

## Active surveillance of prostate cancer with multiparametric magnetic resonance imaging: Review of the literature

Prostat kanserinin aktif izleminde multiparametrik manyetik rezonans görüntüleme: literatür gözden geçirilmesi

Fatih Yanaral<sup>1</sup>, Ufuk Çağlar<sup>2</sup>, Furkan Şendoğan<sup>1</sup>, Murat Binbay<sup>1</sup>

<sup>1</sup> Memorial Şişli Hospital, Department of Urology, Istanbul, Turkey

<sup>2</sup> University of Health Sciences, Haseki Training and Research Hospital, Department of Urology, Istanbul, Turkey



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### Yazışma / Correspondence

Furkan Şendoğan

Kaptan Paşa Mah. Piyale Paşa Bulv.  
Okmeydanı Cd. No: 4, 34384, Şişli  
İstanbul, Türkiye

E-posta: furkandg@hotmail.com

Tel: +90 544 342 63 71

### ORCID

F.Y. 0000-0002-7395-541X  
U.Ç. 0000-0002-4832-9396  
F.Ş. 0000-0001-6865-018X  
M.B. 0000-0001-6675-425X



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### Özet

Günümüzde aktif izlem, düşük riskli prostat kanserine sahip erkeklerde küratif tedaviye alternatif ve kabul edilebilir bir yönetim olarak popülerlik kazanmıştır. Aktif izlem, hastaya gerekli olmayan müdahalelerden kaçınmayı veya önlemeyi, böylece aşırı tedaviyle ilişkili morbiditeyi azaltmayı amaçlar. Güncel kılavuzlarda aktif izlem yaygın olarak kabul görmesine rağmen hem doktor hem de hasta için ileri evre hastalık ve tekrarlayan biyopsi gereksinimi endişesini ortadan kaldıramamaktadır. Bu durum, aktif izlem protokolünde hastalığın durumu hakkında fikir verebilecek, non-invaziv bir yöntem ihtiyacını ortaya çıkarmaktadır. Görüntüleme yöntemlerindeki son teknolojik gelişmeler, modern anatomik ve fonksiyonel sekansların tanımlanması, prostat kanserinin saptanması, risk değerlendirmesi ve takibinde multiparametrik manyetik rezonans görüntülemenin (mpMRG) artan bir role sahip olmasını sağlamıştır. MpMRG'nin başlıca avantajları, üstün anatomik ve kontrast çözünürlüğüne sahip olması, iyonize radyasyonun olmaması ve multi-planar görüntüleme özelliğinin olmasıdır. Ayrıca mpMRG'de PIRADS sınıflaması, prostat kanserinin raporlanmasındaki standardizasyonu sağlamak ve radyologlar arasındaki yorumlara olan güvenilirliği artırarak avantaj sağlamaktadır. Çalışmamız prostat kanserinin aktif izleminde güncel bilgiler ışığında mpMRG'nin rolünü değerlendirmeyi ve özetlemeyi amaçlamaktadır.

**Anahtar Kelimeler:** aktif izlem, prostat kanseri, multiparametrik manyetik rezonans görüntüleme

### Abstract

Nowadays, active surveillance has gained popularity as an acceptable management alternative to definitive treatment for men with low-risk prostate cancer. Active surveillance aims to delay or prevent unnecessary interventions – thereby reducing the morbidity associated with overtreatment. Despite widespread acceptance from current guidelines, active surveillance does not eliminate the concern that the advanced disease and repeat biopsy anxiety for both the clinician and the patient. This situation leads to the search for a method that is non-invasive and can give an idea to the clinician about the status of the disease in the active surveillance protocol. Recent technological advancements and the introduction of modern anatomical and functional sequences have led to a growing role for multiparametric magnetic resonance imaging (mpMRI) in the detection, risk assessment, and monitoring of prostate cancer. The main advantages of MRI are its superior anatomic and contrast resolution, lack of ionizing radiation, and multi-planar capabilities. In addition, standardization of reporting findings such as PI-RADS in mpMRI in prostate cancer provides an advantage by increasing inter-reader reliability among radiologists. This study aims to evaluate and summarize the role of magnetic resonance imaging in the active surveillance of prostate cancer.

**Keywords:** active surveillance, prostate cancer, multiparametric magnetic resonance imaging

**INTRODUCTION**

Prostate cancer is the second most common cancer in men (1). A worldwide prevalence study showed that there were 1,414,259 newly diagnosed prostate cancer patients in 2020 (2). The number of patients diagnosed with prostate cancer has been increasing over the years with the development of diagnostic methods. In parallel with this, the number of patients suitable for low-risk prostate cancer and active surveillance (AS) is increasing.

Active surveillance is a method in which the course of the disease is followed instead of definitive treat-

ment in low-risk prostate cancer. It is applied with a follow-up program determined for patients who meet the appropriate conditions. In contrast to the watchful waiting method, it is necessary to know surgery or other definitive treatment methods may be required in the future for the patients followed up with AS. In the watchful waiting method, patients are given symptomatic treatments, not curative treatment (3). There are many different protocols for patient identification suitable for AS (Table 1).

**Table 1.** Current active surveillance protocols for prostate cancer

Institution	Clinical Stage	Gleason score	Positive cores	Single core positivity	PSA value
JHU	≤T1c	≤6 (3+3)	≤2	≤50%	≤10
ERSPC (PRIAS)	≤T2a	≤6 (3+3)	≤2		≤10
MSKCC	≤T2a	≤6 (3+3)	≤3	≤50%	≤10
UCSF	≤T2a	≤6 (3+3)	≤2		≤10
AUA	≤T2a	≤6 (3+3)	≤3		≤20
NCCN	≤T2a	≤6 (3+3)	≤3		≤10
EAU	≤T2a	≤6 (3+3)			≤10

*JHU: Johns Hopkins University, ERSPC: European Randomized Study of Screening for Prostate Cancer, PRIAS: Prostate Cancer Research International Active Surveillance, MSKCC: Memorial Sloan Kettering Cancer Center, UCSF: University of California, San Francisco, AUA: American Urological Association, NCCN: National Comprehensive Cancer Network, PSA: Prostate specific antigen, EAU: European Association of Urology*

It is very important to evaluate the AS patient correctly. Patients included in AS should be well informed and their demands and thoughts should be evaluated at every stage. Understandably, patients find it difficult to accept a conservative method such as AS after the diagnosis of prostate cancer. In the large-scale study of Miller DC et al. involving 24,450 patients, 55% of the patients chose definitive treatment over AS (4).

As with the patient selection for AS, how AS will be applied also differs between protocols? The DECTECTIVE consensus in the European Association of Urology (EAU) guidelines specified the follow-up protocol as digital rectal examination (at least 1 per year), prostate specific antigen (PSA) (1 per 6 months) and repeat biopsies (5). There is no consensus in the literature on the follow-up protocol. In general, patients are followed up with PSA and repeated biopsy follow-ups.

Follow-up with AS can cause anxiety for both the patient and the clinician. Many studies have been conducted on the reliability of AS. The two most extensive of these were carried out by John Hopkins University and Toronto University. Survival rates in these studies were calculated as 99.9% and 94.3%, respectively (6, 7). With these and similar results, AS before radical prostatectomy is considered in low-risk patients diagnosed with prostate cancer. However, it should not be forgotten that 60% of AS patients will need definitive treatment within 10 years (8). This situation is related to both the progression of the disease over time and the missed clinical significance of cancer at the initial pathology.

Our aim in this review of the literature is to present the use of mpMRI in prostate cancer patients undergoing AS with up-to-date information.

## Methods

We designed our study by conducting a comprehensive literature review written in English, including Embase and Pubmed database. Studies containing the search terms 'active surveillance', 'mpMRI', and 'prostate cancer' were evaluated. In addition, current valid guidelines for prostate cancer were evaluated. First thirty articles and reviews on the role of mpMRI in active surveillance diagnosis and follow-up were reviewed.

### Multiparametric Magnetic Resonance Imaging

For many years, the diagnosis of prostate cancer was made by a biopsy performed blindly from 12 areas of the prostate under the guidance of transrectal ultrasonography (TRUS). MpMRI is an imaging modality that has gained popularity in prostate cancer in recent years. It is frequently used by clinicians in terms of diagnosis, follow-up, and staging of prostate cancer. The term multiparametric describes the addition of diffusion-weighted and dynamic-weighted images to T2 images. Since inflammatory and benign hyperplastic processes are similar to prostate cancer in T2 imaging, a multiparametric system has been adopted for prostate cancer imaging (9). The PI-RADS system for prostate cancer evaluation was defined by the American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR). Lesions are evaluated by scoring increasing according to prostate cancer risk. PI-RADS version 2 was defined in 2015 and PI-RADS version 2.1 was defined in 2019 (10).

MpMRI stands out with its superior anatomical image and high malignancy involvement rates. For localized prostate cancer, it can evaluate all areas of the prostate in detail, not just the peripheral zone. In the study of Schouten G. et al. with 176 patients, patients with a negative prostate biopsy and increased PSA value were examined. Malignant cells were detected in 202 of the 277 lesions marked in mpMRI. One hundred forty-one of these lesions originate from the anterior prostate, which is difficult to reach on standard TRUS biopsy (11). Lawrenceschuk et al. reported that 69% of biopsies taken from suspicious areas in mpMRI in patients with negative TRUS biopsy had tumors in the anterior area. (12). These results show us the im-

portance of having mpMRI-based initial pathology of patients to be AS.

### Role of Multiparametric Magnetic Resonance Imaging in The Decision of Active Surveillance

The clinical characteristics of the patient, pathology result, life expectancy, possible side effects of treatment, and patient preference are important when deciding on AS. In patients followed up with AS, an upgrade stage can be observed in subsequent biopsies. The inaccuracy of the first pathology result and the progression of the disease over time can cause this situation. In the study conducted by Alam R. et al., patients in the low-risk patient group were made biopsy again 2 years later. In 35% of patients, the Gleason stage upgraded compared to biopsy pathology (13). As supported by this study, the application of mpMRI biopsy instead of TRUS biopsy gives the clinician confidence in being close to the actual pathology when making the AS decision.

The decision of AS has been made according to the TRUS biopsy result for a long time. The compatibility of the biopsy result with the actual cancer stage of the prostate is important for the accuracy of the AS decision. In a recent study by Xu N. et al., biopsy pathologies and radical prostatectomy pathologies of patients were evaluated. When all patients were evaluated in the study, there was a 22.7% stage upgrade in radical prostate pathologies compared to biopsy pathologies. In a comparison of mpMRI and TRUS, mpMRI biopsy was found to have higher reliability in predicting the final pathology (14). In the other study conducted by Siddiqui et al. with 582 patients, TRUS biopsy and mpMRI biopsy were performed in the same session. A higher Gleason score was calculated on mpMRI biopsy in 32% of patients (15). The results of these studies show that mpMRI biopsy may be safer for the decision of AS.

With the widespread use of mpMRI, studies on the subject have also increased. In the meta-analysis of Goel et al., the similarity of the mpMRI biopsy result to the final pathology was evaluated. In the analysis in which 1215 patients were evaluated, TRUS biopsy and mpMRI biopsy and radical prostatectomy pathology results were examined. It was observed that the pathological

increase was significantly less in the mpMRI group (16). It is important to reduce the number of patients whose initial biopsy pathology is found to be underestimated and for whom AS is decided. In this respect, confidence in mpMRI biopsy is increasing over time.

Evaluation with mpMRI before the first biopsy can also be predictive of progression. In the study conducted by Vargas et al., 388 patients who were under AS were evaluated. In the study, it was found that patients with a lesion in mpMRI before the first biopsy were more likely to progress than other patients ( $p= 0.001$ ). This study shows us that patients with mpMRI biopsy for AS will be followed more safely in terms of significant prostate cancer (17).

### **Role of Multiparametric Magnetic Resonance Imaging for Patients Followed with Active Surveillance**

In mpMRI evaluation, a PI-RADS score between 1 and 5 is given to each lesion. The PI-RADS score was associated with an increased risk of prostate cancer from 1 to 5. A meta-analysis of 13 studies evaluating patients with suspected or diagnosed prostate cancer examined the sensitivity of mpMRI to clinically significant prostate cancer. Although there was heterogeneity between the results of the studies, the mean positive predictive values of lesions with PI-RADS scores of 3, 4, and 5 were 12%, 48%, and 72%, respectively (18). The aim in AS is not to miss clinically significant prostate cancer, so it can be expected that mpMRI will be included more in the algorithm in patients followed up with AS.

The follow-up of patients managed with AS is as important as the criteria for deciding treatment. Digital rectal examination, one of the procedures included in the standard follow-up protocol, is not an objective evaluation. PSA value is a parameter that is affected by many factors and follows a fluctuating course. Intermittent standard TRUS biopsy is an invasive procedure that affects patient comfort, as well as there is a risk of missing clinically significant cancer as previously stated. For these reasons, there are studies on the development of the AS protocol.

Even if mpMRI is not included in protocols for AS, it is included in many research topics. In a study conducted by Felker ER et al., mpMRI images were added

to the evaluation in addition to PSA value and examination findings in patients followed up with AS. The addition of serial mpMRI images in addition to the PSA value made a significant difference in predicting pathological progression in the study with a mean follow-up of 28 months. In the logistic regression analysis, AUC 0.87 in the evaluation made with PSA value, increased to AUC 0.91 when mpMRI analysis was added ( $p= 0.044$ ) (19). This study showed that AS patients to be followed up with mpMRI will get rid of unnecessary biopsies and evaluate prostate areas that are difficult to reach with biopsy.

MpMRI results are also an interesting subject in the follow-up of patients who are diagnosed with prostate cancer with TRUS biopsy and will be followed up with AS. In the study conducted by Schoots IG et al., 1159 patients were evaluated. Cancer upgrade was observed in 27% of patients who underwent mpMRI target biopsy and systemic biopsy. While only the mpMRI target biopsy cancer upgrade missed 10%, when only a systemic biopsy was evaluated, it was seen to miss 7%. An increase of 35% was observed in patients with positive MRI and 12% in patients with negative MRI (20). This shows that the combination of mpMRI and systemic biopsy is important in the follow-up of AS patients. The success of negative mpMRI findings in excluding prostate cancer provides patients and physicians with the power to continue AS with confidence.

The reliability of negative mpMRI results is very important in patients followed up with AS. MpMRI reports a high negative predictive value (82-95%) in the detection of clinically significant prostate cancer in the literature (21). Therefore, a negative mpMRI result will rule out the presence of occult lesions and confirm that the low-risk disease detected on biopsy is indeed low-risk and shed light on patients followed up with AS (22). In the light of these findings, the AUA guideline was also recommended as an expert opinion in the follow-up of mpMRI AS patients (23).

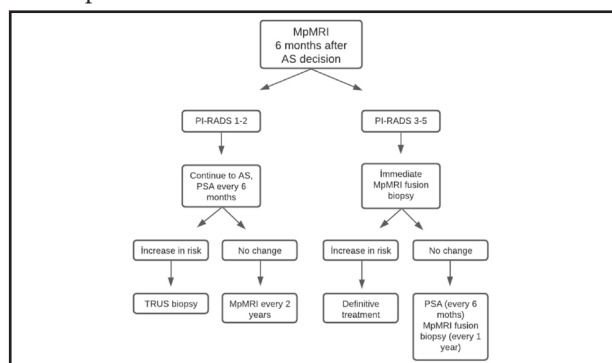
One of the largest studies in the literature on the subject is The Active Surveillance Magnetic Resonance Imaging Study (ASIST). Standard TRUS biopsy and mpMRI biopsy results were evaluated in the follow-up of patients with AS. After two years of follow-up, fewer surveillance failures were observed in the mpMRI arm

(23% and 9.9%) (24). This and similar large-scale studies strengthen the association between AS and mpMRI.

Follow-up of patients with intermittent biopsies is a difficult process to adapt. In addition, prostate biopsy has many complications such as hematuria, rectal bleeding, pain, and sepsis. It has been observed that patients experience adaptation problems over time, even though the process before them is explained when the decision to AS is taken. In a study by Womble R. et al., it was observed that 53.2% of the patients who were AS stopped their prostate biopsy follow-up (25). In another study; Lee EK. et al stated that the patients did not have any problems in compliance with PSA follow-up. However, the rate of discontinuation of intermittent prostate biopsy was reported as 47% in this study (26). The possibility of following AS patients with mpMRI instead of intermittent biopsies will help patients and physicians avoid these problems.

MpMRI can be handled in many ways in the diagnosis and follow-up of AS. Although it is important to avoid unnecessary biopsy in AS patients, the advanced disease should not be missed. MpMRI may also be included in AS protocols in this regard in the future. Even if there is no increase in PSA in active follow-up patients, a new lesion or advanced lesion to be detected in mpMRI may give an early biopsy chance. An active surveillance (AS) algorithm was demonstrated in a review published by Glass AS et al., University of California-Davis Medical Center. Preventing delayed diagnosis with mpMRI will also provide an advantage to clinicians (27). An algorithm that may be appropriate in the light of current data is shown in Figure 1.

**Figure 1.** Active surveillance algorithm of prostate cancer with mpMRI



## CONCLUSION

Today, conservative approaches are gaining importance in prostate cancer as in many diseases. When AS is applied with correct diagnosis and correct follow-up protocols, it prevents patients from facing a major surgery such as radical prostatectomy. However, the discomfort caused by repetitive biopsies and the heterogeneous nature of the PSA value makes physicians think about AS. MpMRI in the diagnosis and follow-up of prostate cancer has led to revolutionary changes. Its place in the diagnosis of prostate cancer is now seen as undisputed. Its place in patients in the AS stage has not been clarified. There are also disadvantages associated with mpMRI. It is not easy to access in every clinic, it is an expensive method, it is related to the radiologist's comments and its interpretation may vary from person to person. In the future, it is possible to follow up patients with AS with mpMRI with high confidence instead of serial biopsies and PSA follow-up. MpMRI can be integrated into the AS follow-up protocol by evaluating the existing literature data. Future prospective studies will also be needed on this topic.

## Conflict of Interest

All authors declared that there is no conflict of interest.

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## Author Contributions

Conception and design; FY, Data acquisition; UÇ, Data analysis and interpretation; UÇ, FŞ, Drafting the manuscript; FY, UÇ, FŞ, Critical revision of the manuscript for scientific and factual content; FY, FŞ, MB, Statistical analysis; UÇ, Supervision; FY, MB.

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