Acta Clin Croat (Suppl. 2) 2019; 58:7-11
doi: 10.20471/acc.2019.58.s2.01

Professional paper

PROSTATE CANCER DIAGNOSIS IN 2019 - CHANGES IN EUROPEAN GUIDELINES AND IMPACT ON DAILY PRACTICE

Igor Tomašković[1,2,3], Sven Nikles[1,3], Miroslav Tomić[1,3], Ivan Pezelj[1,3] and Boris Ružić[1,3.]

[1]Department of Urology, Sestre milosrdnice University Hospital Center, Zagreb;
[2]Faculty of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia;
[3]Referral Center for Prostate Tumors of the Ministry of Health, Republic of Croatia

SUMMARY – Changes in the diagnostic pathway for prostate cancer advised in the most recent Guidelines of the European Association of Urology bring many endeavors for everyday practice. Availability, costs and radiological expertise are still representing a challenge for the adoption of these guidelines in everyday clinical practice. In this article we discuss the current situation regarding these issues and future options.

Key words: *Prostate Cancer, Guidelines, Multiparametric Magnetic Resonance*

Introduction

There were more than 450,000 new cases of prostate cancer (PC) and approximately 107,000 deaths in Europe in the year 2018 (1). Prostate cancer became the most common solid cancer and among three leading causes of mortality from malignancies.

Significant changes have been made in 2019 regarding the diagnosis of prostate cancer in the most recent Guidelines on Prostate Cancer of the European Association of Urology (EU) (2). Through the year 2019, a new concept of prostate cancer screening has emerged also in the EAU Position paper (3). Both have significant impact on a daily urologists' practice.

Diagnosis of prostate cancer

For many years, the standard pathway to diagnose prostate cancer and determine whether it needs to be treated was based on the results of a transrectal ultrasound guided (TRUS) biopsy. This involves multiple needle biopsies to sample tissue across the prostate and possibly detect any cancerous cells. A major disadvantage of this approach, besides discomfort for the patient, was the possibility to miss significant cancer if the part of the prostate with cancer isn't sampled. Also, there was a risk of serious infection. This diagnostic pathway for prostate cancer has resulted in overdiagnosis and consequent overtreatment as well as underdiagnosis and missed diagnoses in many men. Finding a way to improve the number of significant prostate cancers that get caught in time, whilst reducing the number of men who have biopsies unnecessarily, became extremely important. Multiparametric MRI (mp-MRI) of the prostate has been identified as a test that could mitigate both diagnostic errors as well as ensuring that the biopsies are able to be much more targeted to where the cancer is actually located in the prostate (4).

The European Association of Urology (EAU) Guidelines on Prostate Cancer recommended performing prostate mp-MRI before repeated (second) biopsy in 2014. The reason for this change appeared after tremendous work done by the group from the University/College of London (5). Their later land-

Corresponding to: *Assist. Prof. Igor Tomašković, MD, PhD*, Department of Urology, Sestre milosrdnice University Hospital Center, Zagreb; Faculty of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia; Referral Center for Prostate Tumors of the Ministry of Health, Republic of Croatia
e-mail: igor.tomaskovic@kbcsm.hr

mark study PROMIS was the first study that presented blinded data on diagnostic accuracy of both mp-MRI and TRUS-biopsy against an accurate reference test in biopsy-naive men with a suspicion of prostate cancer (6). It was a level 1b evidence for assessment of diagnostic accuracy. The main findings suggested that if mp-MRI was used as a triage test, one-quarter of men might safely avoid prostate biopsy. The high negative predictive value implied that mp-MRI would not miss many clinically significant cancers. Furthermore, over-diagnosis of clinically insignificant cancers might be reduced while detection of clinically significant cancers improved compared with the standard of TRUS-biopsy.

Once the role of mp-MRI against TRUS guided biopsy was elucidated, special attention was given to biopsy-naive man that might have prostate cancer. Three prospective studies evaluated MRI-TBx in biopsy-naive patients: PRECISION, MRI-FIRST trial and The Met Prostaat MRI Meer Mans (4M) study (7, 8,9). PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image guidance or Not?) was a multicenter study designed to determine whether a diagnostic MRI could be used instead of biopsy to rule out prostate cancer. It included 500 men suspected of having prostate cancer after PSA testing. They either received an ultrasound-guided biopsy or MRI without biopsy. Men who had abnormal findings on MRI then went on to have targeted biopsy (7).

There was a 12 percent absolute improvement in the rate of cancer detection for those who had MRI prior to biopsy and MRI targeted biopsy compared to men who just had ultrasound-guided biopsy, while 28 percent of men in the study's MRI group were able to avoid biopsy when their imaging was negative on cancer imaging.

This has subsequently led to a new diagnostic paradigm that implements mp-MRI test before even considering biopsy. Biopsy-naive men with clinical suspicion of prostate cancer should according to new guidelines be first sent to mp-MRI testing based on which further diagnostic work-up can be determined. Summary of the changes in the EAU Guidelines are shown in Table 1.

While recent guidelines suggest a novel diagnostic pathway using mp-MRI before other diagnostic procedures, one should consider limitations to these proofs and barriers that prevent a widespread use of the mp-MRI.

Table 1. Summary of recommendation changes in the EAU Guidelines from 2014 to 2019.

Year	Recommendation for imaging	LE	GR
2014.	When available mp-MRI can be used for targeted repeated prostate biopsy	2b	B
2017.	Perform multiparametric magnetic resonance imaging (mp-MRI) before repeated biopsy when clinical suspicion of PCa persists in spite of negative biopsies.	1a	Strong
2019.	Recommendations in biopsy-naive patients Perform mp-MRI before prostate biopsy.	1a	Weak
2019.	Recommendations in patients with prior negative biopsy Perform mp-MRI before prostate biopsy.	1a	Strong

LE-level of evidence, GR, grade of recommendation

Limitations of Evidence

There are some challenges to accepting mp-MRI as the new standard of care in prostate cancer diagnosis. Although PRECISION trial does provide excellent data on mp-MRI, some important questions remain unanswered. As previously stated, one of the main findings is that 28% of men in the mp-MRI group avoided biopsy, reducing the risk of biopsy complications (sepsis, overdiagnosis etc.). But, as the authors of the study themselves acknowledged, there is no long-term follow-up for these men, and estimates from literature suggest that negative predictive value was 67-88%, meaning that 12% to 33% of those not biopsied harbor high-grade disease (10). Furthermore, PRECISION demonstrates 5.5% absolute risk benefit of MRI-targeted biopsy for detecting the most aggressive cancers (grade group 4 and 5). Their interpretation of this finding is that although mp-MRI may indeed lead to some missed high-grade tumors in patients with false-negative imaging results, this is more than counterbalanced for by the extra high-grade tumors that would be missed by systematic biopsy but that are identified by targeting MRI lesions. As critical editorial in Jama Oncology states, this assumption of oncologic equivalence of high-grade tumors not visible on mp-MRI and high-grade tumors missed by systematic

biopsy is yet to be proved. (11). Some evidence actually suggest that this was not the case. Cumulative incidence of prostate cancer–specific death after 15 years was 0.7% in patients with a negative biopsy result and PSA less than 10 ng/ml in Danish cancer registry and this cohort is very similar to PRECISION (11). This suggests that high-grade cancers missed by systematic biopsy but targeted by mp-MRI are unlikely to be aggressive. On the contrary, the oncologic relevance of high-grade tumors that do not appear on mp-MRI is yet to be fully characterized. Hence, one must consider the drawbacks of these data.

Barriers to Implementing mp-MRI

There are several practical barriers that must be bridged before mp-MRI can be implemented in routine practice. Costs, availability and radiology expertise could hinder the implementation of mp-MRI as the primary diagnostic tool for prostate cancer. It is estimated that by 2020, costs of prostate cancer care in the United States alone will increase to $16.3 billion (12). Obtaining an mp-MRI for every man with an elevated PSA level with a mean cost of mp-MRI of $2550 will sharply accelerate this increase. There are approximately 1.0 - 1.2 million prostate biopsies performed annually in the United States which means that introduction of mp-MRI prior to biopsy would contribute $3 billion annually.

Despite serious costs almost all academic centers in USA perform prostate MRI. On the other hand, only 30% of community hospitals do so (13). Furthermore, only 75% of hospitals perform less than 20 mp-MRIs monthly, with substantial heterogeneity in mp-MRI protocols (13). Interobserver variability between community hospitals and high-volume academic hospitals is substantial and agreement is only 54%. If high standards and accuracy of the test cannot be guaranteed across the country, then the value of the test is questionable.

Situation in Croatia

In a previously reported prospective study, we analyzed diagnostic utility and cost-benefit effect of introducing mp-MRI in diagnostic pathway for prostate cancer in Croatia (14,15). According to contemporary guidelines of that time, the study was designed for patients with indication for mp-MRI in repeated biopsy setting. With the advent of new guidelines recommendation, the cost-benefit effect should be recalculated.

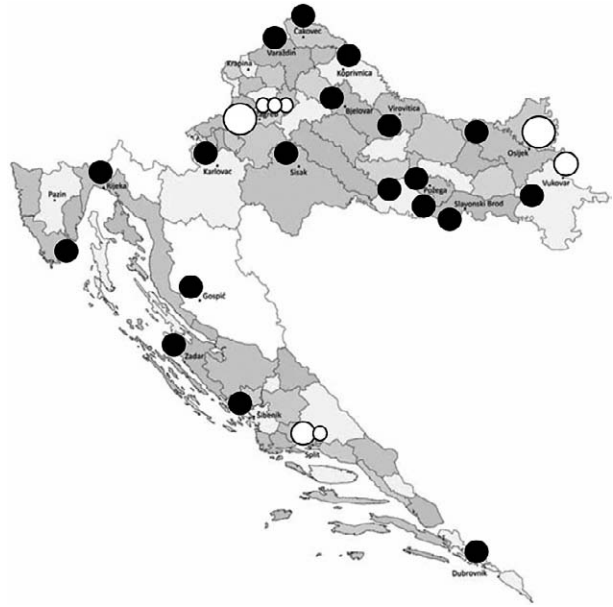

Figure 1. shows availability of mp-MRI in 2019 across Croatia. White dots represent available mp-MRI, black dots unavailable mp-MRI of the prostate.

Regarding availability, mp-MRI is available in most university hospitals and some county hospitals and privately led health practices. In the state-owned facilities the waiting list is 6 months or more while in private settings it is 1-2 weeks. Availability of mp-MRI in September 2019 across the country is presented in Figure 1.

European Association of Urology's Position paper on screening for prostate cancer

On January 22nd, 2019 policy makers, scientific experts, patient groups' representatives with an interest in prostate cancer gathered at the European Parliament to debate the latest evidence and case studies demonstrating the efficacy of prostate cancer screening. It has been stated that prostate cancer mortality has overruled colorectal cancer and is now the second most common cause of cancer-related death in men behind lung cancer. Still, despite the significant public health burden, relatively little is performed on prostate cancer screening at EU level.

However, there is evidence of reducing mortality by multiple rounds of PSA screening, the main obstacle in its implementation at a population level is a huge risk of overdiagnosis and overtreatment. Two large prospective trials, The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Long, Colorectal and Ovarian Cancer Screening Trial (PLCO), evaluated the role of PSA screening (16, 17). In ERSPC, at 16-year follow-up, PSA screening was associated with a relative reduction of 20% in cancer-specific mortality and the absolute difference in PCa mortality between trial arms increased from 14% at 13 years to 18% at 16 years (16). In PLCO after almost 17 years of follow-up, no differences in mortality were detected between the two arms. PLCO was criticized for biased assessment of the efficacy of PSA screening as 80% of control arm received PSA testing at some point. When adjusted for these biases, it seems that PLCO results are consistent with ERSPC. Recent meta-analyses showed PSA screening leads to a small but significant reduction in the risk of dying from PCa over 10 years (19).

In 2019, reflecting the current knowledge about the effects of screening as well as major obstacles such as overdiagnosis and overtreatment, EAU has issued a Position paper (3).

There are several important statements in it:

Statement 1. Screening based on multiple PSA testing rounds reduces PCa-specific mortality in asymptomatic men aged between 55 and 69 years.

Statement 2. Risk of overdiagnosis and overtreatment represent the main barriers for the implementation of PSA screening policies at a population level.

Statement 3. A risk-adapted early detection strategy based on PSA values at the age of 45 years should be offered to well-informed men with life expectancy of 10 years, where screening intervals should be individualized according to baseline PSA levels.

Risk calculators based on PSA, family history, ethnicity, DRE, and prostate volume can assist physicians in the identification of men who should receive prostate biopsy, reducing the risk of overdiagnosis.

Statement 4. Multiparametric MRI can safely improve selection of men for prostate biopsy. The performance of mp-MRI for PCa detection and risk estimation is improved by using it in men at risk of clinically significant disease before prostate biopsy.

Statement 5. Novel tests based on biomarkers and genetic polymorphisms can improve the selection of men with significant PCa and reduce the number of unnecessary prostate biopsies and detection of insignificant disease.

The EAU Position paper concludes that organized, population-based PSA screening programs should be implemented at a European level to reduce PCa mortality, based on a risk-adapted strategy. This should include PSA testing of well-informed men beginning at the age of 45 years, in whom screening intervals should be individualized according to baseline PSA levels. They also include multiparametric MRI in the early detection pathway as a triage test to safely improve selection of men for prostate biopsy. Risk calculators, biomarkers and genetic polymorphisms can further improve the identification of men with significant PCa and reduce the risk of overdiagnosis. The main tool to reduce the risk of overtreatment is an active surveillance in low-risk and some grade group 2 intermediate-risk patients.

Future directions

New diagnostic pathway recommendations issued by the European Association of Urology pose a significant challenge for many European urologists. This approach, both at individual and population level, comes at significant expense. It also takes significant time and resources, both material and human, especially regarding the implementation of MRI. Some countries are still not ready for the full implementation of these guidelines into routine clinical practice. Other tools such as biomarker tests, including free-to-total PSA ratio, Prostate Health Index, and the 4k score can help to further stratify up front need for an MRI and biopsy. This might, at the moment, bridge the lack of resources.

References

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356–87.
2. Mottet N, van den Bergh RCN, Briers E, Cornford P, De Santis M, Fanti S,et al. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. https://uroweb.org/guideline/prostate-cancer.
3. Gandaglia G, Albers P, Abrahamsson PA, Briganti A, Catto JW, Chapple CR, et al. Structured Population-based Prostate-

specific Antigen Screening for Prostate Cancer: The European Association of Urology Position in 2019. Eur Urol. 2019;76 (2):142-150.

4. Stabile A, Giganti F, Rosenkrantz AB, Taneja SS, Villeirs G, Gill IS, et al. Multiparametric MRI for prostate cancer diagnosis: current status and future directions. Nat Rev Urol. 2019; Jul 17.
5. Ahmed H.U., Kirkham A., Arya M., Illing R., Freeman A., Allen C., Emberton M. Is it time to consider a role for MRI before prostate biopsy? Nature Reviews Clinical Oncology 2009;6(4);197-206.
6. Ahmed, H. U. et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017; 389, 815–822.
7. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018;378:1767–77.
8. Rouviere O, *et al.* Added value of prostate systematic and targeted biopsy based on multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective multicentre paired diagnostic study. Lancet Oncol 2018.
9. van der Leest, M., *et al.* Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonanceguided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. Eur Urol, 2018. S0302: 30880.
10. Moldovan PC, Van den Broeck T, Sylvester R, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? a systematic review and meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. Eur Urol. 2017;72(2):250-266.
11. Kim, S. J., Vickers, A. J, Hu, J. C. Challenges in Adopting Level 1 Evidence for Multiparametric Magnetic Resonance Imaging as a Biomarker for Prostate Cancer Screening. JAMA Oncology 2018; 4(12)-.1163-4.
12. Mariotto ABY, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020.J Natl Cancer Inst. 2011;103(2):117-128.
13. Leake JL, Hardman R, Ojili V, et al. Prostate MRI: access to and current practice of prostate MRI in the United States. J Am Coll Radiol. 2014;11(2):156- 160.
14. Pezelj I, Tomašković I, Bolanča Čulo K, Novosel L, Tomić M, Reljić A, et al. Cost-Benefit Analysis of the Introduction of Mp-Mri Guided Biopsies in Croatia. Acta Clin Croat. 2018 Oct;57(Suppl 1):46-49. doi: 10.20471/acc.2018.57.s1.06.
15. Tomašković I, Pezelj I, Bolanča Čulo K, Novosel L, Nikles S, Tomić M, et al. Diagnostic Value of Cognitive-Registration Multiparametric Magnetic Resonance Guided Biopsy for the Detection of Prostate Cancer after Initial Negative Biopsy. Acta Clin Croat. 2018 Oct;57(Suppl 1):40-45. doi: 10.20471/acc.2018.57.s1.05.
16. Hugosson J, Roobol MJ, Mansson M, Tammela TLJ, Zappa M, Nelen V, et al. A 16-yr follow-up of the European randomized study of screening for prostate cancer. Eur Urol 2019;76:43–51.
17. Andriole GL, Crawford ED, Grubb 3rd RL, Buys SS, Chia D, Church et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of followup. J Natl Cancer Inst 2012;104:125–32.
18. Pinsky PF, Miller E, Prorok P, Grubb R, Crawford ED, Andriole G. Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. BJU Int 2019;123:854–60.
19. Ilic D, Djulbegovic M, Jung JH, Hung J, Chang HE, Qi Z, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and metaanalysis. BMJ 2018; 362:k3519.

Sažetak

DIJAGNOSTIKA RAKA PROSTATE U 2019. - PROMJENE U EUROPSKIM SMJERNICAMA I UTJECAJ NA SVAKODNEVNU PRAKSU

I. Tomašković, S. Nikles, M. Tomić, I. Pezelj i *B. Ružić*

Promjene u dijagnostici karcinoma prostate preporučene u najnovijim Smjernicama Europskog udruženja za urologiju donose mnoge izazove u svakodnevnoj praksi. Dostupnost, troškovi i pouzdanost slikovnog nalaza i dalje su izazov za usvajanje ovih smjernica u svakodnevnoj kliničkoj praksi. U ovom članku raspravljamo o trenutnoj situaciji u Hrvatskoj i svijetu i o budućim opcijama.

Ključne riječi: *karcinom prostate, smjernice, multiparametrijska magnetska rezonanca*