Review Article

Role of mpMRI of the prostate in screening for prostate cancer

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Abstract: Prostate cancer screening offers the opportunity to significantly reduce morbidity and mortality from this disease. Currently, serum prostate-specific antigen (PSA) testing is the most widely used screening modality. However, PSA testing continues to have low positive and negative predictive value leading to unnecessary invasive prostate biopsy while missing patients with aggressive forms of the disease. Magnetic resonance imaging (MRI) has been gaining an increasingly large role in the management of patients with early stage prostate cancer including diagnosis in patients with abnormal PSA levels, monitoring of patients on active surveillance, and staging prior to definitive interventions. MRI-based prostate cancer risk assessment has been shown to better distinguish between clinically-significant and insignificant tumors than PSA testing alone or from nomograms. Preliminary data indicate that, among unselected patients, MRI outperforms PSA in the identification of patients with clinically significant prostate cancer. Further work is needed to examine the role of mpMRI in prostate cancer screening.

Keywords: Early detection of cancer; magnetic resonance imaging (MRI); prostatic neoplasms; risk assessment; prostate-specific antigen

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Introduction

Prostate cancer screening using serum prostate specific antigen (PSA) testing continues to be controversial, despite two large randomized studies evaluating whether PSA screening reduces mortality. On one hand, appropriately conducted prostate cancer screening offers the opportunity to reduce morbidity and mortality due to prostate cancer (1). On the other, PSA-based screening is associated with significant over-diagnosis and overtreatment with resultant morbidity (2). Thus, more nuanced approaches to PSA-screening have been sought. These include the use of nomograms, novel biochemical markers, and imaging approaches. These have only been employed among men identified at risk based on an elevated serum PSA level. We review the perspective on the role of multiparametric magnetic resonance imaging (mpMRI) in prostate cancer screening.

Prostate cancer screening: rationale and current controversy

Despite significant stage migration associated with PSA testing (3), prostate cancer remains the third leading cause of cancer death among men in the Western world (4). Two large randomized studies in the U.S. [Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (5)] and Europe [European Randomized Study of Screening for Prostate Cancer (ERSPC) (1)] have been conducted to evaluate whether screening for prostate cancer using serum PSA levels improves overall and prostate cancer mortality. Based on the most recent data from the ERSPC with

13 years of follow up (6), the absolute risk reduction in prostate cancer mortality from PSA screening was 0.11 per 1,000 person years or 1.28 per 1,000 men randomized. This risk reduction has increased with increasing duration of follow up. Additional analysis has shown an absolute risk reduction of developing metastatic disease was 3.1 per 1,000 men randomized (7). In a subgroup of the ERSPC with longer follow-up, the absolute risk reduction in prostate cancer mortality was 4.0 per 1,000 men randomized (8). This corresponds to a number needed to screen of 293 to prevent one prostate cancer death.

The original report of the PLCO study showed no difference in prostate cancer related mortality between formally screened and unscreened men, despite a significant increase in the rate of prostate cancer diagnosis (5). Since that time, further analyses of this cohort have demonstrated similar results. The validity of this dataset has been questioned due to the large degree of contamination of the control group (9) and the poor study power. Thus, it is unlikely that further follow-up studies or additional analyses will change the initial results.

In their review of the literature surrounding PSA-based prostate cancer screening in 2012, the U.S. Preventative Services Task Force (USPSTF) concluded that such screening resulted in minimal decreases in prostate cancer mortality (0 to 1 prostate cancer deaths per 1,000 men screened) with significant harm due to medical evaluation including biopsy, over-diagnosis and overtreatment (2). Thus, the USPSTF concluded, with moderate certainty, that the benefit of PSA-based screening did not outweigh the harms and thus recommended against PSA-based screening for prostate cancer (2). However, currently the USPSTF is reviewing their recommendation and has drafted a position which is more favourable towards screening, based on new follow-up data (10).

In addition to harms of biopsy and intervention, the primary concern regarding PSA-based prostate cancer screening is the inability to distinguish between patients with indolent and aggressive forms of the disease. Prostate cancer screening programs have traditionally used a serum PSA cut-off of 4.0 ng/mL to indicate abnormality. However, many men with PSA values in excess of 4.0 ng/mL do not have prostate cancer, and even fewer have clinically significant prostate cancer. Further, up to 25% of men with PSA levels less than 4.0 ng/mL will be found to have high-grade prostate cancer, if subject to biopsy (11). Thus, PSA-based prostate cancer screening lacks both sensitivity and specificity to identify men with aggressive prostate cancer. As a result, in addition to significant over-diagnosis and overtreatment which has been well recognized, there is a risk for under-diagnosis.

Coinciding with the introduction of PSA testing, prostate cancer mortality has decreased approximately 40% from an epidemiologic perspective (12). Approximately 45–70% of the decline in mortality is attributable to PSA-based prostate cancer screening (13). It is predicted that complete discontinuation of PSA-based screening would result in the prevention of over-diagnosis for 710,000 to 1,120,000 men in the United States over a 12-year period (14). On the other hand, it would result in 36,000 to 57,000 preventable deaths due to prostate cancer over the same period. Thus, as a public health intervention, prostate cancer screening offers the opportunity to decrease prostate cancer related mortality. Current approaches are associated with unacceptably high levels of toxicity, over-diagnosis and overtreatment, and under-diagnosis.

Attempts to overcome limitations of PSA-based screening

Advances and innovations in prostate cancer screening have sought to identify patients with an increased risk of prostate cancer (or clinically significant prostate cancer) among men with an abnormal PSA testing results, to guide biopsy decisions. The most widely adopted of these is the use of nomograms combining demographic details, physician examination findings, and biochemical results. The Prostate Cancer Prevention Trial based nomogram (15) and Sunnybrook Risk Calculator (16) are two well-known examples. Further advances have included the development of the STHLM3, a model combining plasma biomarkers (including PSA), genetic polymorphisms, demographic and clinical data in a population-based cohort of men with serum PSA ≥1 ng/mL (17). In addition, there are a number of other biomarkers currently available to assist with prostate cancer risk stratification and diagnosis, including the 4K score (18), an aggregate score of four kallikreins (total PSA, free PSA, intact PSA, and human kallikrein 2), PCA3 (prostate cancer antigen 3) (19), a non-coding RNA gene product, and PHI (prostate health index, a mathematical combination of total, free and [-2]pro-PSA) (20). A greater number of prognostic biomarkers exist for patients following prostate cancer diagnosis, including Prolaris (21), Oncotype Dx Prostate (22), Decipher (23) and ProMark (24). Despite their value, there are many limitations to the molecular factors which have been examined thus far. Frequently, there

are systematic errors in the design and execution of the discovery studies (25). First, many biomarkers are developed without a clear clinical or research question which they seek to address. This is reflected in the wide variety of outcomes reported in the studies assessing the available tests. Further, the majority have been developed using surrogate endpoints (26), rather than clinically significant outcomes such as distinguishing clinically-relevant disease from the absence of clinically-significant disease (25). Finally, there is a significant publication bias in biomarker development studies with selective non-reporting (25). Thus, new biomarkers currently serve as adjunct tests to PSA and not as new screening instruments.

Magnetic resonance imaging (MRI) of the prostate

Multiparametric prostate magnetic resonance imaging has an increasingly large role in the early detection and staging of prostate cancer. MRI (principally limited to T2-weighted imaging) was initially used as a staging test in patients with prostate cancer for assessment of direct extra-prostatic extension. Significant variability in diagnostic performance, limited ability to detect microscopic disease, and inability to localize the tumor within the gland itself limited its adoption (27). Since that time, and in particular with the addition of diffusion weighted imaging allowing visualization of tumor within the prostate, there has been a migration in the use of MRI earlier in the disease process, and to direct biopsy (28).

When performed in the evaluation of patients with elevated PSA levels with previous negative prostate biopsy, mpMRI has been shown to identify clinically significant prostate cancers which would have been otherwise missed by routine systematic biopsy (29). Among men with an abnormal PSA who have never undergone a prostate biopsy, mpMRI demonstrated promise in both the detection and exclusion of prostate cancer, using an extensive prostate mapping biopsy (median 41 cores) as the referent (30). In a multivariable analysis of an independent cohort including age, family history, prior 5-alpha reductase inhibitor use, digital rectal examination findings, PSA level, PSA density, and MRI score, only MRI score was predictive of clinically significant (Gleason score ≥7) prostate cancer among men without a history of previous prostate biopsy (adjusted OR 40.2, P=0.01) (31). A screening approach using PSA testing followed by MRI for those with an elevated PSA (either ≥1.8 ng/mL or ≥3.0 ng/mL) showed significantly increased specificity compared to a strategy comprising PSA alone (32). Use of a lower PSA threshold prior to MRI significantly increased the testing strategy sensitivity and detection of clinically significant cancer.

Recently Salami *et al.* compared the performance of the PCPT risk calculator and mpMRI in the prediction of clinically significant prostate cancer, among men with an abnormal PSA (33). Prior to biopsy, MRI significantly outperformed the nomogram in identifying patients with clinically significant disease who may benefit from diagnosis and treatment. Thus, as the PCPT risk calculator is used in the initial screening phases for prostate cancer, it is reasonable to examine whether MRI might prove a better screening test.

Pilot study to examining the feasibility of MRI prostate cancer screening

In contrast to previously described approaches, the use of mpMRI in an otherwise unselected population is relatively untested. We recently conducted a pilot study assessing the feasibility of mpMRI as an initial prostate cancer screening test (34). Following a newspaper based call for volunteers, 319 men agreed to participate in this study. Of these, 120 were eligible, 50 were enrolled due to limitations in funding, and 47 completed the study protocol. Serum PSA testing, mpMRI, digital rectal examination, and systematic (+/- targeted) prostate biopsies were performed on all men. Prostate cancer was identified in 18 of 47 men (38.3%). mpMRI (AUC 0.81, 95% CI: 0.67–0.94) significantly outperformed PSA (AUC 0.67, 95% CI: 0.52–0.84) in the prediction of prostate cancer. In multivariable analyses including age, digital rectal examination findings, PSA and MRI score, mpMRI was the only significant predictor for the presence of prostate cancer (adjusted OR 2.7, 95% CI: 1.4–5.4). These findings were even stronger when we sought to predict only clinically significant prostate cancer (Gleason ≥7; adjusted OR 3.5, 95% CI: 1.5–8.3).

Potential advantages of MRI-based screening

The use of MRI as an initial screening test for prostate cancer has a number of potential advantages, compared to an approach which relies upon PSA testing for initial risk stratification. The most important diagnostic characteristic of a screening test is high sensitivity. That is, can MRI can reliably identify clinically significant prostate cancer? Failure to do so would potentially exacerbate the issue

of under diagnosis of prostate cancer highlighted above. The literature in this regard is somewhat conflicting: a recent systematic review demonstrated variable diagnostic accuracy characteristics of MRI in the diagnosis of clinically significant prostate cancer, depending on the thresholds for diagnosis (35). However, sensitivity was generally high (5/8 studies demonstrating sensitivity exceeding 90%). In clinical practice, negative predictive value is of more importance than sensitivity. Thus, the clinically important question is, "*In a patient with a negative MRI, can we be confident that there is no significant prostate cancer present?*". While the available data are based upon those who have undergone pre-screening with PSA testing, a recent review demonstrated that the negative predictive value of mpMRI was highest among populations with the lowest cancer incidence (36). Thus, this parameter is likely to be maximized when MRI is used in a screening context, rather than among pre-screened men. Further, MRI with guided biopsy where a targetable lesion is identified has much higher negative predictive value (96.9%) than standard transrectal ultrasound guided biopsy (37).

Radiologist expertise may also significantly influence the diagnostic characteristics of MRI. In a cohort of 101 patients, Branger *et al.* showed that a negative MRI could not exclude the presence of clinically significant cancer (manifest by Gleason pattern 4 or extraprostatic extension) (38). However, experienced radiologists can exclude significant volumes (core length ≥5 mm) of Gleason score ≥7 prostate cancer with a negative predictive value exceeding 95% (39).

Given the current controversies regarding prostate cancer screening, at least as important as the ability of MRI to detect clinically significant disease is the potential for this screening strategy to reduce the over diagnosis of clinically insignificant prostate cancer. In the report by Priester *et al.*, tumors missed by MRI were significantly lower grade, smaller volume, and shorter in diameter than MRI-visible lesions (40). Thus, while these authors consider MRI to be insensitive for prostate cancer, they have in fact shown that MRI may reduce the issue of over diagnosis of clinically insignificant disease without meaningfully compromising the diagnosis of clinically significant cancer (40). These data corroborate previous evidence that the use of MRI and ultrasound TRUS/MRI fusion imaging in the targeting of prostate biopsy limits the diagnosis of clinically insignificant prostate cancer while simultaneously increasing detection of clinically significant prostate cancer (41). Work in mice models has demonstrated that diffusion weighted imaging (DWI) derived apparent diffusion coefficient (ADC) measurements can distinguish between benign from malignant disease and between well-differentiated and poorly-differentiated cancers (42). This has been further validated in human studies with ADC from mpMRI showing higher Gleason score cancers are associated with lower ADC (43). Work continues on the potential role of ADC as a non-invasive quantitative imaging biomarker for prediction of the presence of clinically significant cancer (44).

Much of the data supporting the potential role for screening MRI is drawn not from the use of MRI in the screening setting but extrapolation from reports among patients with abnormal PSA test results. Thus, further research is required.

Potential disadvantages of MRI-based screening

The primary disadvantage of adoption of an mpMRI-based approach for prostate cancer screening is the associated cost which is considerably higher than a serum PSA test at a population-based level. However, the per-individual costs for a prostate MRI are similar to those for colonoscopy, the recommended screening test for colorectal cancer (45). In addition, in many jurisdictions, the cost of mpMRI is equivalent or marginally higher than genomic tests with the added advantage of providing biopsy guidance. Further, compared to ongoing PSA-based screening, mpMRI-based prostate cancer screening offers the opportunity to significantly reduce the cost and morbidity of prostate cancer screening by reducing the number of biopsies performed and reducing the diagnosis of clinically insignificant prostate cancer, thus reducing overtreatment. In addition, compared to abandoning prostate cancer screening entirely, mpMRI-based prostate cancer screening offers the opportunity to diagnose clinically significant disease while it is localized and amenable to prostate-directed treatments. Such treatment has been shown to decrease progression to metastatic disease (46), which carries significant cost and morbidity (47). Should mpMRI be proven to be a better screening instrument than serum PSA from further studies, comprehensive cost-related studies will be required to determine the feasibility of mpMRI screening for prostate cancer.

Future directions

We are currently undertaking a research ethics board approved (Sunnybrook Health Sciences Centre Research Ethics Board #130-2016) and registered (ClinicalTrials.gov Identifier NCT02799303) randomized trial of PSA-testing

and MRI for prostate cancer screening among an unselected cohort of men. In order to truly examine the performance of MRI in a screening setting, we are recruiting men aged 50 years and older in the general population with a life expectancy of at least 10 years and excluding those with symptomatic lower urinary tract voiding symptoms (IPSS score ≥8), those with a family history of prostate cancer (one or more first degree relatives diagnosed <50 years of age), a history of a previous prostate biopsy, who have undergone a serum PSA determination within 3 years of the recruitment date, an abnormal digital rectal examination of the prostate consistent with prostate cancer, prior or current use of 5-alpha reductase inhibitor medications (finasteride or dutasteride). Patients will be randomized using independent, electronic concealed allocation to prostate cancer screening using multi-parametric MRI (experimental arm) or serum PSA testing (active control).

Patient randomized to MRI-based screening who are found to have one or more lesions scoring PIRADS 4 or 5 will be considered to have a "positive MRI" and be recommended for targeted biopsy using a MRI/TRUS fusion system (Eigen, Artemis, Grass Valley, CA, USA or equivalent), in addition to systematic 12-core prostate biopsy. Patients with no identified PIRADS 4 or 5 lesions will not receive prostate biopsy. They will undergo follow-up by the study nurse. At the end of the study period (3 years from inclusion), patients in the "negative MRI" group will undergo a serum PSA test according to protocol. Patients with a serum PSA level less than 4.0 ng/mL will be managed expectantly with results provided to their primary care physician. Patients with a serum PSA level greater than 4.0 ng/mL will be recommended for systematic 12-core random, systematic prostate biopsy.

Patients randomized to PSA-based screening who have a serum PSA level less than 4.0 ng/mL ("negative PSA") will be managed expectantly with results provided to their primary care physician. Patients with a serum PSA level greater than 4.0 ng/mL ("positive PSA") will be recommended for systematic 12-core prostate biopsy.

All prostate biopsies will be read by genitourinary cancer pathologists in order to determine the presence of clinically-significant prostate cancer (study endpoint; Gleason score ≥7; ISUP Grade Group ≥2). The secondary endpoint will be detection of clinically-insignificant prostate cancer (Gleason score ≤6; ISUP Grade Group 1). Following a cancer diagnosis, patients will receive standard of care consultation with both a urologist and a radiation oncologist to inform their treatment decisions, which are independent of this study.

Based on our pilot study, we anticipated 14% of patients in the PSA group and 21% of those in the MRI group will be diagnosed with clinically-significant cancer. Based on standard assumptions of an alpha =0.05 and beta =0.20 (power =0.80) and a superiority design, we require 918 patients in total (459 in each arm). Allowing for a 10% dropout rate, we are seeking to recruit 1,010 patients. Thus far, we have screened approximately 450 patients and recruited approximately 150 patients.

Technological advancements may make MRI-based prostate cancer screening more feasible. While historically prostate MRI has required the use of an endorectal coil (48), recent advances in MRI technology have obviated the need for the coil (49), thus reducing the cost and burden of the imaging. Further advancement may provide additional benefit. First is a simplified approach to imaging without the administration of contrast and with limited sequences. Such biparametric MRI has been shown to improve the accuracy of detecting clinically significant prostate cancer in men with abnormal PSA results (50). Such an approach requires only half the in-bore time as current mpMRI techniques and is being used in our study. Second, advances in computer aided diagnostics and machine learning have demonstrated that automated interpretation of prostate MRI may be feasible (51,52). This may reduce the burden of radiologist interpretation and allow for greater reliability of interpretation. Recently presented, but not yet published, data show that combining mpMRI and clinical parameters in a nomogram may allow for a more refined selection of patients for prostate biopsy (53), thus reducing health care cost and interventional morbidity.

Together, these innovations have the potential to substantially decrease the cost of prostate MRI, enabling more widespread use. In addition, use of MRI prior to biopsy resulted in a 51% reduction in the number of biopsies performed and decreased the diagnosis of low risk prostate cancer by nearly 90%, among men with elevated PSA (37). Due to the significant costs of biopsy procedures, potentially unnecessary treatment, the management of complications of each of these, and avoidance of costly therapies for advanced disease due to improved diagnosis of intermediate and high-risk prostate cancer, earlier and more widespread use of MRI in prostate cancer may indeed prove cost effective.

Conclusions

Prostate cancer screening offers the opportunity to prevent

morbidity and mortality with significant public health implications. However, PSA-based screening is fraught with concerns regarding both over diagnosis of clinically insignificant disease and under diagnosis. MpMRI exhibits favourable diagnostic characteristics which may make it a useful screening tool. Ongoing trials are underway in order to assess this in a prospective fashion.

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Footnote

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References

1. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
2. Moyer VA, Force U. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2012;157:120-34.
3. Etzioni R, Gulati R, Falcon S, et al. Impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: a surveillance modeling approach. Med Decis Making 2008;28:323-31.
4. Advisory CCSs, Statistics. CoC. Canadian Cancer Statistics 2014. Toronto, ON: Canadian Cancer Society; 2014.
5. Andriole GL, Crawford ED, Grubb RL, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310-9.
6. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027-35.
7. Schröder FH, Hugosson J, Carlsson S, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC) Eur Urol 2012;62:745-52.
8. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725-32.
9. Shoag JE, Mittal S, Hu JC. Reevaluating PSA testing rates in the PLCO trial. N Engl J Med 2016;374:1795-6.
10. Bibbins-Domingo K, Grossman DC, Curry SJ. The US Preventive Services Task Force 2017 Draft Recommendation Statement on Screening for Prostate Cancer: An Invitation to Review and Comment. JAMA 2017. [Epub ahead of print].
11. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004;350:2239-46.
12. Barocas DA, Mallin K, Graves AJ, et al. Effect of the USPSTF grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the United States. J Urol 2015;194:1587-93.
13. Etzioni R, Tsodikov A, Mariotto A, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control 2008;19:175-81.
14. Gulati R, Tsodikov A, Etzioni R, et al. Expected population impacts of discontinued prostate-specific antigen screening. Cancer 2014;120:3519-26.
15. Ankerst DP, Hoefler J, Bock S, et al. Prostate cancer prevention trial risk calculator 2. 0 for the prediction of low- vs high-grade prostate cancer. Urology 2014;83:1362-7.
16. Nam RK, Toi A, Klotz LH, et al. Assessing individual risk for prostate cancer. J Clin Oncol 2007;25:3582-8.
17. Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncol 2015;16:1667-76.
18. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. Eur Urol 2015;68:464-70.
19. Chevli KK, Duff M, Walter P, et al. Urinary PCA3 as a predictor of prostate cancer in a cohort of 3,073 men undergoing initial prostate biopsy. J Urol 2014;191:1743-8.
20. Lepor A, Catalona WJ, Loeb S. The prostate health index: its utility in prostate cancer detection. Urol Clin North Am 2016;43:1-6.
21. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011;12:245-55.
22. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A

17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014;66:550-60.
23. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047-53.
24. Blume-Jensen P, Berman DM, Rimm DL, et al. Development and clinical validation of an in situ biopsy-based multimarker assay for risk stratification in prostate cancer. Clin Cancer Res 2015;21:2591-600.
25. Prensner JR, Rubin MA, Wei JT, et al. Beyond PSA: the next generation of prostate cancer biomarkers. Sci Transl Med 2012;4:127rv3.
26. Martin NE, Mucci LA, Loda M, et al. Prognostic determinants in prostate cancer. Cancer J 2011;17:429-37.
27. Rifkin MD, Zerhouni EA, Gatsonis CA, et al. Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi-institutional cooperative trial. N Engl J Med 1990;323:621-6.
28. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of Mr/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-7.
29. Vourganti S, Rastinehad A, Yerram NK, et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. J Urol 2012;188:2152-7.
30. Abd-Alazeez M, Kirkham A, Ahmed HU, et al. Performance of multiparametric MRI in men at risk of prostate cancer before the first biopsy: a paired validating cohort study using template prostate mapping biopsies as the reference standard. Prostate Cancer Prostatic Dis 2014;17:40-6.
31. Weaver JK, Kim EH, Vetter JM, et al. Presence of Magnetic Resonance Imaging Suspicious Lesion Predicts Gleason 7 or Greater Prostate Cancer in Biopsy-Naive Patients. Urology 2016;88:119-24.
32. Grenabo Bergdahl A, Wilderäng U, Aus G, et al. Role of magnetic resonance imaging in prostate cancer screening: a pilot study within the göteborg randomised screening trial. Eur Urol 2016;70:566-73.
33. Salami SS, Vira MA, Turkbey B, et al. Multiparametric magnetic resonance imaging outperforms the Prostate Cancer Prevention Trial risk calculator in predicting clinically significant prostate cancer. Cancer 2014;120:2876-82.
34. Nam RK, Wallis CJ, Stojcic-Bendavid J, et al. A pilot study to evaluate the role of magnetic resonance imaging for prostate cancer screening in the general population. J Urol 2016;196:361-6.
35. Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? a systematic review of the literature. Eur Urol 2015;68:1045-53.
36. 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. [Epub ahead of print].
37. Pokorny MR, De Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (Mr) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol 2014;66:22-9.
38. Branger N, Maubon T, Traumann M, et al. Is negative multiparametric magnetic resonance imaging really able to exclude significant prostate cancer? The real-life experience. BJU Int 2017;119:449-55.
39. Anastasiadis E, Charman SC, Arumainayagam N, et al. What burden of prostate cancer can radiologists rule out on multiparametric magnetic resonance imaging? a sensitivity analysis based on varying the target condition in template prostate mapping biopsies. Urology 2015;86:544-51.
40. Priester A, Natarajan S, Khoshnoodi P, et al. Magnetic resonance imaging underestimation of prostate cancer geometry: use of patient specific molds to correlate images with whole mount pathology. J Urol 2017;197:320-6.
41. Meng X, Rosenkrantz AB, Mendhiratta N, et al. Relationship between prebiopsy multiparametric magnetic resonance imaging (MRI), biopsy indication, and MRI-ultrasound fusion-targeted prostate biopsy outcomes. Eur Urol 2016;69:512-7.
42. Hill DK, Kim E, Teruel JR, et al. Diffusion-weighted MRI for early detection and characterization of prostate cancer in the transgenic adenocarcinoma of the mouse prostate model. J Magn Reson Imaging 2016;43:1207-17.
43. Hambrock T, Somford DM, Huisman HJ, et al. Relationship between apparent diffusion coefficients at 3. 0-T MR imaging and Gleason grade in peripheral zone prostate cancer. Radiology 2011;259:453-61.

44. Johnston E, Pye H, Bonet-Carne E, et al. INNOVATE: A prospective cohort study combining serum and urinary biomarkers with novel diffusion-weighted magnetic resonance imaging for the prediction and characterization of prostate cancer. BMC Cancer 2016;16:816.
45. Short MW, Layton MC, Teer BN, et al. Colorectal cancer screening and surveillance. Am Fam Physician 2015;91:93-100.
46. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415-24.
47. Seal B, Sullivan SD, Ramsey SD, et al. Comparing hospital-based resource utilization and costs for prostate cancer patients with and without bone metastases. Appl Health Econ Health Policy 2014;12:547-57.
48. Türkbey B, Bernardo M, Merino MJ, et al. MRI of localized prostate cancer: coming of age in the PSA era. Diagn Interv Radiol 2012;18:34-45.
49. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate Mr guidelines 2012. Eur Radiol 2012;22:746-57.
50. Rais-Bahrami S, Siddiqui MM, Vourganti S, et al. Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. BJU Int 2015;115:381-8.
51. Khalvati F, Wong A, Haider MA. Automated prostate cancer detection via comprehensive multi-parametric magnetic resonance imaging texture feature models. BMC Med Imaging 2015;15:27.
52. Giannini V, Mazzetti S, Vignati A, et al. A fully automatic computer aided diagnosis system for peripheral zone prostate cancer detection using multi-parametric magnetic resonance imaging. Comput Med Imaging Graph 2015;46 Pt 2:219-26.
53. Alberts A, Chiu P, Schimmoller L, et al. Multivariable risk-based patient selection for targeted prostate biopsy in case of suspicious Magnetic Resonance Imaging could reduce unnecessary biopsy procedures. European Urology Supplements 2016;15: e1566-e1568.

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