Thomas Jefferson University

Jefferson Digital Commons

Department of Urology Faculty Papers

Department of Urology

10-14-2019

Comparison of MRI- and TRUS-Informed Prostate Biopsy for Prostate Cancer Diagnosis in Biopsy-Naive Men: A Systematic Review and Meta-Analysis.

Hanan Goldberg
University of Toronto; SUNY Upstate Medical University

Ardalan E. Ahmad
University of Toronto

Thenappan Chandrasekar
Thomas Jefferson University

Follow this and additional works at: https://jdc.jefferson.edu/urologyfp

Laurence Klotz
Sunnybrook Health Sciences Centre

Part of the Oncology Commons, and the Urology Commons

Let us know how access to this document benefits you

Mark Emberton
University College London

See next page for additional authors

Recommended Citation

Authors

Hanan Goldberg, Ardalan E. Ahmad, Thenappan Chandrasekar, Laurence Klotz, Mark Emberton, Masoom A. Haider, Samir S. Taneja, Karan Arora, Neil Fleshner, Antonio Finelli, Nathan Perlis, Mark D. Tyson, Zachary Klaassen, and Christopher J.D. Wallis

Author's Accepted Manuscript

Comparison of MRI- and TRUS-Informed Prostate Biopsy for Prostate Cancer Diagnosis in

Biopsy-Naive Men: A Systematic Review and Meta-Analysis

Goldberg H, Ahmad A, Chandrasekar T, Klotz L, Emberton M, Haider MA, Taneja SS, Arora K,

Fleshner N, Finelli A, Perlis N, Tyson MD, Klaassen Z and Wallis CJD

DISCLAIMER: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our subscribers we are providing this early version of the article. The paper will be copy edited and typeset, and proof will be reviewed before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to The Journal pertain.

Embargo Policy

All article content is under embargo until uncorrected proof of the article becomes available online. We will provide journalists with PDF copies on request so that stories can be researched and written. Media inquiries should be directed to LippincottJournalsMedia@Wolterskluwer.com.

1

Comparison of MRI- and TRUS-informed prostate biopsy for prostate cancer diagnosis in biopsy-naïve men: a systematic review and meta-analysis

Hanan Goldberg[1,2]* MD, Ardalan E. Ahmad[1]* MD, Thenappan Chandrasekar[3] MD, Laurence Klotz[4] MD, Mark Emberton[5] MD, Masoom A. Haider[6] MD, Samir S. Taneja[7] MD, Karan Arora[8] MD, Neil Fleshner[1] MD, MPH, Antonio Finelli[1] MS, MSc, Nathan Perlis[1] MD, MSc, Mark D. Tyson[8] MD, Zachary Klaassen[9], MD, MSc, Christopher J.D. Wallis[1] MD, PhD

*Contributed equally

[1] Urology Division, Surgical Oncology Department, Princess Margaret Cancer Center, University Health Network, University of Toronto, Toronto, Ontario, Canada

[2] Department of Urology, SUNY Upstate Medical University, Syracuse, NY, USA

[3] Department of Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia PA, USA

[4] Division of Urology Sunnybrook Health Sciences Centre. Toronto. ON. Canada.

[5] Division of Surgery and Interventional Science, University College London, London, UK.

[6] Department of Medical Imaging, Princess Margaret Cancer Center, Lunenfeld-Tanenbaum Research Institute, University of Toronto, Toronto, Ontario, Canada

[7] Department of Urology and Radiology, NYU Langone Health, New York, NY, USA

[8] Department of Urology, Mayo Clinic Hospital, Phoenix, AZ

[9] Division of Urology, Department of Surgery, Medical College of Georgia, Augusta University, Augusta, GA, USA; Georgia Cancer Center, Augusta, GA, USA.

Correspondence:

Hanan Goldberg, MD
Department of Surgical Oncology, Division of Urology
Princess Margaret Cancer Centre
610 University Ave, Toronto, Ontario, Canada, M5G 2M9
Mobile: +1-647-204-0206
E-Mail: gohanan@gmail.com

Running Head: mpMRI-informed targeted vs. Systematic prostate biopsy meta-analysis

Word count: Abstract: 302, Manuscript: 4009

Figures: 3; **Tables**: 1; **Supplemental Tables**: 2, **Appendix**: 2, **References: 44**

Abstract

Purpose: Multiparametric magnetic resonance imaging (mpMRI) with informed targeted biopsies (TGBX) has changed the paradigm of prostate cancer (PCa) diagnosis. Randomized studies have demonstrated a diagnostic benefit of Clinically significant (CS) for TGBX compared to standard systematic biopsies (SBX). We aimed to evaluate whether mpMRI-informed TGBX has superior diagnosis rates of any-, CS-, high-grade (HG)-, and clinically insignificant (CI)-PCa compared to SBX in biopsy-naïve men.

Methods: Data was searched in Medline, Embase, Web of Science, and Evidence-based medicine reviews-Cochrane Database of systematic reviews from database inception until 2019. Studies were selected by two authors independently, with disagreements resolved by consensus with a third author. Overall 1951 unique references were identified, and 100 manuscripts underwent full-text review. Data were pooled using random-effects models. The meta-analysis is reported according to the PRISMA statement. The study protocol is registered with PROSPERO (CRD42019128468).

Results: Overall 29 studies (13,845 patients) were analyzed. Compared to SBX, use of mpMRI-informed TGBX was associated with a 15% higher rate of any PCa diagnosis (95% CI 10-20%, $p<0.00001$). This relationship was not affected by the study methodology ($p=0.11$). Diagnosis of CS and HG PCa were more common in the mpMRI-informed TGBX group (risk difference of 11%, 95% CI 0-20%, $p=0.05$, and 2%, 95% CI 1-4%; $p=0.005$, respectively) while there was no difference in diagnosis of CI PCa (risk difference of 0, 95% CI -3-3%, $p=0.96$). Notably, the exclusion of SBX in the mpMRI-informed TGBX arm significantly modified the association between a mpMRI strategy and lower rates of CI PCa diagnosis ($p=0.01$) without affecting the diagnosis rates of CS- or HG-PCa.

Conclusions: In comparison to SBX, a mpMRI-informed TGBX strategy results in a significantly higher diagnosis rate of any-, CS-, and HG-PCa. Excluding SBX from

mpMRI-informed TGBX was associated with decreased rates of CI-PCa diagnosis without affecting diagnosis of CS- or HG-PCa.

1. Introduction

Prostate cancer (PCa) diagnosis by systematic random histologic sampling of the prostate has, until recently, been the standard of care[1]. Transrectal ultrasound (TRUS)-guided 12-core template systematic biopsy (SBX) has been widely recommended for men at risk for PCa[2] _ENREF_2. However, SBX templates are limited by inherent random and systematic errors. Specific regions of the prostate are consistently underesampled, including the anterior region and apex[3], and, unless hypoechoic lesions are seen on TRUS, sampling occurs by chance. Thus, SBX can miss up to 20% of CS PCa, resulting in underdiagnosis[4]. Additionally, SBX detects a relatively high percentage of clinically insignificant (CI) PCa (Gleason grade group [GGG] 1), which may result in overtreatment[2], if proper use of active surveillance (AS) is not practiced.

With the introduction of multiparametric prostate magnetic resonance imaging (mpMRI), the pathways for PCa diagnosis have changed. MpMRI is unique in that it can both risk-stratify men for prostate biopsy (PB) and allow anatomic guidance for biopsy. The spatial information provided by mpMRI allows for precise mpMRI-informed targeted biopsy (TGBX), where clinically significant (CS) PCa (≥GGG 2[5]) is detected with fewer biopsy cores[6], and diagnosis of CI PCa decreases[7]. There are randomized studies demonstrating the superior diagnosis rate of TGBX in diagnosing CS PCa in biopsy-naïve men[8, 9]. However, TGBX has limitations, missing CS PCa in 2.1-15% of cases[10-13]. Although the most recent European Association of Urology (EAU)[2] and the National institute for Health and Care Excellence (NICE)[14] guidelines recommend performing mpMRI in biopsy-naïve men with suspected PCa, these recommendations are not

widely adopted in North-America, where mpMRI is usually reserved for men with a previous negative biopsy. Furthermore, the added benefit of combining SBX with TGBX remains unclear with conflicting data supporting both TGBX alone[7, 15] and combining SBX with TGBX[16]. The combination appears to detect more CS PCa than TGBX alone[4, 7]. Both the EAU and American Association of Urology (AUA) guidelines currently recommend adding SBX in men with a suspicious mpMRI lesion undergoing TGBX[2, 17].

To synthesize the available data on these questions, we undertook a systematic review and meta-analysis of all studies comparing SBX and TGBX, either alone or in combination with SBX, to assess the detection rate of any PCa, CS PCa, high grade (HG) PCa (GGG>=4) and CI PCa in biopsy-naïve men.

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[18]. The study protocol was registered with PROSPERO CRD42019128468.

2.1. Research question

Is mpMRI-informed TGBX with or without SBX associated with higher rates of any-, CI-, CS-, and HG-PCa diagnosis than SBX alone in biopsy-naïve men at risk of PCa?

2.2. Types of Studies

Randomized clinical trials and observational cohort studies were included. Other publications including editorials, commentaries, review articles, meeting abstracts and publications not subject to peer-review (ie, reports of data from vital statistics and

dissertations or theses) were excluded. Only studies with paired cohorts, with patients with a positive mpMRI receiving either TGBX alone or together with SBX were included. To prevent duplication of patients used in our analyses, we selected one study (when more than one was published on the same patient cohort), based on contemporary timing, cohort size, and granularity of data reported. Our main interest was to compare the outcomes of mpMRI-informed TGBX alone or in combination with SBX to SBX outcomes in biopsy-naïve men. Thus, studies comparing mpMRI-guided TGBX and SBX in biopsy-naïve men were included and those in men with prior negative biopsy or with prior PCa diagnosis were excluded.

2.3. Outcome measures

The primary outcome of interest was the rate of any PCa diagnosis. Secondary outcomes were rates of CS PCa (GGG ≥ 2), HG PCa (GGG ≥ 4) and CI PCa (GGG=1).

2.4. Search strategy

Medline, EMBASE, Web of Science, Scopus and EBM Reviews Cochrane Database of Systematic Reviews databases were searched using the OvidSP platform for studies indexed from database inception to February 15, 2019 by a professional medical librarian. We used both subject headings and text-word terms for "prostate cancer", "prostate neoplasm", "biopsy"," no prior", "no previous", "naïve", "ultrasound", "magnetic resonance imaging", "systematic", "targeted", and related and exploded terms including MeSH terms in combination with keyword searching. A full search strategy is presented in appendix 1. Only English language publications were included, and all duplicates were excluded.

2.5. Study review methodology

The study selection was conducted by two authors (A.E.A. and T.C.) independently. Disagreements were resolved by consensus with a third author (H.G.). Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion criteria. A data extraction form was created and piloted prior data extraction, which was performed by a single author (A.E.A.) and subsequently verified by two additional authors (H.G. and Z.K.) independently.

2.6. Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias[19] and the Newcastle-Ottawa Scale (NOS) were used for risk of bias assessment in randomized clinical trials and cohort studies, respectively. The NOS assesses risk of bias in three domains[20]: (1) selection of the study groups; (2) comparability of groups; and (3) ascertainment of exposure and outcome[21]. Studies with scores >=7 were considered as having a low risk of bias, scores of 4–6 as having a moderate risk of bias, and scores <4 as having a high risk of bias.

2.7. Assessment of heterogeneity

Heterogeneity was assessed using the Q test, and estimated using the DerSimonian-Laird method, and finally quantified using I^2 values[22]. Given the identified clinical heterogeneity, we employed random effects models for each of our analyses.

2.8. Data synthesis

We expressed the outcome as the risk difference for PCa diagnosis between mpMRI-informed TGBX and SBX. This was determined as the proportion of patients diagnosed with PCa in the SBX group minus the proportion of patients diagnosed in the mpMRI-informed TGBX group. Therefore, a risk difference less than zero (negative risk difference) indicates that PCa diagnosis was more frequent in the mpMRI-informed TGBX group while a risk difference greater than zero (positive risk difference) indicates that PCa diagnosis was more frequent in the SBX group.

We used the Mantel-Haenszel method for meta-analysis of dichotomous data using the risk difference as our measure of effect. For each outcome, we first performed meta-analysis among three strata defined by study methodology (randomized controlled trials, prospective cohort studies, and retrospective cohort studies) as differences in study methodology may reasonably be expected to affect study conclusions. We tested for subgroup differences between strata for each outcome using the Chi-squared test. Where the Chi-squared test for subgroup differences was insignificant, we pooled results for each outcome across the study methodologies to provide a single pooled effect estimate. Where the Chi-squared test for subgroup differences was significant (p<0.05), we deemed it inappropriate to pool results and thus reported pooled results among each stratum individually.

We performed *a priori* subgroup analysis to assess whether inclusion of SBX in the mpMRI-informed TGBX arm would affect the risk difference for PCa diagnosis between mpMRI-informed TGBX and SBX for each outcome. Again, we tested for subgroup differences between strata for each outcome using the Chi-squared test to assess for effect modification due to this factor.

Meta-analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software. Statistical significance was determined at p<0.05.

3. Results

3.1. Literature search results

We identified 1951 unique references (Figure 1). 100 manuscripts underwent full-text review and 29 studies were selected for final analyses. Reasons for exclusion are provided in Figure 1. 19 studies (65.5%) enrolled patients prospectively, however only 5 studies (17.2%) randomly assigned patients to mpMRI-informed TGBX or SBX group. Publication details of all included studies can be found in Appendix 2.

3.2. Characteristics of identified studies

Studies were conducted in 4 continents (65.5% in Europe, 20.7% in Asia, 6.9% in the US, and 6.9% in Australia), and 89.7% were conducted after 2010 (Table 1). 21 studies (72.5%) were from single centers, three studies (10.3%) analyzed two centers and five studies (17.2%) were multicenter.

Across the 29 included studies, there were 13,845 patients, of whom 1,085 (7.8%) patients were enrolled in randomized trials. Nearly all studies included men based on an elevated prostate specific antigen (PSA) and/or an abnormal digital rectal exam (DRE) (Table 1).

With respect to MRI performance and interpretation, 21 studies (72.4%) used 3 Tesla mpMRI and 8 (27.6%) used 1.5 Tesla. The Prostate Imaging Reporting and Data System (PIRADS) was employed in most studies (21 [72.4%]), while 7 studies (24.1%) used the Likert and similar 4- or 5-point scales. 14 studies (48.3%) included SBX in addition to mpMRI-informed TGBX in the mpMRI arm. Targeted biopsy was performed with an ultrasound fusion biopsy technique in 18 studies (62.1%). Cognitive fusion biopsy and in-bore fusion biopsy were used in 8 (27.6%) and 2 studies (7%), respectively. Most studies (24, 82.7%) utilized transrectal biopsy.

All studies reported on overall PCa and CS PCa detection rate, defined based on Gleason score and/or maximum PCa core length (Table 1). However, for our analysis, we considered CS PCa to be GGG>=2 alone[5].

3.3. Risk of bias assessment

All randomized controlled trials included concealed random sequence generation and were similarly at low risk of attrition and reporting bias (Supplementary Table 1). While all studies were unblinded and thus potentially at risk for performance and detection bias, it is improbable that this should influence the outcome of PCa diagnosis.

The risk of bias in the prospective and retrospective cohort studies was low in all included studies (supplementary table 2). In some studies, patients with negative mpMRI were excluded which may have potentially introduced selection bias. As the outcome of interest was overall PCa or CS PCa diagnosis rate, all studies were deemed to have adequate follow up.

3.4. Quantitative synthesis

3.4.1. Any prostate cancer diagnosis

Assessing the association between use of mpMRI-informed TGBX or SBX and rates of any PCa diagnosis, we pooled results from 29 studies representing 31 unique patient cohorts and 13,845 participants. Among randomized controlled trials (5 studies, 1,085 participants), the use of mpMRI-informed TGBX +/- SBX was associated with a 16% increased likelihood of PCa diagnosis (risk difference = -0.16, 95% CI -0.22 to -0.11; p<0.00001; I^2 = 4%) when compared to SBX alone (Figure 2a). Among 14 prospective cohort studies (5,508 participants), the use of mpMRI-informed TGBX +/- SBX was associated with a 20% increased likelihood of PCa diagnosis (risk difference = -0.20, 95% CI -0.27 to -0.12; p<0.00001; I^2 = 89%) compared to SBX alone (Figure 2a). Finally, among 10 retrospective cohort studies (7,252 participants), the use of mpMRI-informed TGBX +/- SBX was associated with a 9% increased likelihood of PCa diagnosis (risk difference = -0.09, 95% CI -0.16 to -0.01; p=0.03; I^2 = 89%) compared to SBX alone (Figure 2a). The test for subgroup differences was insignificant (chi-squared = 4.40, p=0.11; I^2 = 54.5%). Thus, we pooled results across these strata: assessing all 13,845 participants from 29 studies, the use of mpMRI-informed TGBX +/- SBX was associated with a 15% increased likelihood of PCa diagnosis (risk difference = -0.15, 95% CI -0.20 to -0.10; p<0.00001; I^2 = 89%) compared to SBX alone (Figure 2a).

We then assessed whether inclusion of SBX in the mpMRI-informed TGBX arm affected the observed association between mpMRI-informed TGBX and any PCa diagnosis. Among cohorts where data was available for patients in the mpMRI-informed TGBX arm who had targeted biopsy alone (22 studies, 75.9%), the use of mpMRI-informed TGBX was associated with a 12% increased likelihood of PCa diagnosis (risk

difference = -0.12, 95% CI -0.18 to -0.07; p<0.00001; I^2 = 89%) compared to SBX alone (Figure 3a). For cohorts where data was available for patients who received both TGBX and SBX (14 studies, 48.3%), the use of mpMRI-informed TGBX was associated with a 17% increased likelihood of PCa diagnosis (risk difference = -0.17, 95% CI -0.24 to -0.09; p<0.00001; I^2 = 91%) compared to SBX alone (Figure 3a). The test for subgroup differences was insignificant (chi-squared = 0.78, p=0.38; I^2 = 0%) suggesting that the inclusion of SBX in patients undergoing mpMRI-informed TGBX does not modify the association between mpMRI-informed TGBX and rates of any PCa diagnosis.

3.4.2. Clinically significant prostate cancer diagnosis

Twenty-seven studies (13,089 participants) provided data for meta-analysis of the outcome of CS PCa. There was an increased likelihood of CS PCa diagnosis among randomized controlled trials (risk difference = -0.11, 95% CI -0.2 to 0.00; p=0.05; I^2 = 78%), among prospective cohort studies (risk difference = -0.18, 95% CI -0.24 to -0.11; p<0.00001; I^2 = 81%) and among retrospective cohort studies (risk difference = -0.07, 95% CI -0.12 to -0.02; p=0.004; I^2 = 77%) (Figure 2b). However, the test for subgroup differences was significant (chi-squared = 6.35, p=0.04; I^2 = 68.5%). Thus, we did not pool results across strata of study methodology. We found no evidence of effect modification due to inclusion of SBX in the mpMRI-informed TGBX arm on the relationship between mpMRI-informed TGBX, and rates of CS PCa diagnosis (test for subgroup differences chi-squared = 0.18, p=0.67; I^2 = 0%) (Figure 3b).

3.4.3. Clinically insignificant prostate cancer diagnosis

Similarly, 27 studies (13,089 participants) provided data for meta-analysis of the outcome of CI PCa. The use of mpMRI-informed TGBX +/- SBX was associated with no meaningful difference in the likelihood of CI PCa diagnosis, whether assessed among randomized controlled trials (risk difference = 0.01, 95% CI -0.09 to 0.11; p=0.85; I^2 = 82%), prospective cohort studies (risk difference = 0.00, 95% CI -0.05 to 0.05; p=0.99; I^2 = 79%) or retrospective cohort studies (risk difference = -0.01, 95% CI -0.05 to 0.04; p=0.83; I^2 = 84%) (Figure 2c). The test for subgroup differences was insignificant (chi-squared = 0.08, p=0.96; I^2 = 0%). Thus, we pooled results across strata of study methodology and found no meaningful difference in the likelihood of CI PCa diagnosis (risk difference = 0.00, 95% CI -0.03 to 0.03; p=0.96; I^2 = 80%) (Figure 2c).

Interestingly, there was evidence of effect modification due to the inclusion of SBX in the mpMRI-informed TGBX arm for this outcome (test for subgroup differences chi-squared = 6.49, p=0.01; I^2 = 84.6%): while studies which included SBX in the mpMRI-informed TGBX arm demonstrated a 4% higher rate of diagnosis of CI PCa among patients who received mpMRI-informed TGBX+SBX, compared to SBX alone (risk difference = -0.04, 95% CI -0.08 to -0.00; p=0.05; I^2 = 77%), those which utilized TGBX alone demonstrated a 3% lower rate of diagnosis of CI PCa among patients who received mpMRI-informed TGBX, compared to SBX alone (risk difference = 0.03, 95% CI -0.01 to 0.06; p=0.11; I^2 = 75%) (Figure 3c).

3.4.4. High-grade prostate cancer diagnosis

A smaller subset of 19 studies (9,811 participants) provided data for meta-analysis of the outcome of HG PCa. The use of mpMRI-informed TGBX +/- SBX was associated with a significantly higher likelihood of HG PCa diagnosis among

randomized controlled trials, albeit with a small effect size (risk difference = -0.04, 95%

CI -0.07 to -0.01; p=0.004; I^2 = 0%) compared to SBX alone (Figure 2d). Among

prospective cohort studies (risk difference = -0.02, 95% CI -0.05 to 0.01; p=0.23; I^2 =

66%) and retrospective cohort studies (risk difference = -0.02, 95% CI -0.06 to 0.01;

p=0.12; I^2 = 38%) (Figure 2d), this effect was not significant though the direction and

magnitude were similar. The test for subgroup differences was insignificant (chi-squared

= 1.72, p=0.42; I^2 = 0%). Thus, we pooled results across strata of study methodology

and found the use of mpMRI-informed TGBX was associated with a small but

significantly higher likelihood of HG PCa diagnosis (risk difference = -0.02, 95% CI -0.04

to -0.01; p=0.005; I^2 = 47%) compared to SBX alone (Figure 2d). We found no evidence

of effect modification due to inclusion of SBX in the mpMRI-informed TGBX arm on the

relationship between mpMRI-informed TGBX and rates of HG PCa diagnosis (test for

subgroup differences chi-squared = 0.40, p=0.53; I^2 = 0%) (Figure 3d).

4. Discussion

In this meta-analysis of biopsy-naïve patients undergoing a PB, we compared rates of

PCa diagnosis for patients undergoing standard SBX and mpMRI-informed TGBX. Our

analyses demonstrate several findings. First, patients who underwent a mpMRI-

informed TGBX +/- SBX were 15% more likely to be diagnosed with any PCa than

patients who underwent standard SBX. Further, this improved diagnostic yield was not

affected by whether a mpMRI-informed biopsy was performed with TGBX alone or

combined with SBX. Second, patients who underwent mpMRI-informed biopsy were

more likely to be diagnosed with CS PCa and HG PCa, with no difference in the

diagnosis rate of CI PCa compared to those who underwent SBX alone. Third, exclusion of SBX in the mpMRI-informed TGBX arm was associated with decreased rates of CI PCa diagnosis (p=0.01) without meaningfully affecting diagnosis rates of any-, CS-, or HG PCa.

Standard TRUS-guided SBX remains the most common technique used worldwide in biopsy-naïve patients deemed to warrant PB. While affected by characteristics of the population under study, PCa detection rates are approximately 40-45% for SBX[23]. Despite this, TRUS-SBX harbors low sensitivity and specificity in the diagnosis of PCa[12]: repeat biopsy identifies PCa in 10-25% of men with an initially negative biopsy[24]. Further, TRUS-SBX underestimates tumor grade in 36% of men when compared to radical prostatectomy (RP)[25]. With the advent of mpMRI, the sensitivity of PCa imaging has improved[26]. Previous meta-analyses have shown that mpMRI-informed TGBX detects more CS PCA, with fewer cores than utilized in TRUS-guided SBX[13].

More than 70% of studies included in this analysis used 3 tesla mpMRI and incorporated the PIRADS system for interpretation of imaging. However similar results were seen in studies using 1.5 tesla mpMRI, and other reporting systems such as the Likert scale. Included studies utilized numerous strategies for TGBX including ultrasound-, cognitive-, and in-bore-fusion biopsies, all of which have demonstrated an increased detection rate of CS PCa when compared to SBX[27-29]. Presently, there is no consensus on which strategy is superior.

We identified a higher rate of CS PCa diagnosed with mpMRI-informed biopsy compared to SBX ranging from 7 to 18%, with an 11% higher diagnostic rate among

RCTs. This is on par with results of prior meta-analyses[11-13, 30]. Uniquely, this analysis found mpMRI-informed biopsy identified higher rates of HG PCa.

More actionably, we found that exclusion of SBX in the mpMRI-informed TGBX arm significantly modified the association between mpMRI and CI PCa diagnosis (p=0.01), without meaningfully affecting diagnostic rates of CS- or HG PCa. Thus, in contrast to the common hypothesis that the combination of TGBX+SBX yields a higher diagnosis rate of any and CS PCa[31], these data suggest that SBX may be safely omitted in men undergoing mpMRI-guided biopsy. This approach would be expected to decrease the over-detection of clinically indolent PCa. Further, using TGBX only, a lower number of biopsy cores are required to reach a diagnosis, leading to less discomfort and morbidity[32, 33]. Lastly, emerging data suggest that decreased number of biopsy-cores can lead to less blood loss during RP[34].

This analysis strengthens the body of evidence supporting mpMRI as a risk-stratification tool in biopsy-naïve men, showing that a positive mpMRI can lead to a higher detection rate of CS PCa. Our manuscript adds to the current knowledge and supports other recently published meta-analyses demonstrating that TGBX has a clear benefit over SBX alone in the diagnosis of CS PCa[30, 35-37]. Over a million men in the US undergo TRUS-guided SBX each year[38], at a cost of nearly 1 billion dollars, with less than 10% of the 12 million biopsy core samples demonstrating cancer. According to the PROMIS study[39], approximately 25% of the biopsies (250,000) could be avoided in patients with a negative pre-biopsy mpMRI. But, for patients with a positive mpMRI, our study shows that they could go down from a 12-core biopsy to only a 4-core biopsy (provided there is only one mpMRI-targeted lesion), resulting in a reduction of 8 million

cores processed per year. This supports the concept of an mpMRI-first strategy in biopsy-naïve men as an effective and cost-effective approach for the diagnosis of CS PCa[40]. However, we must not forget that if an mpMRI-first strategy in biopsy-naïve men is adopted, the cost of mpMRI must be taken into consideration when analyzing the cost-effectiveness of this entire approach. Taken together, the added benefit of SBX is shown to be questionable in the setting of biopsy-naïve men suspected to have PCa, and its role must be reconsidered, possibly omitted, as recommended in men with a previous negative biopsy[2].

No difference was noted in the diagnosis rate of CI PCa between mpMRI-informed biopsy and SBX. In contrast, three prior meta-analyses have demonstrated a lower rate of CI PCa diagnosis with TGBX when compared to SBX[11, 12, 30] while Valerio et al. showed that most studies demonstrated a higher rate of CI PCa in the mpMRI-informed biopsy pathology[13]. As discussed above, this may be affected using SBX in the TGBX group. In our meta-analysis, TGBX alone or combined with SBX demonstrate an equal rate of CS PCa diagnosis rate but TGBX alone resulted in a 4% reduction in CI PCa diagnosis. The definition of CI PCa varies between studies, ranging from the Epstein criteria[41] to the combination of maximal cancer core length <6 mm with GGG 1[42]. In our analysis, we used the simplified definition of GGG=1 alone, which could explain some of the discrepancies between our analysis and others.

The strength of our analysis includes a comprehensive search strategy and actionable data due to the use of mpMRI protocols in accordance with the current recommended imaging guidelines. However, there are several limitations. First, mpMRI-informed biopsy procedure lacked standardization. There was significant variability

across the studies with regards to the interpretation of suspicious MRI lesions, the

decision on when to biopsy, method of TGBX, the number of cores taken, and the

different stages of the learning curve of the radiologists who interpreted the imaging.

Second, there was significant heterogeneity among many of the comparisons included

in this review. We used random effects models to pool these studies as a result. Third,

this analysis focused on biopsy-naïve men and these results may not be applicable to

those with a previous negative biopsy. Fourth, this analysis only applies to patients with

a positive mpMRI. For patients with a negative mpMRI, the current role of SBX remains

controversial. Notably, previous analyses have demonstrated a CS PCa diagnosis rate

of 12% on systematic biopsy of men with negative mpMRI[43], making the role of SBX far

from obsolete, especially with a negative mpMRI. SBX is still crucial in many settings

and understanding when it is mandatory and when not is imperative. Furthermore, when

considering management with focal therapy, SBX might have a critical role of ruling out

additional disease outside the target lesion. Importantly, aside from the changing

radiologist learning curve of interpreting mpMRI images, the ease of properly obtaining

an mpMRI-targeted biopsy around the world varies due to a plethora of considerations,

and thus the conclusion of this study may not be applicable worldwide. Lastly, there is a

potential methodological error in assuming that one type of biopsy diagnoses more CS-

PCa than another based on the results of PB alone. Deciphering which strategy is better

from a diagnostic perspective, would be to analyze the RP specimens of all patients

who underwent either a TGBX or SBX and compare the rate of CS PCa in the final

specimen to the preoperative biopsy result. Indeed, a recently published study showed

that TGBX can sample the highest grade of a dominant lesion, and perhaps even a

tertiary high-score location. This resulted in reporting a higher biopsy GGG and subsequent downgrading of the final pathologic specimen following RP[44].

5. Conclusions

Based on a comprehensive, current meta-analysis, a mpMRI-informed TGBX strategy in men undergoing their first PB resulted in a significantly higher diagnosis rate of any-, CS-, and HG-PCa, compared to SBX. Furthermore, exclusion of SBX for men undergoing mpMRI-informed TGBX was associated with decreased rates of CI PCa diagnosis without affecting diagnosis rates of CS- or HG PCa.

Author Contributions:

Design and conception: HG, CJDW

Study selection: AEA, TC, HG

Data extraction: AEA, HG, ZK, CJDW

Analysis and interpretation of data: CJDW, HG, AEA

Writing of manuscript: HG, AEA, CJDW

Editing and reviewing of manuscript: ZK, TC, NF, LK, ME, MAH, SST, NP, MDT, CJDW

Figure legends:

Figure 1. – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart

Figure 2. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by study methodology: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

Figure 3. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by inclusion of systematic biopsy in the mpMRI-informed biopsy arm: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

References

1.   Hodge KK, McNeal JE, Terris MK et al: Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989; **142:** 71.

2.   Mottet N, Bellmunt J, Bolla M et al: EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017; **71:** 618.

3.   Kongnyuy M, Sidana A, George AK et al: The significance of anterior prostate lesions on multiparametric magnetic resonance imaging in African-American men. Urol Oncol 2016; **34:** 254.e15.

4.   Schouten MG, van der Leest M, Pokorny M et al: Why and where do we miss significant prostate cancer with multi-parametric magnetic resonance imaging followed by magnetic resonance-guided and transrectal ultrasound-guided biopsy in biopsy-naïve men? Eur Urol 2017; **71:** 896.

5.   Zhao C, Gao G, Fang D et al: The efficiency of multiparametric magnetic resonance imaging (mpMRI) using PI-RADS Version 2 in the diagnosis of clinically significant prostate cancer. Clin Imaging 2016; **40:** 885.

6.   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.

7.   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.

8.   Kasivisvanathan V, Rannikko AS, Borghi M et al: MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018; **378:** 1767.

9.   Porpiglia F, Manfredi M, Mele F et al: Diagnostic pathway with multiparametric magnetic resonance imaging versus standard pathway: results from a randomized prospective study in biopsy-naïve patients with suspected prostate cancer. Eur Urol 2017; **72:** 282.

10.   Borofsky S, George AK, Gaur S et al: What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. Radiology 2018; **286:** 186.

11.   Schoots IG, Roobol MJ, Nieboer D et al: Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015; **68:** 438.

12.   Wegelin O, van Melick HHE, Hooft L et al: Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: a systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? Eur Urol 2017; **71:** 517.

13.   Valerio M, Donaldson I, Emberton M et al: Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. Eur Urol 2015; **68:** 8.

14.   Wise J: NICE recommends MRI for suspected prostate cancer to reduce biopsies. BMJ 2018; **363**: k5290.

15.   Baco E, Rud E, Eri LM et al: A randomized controlled trial to assess and compare the outcomes of two-core prostate biopsy guided by fused magnetic resonance and transrectal ultrasound images and traditional 12-core systematic biopsy. Eur Urol 2016; **69:** 149.

16.   Rosenkrantz AB, Verma S, Choyke P et al: Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol 2016; **196:** 1613.

17.   Fulgham PF, Rukstalis DB, Turkbey IB et al: AUA policy statement on the use of multiparametric magnetic resonance imaging in the diagnosis, staging and management of prostate cancer. J Urol 2017; **198:** 832.

18.   Moher D, Liberati A, Tetzlaff J et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; **62:** 1006.

19.   Higgins JPT, Altman DG, Gøtzsche PC et al: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; **343:** d5928.

20.   Deeks JJ, Dinnes J, D'Amico R et al: Evaluating non-randomised intervention studies. Health Technol Assess 2003; **7:** iii.

21.   Wells GA Shea B, O'Connell D et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, Ontario: Ottawa Hospital Research Institute 2019. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 24, 2019.

22.   Higgins JP, Thompson SG, Deeks JJ et al: Measuring inconsistency in meta-analyses. BMJ 2003; **327:** 557.

23.   Lane BR, Zippe CD, Abouassaly R et al: Saturation technique does not decrease cancer detection during followup after initial prostate biopsy. J Urol 2008; **179:** 1746.

24.   Welch HG, Fisher ES, Gottlieb DJ et al: Detection of prostate cancer via biopsy in the Medicare-SEER population during the PSA era. J Natl Cancer Inst 2007; **99:** 1395.

25.   Epstein JI, Feng Z, Trock BJ et al: Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012; **61:** 1019.

26.   Wu LM, Xu JR, Gu HY et al: Usefulness of diffusion-weighted magnetic resonance imaging in the diagnosis of prostate cancer. Academic radiology 2012; **19:** 1215.

27.   Pinto PA, Chung PH, Rastinehad AR et al: Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol 2011; **186:** 1281.

28.   Moore CM, Robertson NL, Arsanious N et al: Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol 2013; **63:** 125.

29.   Hoeks CM, Schouten MG, Bomers JG et al: Three-Tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers. Eur Urol 2012; **62:** 902.

30.   Kasivisvanathan V, Stabile A, Neves JB et al: Magnetic resonance imaging-targeted biopsy versus systematic biopsy in the detection of prostate cancer: a systematic review and meta-analysis. Eur Urol 2019; **76:** 284.

31.   Mannaerts CK, Kajtazovic A, Lodeizen OAP et al: The added value of systematic biopsy in men with suspicion of prostate cancer undergoing multiparametric MRI-targeted biopsy. Urol Oncol 2019; **37:** 298.e1.

32.   Pepe P and Aragona F: Morbidity after transperineal prostate biopsy in 3000 patients undergoing 12 vs 18 vs more than 24 needle cores. Urology 2013; **81:** 1142.

33.   Simsir A, Kismali E, Mammadov R et al: Is it possible to predict sepsis, the most serious complication in prostate biopsy? Urol Int 2010; **84:** 395.

34.   Carneiro A, Sivaraman A, Sanchez-Salas R et al: Higher number of transrectal ultrasound guided prostate biopsy cores is associated with higher blood loss and perioperative complications in robot assisted radical prostatectomy. Actas Urol Esp 2017; **41:** 155.

35.   Elwenspoek MMC, Sheppard AL, McInnes MDF et al: Comparison of multiparametric magnetic resonance imaging and targeted biopsy with systematic biopsy alone for the diagnosis of prostate cancer: a systematic review and meta-analysis. JAMA Netw Open 2019; **2:** e198427.

36.   Drost FH, Osses D, Nieboer D et al: Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. Eur Urol 2019; doi: 10.1016/j.eururo.2019.06.023.

37.   Woo S, Suh CH, Eastham JA et al: Comparison of magnetic resonance imaging-stratified clinical pathways and systematic transrectal ultrasound-guided biopsy pathway for the detection of clinically significant prostate cancer: a systematic review and meta-analysis of randomized controlled trials. Eur Urol Oncol 2019; doi: 10.1016/j.euo.2019.05.004.

38.   Loeb S, Vellekoop A, Ahmed HU et al: Systematic review of complications of prostate biopsy. Eur Urol 2013; **64:** 876.

39.   Ahmed HU, El-Shater Bosaily A, Brown LC et al: Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017; **389:** 815.

40.   Faria R, Soares MO, Spackman E et al: Optimising the diagnosis of prostate cancer in the era of multiparametric magnetic resonance imaging: a cost-effectiveness analysis based on the Prostate MR Imaging Study (PROMIS). Eur Urol 2018; **73:** 23.

41.   Epstein JI, Walsh PC, Carmichael M et al: Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994; **271:** 368.

42.   Rouvière O, Puech P, Renard-Penna R et al: Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019; **20:** 100.

43.   Rouse P, Shaw G, Ahmed HU et al: Multi-parametric magnetic resonance imaging to rule-in and rule-out clinically important prostate cancer in men at risk: a cohort study. Urol Int 2011; **87:** 49.

44.   Beksac AT, Sobotka S, Xu P et al: Downgrading of grade group after radical prostatectomy: comparison of multiparametric magnetic resonance imaging guided fusion biopsy and standard 12-core biopsy. Urology 2019; **127:** 80.

Table 1-Characteristics of included studies

Author (yr)	Country/ Number of centers	Study interval	Inclusion Criteria	Study size (SBX/ TGBX)	PSA (ng/ml) (SBX/ TGBX)	Age (yr) (SBX / TGBX)	Biopsy approach		Biopsy technique in MRI arm	MRI machi ne	MRI scoring system	TGBX technique	Outcome
							SBX	TGBX					
Randomized controlled trials													
Baco (2016)	Norway/1	9/2011-6/2013	Elevated PSA (PSA 4-20ng/ml) and/or abnormal DRE	175 (89/86)	Median 7.6/Median 6.9	Median 65/Median 64	Transrectal	Transrectal	Systematic + targeted	1.5T	PIRADS v1	Software fusion	Overall PCa CS PCa
Kasivisvanathan (2018)	Multiple/25	2/2016-8/2017	Elevated PSA and/or abnormal DRE	500 (248/252)	Mean 6.5/Mean 6.75	Mean 64.5/Mean 64.4	Transrectal	Transrectal Transperineal	Targeted only	1.5T, 3T	PIRADS v2	Software fusion Cognitive fusion	CS PCa Insignifican t PCa Negative mpMRI
Park (2011)	South Korea/1	7/2008-12/2009	Elevated PSA and/or abnormal DRE	85 (41/44)	Mean 5.6/Mean 6.1	Mean 61/Mean 63	Transrectal	Transrectal	Systematic+ targeted	3T	NR	Cognitive fusion	Overall PCa Positive core rate
Porpiglia (2017)	Italy/2	11/2014-3/2016	Elevated PSA (PSA <=15 ng/ml) Normal DRE	212 (105/107)	Median 6.7/Median 5.9	Median 66/ Median 64	Transrectal	Transrectal Transperineal	Targeted only	1.5T	PIRADS v1	Software fusion	Overall PCa CS PCa
Tonttila (2016)	Finland/1	4/2011-12/2014	Elevated PSA (PSA	113 (60/53)	Median 6.2/Median	Median 62/ Median 63	Transrectal	Transrectal	Systematic+	3T	4-point scale	Cognitive fusion	Overall PCa

			<20 ng/ml or free-to-total PSA ratio <=0.15 and PSA <10 ng/ml in repeated measurement)		6.1					targeted				CS PCa Positive core rate
						Prospective cohort studies								
Borkowetz (2018)	Germany/2	1/2016-12/2017	Elevated PSA and/or abnormal DRE	384 (214/170)	Median 6.22	Median 63	Transrectal	Transperineal	Systematic+ targeted	3T	PIRADS v2	Software fusion	Overall PCa CS PCa Positive core rate
Castellucci (2017)	Spain/1	7/2011-7/2014	Elevated PSA and/or abnormal DRE	254 (168/86)	Mean 8.3	Mean 61.4	Transrectal	Transrectal	Systematic+ targeted	1.5T	PIRADS v1	Cognitive fusion	Overall PCa CS PCa
De Gorski (2015)	France/1	1/2010-5/2014	Elevated PSA (PSA < 10 ng/ml)	232	Mean 6.5	Mean 64	Transrectal	Transrectal	Systematic+ targeted	1.5T	Likert	Software fusion	Overall PCa CS PCa
Delongchamps (2013)	France/1	1/2011-3/2012	Elevated PSA and/or abnormal DRE	605 (391/214)	Mean 8.1/Mean 8.3/Mean 9	Mean 62.7/Mean 64.6/ Mean 64.5	Transrectal	Transperineal	Systematic+ targeted	1.5T	3-point scale	Software fusion Cognitive fusion	Overall PCa Insignificant PCa

Delongchamps (2016)	France/7	6/2014-10/2014	Elevated PSA (PSA >4ng/ml)	108	Median 7.2	Median 65	Transrectal	Transrectal	Systematic+ targeted	1.5T 3T	PIRADS v1	Software fusion	Overall PCa CS PCa
Garcia Bennett (2017)	Spain/4	10/2014-4/2016	Elevated PSA (PSA > 4 ng/mL, a PSA den-sity > 0.18 ng/mL/mL, a PSA velocity > 0.75 ng/mL/year) and/or abnormal DRE	92 (60/32)	Median 7.2	Mean 64.1	Transperineal	Transperineal	Systematic+ targeted	3T	PIRADS v1	Cognitive fusion	Overall PCa CS PCa
Mozer (2015)	France/1	1/2010-9/2013	Elevated PSA (PSA 4-10ng/ml)	152	Median 6	Median 63.7	Transrectal	Transrectal	Systematic+ targeted	1.5T	Likert	Software fusion	CS PCa
Peltier (2015)	Belgium/1	3/2012-9/2013	NR	110	Median 6.9	Median 65.8	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Software fusion	CS PCa
Pokorny (2014)	Australia/1	7/2012-1/2013	Elevated PSA and/or abnormal DRE	365 (223/142)	Median 5.3	Median 63	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Cognitive fusion	Low risk PCa Intermediate/high risk PCa
Quentin (2014)	Germany/1	11/2011-10/2013	Elevated PSA (PSA >4	128	Median 6.7	Median 67	Transrectal	Transrectal	Systematic+	3T	PIRADS v1	In-bore fusion	CS PCa

			ng/ml)						targeted				
Rouviere (2019)	France/16	7/2015-8/2016	Elevated PSA and/or abnormal DRE Family history of PCa	457 (251/206)	Median 6.5	Median 64	Transrectal	Transrectal	Systematic+ targeted	1.5T 3T	Likert	Software fusion Cognitive fusion	CS PCa Insignificant PCa
Shoji (2017)	Japan/1	10/2014-8/2016	Elevated PSA (PSA 4-20ng/ml)	250	Median 6.7	Median 68	Transrectal	Transperineal	Systematic+ targeted	NR	PIRADS v1	Software fusion	Overall PCa CS PCa
Van der Leest (2018)	Netherlands /4	2/2015-2/2018	Elevated PSA (PSA >=3 ng/ml)	626 (309/317)	Median 6.4	Median 65	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v2	In-bore fusion	CS PCa
Zhang (2017)	China/1	12/2014-2/2016	Elevated PSA and/or abnormal DRE	253	Median 69	Median 10.05	Transperineal	Transperineal	Systematic+ targeted	3T	PIRADS v1	Software fusion	Overall PCa CS PCa
Retrospective cohort studies													
Acar (2015)	Turkey/1	1/2012-2/2014	Elevated PSA and/or abnormal DRE Family history of PCa Abnormal	100 (37/63)	Mean 7.6/Mean 5.9	Mean 62.3/Mean 60.4	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Cognitive fusion In-bore fusion	CS PCa

			PSA adjunct tests										
Bryant (2019)	United Kingdom/1	1/2015-7/2017	NR	1789 (997/792)	Median 7.9/Median 7.6	Median 69/Median 68	Transrectal	Transrectal	Systematic+ targeted	1.5T 3T	PIRADS v2	Cognitive fusion	Overall PCa CS PCa CS PCa in patients with negative MRI
Chen (2015)	China/1	6/2008-12/2013	Elevated PSA and/or abnormal DRE	420	Median 9.73	Median 67	Transperineal	Transperineal	Systematic+ targeted	3T	5-point scale	Cognitive fusion	Overall PCa
Choi (2018)	South Korea/1	9/2013-3/2017	Elevated PSA (PSA>=2.5 ng/ml) and/or abnormal DRE	1991 (1786/223)	Median 4.62/Median 4.51	Median 64/ Median 66	Transrectal	Transperineal		3T	PIRADS v2	Software fusion Cognitive fusion	Overall PCa CS PCa
Kam (2018)	Australia/1	6/2014-8/2016	NR	121	Mean 7.44	Mean 65.5	Transrectal	Transrectal Transperineal	Systematic+ targeted	1.5T	PIRADS v2	Software fusion Cognitive fusion	CS PCa
Maxeiner (2018)	Germany/1	1/2012-12/2016	at least one suspicious lesion of the prostate according to the PI-RADS	318	Median 7.14	Median 68	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1 & v2	Software fusion	CS PCa

			classification in mpMRI defined as PI-RADS ≥3										
Mendhiratta (2015)	USA/1	6/2012-6/2015	NR	382	Mean 6.8	Mean 64.5	Transrectal	Transrectal	Systematic+ targeted	3T	Likert	Software fusion	Highest Gleason score CS PCa
Peltier (2016)	Belgium/1	mpMRI 2011-2013, TRUS 2006-2007	Elevated PSA and/or abnormal DRE	119	Median 6.98/Median 6.19	Median 65/Median 63	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Software fusion	Overall PCa CS PCa
Washino (2018)	Japan/2	1/2010-4/2014	Elevated PSA (PSA <15 ng/ml)	496 (281/215)	Median 6.7/Median 6.4	Median 68/Median 68	Transperineal	Transperineal	Systematic+ targeted	1.5T 3T	3-point scale	Cognitive fusion	Overall PCa CS PCa
Yarlagadda (2018)	USA/1	2014-2016	Elevated PSA (PSA > 4ng/ml) and/or abnormal DRE	69	Mean 7.71	Mean 64.33	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v2	Software fusion	Overall PCa

CS=clinically significant; GGG=Gleason grade group; PSA=Prostate specific antigen, NR=Not reported; MRI=magnetic resonance imaging; PIRADS=Prostate Imaging Reporting and Data System; SBX = Systematic biopsy; T=Tesla; TGBX = Targeted biopsy
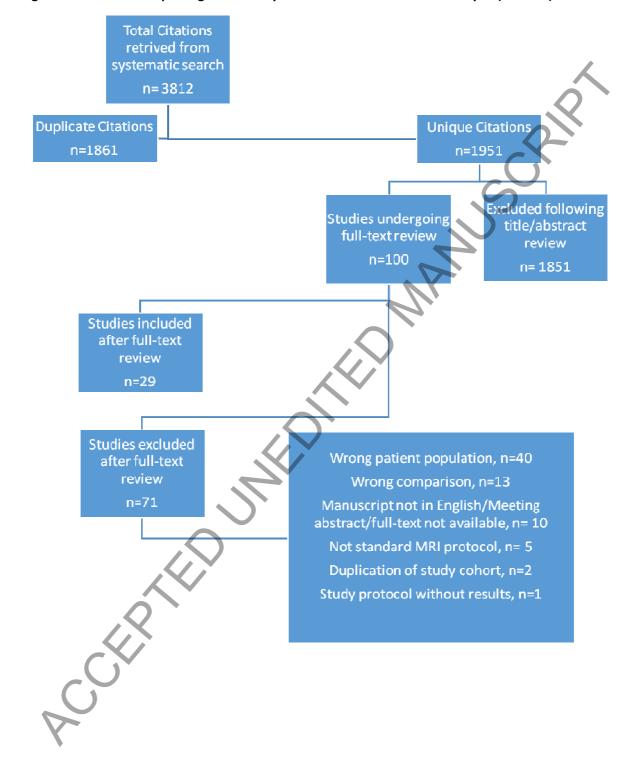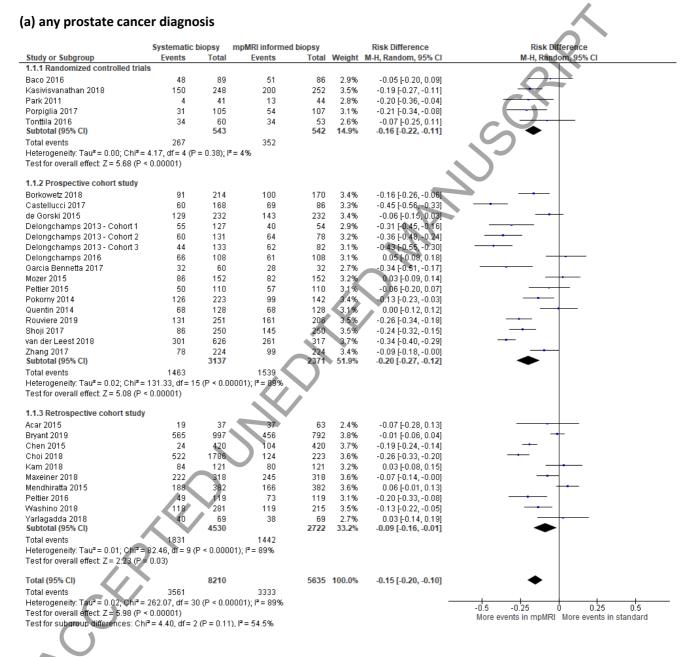
Figure 1. – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart

Total Citations retrived from systematic search
n= 3812

Duplicate Citations
n=1861

Unique Citations
n=1951

Studies undergoing full-text review
n=100

Excluded following title/abstract review
n= 1851

Studies included after full-text review
n=29

Studies excluded after full-text review
n=71

Wrong patient population, n=40

Wrong comparison, n=13

Manuscript not in English/Meeting abstract/full-text not available, n= 10

Not standard MRI protocol, n= 5

Duplication of study cohort, n=2

Study protocol without results, n=1

Figure 2. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by study methodology: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

(a) any prostate cancer diagnosis

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.1.1 Randomized controlled trials						
Baco 2016	48	89	51	86	2.9%	-0.05 [-0.20, 0.09]
Kasivisvanathan 2018	150	248	200	252	3.5%	-0.19 [-0.27, -0.11]
Park 2011	4	41	13	44	2.8%	-0.20 [-0.36, -0.04]
Porpiglia 2017	31	105	54	107	3.1%	-0.21 [-0.34, -0.08]
Tonttila 2016	34	60	34	53	2.6%	-0.07 [-0.25, 0.11]
Subtotal (95% CI)		543		542	14.9%	-0.16 [-0.22, -0.11]
Total events	267		352			
Heterogeneity: Tau² = 0.00; Chi² = 4.17, df = 4 (P = 0.38); I² = 4%						
Test for overall effect: Z = 5.68 (P < 0.00001)						
1.1.2 Prospective cohort study						
Borkowetz 2018	91	214	100	170	3.4%	-0.16 [-0.26, -0.06]
Castellucci 2017	60	168	69	86	3.3%	-0.45 [-0.56, -0.33]
de Gorski 2015	129	232	143	232	3.4%	-0.06 [-0.15, 0.03]
Delongchamps 2013 - Cohort 1	55	127	40	54	2.9%	-0.31 [-0.45, -0.16]
Delongchamps 2013 - Cohort 2	60	131	64	78	3.2%	-0.36 [-0.48, -0.24]
Delongchamps 2013 - Cohort 3	44	133	62	82	3.1%	-0.43 [-0.55, -0.30]
Delongchamps 2016	66	108	61	108	3.1%	0.05 [-0.08, 0.18]
Garcia Bennetta 2017	32	60	28	32	2.7%	-0.34 [-0.51, -0.17]
Mozer 2015	86	152	82	152	3.2%	0.03 [-0.09, 0.14]
Peltier 2015	50	110	57	110	3.1%	-0.06 [-0.20, 0.07]
Pokorny 2014	126	223	99	142	3.4%	-0.13 [-0.23, -0.03]
Quentin 2014	68	128	68	128	3.1%	0.00 [-0.12, 0.12]
Rouviere 2019	131	251	161	206	3.5%	-0.26 [-0.34, -0.18]
Shoji 2017	86	250	145	250	3.5%	-0.24 [-0.32, -0.15]
van der Leest 2018	301	626	261	317	3.7%	-0.34 [-0.40, -0.29]
Zhang 2017	78	224	99	224	3.4%	-0.09 [-0.18, -0.00]
Subtotal (95% CI)		3137		2371	51.9%	-0.20 [-0.27, -0.12]
Total events	1463		1539			
Heterogeneity: Tau² = 0.02; Chi² = 131.33, df = 15 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 5.08 (P < 0.00001)						
1.1.3 Retrospective cohort study						
Acar 2015	19	37	37	63	2.4%	-0.07 [-0.28, 0.13]
Bryant 2019	565	997	456	792	3.8%	-0.01 [-0.06, 0.04]
Chen 2015	24	420	104	420	3.7%	-0.19 [-0.24, -0.14]
Choi 2018	522	1786	124	223	3.6%	-0.26 [-0.33, -0.20]
Kam 2018	84	121	80	121	3.2%	0.03 [-0.08, 0.15]
Maxeiner 2018	222	318	245	318	3.6%	-0.07 [-0.14, -0.00]
Mendhiratta 2015	188	382	166	382	3.6%	0.06 [-0.01, 0.13]
Peltier 2016	49	119	73	119	3.1%	-0.20 [-0.33, -0.08]
Washino 2018	118	281	119	215	3.5%	-0.13 [-0.22, -0.05]
Yarlagadda 2018	40	69	38	69	2.7%	0.03 [-0.14, 0.19]
Subtotal (95% CI)		4530		2722	33.2%	-0.09 [-0.16, -0.01]
Total events	1831		1442			
Heterogeneity: Tau² = 0.01; Chi² = 82.46, df = 9 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Total (95% CI)		8210		5635	100.0%	-0.15 [-0.20, -0.10]
Total events	3561		3333			
Heterogeneity: Tau² = 0.02; Chi² = 262.07, df = 30 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 5.98 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.40, df = 2 (P = 0.11), I² = 54.5%						

Risk Difference M-H, Random, 95% CI: -0.5 -0.25 0 0.25 0.5
More events in mpMRI   More events in standard

(b) clinically-significant prostate cancer diagnosis

Study or Subgroup	TRUS biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.3.1 Randomized controlled trials						
Baco 2016	44	89	38	86	18.7%	0.05 [-0.10, 0.20]
Kasivisvanathan 2018	64	248	95	252	23.9%	-0.12 [-0.20, -0.04]
Park 2011	2	41	11	44	19.0%	-0.20 [-0.35, -0.06]
Porpiglia 2017	14	105	44	107	21.4%	-0.28 [-0.39, -0.16]
Tonttila 2016	18	60	15	53	17.1%	0.02 [-0.15, 0.18]
Subtotal (95% CI)		**543**		**542**	**100.0%**	**-0.11 [-0.23, 0.00]**
Total events	142		203			
Heterogeneity: Tau² = 0.01; Chi² = 16.61, df = 4 (P = 0.002); I² = 76%						
Test for overall effect: Z = 1.94 (P = 0.05)						
1.3.2 Prospective cohort study						
Borkowetz 2018	74	214	81	170	7.4%	-0.13 [-0.23, -0.03]
Castellucci 2017	33	168	41	86	6.8%	-0.28 [-0.40, -0.16]
de Gorski 2015	91	232	113	232	7.6%	-0.09 [-0.18, -0.00]
Delongchamps 2013 - Cohort 1	18	127	18	54	6.2%	-0.19 [-0.33, -0.05]
Delongchamps 2013 - Cohort 2	26	131	33	78	6.5%	-0.22 [-0.35, -0.10]
Delongchamps 2013 - Cohort 3	19	133	27	82	6.9%	-0.19 [-0.30, -0.07]
Delongchamps 2016	38	108	40	108	6.6%	-0.02 [-0.15, 0.11]
Garcia Bennetta 2017	27	60	27	32	5.2%	-0.39 [-0.57, -0.22]
Mozer 2015	34	152	33	152	7.6%	0.01 [-0.09, 0.10]
Peltier 2015	8	110	19	110	7.8%	-0.10 [-0.19, -0.01]
Pokorny 2014	79	223	93	142	7.4%	-0.30 [-0.40, -0.20]
Rouviere 2019	75	251	94	206	7.7%	-0.16 [-0.25, -0.07]
van der Leest 2018	146	626	180	317	8.3%	-0.33 [-0.40, -0.27]
Zhang 2017	35	224	59	224	8.0%	-0.11 [-0.18, -0.03]
Subtotal (95% CI)		**2759**		**1993**	**100.0%**	**-0.18 [-0.24, -0.11]**
Total events	703		858			
Heterogeneity: Tau² = 0.01; Chi² = 70.14, df = 13 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 5.51 (P < 0.00001)						
1.3.3 Retrospective cohort study						
Acar 2015	12	37	28	63	4.5%	-0.12 [-0.31, 0.07]
Bryant 2019	481	997	388	792	13.2%	-0.01 [-0.05, 0.04]
Chen 2015	13	420	43	420	14.0%	-0.07 [-0.10, -0.04]
Choi 2018	323	1786	96	223	11.7%	-0.25 [-0.32, -0.18]
Kam 2018	61	121	61	121	7.6%	0.00 [-0.13, 0.13]
Maxeiner 2018	158	318	175	318	11.0%	-0.05 [-0.13, 0.02]
Mendhiratta 2015	102	382	117	382	12.0%	-0.04 [-0.10, 0.02]
Peltier 2016	19	119	22	119	9.6%	-0.03 [-0.12, 0.07]
Washino 2018	76	281	85	215	10.5%	-0.12 [-0.21, -0.04]
Yarlagadda 2018	24	69	25	69	5.9%	-0.01 [-0.17, 0.15]
Subtotal (95% CI)		**4530**		**2722**	**100.0%**	**-0.07 [-0.12, -0.02]**
Total events	1269		1040			
Heterogeneity: Tau² = 0.00; Chi² = 39.68, df = 9 (P < 0.00001); I² = 77%						
Test for overall effect: Z = 2.87 (P = 0.004)						

Test for subgroup differences: Chi² = 6.35, df = 2 (P = 0.04), I² = 68.5%

Risk Difference M-H, Random, 95% CI

-0.5   -0.25   0   0.25   0.5

More events in mpMRI   More events in standard

(c) clinically-insignificant prostate cancer diagnosis

Study or Subgroup	TRUS biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
1.2.1 Randomized controlled trials							
Baco 2016	4	89	13	86	3.5%	-0.11 [-0.19, -0.02]	
Kasivisvanathan 2018	55	248	23	252	4.0%	0.13 [0.07, 0.19]	
Park 2011	2	41	2	44	3.4%	0.00 [-0.09, 0.09]	
Porpiglia 2017	17	105	10	107	3.4%	0.07 [-0.02, 0.16]	
Tonttila 2016	16	60	19	53	1.9%	-0.09 [-0.26, 0.08]	
Subtotal (95% CI)		543		542	16.3%	0.01 [-0.09, 0.11]	
Total events	94		67				
Heterogeneity: Tau² = 0.01; Chi² = 22.36, df = 4 (P = 0.0002); I² = 82%							
Test for overall effect: Z = 0.19 (P = 0.85)							
1.2.2 Prospective cohort study							
Borkowetz 2018	17	214	19	170	4.1%	-0.03 [-0.09, 0.03]	
Castellucci 2017	27	168	28	86	2.9%	-0.16 [-0.28, -0.05]	
de Gorski 2015	38	232	30	232	4.0%	0.03 [-0.03, 0.10]	
Delongchamps 2013 - Cohort 1	37	127	12	54	2.5%	0.07 [-0.07, 0.21]	
Delongchamps 2013 - Cohort 2	34	131	31	78	2.6%	-0.14 [-0.27, -0.01]	
Delongchamps 2013 - Cohort 3	25	133	35	82	2.7%	-0.24 [-0.36, -0.11]	
Delongchamps 2016	28	108	21	108	3.0%	0.06 [-0.05, 0.18]	
Garcia Bennetta 2017	5	60	1	32	3.4%	0.05 [-0.04, 0.14]	
Mozer 2015	52	152	49	152	3.1%	0.02 [-0.09, 0.13]	
Peltier 2015	42	110	38	110	2.6%	0.04 [-0.09, 0.16]	
Pokorny 2014	47	223	6	142	4.0%	0.17 [0.11, 0.23]	
Rouviere 2019	35	251	23	206	4.1%	0.03 [-0.03, 0.09]	
van der Leest 2018	155	626	81	317	4.1%	-0.01 [-0.07, 0.05]	
Zhang 2017	43	224	40	224	3.8%	0.01 [-0.06, 0.09]	
Subtotal (95% CI)		2759		1993	46.9%	0.00 [-0.05, 0.05]	
Total events	585		414				
Heterogeneity: Tau² = 0.01; Chi² = 60.63, df = 13 (P < 0.00001); I² = 79%							
Test for overall effect: Z = 0.01 (P = 0.99)							
1.2.3 Retrospective cohort study							
Acar 2015	7	37	9	63	2.2%	0.05 [-0.11, 0.20]	
Bryant 2019	84	997	68	792	4.7%	-0.00 [-0.03, 0.02]	
Chen 2015	15	420	61	420	4.5%	-0.11 [-0.15, -0.07]	
Choi 2018	199	1786	28	223	4.4%	-0.01 [-0.06, 0.03]	
Kam 2018	23	121	19	121	3.3%	0.03 [-0.06, 0.13]	
Maxeiner 2018	64	318	50	318	4.1%	0.04 [-0.02, 0.10]	
Mendhiratta 2015	86	382	49	382	4.2%	0.10 [0.04, 0.15]	
Peltier 2016	30	119	51	119	2.8%	-0.18 [-0.29, -0.06]	
Washino 2018	42	281	34	215	4.0%	-0.01 [-0.07, 0.06]	
Yarlagadda 2018	16	69	13	69	2.5%	0.04 [-0.09, 0.18]	
Subtotal (95% CI)		4530		2722	36.8%	-0.01 [-0.05, 0.04]	
Total events	566		382				
Heterogeneity: Tau² = 0.00; Chi² = 55.16, df = 9 (P < 0.00001); I² = 84%							
Test for overall effect: Z = 0.22 (P = 0.83)							
Total (95% CI)		7832		5257	100.0%	0.00 [-0.03, 0.03]	
Total events	1245		863				
Heterogeneity: Tau² = 0.00; Chi² = 143.05, df = 28 (P < 0.00001); I² = 80%							
Test for overall effect: Z = 0.05 (P = 0.96)							
Test for subgroup differences: Chi² = 0.08, df = 2 (P = 0.96), I² = 0%							

-0.2 -0.1 0 0.1 0.2
More events in mpMRI   More events in standard

(d) high-grade prostate cancer diagnosis

Study or Subgroup	TRUS biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.4.1 Randomized controlled trials						
Kasivisvanathan 2018	9	248	23	252	7.3%	-0.05 [-0.10, -0.01]
Park 2011	1	41	5	44	2.2%	-0.09 [-0.19, 0.02]
Porpiglia 2017	3	105	6	107	5.7%	-0.03 [-0.08, 0.03]
Tonttila 2016	4	60	4	53	2.6%	-0.01 [-0.10, 0.09]
Subtotal (95% CI)		**454**		**456**	**17.9%**	**-0.04 [-0.07, -0.01]**
Total events	17		38			
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 2.90 (P = 0.004)						
1.4.2 Prospective cohort study						
Borkowetz 2018	18	214	21	170	4.9%	-0.04 [-0.10, 0.02]
Castellucci 2017	14	168	5	86	4.6%	0.03 [-0.04, 0.09]
Delongchamps 2016	12	108	6	108	3.9%	0.06 [-0.02, 0.13]
Mozer 2015	11	152	11	152	5.2%	0.00 [-0.06, 0.06]
Peltier 2015	0	110	0	110	11.7%	0.00 [-0.02, 0.02]
Pokorny 2014	20	223	21	142	4.2%	-0.06 [-0.13, 0.01]
Rouviere 2019	24	251	21	206	5.6%	-0.01 [-0.06, 0.05]
van der Leest 2018	46	626	42	317	7.3%	-0.06 [-0.10, -0.02]
Zhang 2017	15	224	29	224	5.6%	-0.06 [-0.12, -0.01]
Subtotal (95% CI)		**2076**		**1515**	**52.9%**	**-0.02 [-0.05, 0.01]**
Total events	160		156			
Heterogeneity: Tau² = 0.00; Chi² = 23.56, df = 8 (P = 0.003); I² = 66%						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.4.3 Retrospective cohort study						
Bryant 2019	169	997	129	792	8.6%	0.01 [-0.03, 0.04]
Choi 2018	131	1786	30	223	6.7%	-0.06 [-0.11, -0.01]
Kam 2018	24	121	23	121	2.4%	0.01 [-0.09, 0.11]
Maxeiner 2018	85	318	106	318	4.0%	-0.07 [-0.14, 0.01]
Washino 2018	25	281	26	215	5.6%	-0.03 [-0.09, 0.02]
Yarlagadda 2018	11	69	9	69	1.8%	0.03 [-0.09, 0.15]
Subtotal (95% CI)		**3572**		**1738**	**29.2%**	**-0.02 [-0.06, 0.01]**
Total events	445		323			
Heterogeneity: Tau² = 0.00; Chi² = 8.04, df = 5 (P = 0.15); I² = 38%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Total (95% CI)		**6102**		**3709**	**100.0%**	**-0.02 [-0.04, -0.01]**
Total events	622		517			
Heterogeneity: Tau² = 0.00; Chi² = 33.96, df = 18 (P = 0.01); I² = 47%						
Test for overall effect: Z = 2.78 (P = 0.005)						
Test for subgroup differences: Chi² = 1.72, df = 2 (P = 0.42), I² = 0%						

Risk Difference M-H, Random, 95% CI

-0.2 -0.1 0 0.1 0.2
More events in mpMRI   More events in standard

Figure 3. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by inclusion of systematic biopsy in the mpMRI-informed biopsy arm: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

(a) any prostate cancer diagnosis

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.5.1 Targeted biopsy only						
Acar 2015	19	37	37	63	2.0%	-0.07 [-0.28, 0.13]
Castellucci 2017	60	168	48	86	2.6%	-0.20 [-0.33, -0.07]
Chen 2015	24	420	41	420	3.1%	-0.04 [-0.08, -0.00]
Choi 2018	522	1786	124	223	3.0%	-0.26 [-0.33, -0.20]
de Gorski 2015	129	232	126	232	2.8%	0.01 [-0.08, 0.10]
Delongchamps 2013 - Cohort 1	55	127	40	54	2.4%	-0.31 [-0.45, -0.16]
Delongchamps 2013 - Cohort 2	60	131	64	78	2.6%	-0.36 [-0.48, -0.24]
Delongchamps 2013 - Cohort 3	44	133	62	82	2.6%	-0.43 [-0.55, -0.30]
Delongchamps 2016	66	108	61	108	2.5%	0.05 [-0.08, 0.18]
Garcia Bennetta 2017	32	60	28	32	2.2%	-0.34 [-0.51, -0.17]
Kam 2018	84	121	80	121	2.6%	0.03 [-0.08, 0.15]
Kasivisvanathan 2018	150	248	200	252	2.9%	-0.19 [-0.27, -0.11]
Maxeiner 2018	222	318	213	318	3.0%	0.03 [-0.04, 0.10]
Mendhiratta 2015	188	382	166	382	3.0%	0.06 [-0.01, 0.13]
Mozer 2015	86	152	82	152	2.7%	0.03 [-0.09, 0.14]
Peltier 2015	50	110	57	110	2.5%	-0.06 [-0.20, 0.07]
Pokorny 2014	126	223	99	142	2.8%	-0.13 [-0.23, -0.03]
Porpiglia 2017	31	105	54	107	2.5%	-0.21 [-0.34, -0.08]
Quentin 2014	68	128	68	128	2.6%	0.00 [-0.12, 0.12]
Rouviere 2019	131	251	104	206	2.8%	0.02 [-0.08, 0.11]
Shoji 2017	86	250	145	250	2.9%	-0.24 [-0.32, -0.15]
van der Leest 2018	301	626	247	317	3.0%	-0.30 [-0.36, -0.24]
Washino 2018	118	281	119	215	2.9%	-0.13 [-0.22, -0.05]
Yarlagadda 2018	40	69	38	69	2.2%	0.03 [-0.14, 0.19]
Subtotal (95% CI)		6466		4147	64.3%	-0.12 [-0.18, -0.07]
Total events	2692		2303			

Heterogeneity: Tau² = 0.02; Chi² = 218.61, df = 23 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.21 (P < 0.0001)

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.5.2 Targeted + systematic biopsy						
Baco 2016	48	89	51	86	2.4%	-0.05 [-0.20, 0.09]
Borkowetz 2018	91	214	100	170	2.8%	-0.16 [-0.26, -0.06]
Bryant 2019	565	997	456	792	3.1%	-0.01 [-0.06, 0.04]
Castellucci 2017	60	168	69	86	2.7%	-0.45 [-0.56, -0.33]
Chen 2015	24	420	104	420	3.1%	-0.19 [-0.24, -0.14]
de Gorski 2015	129	232	143	232	2.9%	-0.06 [-0.15, 0.03]
Maxeiner 2018	222	318	245	318	3.0%	-0.07 [-0.14, -0.00]
Park 2011	4	41	13	44	2.3%	-0.20 [-0.36, -0.04]
Peltier 2016	49	119	73	119	2.6%	-0.20 [-0.33, -0.08]
Rouviere 2019	131	251	161	206	2.9%	-0.26 [-0.34, -0.18]
Tonttila 2016	34	60	34	53	2.1%	-0.07 [-0.25, 0.11]
van der Leest 2018	301	626	261	317	3.1%	-0.34 [-0.40, -0.29]
Zhang 2017	78	224	99	224	2.8%	-0.09 [-0.18, -0.00]
Subtotal (95% CI)		3759		3067	35.7%	-0.17 [-0.24, -0.09]
Total events	1736		1809			

Heterogeneity: Tau² = 0.02; Chi² = 130.91, df = 12 (P < 0.00001); I² = 91%
Test for overall effect: Z = 4.37 (P < 0.0001)

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Total (95% CI)		10225		7214	100.0%	-0.14 [-0.19, -0.09]
Total events	4428		4112			

Heterogeneity: Tau² = 0.02; Chi² = 358.56, df = 36 (P < 0.00001); I² = 90%
Test for overall effect: Z = 6.06 (P < 0.00001)
Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%

More events in mpMRI More events in standard

(b) clinically-significant prostate cancer diagnosis

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.10.1 Targeted biopsy only						
Acar 2015	12	37	28	63	1.9%	-0.12 [-0.31, 0.07]
Castellucci 2017	33	168	30	86	2.7%	-0.15 [-0.27, -0.04]
Chen 2015	13	420	18	420	3.6%	-0.01 [-0.04, 0.01]
Choi 2018	323	1786	96	223	3.3%	-0.25 [-0.32, -0.18]
de Gorski 2015	91	232	102	232	3.0%	-0.05 [-0.14, 0.04]
Delongchamps 2013 - Cohort 1	18	127	18	54	2.4%	-0.19 [-0.33, -0.05]
Delongchamps 2013 - Cohort 2	26	131	33	78	2.6%	-0.22 [-0.35, -0.10]
Delongchamps 2013 - Cohort 3	19	133	27	82	2.7%	-0.19 [-0.30, -0.07]
Delongchamps 2016	38	108	40	108	2.6%	-0.02 [-0.15, 0.11]
Garcia Bennetta 2017	27	60	27	32	2.0%	-0.39 [-0.57, -0.22]
Kam 2018	61	121	61	121	2.6%	0.00 [-0.13, 0.13]
Kasivisvanathan 2018	64	248	95	252	3.1%	-0.12 [-0.20, -0.04]
Maxeiner 2018	158	318	140	318	3.1%	0.06 [-0.02, 0.13]
Mendhiratta 2015	102	382	117	382	3.3%	-0.04 [-0.10, 0.02]
Mozer 2015	34	152	33	152	3.0%	0.01 [-0.09, 0.10]
Peltier 2015	8	110	19	110	3.1%	-0.10 [-0.19, -0.01]
Pokorny 2014	79	223	93	142	2.9%	-0.30 [-0.40, -0.20]
Porpiglia 2017	14	105	44	107	2.7%	-0.28 [-0.39, -0.16]
Rouviere 2019	75	251	81	206	3.0%	-0.09 [-0.18, 0.01]
van der Leest 2018	146	626	159	317	3.3%	-0.27 [-0.33, -0.20]
Washino 2018	76	281	85	215	3.1%	-0.12 [-0.21, -0.04]
Yarlagadda 2018	24	69	25	69	2.2%	-0.01 [-0.17, 0.15]
Subtotal (95% CI)		**6088**		**3769**	**62.0%**	**-0.13 [-0.18, -0.07]**
Total events	1441		1371			

Heterogeneity: Tau² = 0.01; Chi² = 179.39, df = 21 (P < 0.00001); I² = 88%
Test for overall effect: Z = 4.70 (P < 0.00001)

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.10.2 Targeted + systematic biopsy						
Baco 2016	44	89	38	86	2.3%	0.05 [-0.10, 0.20]
Borkowetz 2018	74	214	81	170	2.9%	-0.13 [-0.23, -0.03]
Bryant 2019	481	997	388	792	3.4%	-0.01 [-0.05, 0.04]
Castellucci 2017	33	168	41	86	2.6%	-0.28 [-0.40, -0.16]
Chen 2015	13	420	43	420	3.5%	-0.07 [-0.10, -0.04]
de Gorski 2015	91	232	113	232	3.0%	-0.09 [-0.18, -0.00]
Maxeiner 2018	158	318	175	318	3.1%	-0.05 [-0.13, 0.02]
Park 2011	2	41	11	44	2.4%	-0.20 [-0.35, -0.06]
Peltier 2016	19	119	22	119	2.9%	-0.03 [-0.12, 0.07]
Rouviere 2019	75	251	94	206	3.0%	-0.16 [-0.25, -0.07]
Tonttila 2016	18	60	15	53	2.1%	0.02 [-0.15, 0.18]
van der Leest 2018	146	626	180	317	3.3%	-0.33 [-0.40, -0.27]
Zhang 2017	35	224	59	224	3.2%	-0.11 [-0.18, -0.03]
Subtotal (95% CI)		**3759**		**3067**	**38.0%**	**-0.11 [-0.17, -0.05]**
Total events	1189		1260			

Heterogeneity: Tau² = 0.01; Chi² = 92.12, df = 12 (P < 0.00001); I² = 87%
Test for overall effect: Z = 3.59 (P = 0.0003)

Total (95% CI)		**9847**		**6836**	**100.0%**	**-0.12 [-0.16, -0.08]**
Total events	2630		2631			

Heterogeneity: Tau² = 0.01; Chi² = 266.65, df = 34 (P < 0.00001); I² = 87%
Test for overall effect: Z = 6.20 (P < 0.00001)
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%

Risk Difference M-H, Random, 95% CI

-0.5 -0.25 0 0.25 0.5
More events in mpMRI   More events in standard

(c) clinically-insignificant prostate cancer diagnosis

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
1.9.1 Targeted biopsy only							
Acar 2015	7	37	9	63	2.6%	0.05 [-0.11, 0.20]	
Castellucci 2017	27	168	18	86	4.0%	-0.05 [-0.15, 0.05]	
Chen 2015	15	420	23	420	6.6%	-0.02 [-0.05, 0.01]	
Choi 2018	199	1786	28	223	6.1%	-0.01 [-0.06, 0.03]	
de Gorski 2015	38	232	24	232	5.5%	0.06 [-0.00, 0.12]	
Delongchamps 2013 - Cohort 1	37	127	12	54	3.0%	0.07 [-0.07, 0.21]	
Delongchamps 2013 - Cohort 2	34	131	31	78	3.1%	-0.14 [-0.27, -0.01]	
Delongchamps 2013 - Cohort 3	25	133	35	82	3.3%	-0.24 [-0.36, -0.11]	
Delongchamps 2016	28	108	21	108	3.7%	0.06 [-0.05, 0.18]	
Garcia Bennetta 2017	5	60	1	32	4.4%	0.05 [-0.04, 0.14]	
Kam 2018	23	121	19	121	4.2%	0.03 [-0.06, 0.13]	
Kasivisvanathan 2018	55	248	23	252	5.5%	0.13 [0.07, 0.19]	
Maxeiner 2018	64	318	54	318	5.6%	0.03 [-0.03, 0.09]	
Mendhiratta 2015	86	382	49	382	5.8%	0.10 [0.04, 0.15]	
Mozer 2015	52	152	49	152	3.9%	0.02 [-0.09, 0.13]	
Peltier 2015	42	110	38	110	3.3%	0.04 [-0.09, 0.16]	
Pokorny 2014	47	223	6	142	5.5%	0.17 [0.11, 0.23]	
Porpiglia 2017	17	105	10	107	4.5%	0.07 [-0.02, 0.16]	
Rouviere 2019	35	251	23	206	5.5%	0.03 [-0.03, 0.09]	
van der Leest 2018	155	626	88	317	5.6%	-0.03 [-0.09, 0.03]	
Washino 2018	42	281	34	215	5.4%	-0.01 [-0.07, 0.06]	
Yarlagadda 2018	16	69	13	69	3.0%	0.04 [-0.09, 0.18]	
Subtotal (95% CI)		6088		3769	100.0%	0.03 [-0.01, 0.06]	
Total events	1049		608				

Heterogeneity: Tau² = 0.00; Chi² = 82.48, df = 21 (P < 0.00001); I² = 75%
Test for overall effect: Z = 1.62 (P = 0.11)

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
1.9.2 Targeted + systematic biopsy							
Baco 2016	4	89	13	86	7.6%	-0.11 [-0.19, -0.02]	
Borkowetz 2018	17	214	19	170	9.6%	-0.03 [-0.09, 0.03]	
Bryant 2019	84	997	68	792	11.8%	-0.00 [-0.03, 0.02]	
Castellucci 2017	27	168	28	86	6.0%	-0.16 [-0.28, -0.05]	
Chen 2015	15	420	61	420	11.1%	-0.11 [-0.15, -0.07]	
de Gorski 2015	38	232	30	232	9.2%	0.03 [-0.03, 0.10]	
Maxeiner 2018	64	318	50	318	9.6%	0.04 [-0.02, 0.10]	
Park 2011	2	41	2	44	7.4%	0.00 [-0.09, 0.09]	
Peltier 2016	30	119	51	119	5.7%	-0.18 [-0.29, -0.06]	
Tonttila 2016	16	60	19	53	3.6%	-0.09 [-0.26, 0.08]	
van der Leest 2018	155	626	81	317	9.7%	-0.01 [-0.07, 0.05]	
Zhang 2017	43	224	40	224	8.7%	0.01 [-0.06, 0.09]	
Subtotal (95% CI)		3508		2861	100.0%	-0.04 [-0.08, -0.00]	
Total events	495		462				

Heterogeneity: Tau² = 0.00; Chi² = 48.28, df = 11 (P < 0.00001); I² = 77%
Test for overall effect: Z = 1.97 (P = 0.05)

Test for subgroup differences: Chi² = 6.49, df = 1 (P = 0.01), I² = 84.6%

-0.5   -0.25   0   0.25   0.5
More events in mpMRI   More events in standard

(d) high-grade prostate cancer diagnosis

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.11.1 Targeted biopsy only						
Castellucci 2017	14	168	3	86	4.9%	0.05 [-0.01, 0.11]
Choi 2018	131	1786	30	223	6.1%	-0.06 [-0.11, -0.01]
Delongchamps 2016	12	108	6	108	3.6%	0.06 [-0.02, 0.13]
Kam 2018	24	121	23	121	2.3%	0.01 [-0.09, 0.11]
Kasivisvanathan 2018	9	248	23	252	6.6%	-0.05 [-0.10, -0.01]
Maxeiner 2018	85	318	75	318	4.0%	0.03 [-0.04, 0.10]
Mozer 2015	11	152	11	152	4.8%	0.00 [-0.06, 0.06]
Peltier 2015	0	110	0	110	10.1%	0.00 [-0.02, 0.02]
Pokorny 2014	20	223	21	142	3.9%	-0.06 [-0.13, 0.01]
Porpiglia 2017	3	105	6	107	5.2%	-0.03 [-0.08, 0.03]
Rouviere 2019	24	251	21	206	5.1%	-0.01 [-0.06, 0.05]
van der Leest 2018	46	626	42	317	6.6%	-0.06 [-0.10, -0.02]
Washino 2018	25	281	26	215	5.1%	-0.03 [-0.09, 0.02]
Yarlagadda 2018	11	69	9	69	1.7%	0.03 [-0.09, 0.15]
Subtotal (95% CI)		4566		2426	70.2%	-0.01 [-0.04, 0.01]
Total events	415		296			

Heterogeneity: Tau² = 0.00; Chi² = 29.46, df = 13 (P = 0.006); I² = 56%
Test for overall effect: Z = 1.37 (P = 0.17)

Study or Subgroup	Systematic biopsy Events	Total	mpMRI informed biopsy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.11.2 Targeted + systematic biopsy						
Borkowetz 2018	18	214	21	170	4.5%	-0.04 [-0.10, 0.02]
Bryant 2019	169	997	129	792	7.7%	0.01 [-0.03, 0.04]
Castellucci 2017	14	168	5	86	4.2%	0.03 [-0.04, 0.09]
Maxeiner 2018	85	318	106	318	3.8%	-0.07 [-0.14, 0.01]
Park 2011	1	41	5	44	2.1%	-0.09 [-0.19, 0.02]
Tonttila 2016	4	60	4	53	2.5%	-0.01 [-0.10, 0.09]
Zhang 2017	15	224	29	224	5.2%	-0.06 [-0.12, -0.01]
Subtotal (95% CI)		2022		1687	29.8%	-0.03 [-0.06, 0.00]
Total events	306		299			

Heterogeneity: Tau² = 0.00; Chi² = 10.16, df = 6 (P = 0.12); I² = 41%
Test for overall effect: Z = 1.69 (P = 0.09)

Total (95% CI)		6588		4113	100.0%	-0.02 [-0.04, -0.00]
Total events	721		595			

Heterogeneity: Tau² = 0.00; Chi² = 39.48, df = 20 (P = 0.006); I² = 49%
Test for overall effect: Z = 2.16 (P = 0.03)
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%

Risk Difference M-H, Random, 95% CI

-0.2 -0.1 0 0.1 0.2
More events in mpMRI   More events in standard