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

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

<text>

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 Evidencebased 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 care¹. Transrectal ultrasound (TRUS)-guided 12-core template systematic biopsy (SBX) has been widely recommended for men at risk for PCa² <u>ENREF 2</u>. However, SBX templates are limited by inherent random and systematic errors. Specific regions of the prostate are consistently underesampled, including the anterior region and apex³, and, unless hypoechoic lesions are seen on TRUS, sampling occurs by chance. Thus, SBX can miss up to 20% of CS PCa, resulting in underdiagnosis⁴. Additionally, SBX detects a relatively high percentage of clinically insignificant (CI) PCa (Gleason grade group [GGG] 1), which may result in overtreatment², 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 2⁵) is detected with fewer biopsy cores⁶, and diagnosis of CI PCa decreases⁷. 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 cases¹⁰⁻¹³. 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

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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 TGBX¹⁶. 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) statement¹⁸. 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 \geq 2), HG PCa (GGG \geq 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 bias¹⁹ 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 domains²⁰: (1) selection of the study groups; (2) comparability of groups; and (3) ascertainment of exposure and outcome²¹. 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 I² values²². Given the identified clinical heterogeneity, we employed random effects models for each of our analyses.

2.8. Data synthesis

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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.

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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 alone⁵.

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 mpMRIinformed 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 mpMRIinformed TGBX was associated with a 12% increased likelihood of PCa diagnosis (risk

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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 = -0.18, 95% CI -0.24 to -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 0.05; 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 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 metaanalysis 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 SBX²³. Despite this, TRUS-SBX harbors low sensitivity and specificity in the diagnosis of PCa¹²: repeat biopsy identifies PCa in 10-25% of men with an initially negative biopsy²⁴. 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 improved²⁶. Previous meta-analyses have shown that mpMRI-informed TGBX detects more CS PCA, with fewer cores than utilized in TRUS-guided SBX¹³.

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 SBX²⁷⁻²⁹. 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 PCa³¹, 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 RP³⁴.

This analysis strengthens the body of evidence supporting mpMRI as a riskstratification 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 year³⁸, 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 study³⁹, 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 PCa⁴⁰. 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 biopsy².

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 pathology¹³. 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 criteria⁴¹ to the combination of maximal cancer core length <6 mm with GGG 1⁴². 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, mpMRIinformed biopsy procedure lacked standardization. There was significant variability

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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 mpMRI⁴³, 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 RP⁴⁴.

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

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Conflict of Interests: None

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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.

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 Table 1-Characteristics of included studies

	Country/	Study	Inclusion	Study size	PSA (ng/ml)	Age (yr)	Biopsy	y approach	Biopsy	MRI	MRI scoring	TGBX	
Author (yr)	Number of centers	interval	Criteria	(SBX/ TGBX)	(SBX/ TGBX)	(SBX / TGBX)	SBX	TGBX	- technique in MRI arm	machi ne	system	technique	Outcome
						Randomized cont	rolled trials	C,	,				· · · · · ·
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		6.1				targeted				CS PCa
			free-to-total										Positive
			PSA ratio										core rate
			<=0.15 and						\wedge				
			PSA <10						R				
			ng/ml in					0					
			repeated					SCA					
			measurement)										
						Prospective coh	ort studies	2					
							2						Overall PCa
			Elevated PSA					Ϋ́					CS PCa
Borkowetz	Germany/2	1/2016-	and/or	384 (214/170)	Median 6.22	Median 63	Transrectal	Transperineal	Systematic+	3T	PIRADS	Software	Corca
(2018)	Germany/2	12/2017	abnormal	504 (214/170)	Weddan 0.22	Wedian 05	Tunarectur	Transpermear	targeted	51	v2	fusion	Positive
			DRE						-				core rate
			Elevated PSA										Overall PCa
Castellucci		7/2011-	and/or						Systematic+		PIRADS	Cognitive	
(2017)	Spain/1	7/2014	abnormal	254 (168/86)	Mean 8.3	Mean 61.4	Transrectal	Transrectal		1.5T	vl	fusion	CS PCa
(2017)			DRE						targeted			TROTOT	
						\mathbf{O}							
		1/2010-	Elevated PSA										Overall PCa
De Gorski	France/1	5/2014	(PSA < 10	232	Mean 6.5	Mean 64	Transrectal	Transrectal	Systematic+	1.5T	Likert	Software	CS PCa
(2015)			ng/ml)						targeted			fusion	
			8)		K								
					·	Mean							
			Elevated PSA	U'	Mean	62.7/Mean						Software	Overall PCa
Delongchamps	France/1	1/2011-	and/or	605 (391/214)	8.1/Mean	64.6/ Mean	Transrectal	Transparingal	Systematic+	1.5T	3-point	fusion	Insignifican
(2013)	Fiance/1	3/2012	abnormal	003 (391/214)	8.3/Mean 9	64.5		Transperineal	targeted	1.51	scale	Cognitive	t PCa
			DRE		0.5/1v1Call 7				Ŭ			fusion	
											1		

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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	3Т	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	3Т	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 Intermediat e/high risk PCa
Quentin (2014)	Germany/1	11/2011- 10/2013	Elevated PSA (PSA >4	128	Median 6.7	Median 67	Transrectal	Transrectal	Systematic+	3Т	PIRADS v1	In-bore fusion	CS PCa

ng/ml) targeted Elevated PSA and/or CS PCa Software 7/2015abnormal Systematic+ Transrectal Transrectal 1.5T fusion Insignifican 8/2016 DRE 457 (251/206) Rouviere (2019) France/16 Median 6.5 Median 64 Likert t PCa targeted 3T Cognitive Family fusion history of PCa Overall PCa 10/2014-Elevated PSA Transperineal Transrectal Systematic+ PIRADS Software 8/2016 Shoji (2017) Japan/1 (PSA 4-250 Median 6.7 Median 68 NR CS PCa v1fusion targeted 20ng/ml) Elevated PSA Transrectal Transrectal CS PCa Systematic+ Van der Leest Netherlands 2/2015-PIRADS (PSA >=3 626 (309/317) Median 6.4 Median 65 3T In-bore fusion (2018) /4 2/2018 v2 targeted ng/ml) Overall PCa Elevated PSA Transperineal Transperineal Systematic+ 12/2014and/or PIRADS Software Zhang (2017) 253 Median 69 Median 10.05 3T CS PCa China/1 2/2016 abnormal v1fusion targeted DRE Retrospective cohort studies Elevated PSA and/or abnormal Cognitive Mean DRE Systematic+ CS PCa 1/2012-PIRADS Mean fusion Acar (2015) Turkey/1 100 (37/63) 62.3/Mean Transrectal Transrectal 3T 2/2014 7.6/Mean 5.9 v1 Family targeted 60.4 In-bore fusion history of PCa Abnormal

			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	Transrectat	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	348	Median 7.14	Median 68	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1 & v2	Software fusion	CS PCa

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			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	3Т	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

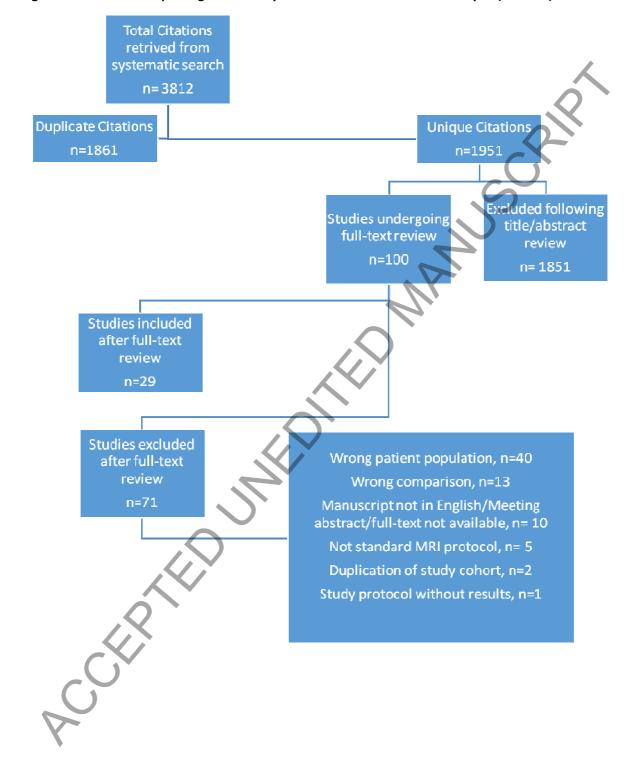
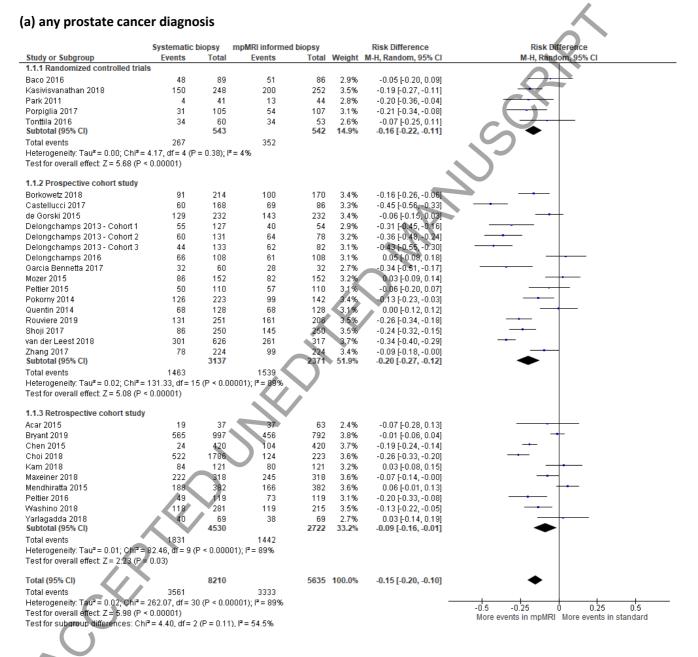


Figure 1. – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart

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.



(b) clinically-significant prostate cancer diagnosis

	TRUS bi	onev	mpMRI informed bi	onev		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.3.1 Randomized controlled tria		Total	Erento	Total	Troight	m-n, rundon, oon or	
Baco 2016	44	89	38	86	18.7%	0.05 [-0.10, 0.20]	
Kasivisvanathan 2018	64	248	95	252		-0.12 [-0.20, -0.04]	
Park 2011	2	41	95 11	44		-0.20 [-0.35, -0.06]	
Porpiglia 2017	14	105	44	107	21.4%	-0.28 [-0.39, -0.16]	
Tonttila 2016	14	60	15	53	17.1%		
Subtotal (95% CI)	10	543	10		100.0%	0.02 [-0.15, 0.18] - 0.11 [-0.23, 0.00]	
	142	343	203	342	100.070	-0.11[-0.25, 0.00]	
Total events Heterogeneity: Tau ² = 0.01; Chi ² = Test for overall effect: Z = 1.94 (P =	16.61, df=	= 4 (P =					-C
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	34	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	223	93 94	206	7.4%	-0.16 [-0.25, -0.07]	
van der Leest 2018	75 146	626	94 180	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)	50	2759	29	1993		-0.18 [-0.24, -0.11]	
Total events	703	2100	858	1000			•
Heterogeneity: Tau ² = 0.01; Chi ² = Test for overall effect: Z = 5.51 (P <	70.14, df=			<	$\langle \cdot \rangle$		
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 Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 2.87 (P =		= 9 (P <	1040 0.00001); I² = 77%				
	$\langle \cdot \rangle$					+	0.5 -0.25 0 0.25 0.5
Test for subgroup differences: Ch	i² = 6.35, d	f= 2 (P	= 0.04), I ² = 68.5%				More events in mpMRI More events in standard
Test for subgroup differences: Ch							

(c) clinically-insignificant prostate cancer diagnosis

	TRUS bi	opsy	mpMRI informed b	iopsy		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.2.1 Randomized controlled tria	s				-		
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: Tau ² = 0.01; Chi ² = Test for overall effect: Z = 0.19 (P =		= 4 (P =	0.0002); I² = 82%				
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		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		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	40.00	414		\sim		
Heterogeneity: Tau ² = 0.01; Chi ² = Test for overall effect: Z = 0.01 (P =		:13 (P ·	< 0.00001); I*= 79%				
1.2.3 Retrospective cohort study	1						
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)	500	4530		2722	36.8%	-0.01 [-0.05, 0.04]	
Total events	566 55 4 6 alfa	0.00	382				
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 0.22 (P =		9 (P <	0.00001);				
Total (95% CI)		7832		5257	100.0%	0.00 [-0.03, 0.03]	•
Total events	1245		863				T
Heterogeneity: Tau ² = 0.00; Chi ² =		= 28 (P		6			
				•			-0.2 -0.1 Ó 0.1 0.2
Test for subgroup differences: Ch	1 ² = 0.08, d	f= 2 (P	= 0.96), I ² = 0%				More events in mpMRI More events in standard
Test for overall effect: Z = 0.05 (P Test for subgroup differences: Ch							
•							

(d) high-grade prostate cancer diagnosis

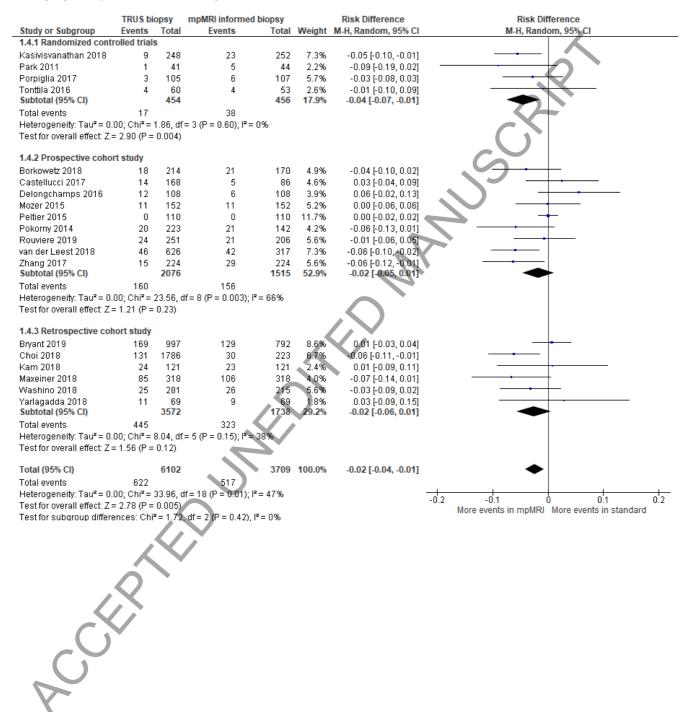


Figure 3. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by inclusion of systematic biopsy in the mpMRI-informed biopsy arm: (a) any prostate cancer diagnosis, (b) clinically-significant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

(a) any prostate cancer diagnosis

X

	Systematic		mpMRI informed		Mainte	Risk Difference	Risk Difference
itudy or Subgroup	Events	Total	Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
.5.1 Targeted biopsy only							
car 2015	19	37	37	63	2.0%	-0.07 [-0.28, 0.13]	
astellucci 2017	60	168	48	86	2.6%	-0.20 [-0.33, -0.07]	
hen 2015	24	420	41	420	3.1%	-0.04 [-0.08, -0.00]	
>hoi 2018	522	1786	124	223	3.0%	-0.26 [-0.33, -0.20]	
le Gorski 2015	129	232	126	232	2.8%	0.01 [-0.08, 0.10]	
)elongchamps 2013 - Cohort 1	55	127	40	54	2.4%	-0.31 [-0.45, -0.16]	
)elongchamps 2013 - Cohort 2	60	131	64	78	2.6%	-0.36 [-0.48, -0.24]	
elongchamps 2013 - Cohort 3 🤅	44	133	62	82	2.6%	-0.43 [-0.55, -0.30]	
)elongchamps 2016	66	108	61	108	2.5%	0.05 [-0.08, 0.18]	
∂arcia Bennetta 2017	32	60	28	32	2.2%	-0.34 [-0.51, -0.17]	
(am 2018	84	121	80	121	2.6%	0.03 [-0.08, 0.15]	
(asivisvanathan 2018	150	248	200	252	2.9%	-0.19 [-0.27, -0.14]	
faxeiner 2018	222	318	213	318	3.0%	0.03 (-0.04, 0.10)	
1endhiratta 2015	188	382	166	382	3.0%	0.06 [-0.01, 0.13]	
lozer 2015	86	152	82	152	2.7%	0.03 [-0.09, 0.14]	
eltier 2015	50	110	57	110	2.5%	-0.06 [-0.20, 0.07]	
okorny 2014	126	223	99	142	2.8%	-0.13 [-0.23, -0.03]	
orpiglia 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%		
an der Leest 2018	301	626	247	317	3.0%	-0.30 [-0.36, -0.24]	
Vashino 2018	118	281	119	215	2.9%	-0.13 [-0.22, -0.05]	
arlagadda 2018	40	69	38	69	2.2%	0.03 [-0.14, 0.19]	
Subtotal (95% CI)	10	6466		4147	64.3%	-0.12 [-0.18, -0.07]	•
otal events	2692		2303				•
leterogeneity: Tau ² = 0.02; Chi ² =		3 (P < 0 00					
lotorogeneny. rua = 0.02, om =		0 (1 - 0.00	10017,1 = 0070				
est for overall effect: 7 = 4 21 (P ≤	< 0.0001)			\mathbf{v}			
'est for overall effect: Z = 4.21 (P <	< 0.0001)						
			\sim				
.5.2 Targeted + systematic biop	sy	80 4	51	86	7.1%	-0.05 (-0.20, 0.00)	
.5.2 Targeted + systematic biops acco 2016	sy 48	89 214	51	86	2.4%	-0.05 [-0.20, 0.09]	
.5.2 Targeted + systematic biops laco 2016 lorkowetz 2018	sy 48 91	214	100	170	2.8%	-0.16 [-0.26, -0.06]	
.5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 loyant 2019	sy 48 91 565	214 997	100 456	170 792	2.8% 3.1%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04]	
.5.2 Targeted + systematic biop: laco 2016 lorkowetz 2018 lyant 2019 castellucci 2017	sy 48 91 565 60	214 997 168	100 456 69	170 792 86	2.8% 3.1% 2.7%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33]	
.5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 livant 2019 lastellucci 2017 chen 2015	sy 48 91 565 60 24	214 997 168 420	100 456 69 104	170 792 86 420	2.8% 3.1% 2.7% 3.1%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14]	
.5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 liyant 2019 lastellucci 2017 chen 2015 le Gorski 2015	sy 48 91 565 60 24 129	214 997 168 420 232	100 456 69 104 143	170 792 86 420 232	2.8% 3.1% 2.7% 3.1% 2.9%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03]	
.5.2 Targeted + systematic biops laco 2016 iorkowetz 2018 inyant 2019 castellucci 2017 hen 2015 le Gorski 2015 faxeiner 2018	sy 48 91 565 60 24	214 997 168 420 232 318	100 456 69 104 143 245	170 792 86 420 232 318	2.8% 3.1% 2.7% 3.1% 2.9% 3.0%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00]	
5.2 Targeted + systematic biop laco 2016 lorkowetz 2018 liyant 2019 lastellucci 2017 lihen 2015 le Gorski 2015 laxeiner 2018 lark 2011	sy 48 91 565 60 24 129 222 4	214 997 168 420 232 318 41	100 456 69 104 143 245 13	170 792 86 420 232 318 44	2.8% 3.1% 2.7% 3.1% 2.9% 3.0% 2.3%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04]	
5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 lyrant 2019 castellucci 2017 chen 2015 le Gorski 2015 laxeiner 2018 lark 2011 'ettier 2016	sy 48 91 565 60 24 129 222 4 4	214 997 168 420 232 318 41 119	100 456 69 104 143 245 13 73	170 792 86 420 232 318 44 119	2.8% 3.1% 2.7% 3.1% 2.9% 3.0% 2.3% 2.6%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08]	
5.2 Targeted + systematic biop laco 2016 lorkowetz 2018 livyant 2019 lastellucci 2017 chen 2015 le Gorski 2015 laxeiner 2018 lark 2011 lettler 2016 Rouviere 2019	sy 48 91 565 60 24 129 222 4 49 131	214 997 168 420 232 318 41 119 251	100 456 69 104 143 245 13 73 161	170 792 86 420 232 318 44 119 206	2.8% 3.1% 2.7% 3.1% 2.9% 3.0% 2.3% 2.6% 2.9%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18]	
5.2 Targeted + systematic biops lace 2016 lorkowetz 2018 liyant 2019 lastellucci 2017 chen 2015 le Gorski 2015 laxeiner 2018 larki 2011 'ettier 2016 louviere 2019 lonttila 2016	sy 48 91 565 60 24 129 222 4 49 131 34	214 997 168 420 232 318 41 119 251 60	100 456 69 104 143 245 13 73 161 34	170 792 86 420 232 318 44 119 206 53	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.9% 2.1%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.26 [-0.34, -0.18] -0.26 [-0.34, -0.18]	
5.2 Targeted + systematic biop laco 2016 lorkowetz 2018 linyant 2019 lastellucci 2017 then 2015 le Gorski 2015 laxeiner 2018 lark 2011 leitier 2016 Rouviere 2019 lonttila 2016 an der Leest 2018	sy 48 91 565 60 24 129 222 4 4 131 34 301	214 997 168 420 232 318 41 119 251 60 626	100 456 69 104 143 245 13 73 161 34 261	170 792 86 420 232 318 44 119 206 53 317	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.1% 3.1%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.34, -0.18] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29]	
5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 livyant 2019 castellucci 2017 then 2015 le Gorski 2015 laxeiner 2018 lark 2011 'ettier 2016 louwiere 2019 ionttila 2016 an der Leest 2018 thang 2017	sy 48 91 565 60 24 129 222 4 49 131 34	214 997 168 420 232 318 41 119 251 60 626 224	100 456 69 104 143 245 13 73 161 34	170 792 86 420 232 318 44 119 206 53 317 224	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.1% 3.1% 2.8%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00]	
5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 livpant 2019 castellucci 2017 then 2015 le Gorski 2015 laxeiner 2018 lark 2011 lettier 2016 louviere 2019 lonttila 2016 an der Leest 2018 lhang 2017 lubtotal (95% CI)	sy 48 91 565 60 24 129 222 4 49 131 34 301 78	214 997 168 420 232 318 41 119 251 60 626	100 456 69 104 143 245 13 73 161 34 261 99	170 792 86 420 232 318 44 119 206 53 317	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.1% 3.1%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.19 [-0.24, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.34, -0.18] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29]	
5.2 Targeted + systematic biops laco 2016 loorkowetz 2018 livyant 2019 castellucci 2017 chen 2015 le Gorski 2015 laxeiner 2018 laxeiner 2018 loorki 2016 Rouviere 2019 conttila 2016 an der Leest 2018 lhang 2017 lubtotal (95% CI) otal events	sy 48 91 565 60 24 129 222 4 49 131 34 301 78 1736	214 997 168 420 232 318 41 119 251 60 626 224 3759	100 456 69 104 143 245 13 73 161 34 261 99 1809	170 792 86 420 232 318 44 119 206 53 317 224	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.1% 3.1% 2.8%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00]	
5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 linyant 2019 lastellucci 2017 then 2015 lastellucci 2017 lastellucci 2017 lastellucci 2015 lastellucci 2015 lastellucci 2015 lastellucci 2018 lastellucci 2018 lastellucci 2018 lore 2019 lorttila 2016 an der Leest 2018 lhang 2017 lubtotal (95% CI) lotal events leterogeneity. Tau ² = 0.02; Chi ² =	sy 48 91 565 60 24 129 222 4 4 131 34 301 78 1736 130.91, df = 1	214 997 168 420 232 318 41 119 251 60 626 224 3759	100 456 69 104 143 245 13 73 161 34 261 99 1809	170 792 86 420 232 318 44 119 206 53 317 224	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.1% 3.1% 2.8%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00]	
5.2 Targeted + systematic biops laco 2016 loorkowetz 2018 livyant 2019 castellucci 2017 chen 2015 le Gorski 2015 laxeiner 2018 laxeiner 2018 loorki 2016 Rouviere 2019 conttila 2016 an der Leest 2018 lhang 2017 lubtotal (95% CI) otal events	sy 48 91 565 60 24 129 222 4 4 131 34 301 78 1736 130.91, df = 1	214 997 168 420 232 318 41 119 251 60 626 224 3759	100 456 69 104 143 245 13 73 161 34 261 99 1809	170 792 86 420 232 318 44 119 206 53 317 224	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.1% 3.1% 2.8%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00]	
5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 lyrant 2019 castellucci 2017 then 2015 le Gorski 2015 laxeiner 2018 lark 2011 lettier 2018 lark 2011 lettier 2016 louviere 2019 lonttila 2016 an der Leest 2018 lhang 2017 lubtotal (95% CI) otal events leterogeneity: Tau ² = 0.02; Chi ² = let for overall effect; Z = 4.37 (P <	sy 48 91 565 60 24 129 222 4 4 131 34 301 78 1736 130.91, df = 1	214 997 168 420 232 318 41 119 251 60 626 626 224 3759 2 (P < 0.00	100 456 69 104 143 245 13 73 161 34 261 99 1809	170 792 86 420 2318 44 119 206 53 317 224 3067	2.8% 3.1% 2.7% 3.1% 2.9% 2.6% 2.9% 2.1% 3.1% 3.1% 3.5.7%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00] -0.17 [-0.24, -0.09]	
5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 linyant 2019 lastellucci 2017 then 2015 lastellucci 2017 lastellucci 2017 lastellucci 2015 lastellucci 2015 lastellucci 2015 lastellucci 2018 lastellucci 2018 lastellucci 2018 lore 2019 lorttila 2016 an der Leest 2018 lhang 2017 lubtotal (95% CI) lotal events leterogeneity. Tau ² = 0.02; Chi ² =	sy 48 91 565 60 24 129 222 4 4 131 34 301 78 1736 130.91, df = 1	214 997 168 420 232 318 41 119 251 60 626 224 3759	100 456 69 104 143 245 13 73 161 34 261 99 1809	170 792 86 420 2318 44 119 206 53 317 224 3067	2.8% 3.1% 2.7% 3.1% 2.9% 2.3% 2.6% 2.9% 2.1% 3.1% 2.8%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00]	
5.2 Targeted + systematic biops laco 2016 lorkowetz 2018 lyrant 2019 castellucci 2017 then 2015 le Gorski 2015 laxeiner 2018 lark 2011 lettier 2018 lark 2011 lettier 2016 louviere 2019 lonttila 2016 an der Leest 2018 lhang 2017 lubtotal (95% CI) otal events leterogeneity: Tau ² = 0.02; Chi ² = let for overall effect; Z = 4.37 (P <	sy 48 91 565 60 24 129 222 4 4 131 34 301 78 1736 130.91, df = 1	214 997 168 420 232 318 41 119 251 60 626 626 224 3759 2 (P < 0.00	100 456 69 104 143 245 13 73 161 34 261 99 1809	170 792 86 420 2318 44 119 206 53 317 224 3067	2.8% 3.1% 2.7% 3.1% 2.9% 2.6% 2.9% 2.1% 3.1% 3.1% 3.5.7%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00] -0.17 [-0.24, -0.09]	
5.2 Targeted + systematic biop: acc 2016 orkowetz 2018 ryant 2019 asstellucci 2017 then 2015 e Gorski 2015 laxeiner 2018 ark 2011 eltier 2016 touviere 2019 onttila 2016 an der Leest 2018 hang 2017 ubtotal (95% CI) otal events leterogeneity: Tau ² = 0.02, ChP = est for overall effect; Z = 4.37 (P < otal (95% CI) otal events	sy 48 91 565 60 24 129 222 4 49 131 34 301 78 1736 130.91, df = 1 < 0.0001)	214 997 168 420 232 318 41 119 251 60 626 224 3759 2 (P < 0.00 10225	100 456 69 104 143 245 13 73 161 34 261 99 1809 1001); I [≠] = 91%	170 792 86 420 2318 44 119 206 53 317 224 3067	2.8% 3.1% 2.7% 3.1% 2.9% 2.6% 2.9% 2.1% 3.1% 3.1% 3.5.7%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00] -0.17 [-0.24, -0.09]	
5.2 Targeted + systematic biops acc 2016 iorkowetz 2018 ivyant 2019 castellucci 2017 then 2015 e Gorski 2015 faxeiner 2018 ark 2011 ettier 2016 touviere 2019 onttila 2016 an der Leest 2018 hang 2017 ubtotal (95% CI) otal events leterogeneity: Tau ² = 0.02, Chi ² = est for overall effect; Z = 4.37 (P <	sy 48 91 565 60 24 129 222 4 49 131 34 301 78 1736 130.91, df = 1 <0.0001) 4428 358.56, df = 3	214 997 168 420 232 318 41 119 251 60 626 224 3759 2 (P < 0.00 10225	100 456 69 104 143 245 13 73 161 34 261 99 1809 1001); I [≠] = 91%	170 792 86 420 2318 44 119 206 53 317 224 3067	2.8% 3.1% 2.7% 3.1% 2.9% 2.6% 2.9% 2.1% 3.1% 3.1% 3.5.7%	-0.16 [-0.26, -0.06] -0.01 [-0.06, 0.04] -0.45 [-0.56, -0.33] -0.06 [-0.14, -0.14] -0.06 [-0.15, 0.03] -0.07 [-0.14, -0.00] -0.20 [-0.36, -0.04] -0.20 [-0.33, -0.08] -0.26 [-0.34, -0.18] -0.07 [-0.25, 0.11] -0.34 [-0.40, -0.29] -0.09 [-0.18, -0.00] -0.17 [-0.24, -0.09]	

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(b) clinically-significant prostate cancer diagnosis

	Systematic I		mpMRI informed I			Risk Difference	Risk Difference
udy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
10.1 Targeted biopsy only							
ar 2015	12	37	28	63	1.9%	-0.12 [-0.31, 0.07]	· · · · · · · · · · · · · · · · · · ·
astellucci 2017	33	168	30	86	2.7%	-0.15 [-0.27, -0.04]	/
nen 2015	13	420	18	420	3.6%	-0.01 [-0.04, 0.01]	*
noi 2018	323	1786	96	223	3.3%	-0.25 [-0.32, -0.18]	
e Gorski 2015	91	232	102	232	3.0%	-0.05 [-0.14, 0.04]	
elongchamps 2013 - Cohort 1	18	127	18	54	2.4%	-0.19 [-0.33, -0.05]	
elongchamps 2013 - Cohort 2	26	131	33	78	2.6%	-0.22 [-0.35, -0.10]	
elongchamps 2013 - Cohort 3	19	133	27	82	2.7%	-0.19 [-0.30, -0.07]	
elongchamps 2016	38	108	40	108	2.6%	-0.02 [-0.15, 0.11]	
arcia Bennetta 2017	27	60	27	32	2.0%	-0.39 [-0.57, -0.22]	
am 2018	61	121	61	121	2.6%	0.00 [-0.13, 0.13]	
asivisvanathan 2018	64	248	95	252	3.1%	-0.12 [-0.20, -0.04]	
axeiner 2018	158	318	90 140	318	3.1%		
						0.06 [-0.02, 0.13]	
endhiratta 2015	102	382	117	382	3.3%	-0.04 [-0.10, 0.02]	
ozer 2015	34	152	33	152	3.0%	0.01 [-0.09, 0.10]	
eltier 2015	8	110	19	110	3.1%	-0.10 [-0.19, -0.01]	
okorny 2014	79	223	93	142	2.9%	-0.30 [-0.40, -0.20]	
orpiglia 2017	14	105	44	107	2.7%	-0.28 [-0.39, -0.16]	
ouviere 2019	75	251	81	206	3.0%	-0.09 [-0.18, -0.01]	
n der Leest 2018	146	626	159	317	3.3%	-0.27 [-0.33, -0.20]	
ashino 2018	76	281	85	215	3.1%	-0.12 [-0.21, -0.04]	
arlagadda 2018	24	69	25	69	2.2%	-0.01 [-0.17, 0.15]	
ubtotal (95% CI)		6088		3769	62.0%	-0.13 [-0.18, -0.07]	◆
otal events	1441		1371				
eterogeneity: Tau ² = 0.01; Chi ² =	179.39, df = 2 ⁴	1 (P < 0.00	001); I ^z = 88%				
est for overall effect: Z = 4.70 (P =		`					
•••••	,						
10.2 Targeted + systematic bio	DSV						
aco 2016	44	89	38	86	2.3%	0.05 [-0.10, 0.20]	
prkowetz 2018	74	214	81	170	2.9%	-0.13 [-0.23, -0.03]	
vant 2019	481	997	388	792	3.4%	• • •	
,					_	-0.01 [-0.05, 0.04]	
astellucci 2017	33	168	41	86	2.6%	-0.28 [-0.40, -0.16]	
nen 2015	13	420	43	420		-0.07 [-0.10, -0.04]	
e Gorski 2015	91	232	113	232	3.0%	-0.09 [-0.18, -0.00]	
axeiner 2018	158	318	175	318	3.1%	-0.05 [-0.13, 0.02]	
ark 2011	2	41	11	44	2.4%	-0.20 [-0.35, -0.06]	
eltier 2016	19	119	22	119	2.9%	-0.03 [-0.12, 0.07]	
ouviere 2019	75	251	94	206	3.0%	-0.16 [-0.25, -0.07]	
onttila 2016	18	60	15	53	2.1%	0.02 [-0.15, 0.18]	
n der Leest 2018	146	626	180	317	3.3%	-0.33 [-0.40, -0.27]	(
ang 2017	35	224	59	224	3.2%	-0.11 [-0.18, -0.03]	
ubtotal (95% CI)		3759		3067	38.0%	-0.11 [-0.17, -0.05]	◆
otal events	1189		1260				
eterogeneity: Tau ² = 0.01; Chi ² =		(P < 0.000	01): I² = 87%				
est for overall effect: Z = 3.59 (P =							
	,						
otal (95% CI)		9847		6836	100.0%	-0.12 [-0.16, -0.08]	•
tal events	2630		2631				•
eterogeneity: Tau² = 0.01; Chi² =	2000 200 05 df - 2		2001				
eterogenenty: rau-= 0.01, Chi-= est for overall effect: Z = 6.20 (P =	200.00, ui = 34	4 (F < 0.00	001), 1 = 07 %				-0.5 -0.25 0 0.25 0
est for overall effect. $Z = 6.20$ (P =		(D 0.07)	17 000				More events in mpMRI More events in standard
st for subgroup differences: Chi	~=10.18, at = 1	(P = 0.67)	, 17 = 0%				
	Ť						
C C C C C C C C C C C C C C C C C C C							
C							
st for overall effect: Z = 6.20 (P st for subgroup differences: Chi							

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(c) clinically-insignificant prostate cancer diagnosis

Study of Sub-	Systematic I		mpMRI informed		147-1-1-4	Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.9.1 Targeted biopsy only	7	37			0.000	0.057.044.0.001	
Acar 2015 Castellucci 2017	27	37 168	9 18	63 86	2.6% 4.0%	0.05 [-0.11, 0.20]	
Chen 2015	15	420	23	420	4.0% 6.6%	-0.05 [-0.15, 0.05] -0.02 [-0.05, 0.01]	
Choi 2018	199	420	23	420 223	0.0% 6.1%		4
de Gorski 2015	38	232	20	223	5.5%	-0.01 [-0.06, 0.03] 0.06 [-0.00, 0.12]	
Delongchamps 2013 - Cohort 1	30	127	12	232 54	3.0%	0.07 [-0.07, 0.21]	
	34	131	31	54 78	3.1%		
Delongchamps 2013 - Cohort 2 Delongchamps 2013 - Cohort 3	34 25	131	35	/ 8 82	3.3%	-0.14 [-0.27, -0.01] -0.24 [-0.36, -0.11]	
Delongchamps 2013 - Conon 3 Delongchamps 2016	25	108	21	108	3.3%	0.06 [-0.05, 0.18]	
Garcia Bennetta 2017	20 5	60	1	32	4.4%	0.05 [-0.04, 0.14]	
Kam 2018	23	121	19	121	4.4%	0.03 [-0.04, 0.14]	
Kasivisvanathan 2018	25 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	49 38	110	3.3%	0.02 [-0.09, 0.15]	
Pokorny 2014	42	223	6	142	5.5%	0.17 [0.11, 0.23]	
Porpiglia 2017	47	105	10	142	0.0% 4.5%	0.07 [0.17, 0.23]	
Rouviere 2019	35	251	23	206	4.0% 5.5%	0.03 [-0.03, 0.09]	
van der Leest 2018	35 155	251 626	23	206	5.6%	-0.03 [-0.09, 0.03]	
Washino 2018	42	281	34	215	5.4%	-0.03 [-0.09, 0.03]	_
Yarlagadda 2018	42	201	13	215	3.0%	0.04 [-0.09, 0.18]	
Subtotal (95% CI)	10	6088	15		100.0%	0.03 [-0.01, 0.06]	
Total events	1049	0000	608	5105	100.070	0.001.0.01.0.001	•
Heterogeneity: Tau² = 0.00; Chi² =		/D ~ 0 00					
Test for overall effect: Z = 1.62 (P =		(i < 0.00	001),1 = 73.0				
1.9.2 Targeted + systematic biop			10	00	7.00		
Baco 2016 Barkeweta 2010	4	89	13	86	7.6% 9.6%	-0.11 [-0.19, -0.02]	
Borkowetz 2018	17	214	19	170		-0.03 [-0.09, 0.03]	T
Bryant 2019 Castellucci 2017	84 27	997 168	68	792	11.8% 6.0%	-0.00 [-0.03, 0.02]	1
	15	420	28	86	11.1%	-0.16 [-0.28, -0.05]	
Chen 2015 de Gorski 2015	38	232	61 30		9.2%	-0.11 [-0.15, -0.07]	-
	50 64	318	50	232 31.8		0.03 [-0.03, 0.10]	
Maxeiner 2018 Devis 2014	2	41	50		9.6%	0.04 [-0.02, 0.10]	
Park 2011 Peltier 2016	30	119	51	44 119	7.4%	0.00 [-0.09, 0.09]	
Tonttila 2016	30 16	60	1.9	53	5.7% 3.6%	-0.18 [-0.29, -0.06]	
		626	81	P		-0.09 [-0.26, 0.08]	
van der Leest 2018 Zhong 2017	155 43		40	317	9.7% 8.7%	-0.01 [-0.07, 0.05]	1
Zhang 2017 Subtotal (95% CI)	43	224 3508	40	224 2861	100.0%	0.01 [-0.06, 0.09] - 0.04 [-0.08, -0.00]	
	495	5500	462	2001	100.070	-0.04 [-0.00, -0.00]	•
Total events Notarogeneity: Touž – 0.00: Chiž –		/D → 0 00					
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 1.97 (P =		(F = 0.00	001), 1 = 77%				
						-	-0.5 -0.25 0 0.25 0.5
Test for subgroup differences: Ch	i² = 6.49, df = 1	(P = 0.01), l² = 84.6%				More events in mpMRI More events in standard
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(d) high-grade prostate cancer diagnosis

Study of Subgroup	Systematic		mpMRI informed b		Weight	Risk Difference	Risk Difference
Study or Subgroup 1.11.1 Targeted biopsy	Events	Total	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
	-	400	2		4.000	0.051.0.04.0.441	
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 9	121	23	121	2.3%	0.01 [-0.09, 0.11]	
Kasivisvanathan 2018		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 6	142	3.9%	-0.06 [-0.13, 0.01]	
Porpiglia 2017 Rouviere 2019	3 24	105 251	21	107 206	5.2% 5.1%	-0.03 [-0.08, 0.03]	
van der Leest 2018	46	626	42	317	5.1% 6.6%	-0.01 [-0.06, 0.05] -0.06 [-0.10, -0.02]	
Washino 2018	40 25	281	42 26	215	5.1%		
Yarlagadda 2018	11	201	20	69	1.7%	-0.03 [-0.09, 0.02] 0.03 [-0.09, 0.15]	
Subtotal (95% CI)	11	4566	9	2426	70.2%	-0.01 [-0.04, 0.01]	
	415	4300	296	2420	10.2/0	-0.01[-0.04, 0.01]	
Total events Heterogeneity: Tau ² = 0.0		C 4f - 10					
		•	(P = 0.000), F = 565	6			
Test for overall effect: Z =	= 1.37 (P = 0.1	0					
1.11.2 Targeted + syste	matic bioney						
		24.4	24	470	1.50	0.04.0.40.0.0	
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 Subtotal (05% CI)	15	224 2022	29	224 1687	5.2% 29.8%	-0.06 [-0.12, -0.01]	
Subtotal (95% CI)	200	2022	200	1007	23.0%	-0.03 [-0.06, 0.00]	
Total events	306 00: 01:3-40.4	e 46- e 0	299			$\langle \rangle$	
Heterogeneity: Tau ² = 0.0			P = 0.12); I= = 41%				
Test for overall effect: Z =	= 1.69 (P = 0.0	9)			K .		
Total (95% CI)		6588		4113	100.0%	-0.02 [-0.04, -0.00]	
	721	0300	595	4113	100.076	-0.02 [-0.04, -0.00]	•
Total events Heterogeneity: Tau ² = 0.0		0 df - 20		e 🔪			
Test for overall effect: Z =			(F = 0.000), 1 = 49	°			-0.2 -0.1 0 0.1 0.2
Test for subgroup differe	-2.10 (1 = 0.0 nres: Chi≅ = 0	-) ∕10_df=1	(P = 0.53) IZ = 0%				More events in mpMRI More events in standard
		.+0, 01 = 1	(1 = 0.00), 1 = 0.0				
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