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Effects of Magnetic Resonance Imaging Targeting on Overdiagnosis and Overtreatment of Prostate Cancer

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Abstract

Background: It has been suggested that targeting prostate lesions identified on magnetic resonance imaging (MRI) will improve the sensitivity of prostate biopsy for high-grade disease. The clinical significance of high-grade tumors found on MRI but missed on systematic biopsy is open to question.

Objective: To determine the risk of mortality for high-grade cancers identified by MRI targeting in men who had benign systematic biopsy findings.

Design, setting, and participants: We used data from 999 men with negative systematic biopsy and concurrent MRI-targeted biopsy in the National Cancer Institute MRI study. The comparison group consisted of 3056 men followed for 11 yr after negative sextant biopsy in the European Randomized Trial of Screening for Prostate Cancer (ERSPC).

Outcome measurements and statistical analysis: We calculated the number of patients needed to be diagnosed (NND) and treated (NNT) following targeted biopsy in order to prevent one prostate cancer death at 11 yr. We used a simple modeling approach that involved several assumptions, such as the proportion of the deaths in ERSPC preventable by earlier detection with MRI-guided biopsy. We then varied these assumptions to assess the effects on the results.

Results and limitations: NND and NNT were 89 and 57 for the scenario involving assumptions favorable to MRI, and 169 and 127 for a more neutral set of assumptions,

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respectively. Results were only more encouraging for MRI targeting under unlikely scenarios, such as 100% sensitivity for MRI and a cure rate of 100% for treatment.

Conclusions: Although MRI may be of benefit overall, considering the decrease in overdiagnosis among men with negative MRI findings, targeting biopsy needles to MRI-detected lesions results in a large number of men diagnosed and treated per death prevented. Consideration should be given to changing guidelines on grading of MRI cores and those regarding treatment of MRI-detected high-grade prostate cancer.

Patient summary: We carried out a modeling study to assess how magnetic resonance imaging (MRI) scan results used to target prostate cancer lesions during biopsy can affect outcomes. The model results show that if MRI-visible tumors are targeted during prostate biopsy, a large number of men need to be diagnosed and treated for prostate cancer in order to avoid just one prostate cancer death.

Keywords

Prostate cancer; MRI; overdiagnoses

1. Introduction

Several recent guidelines, including those of the European Association of Urology [1], recommend routine use of multiparametric magnetic resonance imaging (MRI) before diagnostic prostate biopsy. MRI may be of benefit in two separate ways: (1) it may improve specificity by reducing both unnecessary biopsy and overdiagnosis of low-grade disease for men with negative MRI findings; and (2) for men with positive MRI findings, it may improve sensitivity by targeting of lesions, thereby finding tumors that would be missed by systematic biopsy.

The data on MRI and specificity are relatively straightforward. Sathianathen and colleagues [2] reported a meta-analysis of 42 studies in which patients underwent MRI and subsequent systematic biopsy. The overall negative predictive value was 91%, although significant heterogeneity between studies suggests variation between institutions. It seems reasonable to conclude that while MRI does have a role in avoiding unnecessary biopsy, with a consequent reduction in overdiagnosis of low-grade disease, caution should be exercised in the choice of MRI facility and attention paid to standardizing MRI techniques and radiological assessment. The data on MRI and sensitivity of prostate biopsy are far more problematic. In a typical study, results for MRI scans and systematic biopsy are compared grade-by-grade to determine the effects of MRI on detection of low- and high-grade prostate cancer. The difficulty with this approach is that it assumes that cancers of equivalent grade are of equivalent oncologic risk, irrespective of the method of detection. There are various reasons for believing that this is not the case. Perhaps most importantly, the recommended approach to grading of multiple cores obtained from a single MRI-targeted lesion is to use the core with the highest grade. It is a matter of simple geometry to show that this will lead to upgrading of tumors compared to systematic biopsy [3]. In the well-known PRECISION trial, the authors reported that MRI led to more high-grade and fewer low-grade cancers and concluded that MRI ameliorates both overdiagnosis and underdetection.

However, the total number of cancers was almost identical in both arms, and thus similar findings would have been reported for an approach that simply upgraded some low-grade tumors [4]. The National Cancer Institute (NCI) study [5] of concurrent MRI and transrectal ultrasound (TRUS) biopsy for men with a clinical indication for prostate biopsy—elevated prostate specific antigen (PSA) or positive digital rectal examination—presents a unique opportunity to study the improvements in sensitivity associated with MRI targeting. This is because participants underwent both MRI-targeted and 12-core systematic TRUS biopsy. In particular, the NCI study reports the results of MRI targeting for 999 men for whom concurrent TRUS biopsy was negative.

Here we compare the findings for these 999 men with an 11-yr follow-up study of 3056 men who had negative sextant TRUS biopsy during the first round of the European Randomized Trial of Screening for Prostate Cancer (ERSPC). These men received repeat PSA measurements at 4 and 8 yr, with repeat biopsy if PSA remained elevated [6]. A comparison of MRI results for men with concurrent negative systematic biopsy versus long-term prostate cancer mortality among men with negative systematic biopsy provides an insight into the oncologic risk of cancers detected only by MRI targeting.

2. Patients and methods

In the NCI study, there were 999 men with negative TRUS biopsy; 208 were diagnosed with cancer on MRI targeting, of whom 134 had high-grade disease (grade group ≥2) and 37 had the very highest risk cancers of grade group 4 or 5. The headline result of the ERSPC study is that prostate cancer mortality is extremely low among men with negative biopsy: seven deaths occurred in the group of 3056 patients with negative biopsy, representing an 11-yr probability of 0.2%, which is lower than the population average. The authors also reported that 1395 biopsies were conducted during subsequent follow-up, with 287 cancers found. Baseline data for the two cohorts are given in the Supplementary material.

As more cancers were detected by MRI-targeted biopsy in the NCI study than were diagnosed during ERSPC follow-up (208 per 999 vs 287 per 3056), but there were some deaths in ERSPC, we sought to estimate the number of additional patients diagnosed (number needed to diagnose, NND) and treated (number needed to treat, NNT) for MRI-targeted biopsy to prevent one death at 11 yr. Several assumptions are required to do so. For instance, we need to make assumptions as to how many of the seven deaths in the ERSPC trial would have been prevented by earlier diagnosis had initial biopsy been MRI-guided, and what proportion of the 287 cancers diagnosed during ERSPC follow-up would have been detected by MRI at initial biopsy. The key point is to vary the assumptions and see how doing so impacts the value of MRI.

We chose as the base case a set of assumptions that are broadly favorable to MRI (Table 1). In the case of assumption 1, if not all patients with grade group 1 cancer found by MRI are put on active surveillance, or if crossover on active surveillance is taken into consideration, the number of patients who undergo treatment as a result of MRI is higher, and the effect would be an increase in NNT. Assumption 2 ignores that grade is generally higher on MRI-targeted than on systematic biopsy, so the number of patients who would be treated

during follow-up after negative systematic biopsy is overestimated and therefore the NNT for MRI decreases. Assumption 3 is that MRI has very high sensitivity of MRI and that almost all cancers diagnosed over 11 yr of a screening program are detectable at baseline, with few de novo cancers. This association is strengthened for fatal tumors in assumption 4. With respect to assumption 5, no randomized trial has shown anywhere close to a relative risk of 0.25 for curative treatment: the SPCG-4 [7] and PIVOT estimates [8] were 0.56 and 0.92, respectively. If treatment is less effective, fewer deaths are avoided by MRI detection and NND and NNT both rise. Assumption 6 implies that a single unnecessary biopsy is equally harmful as several years of erectile dysfunction after treatment for prostate cancer; if this assumption were not made, we would have to consider extra years of treatment-related morbidity caused by MRI. Assumption 7 favors MRI because it assumes that none of the deaths in ERSPC occurred in men with a tumor that would have been detected on 12-core but not six-core biopsy. Assumption 8 may be considered reasonable on the grounds that the authors of the NCI study reported only “small differences” by prior biopsy status. Further discussion of baseline differences between the groups is provided in the Supplementary material. Assumption 9 is favorable to MRI because it seems plausible that some men who died in the ERSPC trial would have been saved had a subsequent biopsy been MRI-guided. Finally, assumption 10 is favorable to MRI because it assumes that there have not been any improvements in treatment, such as higher radiotherapy doses or novel chemotherapy agents, since ERSPC.

To calculate the NNT and NND for MRI targeting, we start with the difference in the rate of cancer in NCI and ERSPC. In the NCI trial, 208 men with negative TRUS biopsy had cancer on MRI targeting, a rate of 2082 cases per 10 000; in ERSPC, 287 cases were diagnosed during follow-up of 3056 men, representing a rate of 939 cases per 10 000. We then need to make an assumption about the proportion of these cases that would have been detectable by MRI at baseline: MRI is not 100% sensitive and some men may have developed cancer during follow-up that would not have been detectable at baseline. In the base case, we assume that 75% of the cancers found during follow-up in ERSPC would have been detectable at baseline. Hence, the increase in cancer associated with MRI is 2082 – 939 x 75% = 1378. To calculate the number of extra treatments resulting from MRI, we multiply the number of additional cancers by a treatment rate. In the base case, we use the empirical rate of grade group ≥2 cancers in the NCI trial and assume that 64.42% of cancers are treated, giving an increase of 1378 x 64.42% = 888.

To calculate the number of deaths avoided by MRI, we multiply the proportion of fatal cancers detected by MRI at baseline by the relative risk reduction for treatment. In the base case, we used favorable assumptions that MRI would detect 90% of subsequently fatal cancers and that immediate treatment would lower the risk of death by 75%. This gives 90% x 75% = 68% of subsequent deaths avoided had MRI been used at baseline. There were seven deaths in ERSPC, representing a rate of 22.9 per 10 000. Hence, under the base-case scenario, we assume that MRI would have reduced this death rate by 68%, which represents 15.5 deaths per 10 000. To obtain NND and NNT, we simply divide the number of additional cases associated with MRI and number of additional treatments by the number of deaths. As pointed out, it is advisable to vary the assumptions and determine the consequent effect on the results, on the grounds that any of the assumptions can be

reasonably questioned. First, because our base case was favorable to MRI, we used a more neutral set of assumptions, slightly reducing the proportion of subsequent diagnoses avoided by immediate MRI, increasing the proportion of patients subject to treatment, and reducing the effectiveness of treatment. We created an extreme scenario—assuming perfect properties of MRI (preventing all subsequent diagnoses and identifying all of those destined to die from disease), perfect treatment (100% risk reduction), and moderate treatment rates (50%)—and a fourth scenario with a more conservative estimate of the treatment effect (25% risk reduction). We also explored the effects of assuming: (1) a dramatic reduction in treatment rates (35%); (2) contemporary 12-core biopsy finds 20% more cancers, although none of the additional cancers are fatal; (3) contemporary 12-core biopsy finds 20% of both fatal and nonfatal cancers; and (4) clinical use of MRI in patients with continuously rising PSA but negative biopsy would avoid 25% of the deaths that would be preventable by immediate MRI. These four scenarios were applied to the base case and to the case with more neutral assumptions. As the math behind the modeling approach is straightforward, it was implemented in a Microsoft Excel spreadsheet. This is included in the Supplementary material so that any reader can replace the parameters with their own assumptions to determine the effects on the findings.

3. Results

The results for the base case are shown in Table 2. Although this scenario involves favorable assumptions, NND and NNT are 89 and 57, respectively. By way of general comparison, the NND at 9 yr for PSA screening is 48 [9], an estimate that is generally considered to be too high, but that is approximately half of the NND for MRI targeting at 2-yr-shorter follow-up. Using a more neutral set of assumptions, the degree of overdiagnosis and overtreatment becomes substantial (NND = 169, NNT = 127). Even in the extreme and unrealistic scenario —assuming 100% of the cancers diagnosed over the subsequent 11 yr would be detected by MRI at baseline, a cure rate of 100%, and ~50% of grade group 2 cancers would never undergo treatment—the numbers needed to diagnose and treat remain relatively high (NND = 50, NNT = 25).

Changing the other assumptions failed to change the conclusion that excess overdiagnosis and overtreatment are associated with MRI (Tables 2, 3, and 4). We only found more encouraging results for MRI targeting (NND = 89, NNT = 31) under the unlikely scenario that most patients with grade group 2 disease are managed conservatively, with zero crossover to active treatment and zero deaths. Moreover, these results were only found under scenarios for which the other assumptions were highly favorable for MRI and not under the more neutral case.

4. Discussion

We found that MRI targeting detects a large number of cancers, including those that would be treated under current guidelines, in patients with a concurrent negative systematic biopsy. This group has a very low rate of prostate cancer mortality, and therefore MRI targeting has an unfavorable benefit-to-harm ratio.

Our findings are consistent with other studies in the literature. For 20-yr follow-up of 452 men with negative biopsy in the Goteborg ERSPC center, Palmstedt et al [10] reported five deaths. Two of these men had very high PSA (34 and 73 ng/ml) and would undoubtedly have been subject to follow-up MRI in contemporary practice if a systematic biopsy was negative. Two men were diagnosed in their 70s after ceasing testing at age 70 yr, even though they had elevated PSA, which again is inconsistent with contemporary practice. The final death occurred 17 yr after a negative biopsy with PSA of 12.5 ng/ml. Hence, it is unclear whether immediate MRI compared to careful follow-up would have saved the lives of any of these men. In a population-based study from Denmark, the cumulative incidence of prostate cancer mortality among men with a negative biopsy and PSA <10 ng/ml was 0.7% at 15 yr [11]. Both of these studies support the finding that the risk of mortality is very low if systematic biopsy is negative. On the MRI side, PRECISION reported an absolute 12% increase in the number of high-grade cancers found by MRI compared to systematic biopsy [4]. Although we do not know how many of these cancers were upgraded from low grade compared to benign, the results are broadly comparable to those from the NCI study.

The major limitation of our study is that it is a comparison based on statistical modeling. It is obviously unethical to follow patients with negative systematic biopsy who have high-grade cancer on MRI-targeted biopsy without treatment, so we cannot ever know the true natural history of such patients. Thus, a modeling approach is our only option. There are several differences between the ERSPC and NCI studies (Supplementary material), including presentation (many patients in the NCI trial had a previous biopsy), TRUS biopsy technique (sextant vs extended biopsy), and follow-up, with ERSPC patients treated 20 yr ago or more. However, the scientifically preferable way to treat such differences is not to simply declare the studies “incomparable” and give up, but to carefully and quantitatively explore their possible effects on findings. It is clear, for example, that many of the differences between ERSPC and NCI would lead to an increase in the apparent benefit from MRI, the assumption of no improvement in treatment being an obvious example. Moreover, the results are so extreme (eg, NND = 169) and so robust to changes in the key assumptions that differences between the NCI and ERSPC cohorts, such as with respect to baseline risk, are unlikely to affect our findings.

A second limitation is that the 11-yr outcome might be considered too short. Again, the results are so extreme that longer follow-up is unlikely to change the conclusions. Moreover, longer follow-up would introduce other factors that disfavor MRI targeting. These include an increasing length of time living with treatment-related morbidity for patients treated immediately after MRI-detected high-grade cancer, and deaths from cancers that could not have been detectable at baseline. A final limitation is that MRI techniques continue to develop—transperineal biopsy being an obvious example—and our findings are limited to MRI as used in the NCI study.

These findings have no bearing on the use of MRI targeting in the clear clinical indication for a patient with high clinical suspicion of aggressive disease (eg, PSA 25 ng/ml) following a negative biopsy. Moreover, it may be that overall, MRI does more good than harm because the increase in overdiagnosis for men with positive MRI is offset by larger decreases in overdiagnosis for men with negative MRI who avoid biopsy. Such a possibility could be

explored in further modeling research. Our findings also do not touch on other current clinical uses of MRI—such as focal therapy or planning of definitive treatment—or plausible future uses, such as targeting areas of the prostate for genomic sampling [12]. That said, the results do address a pertinent clinical question, namely, whether or not to target lesions in men with positive MRI results. Note that because our comparison is between men who received only a systematic biopsy and those who underwent both systematic and targeted biopsies at the same time, our results are applicable to biopsy-naïve patients: we are not investigating the value of whether or not to perform MRI following a negative biopsy, but the value of MRI targeting concurrent with systematic biopsy.

Our finding that targeting probably does more harm than good critically depends on current approaches to pathologic grading and treatment. Pathologic grading guidelines are to use the core with the highest grade, while treatment guidelines recommend treatment for patients with any pattern 4 disease; in particular, treatment is considered mandatory for grade groups 3 and 4. Take the case of a patient with a low-volume lesion that is predominately pattern 3 with a small focus of pattern 4. Such a patient is most likely to be placed on active surveillance following systematic biopsy because his cancer would either be graded as grade group 1 or be considered low-risk grade group 2. There is copious evidence that this is a perfectly safe strategy for such a patient [13,14]. By contrast, placing multiple needles into such a lesion is likely to result in one directly hitting the area of pattern 4, leading to a diagnosis of grade group 3 or 4 and a firm recommendation for treatment [3]. This harmful result would be avoided if the rules for pathologic grading gave the patient a lower grade group, or if treatment guidelines depended on whether a tumor was detected by systematic biopsy or MRI targeting.

5. Conclusions

In conclusion, the NCI trial provides evidence that MRI targeting leads to overdiagnosis and overtreatment as it detects a large number of cancers, including those that would be treated under current guidelines, in a patient group known to have a very low rate of prostate cancer mortality. Even when using extremely favorable assumptions for MRI, the NND and NNT to prevent one prostate cancer death are large. Further research is urgently needed to stratify the prebiopsy risk of aggressive prostate cancer and optimize how best to incorporate MRI in the diagnostic pathway. Consideration should be given to changing guidelines on grading of MRI cores and guidelines regarding treatment of high-grade prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1 –

Assumptions for the base case

Assumption	Description
1	Patients with grade group 1 disease are managed conservatively whereas those with grade group ≥2 receive curative therapy. No patients on conservative management cross over to treatment.
2	The grade distribution of cancers identified during follow-up in the ERSPC study is similar to that of the MRI-detected cancers in patients in the NCI study who had no cancer on TRUS biopsy.
3	MRI would have detected 75% of the tumors subsequently diagnosed in later rounds of the ERSPC trial.
4	Of the men with negative systematic biopsy who died in the ERSPC study, MRI targeting would have detected 90% of the tumors.
5	Immediate treatment of patients with cancers detected on MRI targeting reduces the risk of prostate cancer death by 75%.
6	Any benefits from MRI in avoiding repeat biopsy are approximately equivalent to MRI-induced harms of additional years with treatment-related morbidity related to earlier diagnosis and treatment.
7	Sextant biopsy used in ERSPC is roughly equivalent in terms of high- and low-grade cancers missed compared to the contemporary 12-core biopsy used in the NCI study.
8	The NCI trial included men with prior PSA screening, both biopsy-naïve men and those with prior biopsy, both positive and negative. The ERSPC study included men who were both PSA- and biopsy-naïve. We assume that the distribution of benign and low- and high-grade cancers is similar in the two settings.
9	No MRI is available in the systematic biopsy group, even where clinically indicated, such as a man with PSA of 25 ng/ml following negative systematic biopsy.
10	No patient who died in ERSPC before 11 yr would have survived beyond 11 yr had they been given contemporary treatment.

ERSPC = European Randomized Trial of Screening for Prostate Cancer; MRI = magnetic resonance imaging; NCI = National Cancer Institute; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

Table 2 –

Effects of MRI on prostate cancer diagnoses and prostate cancer mortality, standardized to 10 000 men

	Base case with favorable assumptions for MRI	NAS for MRI properties and Tx effects	Extreme case of MP MRI properties and Tx effects	NAS for MRI properties, CAS for Tx effects
(A) Proportion of subsequent diagnoses avoided (%) [a]	75	67	100	67
Additional diagnoses associated with MRI [b]	1378	1453	1143	1453
(B) Proportion of cases subject to treatment (%) [a]	64	75	50	75
Additional treatments [c]	882	1090	571	1090
(C) Proportion of cancers detected by MRI in patients destined to die of prostate cancer (%) [a]	90	75	100	75
(D) Relative risk reduction for immediate Tx (%) [a]	75	50	100	25
Proportion of deaths avoided using MRI (%) [d]	68	37.5	100	18.8
Deaths avoided [e]	15.5	8.6	22.9	4.3
Number needed to diagnose [f]	89.1	169.1	49.9	338.3
Number needed to treat [g]	57.0	126.9	24.9	253.7

CAS = conservative assumptions; ERSPC = European Randomized Trial of Screening for Prostate Cancer; MP = maximally perfect; MRI = magnetic resonance imaging; NAS = neutral assumptions; NCI = National Cancer Institute; Tx = treatment.

[a] Assumptions about MRI and treatment that can be varied.

[b] Calculated from the difference between the number of cases found in the NCI (2082 cases per 10 000) and ERSPC studies (939 cases per 10 000), where the latter is multiplied by assumption (A) concerning the proportion of subsequent diagnoses found by MRI.

[c] Calculated from the number of additional diagnoses multiplied by assumption (B), the proportion of cases subject to treatment: 64% if grade group ≥2 treated and zero crossover; 75% assuming some crossover to treatment by men on active surveillance; 50% if ~50% of men with grade group 2 on active surveillance and zero crossover.

[d] Calculated by multiplying the proportion of lethal cancers found by MRI (assumption C) by the relative risk reduction for treatment (assumption D).

[e] Calculated by multiplying the death rate of 22.9 per 10 000 in the ERSPC study by the proportion of deaths avoided.

[f] Calculated by dividing the number of additional diagnoses by the number of deaths avoided.

[g] Calculated by dividing the number of additional treatments by the number of deaths avoided.

Table 3 –

Sensitivity analysis using the base case with favorable assumptions for MRI [a]

	Dramatic reduction in Tx rates but same cure rates	**12CB finds more disease, but no FC**	**12CB finds more disease, including some FC**	**Some deaths avoided by clinical use of MRI in men with negative Bx and high PSA**
Proportion of subsequent diagnoses avoided (%)	75	75	75	75
Additional diagnoses associated with MRI	1378	**1237**	**1237**	1378
Proportion of cases subject to treatment (%)	**35**	64	64	64
Additional treatments	482	**797**	**797**	888
Proportion of cancers detected by MRI in patients destined to die of prostate cancer (%)	90	90	90	90
Relative risk reduction for immediate Tx (%)	75	75	75	75
Proportion of deaths avoided using MRI (%)	68	68	68	68
Deaths avoided	15.5	15.5	**12.9**	**11.6**
Number needed to diagnose	89.1	80.0	96.0	118.8
Number needed to treat	31.2	51.5	61.8	76.5

12CB = 12-core biopsy; Bx = biopsy; FC = fatal cancer; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; Tx = treatment.

[a]Estimates changed by varying the assumptions are in bold font.

Table 4 –

Sensitivity analysis using neutral assumptions [a]

	Dramatic reduction in Tx rates but same cure rates	12CB finds more disease, but no FC	12CB finds more disease, including some FC	Some deaths avoided by clinical use of MRI in men with negative Bx and high PSA
Proportion of subsequent diagnoses avoided (%)	67	67	67	67
Additional diagnoses associated with MRI	1453	**1327**	**1327**	1453
Proportion of cases subject to treatment (%)	**35**	75	75	75
Additional treatments	509	**995**	**995**	1090
Proportion of cancers detected by MRI in patients destined to die of prostate cancer (%)	75	75	75	75
Relative risk reduction for immediate Tx (%)	50	50	50	50
Proportion of deaths avoided using MRI (%)	37.5	37.5	37.5	37.5
Deaths avoided	8.6	8.6	**7.2**	**6.4**
Number needed to diagnose	169.1	154.5	185.4	225.5
Number needed to treat	59.2	115.9	139.0	169.1

12CB = 12-core biopsy; Bx = biopsy; FC = fatal cancer; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; Tx = treatment.

[a]Estimates changed by varying the assumptions are in bold font.