Association Between Multiparametric Magnetic Resonance Imaging of the Prostate and Oncological Outcomes after Primary Treatment for Prostate Cancer: a Systematic Review and Meta-analysis

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Abstract

Context: the diagnostic accuracy of multiparametric magnetic resonance imaging (mpMRI) for prostate cancer (PCa) diagnosis has been extensively explored. Little is known about the prognostic value of mpMRI suspicion scores and other quantitative mpMRI information.

Objective: we aimed to systematically review the current literature assessing the relationship between pre-treatment mpMRI and oncological outcomes after primary treatment for PCa in order to assess the role of mpMRI as a prognostic tool.

Evidence acquisition: a computerized bibliographic search of Medline/PubMed, EMBASE, Scopus, and Cochrane Library's Central databases was performed for all studies assessing the relationship between mpMRI and oncological outcomes after primary treatment for PCa. The review protocol was published in the PROSPERO database (CRD42020209899).

Evidence synthesis: a total of 6 studies were included. Reliable evidence is still limited in this field. The PI-RADS score represented an independent predictor of biochemical recurrence (BCR) after radical prostatectomy (RP) in the majority of the included studies. The tumor volume at mpMRI was not significantly associated with BCR after RP for PCa. Data on disease progression and PCa specific mortality is limited. Heterogeneity among studies was substantial.

Conclusions: PI-RADS score appears, from this review, to provide information on the future likelihood of cancer recurrence or progression at least in men receiving RP. We are of the view that this information should be taken into account to identify men at higher risk of unfavorable outcomes.

Patient summary: higher PI-RADS score seems to be positively associated with oncological failure and should be incorporated into future risk models.

1. Introduction

The use of multiparametric magnetic resonance imaging (mpMRI) for prostate cancer (PCa) diagnosis has significantly increased [1], and nowadays its use is strongly suggested before prostate biopsy in any clinical setting [2]. Furthermore, mpMRI has also been used to improve PCa staging accuracy [3,4]. Nonetheless, there is still a lack of evidence supporting the value of mpMRI suspicion score in predicting oncological outcomes after primary treatment for PCa. In fact, most of the existing predictive tools still rely on clinical and pathological findings [5]. A recent meta-analysis showed that mpMRI findings significantly affect PCa outcomes after primary treatment with radiotherapy [6]. Nonetheless, most of the studies included in this work were carried out before mpMRI protocol standardization [7] and none of the findings that currently are considered to be crucial in mpMRI reporting were tested. Indeed, mpMRI reporting assessment provides standardized information based on the interpretation of the different sequences according to a Likert score [8] or the more standardized Prostate Imaging Reporting and Data System [7,9,10]. These suspicion scores are in fact well-known predictors for the presence of PCa among other predictors such as apparent diffusion coefficient (ADC) and tumor volume that are usually provided by mpMRI [11,12].

When considering treatment for PCa, an accurate risk assessment is pivotal to properly counsel patients, helping to identify those men at higher risk of adverse clinical outcomes. Bearing this in mind, and given the crucial role that mpMRI has gained in the diagnosis and staging of PCa, the inclusion of mpMRI metrics within the risk assessment process of patients referred for PCa treatment needs to be addressed.

This study aimed to systematically review the studies assessing the relationship between measures of mpMRI suspicion and oncological outcomes after primary treatment for PCa in order to explore whether the role of mpMRI as a prognostic tool in this setting should be supported.

2. Evidence acquisition

2.1. Objective

We aimed to systematically review the current literature assessing the relationship between pre-treatment mpMRI findings and oncological outcomes after primary treatment for PCa.

2.2. Search strategy

Data collection was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [13]. A computerized bibliographic search of Medline/PubMed, EMBASE, Scopus, and Cochrane Library's Central databases was performed from inception to September 1st, 2020. From this date onwards, eventual relevant studies published were included in the analyses. The search strategy used is summarized in Supplementary Methods – Appendix 1. The review protocol was registered in the PROSPERO database (registration number: CRD42020209899).

2.3. Inclusion and exclusion criteria

As recommended by the PRISMA guidelines, we used the population, intervention, comparator, and outcome (PICO) approach to define study eligibility [13]. Reports were

considered relevant if they provided data regarding the relationship between mpMRI and oncological outcomes after primary treatment for PCa (i.e. radical prostatectomy [RP], external beam radiotherapy [EBRT], focal therapy, brachytherapy, others). More specifically, only studies assessing the relationship between pre-treatment mpMRI information related with the PCa index lesion (e.g. scoring system, index lesion tumor volume [TV], ADC, etc.) and oncological outcomes were included. Oncological outcomes were defined as one of the following: biochemical recurrence (BCR) after radical treatment (RP and/or EBRT), disease progression (defined according to the criteria suggested by Prostate Cancer Clinical Trials Working Group 2 [14]), metastatic failure (appearance of metastasis after treatment), overall- or cancer specific-mortality.

The studies with the following characteristics were excluded: 1) studies that did not use or provide any information regarding the mpMRI assessment/scoring system and did not rely on standardized systems for reporting MRI (i.e. Prostate Imaging – Reporting And Data System [PI-RADS] v1 or higher); 2) studies only assessing the prognostic value of mpMRI staging; 3) studies with insufficient survival data needed for meta-analysis; 4) when multiple studies relied on duplicated cohort, the one providing the most comprehensive information was included; 5) case reports, editorials, letters, review articles, and meeting abstracts.

2.4. Systematic review process and data extraction

Three authors (A.S., E.M. and G.C.) independently reviewed a total of 2,036 abstracts and selected 107 studies that were considered eligible for full-text evaluation and eventual inclusion in the systematic review. Fig. 1 shows the PRISMA flowchart

describing the selection process. Data were independently extracted from all included studies by the same authors. Discrepancies between reviewers were resolved via consensus, adjudicated by a third reviewer (E.M.).

2.5. Data analysis

The outcomes considered were BCR, disease progression, overall- and cancer specific-mortality. A pooled analysis was performed when more than one study testing the same mpMRI predictor and the same outcome was available. Alternatively, narrative synthesis of the studies was performed. The effect size of mpMRI factors associated with the outcomes was measured in terms of hazard ratios (HRs). The HRs and the corresponding standard errors for each predictor were extracted from each study included when available. Pooled analyses of the HRs for each mpMRI factor and the related outcome were performed using the inverse variance technique for meta-analysis of HRs, specifically the random-effects model according to DerSimonian and Laird [15,16]. In order to test mpMRI factors as predictors of oncological outcomes after treatment for PCa, as suggested by Cochrane Handbook for Meta-Analyses [15], only studies providing adjusted HRs were included for pooled analyses, whereas studies providing unadjusted estimates were excluded from the main analysis. Heterogeneity between studies was measured using the I^2 statistics and the extent of the variation among the effects observed in different studies (between-study variance) using τ^2 from random-effect analyses [17]; p values of < 0.05 were considered to indicate statistical significance. Where the same study provided different HRs for different cut-offs/populations, the same study was duplicated in the analysis accordingly. All statistical analyses were performed using the RStudio graphical

interface v.1.2.5033 for R software environment v.3.6.3. (packages included “metafor”, “meta” and “rms”).

2.6. Risk of bias assessment

The risk of bias assessment of individual studies was assessed independently by the same two authors using the Quality in Prognostic Studies tool [18] (Fig. 2).

3. Evidence synthesis

Overall, 2,036 studies were initially screened after duplicates removal. If it was not clear from the abstract whether the paper might contain relevant data, the full paper was assessed. After full paper evaluation of the eligible studies (n = 107), six articles were included in the final qualitative analysis according to the pre-specified inclusion criteria (Fig. 1). Only studies reporting outcomes after radical prostatectomy (RP) were included in the quantitative synthesis (i.e. meta-analysis). Given the significant between-studies heterogeneity that may not be accounted for in a pooled meta-analysis, data on PI-RADS score as a predictor of oncological outcomes was exclusively described in the qualitative synthesis. Particularly, 5 studies were included in the narrative description on the effect of PI-RADS score on BCR after RP and 2 studies in the meta-analysis testing the effect of tumor volume at mpMRI on BCR after RP. Furthermore, one study tested the PI-RADS score as a predictor for disease progression and one tested PI-RADS score as repdictor for BCR in a cohort of men receiving radiotherapy.

3.1. Study and patient characteristics

Single studies are described in detail in Table 1. A total of 6 studies including 1770 patients were included in the qualitative synthesis. The median age ranged between 59 [19] and 69 [20] yr. A total of 1647 (93%) and 123 (7%) patients received radical prostatectomy and radiotherapy, respectively. Among 1612 patients for whom clinical stage was available, 1143 (71%), 323 (20%) and 146 (9%) had clinical T1, T2 and T3 disease, respectively. Among 1770 patients for whom Gleason score was available, 444 (25%), 1108 (63%) and 218 (12%) had PCa with Gleason score 6, 7 and ≥8, respectively.

3.2. Risk of bias within studies

The overall risk of bias according to the Quality in Prognostic Studies tool [18] is given in Fig.2. The overall methodological quality of the studies was moderate, with the most significant issues concerning the study attrition and prognostic factors and measurement domains mainly due to the retrospective nature of studies included and the heterogeneity of the confounders considered within the adjusted analyses (Table 1 – Supplementary Table 1). Supplementary Fig 1 shows the risk of bias for each study.

3.3. Biochemical recurrence

In total, 5 studies assessing mpMRI as a predictor of BCR after RP were included in the qualitative synthesis. Specifically, 5 studies tested the mpMRI scoring system [19,21–24], 2 studies tested the mpMRI TV [19,25], and one study measured the ADC of the suspicious lesion as a predictor of BCR [20], respectively (Table 1). Two studies testing the effect of mpMRI TV on outcomes were pooled in a quantitative meta-analysis.

Detailed characteristics of the 5 studies testing the predictive value of mpMRI scoring system is shown in Table 1 and in Supplementary Figure 1. Three [19,23,24] and two studies [20,22] tested this predictor as a categoric and continuous variable, respectively (Fig. 3). Among studies using PI-RADS score as categorical variable, Gandaglia et al. (804 patients) [19] recorded higher risk of BCR in patients with PI-RADS 5 vs 3 (HR 2.86, 95%CI 1.14-7.20, p = 0.04) but not in patients with PI-RADS 4 vs 3 (HR 1.48, 95%CI 0.60-3.64, p=0.3) at mpMRI. Hattori et al. [23] (314 patients) confirmed higher risk of BCR in patients with PI-RADS ≥ 3 vs < 3 (HR 6.19, 95%CI 1.41-27.1, p=0.016) at mpMRI. Similarly, Kim et al. [24] (166 patients) demonstrated higher probability of BCR in patients with PI-RADS 5 vs < 5 (HR 1.75, 95%CI 1.05-2.93, p=0.033) and in patients with PI-RADS ≥ 3 vs < 3 (HR 5.58, 95%CI 1.34-23.2, p=0.018) at mpMRI, while no statistically significant differences were recorded in patients with PI-RADS ≥ 4 vs < 4 at mpMRI (HR 2.03, 95%CI 0.95-4.36, p=0.069).

Among studies using PI-RADS score as continuous variable, Park et al. [22] relied on 158 patients whose mpMRI were evaluated by two different radiologists. Here, PI-RADS score resulted as independent predictor of BCR when mpMRI were evaluated by the second reader (HR 2.78, 95%CI 1.18-6.92, p=0.028), but such predictive effect was not statistically significant when mpMRI were evaluated by the first reader (HR 2.46, 95%CI 0.95-6.41, p>0.05). Lastly, Zhang et al. [20] (205 patients) demonstrated that a higher PI-RADS score was significantly associated with higher risk of BCR (HR 4.12, 95%CI 1.07-15.8, p=0.039).

Forest plot for the predictive value of mpMRI TV is shown in Fig. 4. Two [19,22] studies assessed mpMRI TV after RP. Overall, mpMRI TV was not significantly associated with BCR after RP for PCa (HR: 0.99; 95% CI: 0.92-1.07; p=0.84)

Only one study [20] assessed ADC as a predictor of BCR providing an adjusted HR, showing that the ADC value was negatively correlated with BCR-free survival (HR: 1.747; 95% CI: 1.136-2.685; p=0.011) meaning that a lower ADC value of the tumor before treatment was associated with a worse outcome.

3.4. Disease progression

In total, one study assessing mpMRI as a predictor of disease progression after RP was included [24]. In this study, Kim et al. relied on a population of 166 men receiving RP for PCa. With a median follow-up of 9.1 years, the authors demonstrated that PI-RADS v2 was an independent predictor of disease progression (defined as local recurrence [appearance of a new lesion in the prostatectomy bed], a new target lesion, lymph node metastasis [≥ 2 cm in diameter], a bony lesion [appearance of two or more new lesions on bone scan], and requirement for other therapies), after accounting for age, preoperative PSA, performance status, clinical stage, biopsy Gleason score and number of positive biopsy cores. More specifically, PI-RADS < 3 vs. ≥ 3, and PI-RADS < 4 vs. ≥ 4, and PI-RADS < 5 vs. 5 at multivariable Cox regression models were related with the rate of disease progression with the following HRs: 3.99 (95% CI: 0.96-16.59, p=0.047), 2.02 (95% CI: 0.85-4.82, p=0.113), and 2.31 (95% CI: 1.30-4.09, p=0.04), respectively.

3.5. Biochemical recurrence in patients treated with radiotherapy

Overall, one study tested the role of mpMRI in predicting BCR in patients treated with EBRT [26]. In this study, 76 patients treated with EBRT were stratified according to PI-RADS score ≤4 or >4 at pre-EBRT mpMRI. At multivariable Cox model, patients with PI-RADS ≥ 4 treated with EBRT had higher rate of BCR (HR 5.37, 95% CI: 1.55-25.3) compared to patients with PI-RADS score ≤ 4 at pre-EBRT mpMRI.

4. Discussion

The growing interest in the use of mpMRI for PCa diagnosis and the subsequent amount of evidence supporting the accuracy of this test in predicting PCa aggressiveness [11,27,28] has had a significant impact on the diagnostic pathway of this disease [2].

When considering the field of PCa treatment and oncological outcomes, several efforts are being made to provide evidence supporting the use of biomarkers to improve patients' risk stratification and treatment choice [29,30]. Nonetheless, despite the strong role of mpMRI as an independent predictor of clinically significant PCa (csPCa) [11,31,32], data supporting the use of mpMRI endotypes, categorizing mpMRI severity based on suspicion scale, as a prognostic factor of oncological outcomes after primary treatment is still scarce.

A recently published meta-analysis assessing the role of mpMRI in predicting oncological outcomes after EBRT showed that extracapsular extension, seminal vesicle invasion, larger TV, and involvement of the prostate apex were significantly associated with BCR rate [6]. Furthermore, the authors showed that lymph-node invasion at mpMRI was significantly associated with prostate cancer specific-mortality (PCSM). Nonetheless, this study was limited by some issues that deserve discussion: 1) the authors were not able

to test some of the mpMRI factors that are currently considered the main predictors of PCa aggressiveness (e.g. PI-RADS score) but differently the study assessed the prognostic value of mpMRI staging parameters rather than qualitative characteristics of the mpMRI abnormality; 2) pooled analyses of HRs were performed including non-adjusted analyses that might have introduced significant bias leading to unreliable results; 3) only studies relying on EBRT cohorts were included.

Given the high heterogeneity of studies in this field, we aimed to identify qualitative or quantitative mpMRI factors that could represent independent predictors of oncological outcomes to support their inclusion in the risk assessment of patients referred for treatment for PCa.

Based on our findings, several observations can be made. First, the standardized PI-RADS scoring system, represented an independent predictor of BCR after RP in the majority of the included studies particularly when PI-RADS score was tested as a continuous variable, even when adjusting for disease aggressiveness. Of note, despite all the studies relied on PI-RADS score, residual heterogeneity, mainly due to differences in cut-offs of PI-RADS category stratification, prevented the calculation of a pooled HR for mpMRI scoring system. Nonetheless, we showed that a higher PI-RADS score was associated with increased risk of BCR after RP, particularly when PI-RADS 5 and PI-RADS 3 lesions were compared to lesions with lower PI-RADS score and with negative mpMRI, respectively [19,24].

The clinical implication of these findings are twofold: 1) the inclusion of PI-RADS score in post-operative outcomes predictive tools should be reinforced. This will likely allow to more accurately identify patients with a higher risk of unfavorable outcomes after

treatment in order to better counsel patients willing to receive treatment and draw patient-tailored therapeutic decisions; 2) as suggested by previous studies [33–35], PCa lesions' features at mpMRI, and more specifically their grade of suspicion defined according to standardized reporting systems [9] might be related to aggressiveness at a sub-cellular level (e.g. genomic, metabolic). However, due to the high between-studies heterogeneity which did not allow to perform a pooled meta-analysis of the mpMRI grading score on post-operative outcomes, an overall figure of the cumulative effect of mpMRI PI-RADS score on BCR could not be assessed.

Second, we failed to demonstrate a statistically significant relationship between mpMRI TV and BCR after RP for PCa (HR: 0.99; p=0.84). Nowadays, providing reliable results regarding the role of mpMRI TV as an oncological prognostic factor is key, particularly given the growing interest and evidence on tissue-preserving therapies like focal therapy for PCa and its promising mid-term results [36]. Historically, PCa TV, measured at whole-mount pathology, has been always considered both a predictor of PCa aggressiveness [37] and disease recurrence as also demonstrated in a meta-analysis carried out by Meng et al. [38]. When considering PCa TV measured at mpMRI, results are controversial. Recently, Woo et al. [6] showed that mpMRI TV was significantly correlated with BCR after EBRT. However, as aforementioned, Woo et al. provided pooled-analyses that suffered by some limitations [15]. Our findings might be explained by the known issues with the reliability of PCa TV when measured at mpMRI. First, most of the studies assessing the ability of mpMRI in estimating tumor volume measured at whole-mount pathology showed a significant underestimation, particularly for small lesions [39–42]. Second, the mpMRI sequence that best estimates tumor volume still needs to be defined,

with the most reliable method appearing to be to measure PCa TV in the sequence where the index lesion is best visible [43,44]. Lastly, even though mpMRI reaches good accuracy in detecting PCa index lesions, the per-lesion sensitivity, namely the ability to identify smaller PCa foci, is moderate at best [45,46]. In light of our findings, the use of PCa TV measured at mpMRI needs to be further investigated and standardized in order to become a useful and reliable predictive tool for oncological outcomes after treatment.

Finally, when attempting to explore outcomes with a more significant clinical impact as disease progression or cancer-specific mortality, few or no reliable studies were found. Therefore, no conclusions can be driven by these results.

Despite its strengths, mainly due to the strict selection criteria for the studies included, this study is not devoid of limitations. First, due to the retrospective nature and the wide range of study periods, against the relatively recent introduction of mpMRI for diagnostic purposes, the heterogeneity among studies is significant [47]. Also, most of the studies did not provide any information regarding mpMRI-targeted biopsy. Second, given that the majority of studies assessed cohorts of men receiving RP, pooled analyses on the role of mpMRI in men receiving other treatments were not possible. For this specific reason our findings should be carefully considered when different primary treatments are taken into account. Third, the median follow-up of the studies included was probably too short to provide meaningful oncological outcomes in the field of PCa (range: 25 – 109 months). Furthermore, the numbers of men experiencing the outcomes tested were quite low to provide highly reliable adjusted analyses (Table 1). Fourth, given the multi-center nature of this study, it was not possible to take into account the inter-reader agreement of mpMRI reporting among different centers. Finally, few or no studies assessing mpMRI as a

predictor of either disease progression or PCSM met the inclusion criteria for the purpose of a meta-analysis. This limitation prevented us from drawing any reliable conclusion for these specific topics.

5. Conclusions

Among the clinical predictors of oncological outcomes after RP for PCa, PI-RADS score seems to represent a promising independent prognostic factor. More specifically, the PI-RADS score is significantly correlated with the rate of BCR in most of the studies and it should be taken into account to identify men at higher risk of unfavorable outcomes. On the other hand, there is no evidence to support the role of PCa TV at mpMRI as a predictor of oncological outcomes after RP for PCa. Widespread of standardized, high-quality mpMRI protocols and further investigation in the emerging field of artificial intelligence is mandatory [47]. Further studies are needed to clarify the role of mpMRI suspicion as a potential contributing factor in predictive models.

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Figure legend

Figure 1: Flow diagram showing the outcome of the intial searches resulting in the full studies included in the review (from databases inception until September 1° 2020)

* A study can assess relationship between mpMRI scoring system and/or tumor and BCR or other survival outcomes.

Figure 2: Overall summary of risk of bias assessment across studies based on QUIPS criteria. QUIPS = Quality in Prognostic Studies tool

Figure 3: Forest plot for predictive value of mpMRI scoring system for biochemical recurrence. RP = radical prostatectomy

Figure 4: Forest plot for predictive value of mpMRI tumor volume for biochemical recurrence. RP = radical prostatectomy; TS = tumor size; TV = tumor volume; HIFU = High intensity focused ultrasound

Suppl Figure 1: Risk of bias assessment for each study according based on QUIPS criteria. QUIPS = Quality in Prognostic Studies tool

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