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Multiparametric magnetic resonance imaging prior to radical prostatectomy identifies intraductal and cribriform growth pattern of prostate cancer

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Abstract

Objectives

To evaluate the diagnostic value of multiparametric prostate magnetic resonance imaging (MP-MRI) prior to radical prostatectomy with curative intent for detection of cribriform architecture (CA) and intraductal prostate cancer (IDC), which have recently been demonstrated to be adverse pathologic factors.

Patients and Methods

This study included 124 men who underwent MP-MRI prior to radical prostatectomy at our centre. Preoperative MP-MRI, prostatectomy histology, and clinical follow-up details were reviewed retrospectively. The diagnostic value of MP-MRI was evaluated on the basis of the detection rate. Secondly, the prognostic significance of CA/IDC among grade group 2 cancers with regard to biochemical recurrence-free survival was assessed using Kaplan-Meier analysis with the log rank test and Fisher's exact test.

Results

Pathologic examination of radical prostatectomy specimens identified CA/IDC in 89 (71%) of 124 cases and MP-MRI identified 86/95 of tumours including any CA/IDC with a sensitivity of 90.5% (95% confidence interval 82.8%–95.6%). When localization of the lesions was compared, there was an association between the highest Prostate Imaging-Reporting and Data System (PI-RADS) classification and the highest pathologic grade in 106 (85.5%) of the 124 cases. In patients with grade group 2 lesions, biochemical recurrence occurred in 11 of 31 (35.5%) with CA/IDC and 2 of 21 (9.5%) without CA/IDC (p=0.034).

Conclusion

MP-MRI has good sensitivity for detection of pathologic primary prostate cancer, including most cases with CA/IDC. However, reliable prediction of grade group 2 tumours with CA/IDC for individual risk stratification remains challenging.

Keywords: multiparametric magnetic resonance imaging, prostate cancer, cribriform growth pattern, intraductal prostate cancer

Introduction

Multiparametric prostate magnetic resonance imaging (MP-MRI) is increasingly used for diagnosis of prostate cancer and risk stratification (1). Risk stratification with MP-MRI is based on the visibility, size, location, suspicion of extraprostatic extension and functional imaging properties of the MRI-target.

According to 2014 ISUP Grade group definitions grade group 2 (GG2 i.e. Gleason Score 3+4=7) is now the most common prostate biopsy and prostatectomy finding (2,3). In recent studies, the limit of clinical significance has been set to GG2 or GG3 (2,3). Risk stratification of GG2 prostate cancer is highly variable and remains challenging. Four subtypes (i.e., cribriform, poorly formed, fused and glomeruloid) are now recognized within the Gleason pattern 4. The cribriform architecture (CA) subtype, along with intraductal prostate cancer (IDC), have recently been associated with significantly higher rates of extraprostatic extension, metastasis, and prostate cancer-related mortality (4-6). The presence of CA or IDC has been proposed as an exclusion criterion for active surveillance (7). However, GG2 with small amounts of Gleason pattern 4 without CA/IDC probably has the same prognosis as GG1 (6).

Predicting the presence of CA or IDC would be important for risk assessment and treatment planning. The prevalence of CA/IDC in prostatectomy histology specimens was reported to be 51.8% in a prospective prostatectomy dataset and 74.5% in a retrospective targeted biopsy group (8,9). Unfortunately, the sensitivity of standard biopsy for detection of CA/IDC is reported to be low (20.7%–42.2%) and that of targeted biopsy to be only moderate (28.6%–61.2%) (8-10). Furthermore, there are reports of poor visualization of carcinomas with a predominance of CA/IDC on MP-MRI (10).

The aim of this study was to determine the MRI visibility of CA/IDC pathology and its prognostic significance in 124 consecutive prostatectomies with preoperative 3-T MP-MRI.

Patients and Methods

Study design

This retrospective chart review was approved by the Northern Osthrobothnia Hospital District Ethics Council (Oulu, Finland), with institutional registration number 200/2016, and performed according to Finnish law. The informed consent requirement was waived by the Ethics Council. We collected data for 124 consecutive men who had undergone 3-T prostate MRI and diffusion-weighted imaging with or without dynamic contrast enhancement before radical prostatectomy between August 2014 and November 2016. The indication for MRI was preoperative staging (79.8%), diagnostic MRI after a negative standard biopsy (9.7%), pre-biopsy MRI (5.6%), and part of active surveillance (4.8%). Before January 2016, staging MRI was performed only for high-risk cases (n=35) and thereafter

routinely. Consequently, there was 15/35 (42.9%) cases with GG5 prostate cancer among the first staging MRIs and 16/89 (18.0%) in the rest of the study cohort. Four patients who underwent 1.5-T MRI (because of a hip prosthesis) and one patient with nondiagnostic MRI were excluded.

Patient age, clinical staging, the serum prostate-specific antigen (PSA) level before prostatectomy, MRI volume-based PSA density, and serum PSA levels during follow-up were recorded. Biochemical recurrence (BCR) was defined as the time point when the serum PSA level was ≥0.1 ng/ml after prostatectomy. Twenty-eight patients with PSA level ≥0.1 ng/ml at first control visit 1-3 months after prostatectomy were included in the analysis. Prostate biopsies confirming cancer were performed at several referring centres and not re-evaluated.

MRI protocol and image analysis

MRI was performed using a 3-T magnet (Magnetom® Skyra Siemens AG, Munich, Germany) with body and spine matrix surface coils. The protocol included T1-weighted and T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast enhancement. Diffusion-weighted imaging was performed with b values of 50, 300, 800, and 1500 s/mm². Apparent diffusion coefficient (ADC) maps were generated using the manufacturer`s software. Dynamic contrast enhancement was not performed for 73 preoperative MRI scans. The MRI protocol is described in Table S1.

The MRI studies were reviewed and interpreted in consensus by two experienced radiologists (EP, MK), both with >100 prostate MRI reads/year for over six years. PI-RADS v2 (Prostate Imaging-Reporting and Data System version 2) scoring was used, and suspicious PI-RADS 3–5 lesions were drawn on a region of interest sector map with 16 separate sectors (11). The dimensions of the lesion (maximal axial, perpendicular to that and coronal plane when available) were measured individually. The ADC values for suspicious lesions were measured by placing a region of interest on the ADC map. The size of the region of interest varied according to the size of the lesion but covered the largest area of the lesion possible. Mean and minimum ADC values were registered. The maximum of two targets, i.e., index lesion and secondary lesion, were drawn. The radiologists were blinded to the pathologic results and previous MRI readings but were aware that the patients had prostate cancer and that prostatectomy had been performed.

The histologic and radiologic regions of interest sector maps were compared for each case and target. If the MRI target matched the sector containing the tumour, it was classified as true-positive. For tumours extending across several sectors, if the MRI target was drawn on any of the sectors, it was also registered as true-positive. A finding of two separate MRI targets within the same large tumour area was also interpreted as true-positive. If this was the case, the ADC value and MRI target sizes were registered along with the radiologists' perception of the primary target. GG1 tumours with a maximum diameter of <5 mm were considered undetectable on MRI (12).

Histopathologic analysis

All the prostatectomy pathology specimens were re-evaluated by two pathologists (PH, AA) in consensus while blinded to the MRI data. Clinical significance was set to a GG ≥2. All the tumour areas were drawn on a sector map analogous to that used for MRI targets. GG1 tumours <5 mm were included and drawn only if the cancer was a solitary finding. The largest diameter of each lesion was measured. Prostatectomy lesions, when present, were arranged first by grade group and then by size as index, secondary, tertiary or quaternary. CA/IDC was diagnosed based on established criteria (13). We did not differentiate CA from IDC in the analysis because the prognostic value of each has been estimated to be similar (14,15).The presence and percentage of Gleason pattern 3, 4, and 5 and CA/IDC in each lesion were estimated visually. Localization of CA/IDC was registered as central, peripheral, intermixed, or pure (i.e., ≥80% of lesion volume). Cribriform tumours with comedonecrosis were analysed within the CA/IDC group but were classified as Gleason pattern 5 in GG analysis. Other Gleason pattern 4 subtypes were not analysed separately.

Statistical analysis

The summary measurements are presented as the median (interquartile range) and the ADC values as the mean ± standard deviation. The study groups were compared using the Student's t-test (for continuous variables) and chi-square test or Fisher's exact test (for categorical variables). The impact of adverse histology on BCR-free survival was assessed using Kaplan-Meier analysis. P-values were calculated using the log rank test. Only sensitivity of MRI detection of CA/IDC was calculated because all MRIs were performed in men with prostate cancer; therefore, it was not possible to calculate specificity. Two-tailed P-values are reported. All statistical analyses were performed using SPSS for Windows (version 25; IBM Corp., Armonk, NY, USA).

Results

The clinicopathological characteristics of the study population are shown in Table 1. Figure S1 illustrates histology and corresponding MRI-findings of a 68-year-old man with representative bilateral prostate cancer.

Prostatectomy pathology CA/IDC and its detection on MRI

On pathologic examination, CA/IDC was identified in the majority of radical prostatectomy specimens (89/124, 71%). Distribution of tumours with (n=95) or without (n=97) CA/IDC and tumour identification on MRI is shown in Table 2. MRI identified 86 of 95 tumours that included any CA/IDC with a sensitivity of 90.5% (95% confidence interval 82.8-95.6). MRI identified all the 21 tumours with predominantly CA/IDC (≥50%). Four of the 10 tumours with pure CA/IDC were PI-RADS 4 (prostatectomy lesion diameters 12, 13, 14, and 20 mm) and 6 were PI-RADS 5 (prostatectomy lesion diameters 16–39 mm). Characteristics of missed lesions with CA/IDC, the

presence of CA/IDC on different prostatectomy grade group lesions as well as localization of CA/IDC growth is presented in Tables S2 and S3 and in text after Table S3.

Detection of prostatectomy pathology lesions on MRI

There was an association of the MRI index lesion with the prostatectomy index lesion and with the prostatectomy secondary lesion in 106/124 (85.5%) and 9/54 (16.7%) cases, respectively. Further, the MRI secondary lesion associated with the prostatectomy index lesion and with the prostatectomy secondary lesion in 1/124 (0.8%) and 6/54 (11.1%) cases, respectively. No tertiary/quaternary tumours were identified by MRI. Two MRI index lesions and two MRI secondary lesions were false-positive targets. One of the MRI index lesions associated with a solitary prostatectomy index lesion GG1 tumour measuring <5mm and was defined as false-positive.

Radical prostatectomy identified 1, 2, 3, and 4 foci of cancer (pathology lesions) in 70 (55.5%), 42 (33.9%), 10 (8.1%), and 2 (1.6%) cases, respectively. MRI identified 122/192 (63.5%) of the final prostatectomy pathology lesions.

MRI missed 17 prostatectomy index lesions (13.7%). These included 8 GG1 and GG2 tumours with a maximum 10% Gleason pattern 4 without CA/IDC and minor clinical significance, and 9 clinically significant tumours (five GG2, two GG3, and two GG5); the four GG3–5 tumours measured 1, 5, 8, and 12 mm, respectively. MRI identified prostatectomy secondary lesion in eight of nine men in whom a clinically significant prostatectomy index lesion was missed; seven of these eight tumours were ≥GG2. MRI-positive prostatectomy index lesions were larger than missed prostatectomy index lesions (median 23.0 [16.0–28.0] mm vs 10.5 [5.0–13.0] mm; p<0.001). All 11 prostatectomy index lesions <12 mm were MRI-negative; eight of these tumours were ≥GG2.

ADCs in tumour grading

There were no significant differences in mean ADCs and mean minimum ADCs for MRI-positive GG2 and GG3 lesions with and without CA/IDC (Table S4 and text in Table S4 file). We further analysed the effect of Gleason pattern 3 percentage on ADCs in order to evaluate the validity of our measurements (text in Table S4 file). Higher ADCs were detected for less aggressive tumours, which is in line with earlier publications.

Prognostic significance of CA/IDC

There were no cases of BCR in men with GG1 prostate cancer. We further analysed the prognostic significance of the presence or absence of CA/IDC on BCR-free survival in men with GG2 prostate cancer using Kaplan-Meier analysis (Figure 1). The median follow-up duration was 29 months (interquartile range, 24–34). CA/IDC in prostatectomy index lesion in patients with GG2 prostate cancer was linked to BCR. There was 11/31 (35.5%) and 2/21 (9.5%) BCRs in patients with GG2

tumours with CA/IDC and GG2 tumours without CA/IDC, respectively (p=0.034). Furthermore, all the GG2 cases with metastases (n=2) and those on ongoing androgen derivation therapy without diagnosed metastases (n=2) had CA/IDC. Kaplan-Meier analysis of BCR-free survival in patients who had GG2 prostate cancer with and without CA/IDC revealed a tendency for poorer BCR-free survival in the patients with CA/IDC; however, the difference was not statistically significant (p=0.057).

Discussion

In the present study, we evaluated the presence and detection of CA/IDC on MP-MRI performed before prostatectomy with curative intent. We focused specifically on prostate tumours containing CA/IDC in view of the conflicting results regarding visualization of these lesions by MRI. The definitions of clinically significant and insignificant cancers based on biopsy data vary from study to study. In particular, there is a general lack of agreement regarding MRI-targeted biopsies (16). Furthermore, a histologic prostate cancer grading system has been evolving, such that old study results concerning sextant or 12-core biopsies and even prostatectomy histology are not necessarily valid today (1). There is mounting evidence showing a strong association of CA/IDC with PSA failure, metastasis, and prostate cancer death, which is prognostically meaningful in any amount ($<5\%$, ≥ 1 mm²) (4,5,14,15). The 2014 International Society of Urological Pathology grading committee agreed that all CA should be staged as Gleason pattern 4. Despite the short follow-up duration, our results are in line with the published reports of a worse prognosis for GG2 cancer that contains CA/IDC (4,5,6).

Agreement on the histologic grading of CA/IDC has been shown to be more reliable than for the other Gleason pattern 4 subtypes (17). Differential diagnosis between CA and IDC requires immunohistochemistry, which was not systematically performed in this retrospective study. In a study by Trudel *et al*, which included 246 patients who underwent prostatectomy and were followed up for 130 months, there was no difference in the BCR-free rates between CA and IDC (14). The differential diagnosis between hyperplastic cribriform glands and CA/IDC is not difficult because benign lesions lack cytologic atypia. Separation of CA/IDC from premalignant cribriform lesions, such as high-grade intraepithelial neoplasia, is based on basic histologic features of malignancy. Immunostaining can help to make the differential diagnosis (18,19).

Prostate cancer is typically multifocal. Separate tumour foci do not seem to have common mutations (20). Genomic profiling has linked IDC to prostate cancer metastases (21). Furthermore, CA/IDC has been associated with a lethal genetic profile and increased genetic instability that may also extend to the adjacent non-cribriform tumour glands (22,23).

Recognizing CA/IDC and/or Gleason pattern 5 at the time of diagnosis would be valuable for risk stratification. Our data indicate that MRI identifies prostatectomy index lesions quite reliably in that only 13 (11.0%) of 118 GG≥2 index lesions were missed. Furthermore, 85/91 (93.4%) and 36/38 (94.7%) of CA/IDC and Gleason pattern 5 cases, respectively, were MRI-positive. Most of the CA/IDC pathology seemed to be identifiable with MRI even if the tumour was almost exclusively CA/IDC, which is conflicting to the report by Truong *et al*. Truong *et al* retrospectively examined 47 prostatectomy specimens with 51/180 tumour foci containing CA/IDC, including 23 in pure form. Only 17.7% of the CA/IDC tumours in pure form were identified by MRI (9). Their data is concentrated by primary negative biopsy cases and only one with GG5. In our material high-grade cases are somewhat overexpressed. Our results are analogous to those of Prendeville *et al* with regard to visualization of CA/IDC on MRI scans (24). However, unlike in our study, they were unable to correlate their findings with the final histopathology. Previous researchers have shown an inverse correlation of the ADC with high-grade cancer (25). We noticed a similar correlation in our data with a range so wide that the clinical value is limited. Hurrel *et al* did not find a significant difference between the ADCs for Gleason pattern 4 with and without CA/IDC (26). In our study, there was no statistically significant difference in the mean ADCs between patients with GG2 prostate cancer and CA/IDC and their counterparts without CA/IDC (Supporting information Table 4). It seems that ADC is not the key to differentiation of GG2 cancers with CA/IDC.

Negative predictive value of biopsies excluding CA/IDC seems to be at most modest. The prevalence of CA/IDC in biopsies was 26.9%, which is considerably less than the prevalence of 51.8% found on prostatectomy histology in a prospective biopsy and prostatectomy database (8). In that study, patients with or without CA/IDC on biopsy had more advanced disease if CA/IDC was found in the final prostatectomy histology. In another study, the relative value of standard biopsies and targeted biopsies for detecting CA pathology was compared in a retrospective analysis of 103 patients. CA/IDC was found in 23 biopsy specimens, in 22 targeted biopsies, and in only 3 standard biopsies of MRI-negative regions (24). In the study by Truong *et al*, which included 47 prostatectomy specimens, standard biopsies, targeted biopsies, and a combination of standard and targeted biopsies detected CA/IDC in 20.7%, 28.6%, and 37.1% of cases, respectively, whereas CA/IDC was found in 74.5% of prostatectomy histology specimens (9). In our study, the localization of CA/IDC was intermixed or peripheral in 77.9% of tumours. Further studies are needed to clarify if multiple targeted biopsies around the MRI target or genomic profiling of tumour tissue could improve our diagnostics.

As far as we know, only Truong *et al* have published research on the correlation between the diagnostic ability of MRI in CA/IDC prostate cancer targets and lesion-based final histopathology (10). Our results are considerably different from those of Truong *et al*. Furthermore, our patient cohort was larger and arguably more representative.

This study has several limitations. First, it had a retrospective design and was performed at a single centre. Second, histologic prostate sampling was performed as part of the routine hospital work flow so was not standardized and the axial orientation of MRI and tissue slicing were not identical. Estimations of tumour and MRI target size are not as accurate as axial area or volume measurements; however, the latter would have required special software and/or digital imaging of pathologic samples. Third, indications for MRI were variable and there was some over-representation of high-risk prostate cancer cases in this study, although it was not part of our aim to describe an unselected cohort. Finally, the study had a limited follow-up duration.

In conclusion, MP-MRI has good sensitivity for detecting the pathologic primary target of prostate cancer, including most cases with CA/IDC. However, prediction of GG2 tumours with CA/IDC for individual risk stratification remains challenging, as prostate biopsies are unreliable to detect or exclude CA/IDC.

Conflicts of interest: Dr. Tonttila reports personal fees from Finnish Urological Association, personal fees from Scholarship Fund of the University of Oulu (Maija-Liisa Kovala Fund), during the conduct of the study. The other authors have nothing to disclose.

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Figure legend

Figure 1. Kaplan-Meier analysis of biochemical recurrence-free survival in men with grade group 2 prostate cancer. BCR, biochemical recurrence; CA, cribriform architecture; IDC, intraductal prostate cancer

Table 1. Clinicopathological characteristics of the study population

Parameter	Result
Median age, years (range)	64.0 (59.0-69.0)
Median time from MRI to prostatectomy, days	29.0 (16-64)
Median prostate-specific antigen level, ng/ml	8.1 (5.5-13.1)
Preoperative clinical stage	
cT1c	51 (41%)
cT2	52 (42%)
cT3	21 (17%)
Median MRI prostate volume, cm^3	36 (30.8-44.9)
Median MRI prostate-specific antigen density, ng/ml/cm^3	0.25 (0.17-0.36)
Median MRI index lesion* diameter, mm (n=106)	17 (13-23)
Median pathology index lesion** diameter, mm (n=124)	20.0 (14-26)
Median MRI non-index lesion diameter, mm (n=15)	9.0 (7-12)
Median pathology non-index lesion diameter, mm (n=67)	11.0 (7-13)
Histopathology, grade group	
Index pathologic lesions (n=124)	
1	6 (5%)
2	51 (41%)
3	28 (23%)
4	8 (7%)
5	31 (25%)
Non-index pathologic lesions (n=68)	
1	28 (41%)
2	32 (47%)
3	4 (6%)
4	2 (3%)
5	2 (3%)
Indication for multiparametric MRI	
Preoperative staging	99 (80%)
Diagnostic, after negative standard biopsy	12 (10%)
Pre-biopsy MRI	7 (6%)
As part of active surveillance	6 (5%)
Index MRI lesion PI-RADS score	
MRI-negative	17 (14%)
3	1 (1%)
4	38 (31%)
5	68 (55%)
Solitary tumor	70 (56%)
2 foci	42 (34%)
3 foci	10 (8%)

4 foci	2 (2%)

The data are presented as the number and interquartile range or number (percentage). *The MRI index lesion was the target with the highest PI-RADS score. If there were two targets with the same PI-RADS score, the one judged clinically to be more suspicious by the radiologist was recorded as index lesion. **The pathology index lesion was the one with the highest grade group classification and secondarily the lesion with the largest maximal diameter. MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System

Table 2. Distribution of cribriform architecture (CA) and intraductal prostate cancer (IDC) among the tumours analysed and their identification on MRI.

	MRI visible tumours, n=122	MRI invisible tumours, n=70	
no CA/IDC	36	61	P<0.001*
CA/IDC <50%	65	9	
CA/IDC≥50%	21	0	
any CA/IDC	86	9	

* P-value for no CA/IDC vs any CA/IDC.

Number of patients at risk

no CA/IDC	21	19	17	6
CA/IDC present	31	25	22	12