# Can 3T multiparametric magnetic resonance imaging accurately detect prostate cancer extracapsular extension?

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## Abstract

**Background:** Accurate staging is essential to determine the correct management of patients diagnosed with prostate cancer. We assess the accuracy of 3T multiparametric magnetic resonance imaging (MRI) with endorectal coil (3TemMRI) in detecting prostate cancer local extension.

**Methods:** We retrospectively reviewed charts from January 2008 to July 2012 from all patients undergoing radical prostatectomy. Patients were only included if 3TemMRI and radical prostatectomy were performed at our institution. Based on the presence of extracapsular extension (ECE) at 3TemMRI, prostate cancer was dichotomized into locally advanced or organ-confined disease. The accuracy of 3TemMRI local staging was then evaluated using definitive pathology as a reference.

**Results:** Overall, 177 radical prostatectomies were performed within the timeframe. After applying exclusion criteria, 60 patients were included in the final analysis. The mean patient age was 67 ± 7 (standard deviation) years. Mean prostate-specific antigen value was 12.7 ± 12.7 ng/L. Based on preoperative characteristics, we considered 38 of the 60 patients (63%) patients high risk. 3TemMRI identified an organ-confined tumour in 46 patients and locally advanced disease in 14 patients. When correlated to final pathology, 3TemMRI specificity, sensitivity, negative and positive predictive values, and accuracy in detecting locally advanced prostate cancer were 90%, 35%, 57%, 79% and 62%, respectively.

**Interpretation:** This study shows that the use of preoperative 3TemMRI can be used to identify organ-confined prostate cancer when locally advanced disease is suspected.

## Introduction

Curative treatment options for localized prostate cancer include radical prostatectomy, radiation therapy, and active surveillance. Patient selection is mainly based on life expectancy and preoperative staging. At present, the diagnosis of relies on prostate-specific antigen (PSA) level, digital rectal examination (DRE) and transrectal ultrasound (TRUS)-guided biopsy of the prostate.[1] The development of nomograms has improved the accuracy of prostate cancer risk stratification;[2] nonetheless, these tools are still unsatisfactory in predicting extra-capsular extension (ECE). This crucial preoperative information dictates not only the adequate patient management, but also the correct surgical approach, thereby influencing the functional outcome. The decision on preserving neurovascular bundles (NVB) relies on accurate local staging.[3,4] Previous trials have shown that 27% of patients clinically diagnosed with ECE have locally confined disease, and 25% to 30% of patients diagnosed with organ-confined disease have ECE at final pathology.[5,6] To overcome this lack of precise local staging, magnetic resonance imaging (MRI) is considered the most promising way to detect and stage prostate cancer.[7] Despite encouraging results in identifying clinically significant disease within the prostate, previous studies investigating the role of 1.5T endorectal coil MRI in detecting ECE have shown a wide range of sensitivity and specificity, between 13% and 95% and 49% and 97%, respectively.[7] Consequently, systematic preoperative MRI remains contentious.[4,8] Recently, multiparametric 1.5T MRI, combining dynamic contrast-enhanced and diffusion-weighted imaging (DWI) with spectroscopy, has shown promising results in prostate cancer detection.[9] The clinical relevance of these technical advances combined with an improved signal resolution by using 3T endorectal coil multiparametric MRI (3TemMRI) in predicting ECE has not yet been investigated. In this study, we evaluate the accuracy of 3TemMRI in detecting locally advanced prostate cancer by using radical prostatectomy specimen as a reference.

## Methods

After approval from our hospital review board, we retrospectively analyzed the diagnostic accuracy of 3TemMRI in

predicting ECE. The results of this study are reported according to the STARD (Standards for Reporting of Diagnostic Accuracy) statement.[10] All patients undergoing radical prostatectomy at our tertiary care centre from January 2008 to July 2012 were considered eligible. Only patients in whom preoperative 3TemMRI was performed in our centre were included. Patients in whom 3TemMRI was performed less than 21 days after biopsies were excluded to avoid possible bias related to post-biopsy artifacts.[11] In addition, 3TemMRI performed more than 6 months before surgery were not included due to possible bias related to disease progression. Prostate cancer was histologically diagnosed by TRUS-guided, 12 cores biopsy in a standardized protocol, based on pathological PSA values and/or DRE findings.[4] The decision to undertake a 3TemMRI was based on preoperative suspicion of locally advanced disease after multidisciplinary discussion at the local prostate cancer unit.

If a patient was selected for surgery, open radical prostatectomy was performed as per the standardized technique.[12] At final pathology, Gleason score, TNM stage, tumour volume, maximal tumour size, presence of ECE, seminal vesicle invasion, and margin status were recorded. Tumours were then dichotomized into either organ-confined (pT2a-b-c) or locally advanced (pT3a-b or pT4) by 1 pathologist specializing in genitourinary oncology. Definitive pathology was correlated to 3TemMRI with respect to local extension. Two groups were compared: (1) patients in whom final pathology either disagreed with or (2) patients with confirmed radiological stage.

## 3TemMRI

T1-, T2- and diffusion-weighted, as well as dynamic contrast-enhanced images, were acquired with a Magnetom Verio 3TMRI system (Siemens, Germany), using an endorectal coil (eCoil Endo Rectal, Medrad, Warrendale, PA). The prostate was imaged with T2-weighted fast spin-echo acquisitions in coronal, sagittal and axial planes and T1-weighted fat saturated images before and after intravenous administration of 0.2 mL/kg gadopentetate dimeglumine at a concentration of 0.5 mmol/mL in a dynamic phase (Dotarem, Guebert S.A., France). All images were studied by 2 experienced urogenital radiologists. The presence of a tumour was defined by fulfilling at least 2 of 3 criteria: (1) low signal intensity on T2-weighted images; (2) homogeneous enhancing lesion; or (3) reduced diffusion coefficient on DWI. An irregular capsule bulge, a periprostatic fat infiltration, an obliteration of the retroprostatic angle and/or an asymmetry of NVB were used as ECE features.[13] Based on these results, the tumour was classified as either organ-confined (cT2a-b-c) or locally advanced (cT3a-b or cT4).

## Statistics

A contingency table was used to calculate the accuracy (defined by the sum of true positives and true negatives divided by the total number of patients) of 3TemMRI in identifying ECE. Descriptive statistics are reported as median (range) or mean (±standard deviation) for continuous variables, and absolute or relative frequencies for categorical variables. Results are given with 95% confidence interval to show the reliability of estimates. Prism 5.2 (GraphPad, CA) was used for the analysis.

# Results

After applying the exclusion criteria, 60 patients were included in the present study. We illustrate the selection process and STARD flow diagram (Fig. 1). We also tallied the preoperative characteristics and biopsy findings (Table 1).

MRI identified two cT4, 12 cT3a, 12 cT2c (Fig. 2), 11 cT2b and 23 cT2a tumours. The mean maximal tumour size was 17 ± 8 mm. Hyposignal on T2 imaging was always present. Reduced diffusion coefficient was the second most often fulfilled criteria of tumour presence (50 cases). A contrast-enhancing lesion was seen on 41 3TemMRI. Median time from MRI to surgery was 74 days (range: 0-174).

At final pathology, 2 tumors were classified as pT4, 7 as pT3b, 22 as pT3a, 25 as pT2c, 1 as pT2b and 3 as pT2a

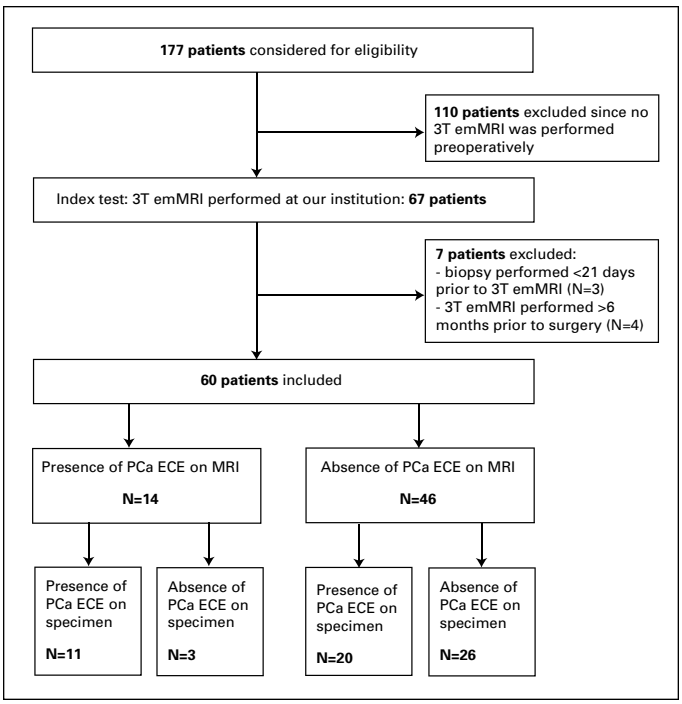


***Fig. 1.*** Standards for Reporting of Diagnostic Accuracy (STARD) flow diagram showing the selection process and the outcome. 3T emMRI: 3 tesla endorectal coil multiparametric magnetic resonance imaging; PCa: prostate cancer; ECE: extra-capsular extension.

| Table 1. Patients' characteristics and biopsy findings | |
|---|---|
| No. patients | 60 |
| Age (years) | 67 ± 7 |
| PSA (ng/L) | 12.7 ± 12.7 |
| DRE | |
| Normal | 24 |
| Palpable | 34 |
| ECE | 2 |
| No. cores | 12 ± 2 |
| No. positive cores | 5 ± 3 |
| Maximum % cancer per core | 38 ± 29 |
| Gleason score | |
| 6 | 16 |
| 7 | 24 |
| ≥8 | 20 |

PSA: prostate-specific antigen; DRE: digital rectal examination; ECE: extracapsular extension.

tumours. The mean tumour volume was 27 ± 18% of the gland. The mean maximal tumour size was 30 ± 16 mm. Microscopic positive margins were found in 26 patients (43%). Of these patients, 20 had ECE and the others had pT2c stage.

When 3TemMRI findings were compared to final pathology, specificity and sensitivity of MRI in detecting ECE was 90% (95% CI 73%-98%) and 35% (19%-55%), respectively, allowing for an overall accuracy of 62%. The negative and positive predictive values were 57% (41%-71%) and 79% (49%-95%), respectively. The correct clinical stage was confirmed in 37 patients. Three patients were overstaged to locally advanced tumour and 20 patients were understaged to organ-confined tumour by 3TemMRI.

## Discussion

Our study found a high specificity of 90%, while sensitivity and accuracy of 3TemMRI in detecting locally advanced prostate cancer were 35% and 62%, respectively, within the range previously published using 1.5T endorectal MRI.[14] These findings suggest that 3TemMRI can precisely detect ECE. An increased accuracy in staging prostate cancer would be expected by using the latest technology. Indeed, 3TemMRI not only reinforces quantitative measures, but also allows for a better spatial and spectral resolution, which should increase the accuracy in staging.[15]

The accuracy of 3TemMRI depends entirely on how the presence of ECE is defined. In this study, the presence of locally advanced disease was binary (yes or no). This does not represent the standard approach, which consists in using a 5-point scale, which allows for probabilistic diagnosis.[16] While this method might be seen as a limitation, we believe that our approach is more straightforward.

Overall, the diagnostic accuracy of preoperative 3TemMRI with low sensitivity and high specificity suggests that this imaging should not be used as a first-line test to assess locally advanced prostate cancer. Indeed, a high sensitivity is a basic requirement to employ a test for screening. Another first-line assessment seems appropriate in this setting. A specific nomogram was developed to predict ECE.[17] It is based on PSA, DRE and biopsy findings, and has shown a high sensitivity at 88%, with a low positive predictive value at 22%. Based on these results and given the lack of a unique accurate preoperative assessment, a straightforward approach in high-risk patients would be to combine this sensitive nomogram with the specific value of 3TemMRI to determine true positives. Prospective studies using this strategy are needed to verify the overall accuracy of this compound approach.

The use of preoperative MRI for NVB preservation remains appealing. The preservation of NVB is now based on patients' clinical characteristics and intraoperative findings. Bilateral nerve-sparing surgery should be offered to all men with normal erectile function and organ-confined prostate cancer. MRI has already shown its ability to detect NVB involvement. In one study, the use of preoperative MRI changed the surgical approach in 44% of patients. MRI correlated well with histopathological findings and was considered an excellent tool to plan operative strategy.[18] Based on our results, 3TemMRI can reliably identify locally advanced disease. Therefore, if 3TemMRI shows ECE, NVB preservation should not be attempted.

Before implementing these findings into clinical practice, the limitations that may have impaired this study must be discussed.

First, a selection bias was obviously present. Half of the patients (31/60) included had locally advanced disease. Preoperative criteria for high-risk disease are a Gleason score >7, a PSA >20 or a suspected cT3/4. When these criteria are applied to our series, 38 patients (63%) are deemed high-risk. Evidence points out that emMRI might be more accurate (i.e., >80% accuracy) in detecting clinically significant organ-confined disease.[19] Indeed, while the detection of intraprostatic prostate cancer is based on reliable features, the prediction of ECE is not based on the same criteria, and is more challenging to detect. As a consequence, a higher proportion of high-risk patients could result in a decreased accuracy. This hypothesis is reinforced by Brajtbord and colleagues.[7] In their study, they found that 39% of patients had pT3/4 disease. They found a staging accuracy of 64%, which is comparable to our results. However, it cannot be definitely stated that MRI is a poor tool in preoperatively assessing patients with high-risk prostate cancer. It has been previously demonstrated that microscopic ECE does not affect the oncological outcome of patients with prostate cancer; so, in this case a false negative MRI would not contraindicate surgery.[20] This argument is sustained by the study from Cornud and colleagues in which MRI achieved an accuracy of 88% in detecting extensive ECE, whereas the accuracy was significantly decreased in detecting microscopic ECE.[21]

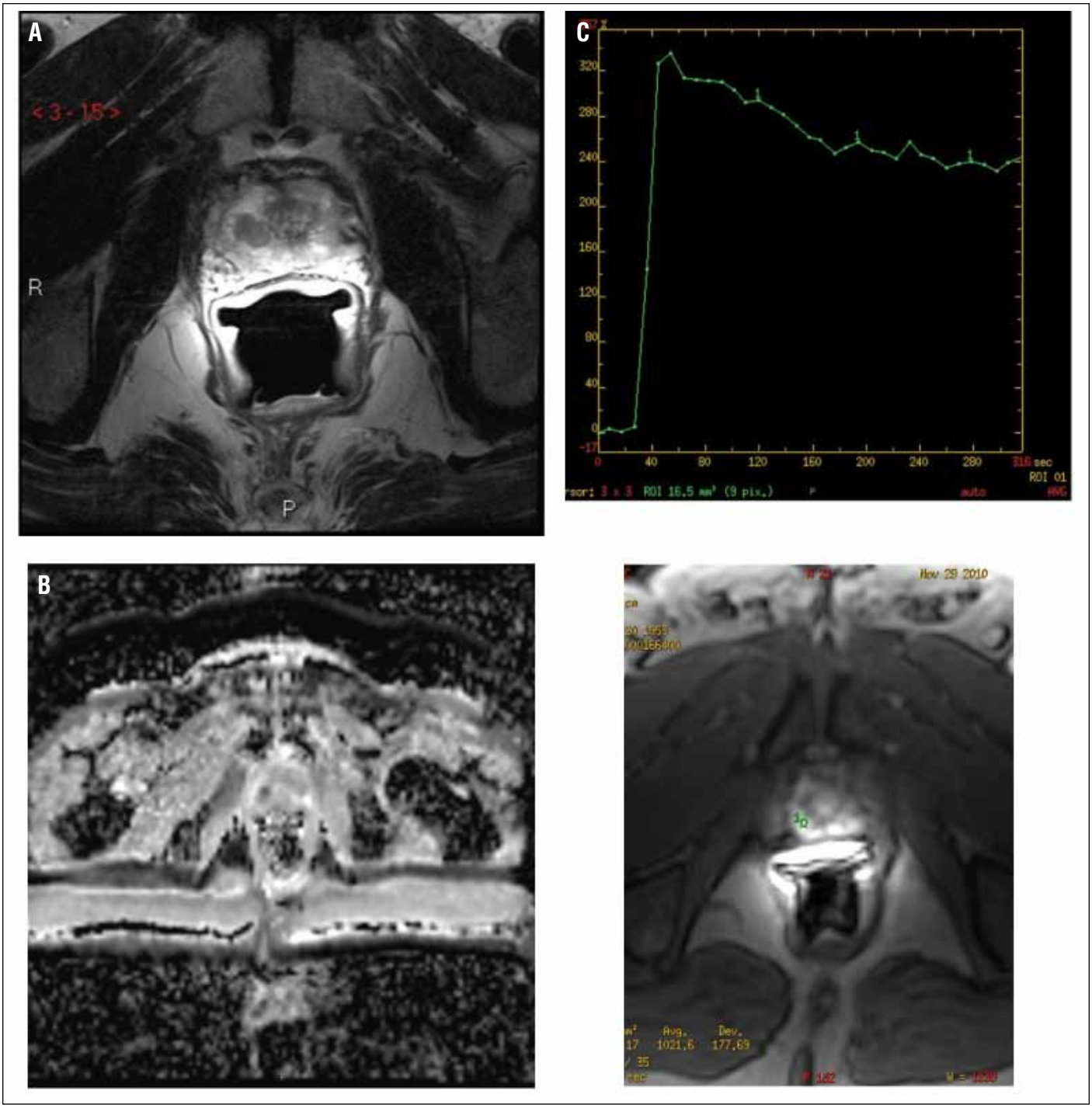


***Fig. 2.*** 3T emMRI appearance of localized prostate cancer classified cT2c. These specific sequences show hyposignal on T2 imaging (2A), restriction of diffusion imaging (2B) and rapid and homogenous contrast enhancing with rapid washout (2C). No extracapsular extension features are seen in these images. 3T emMRI: 3 tesla endorectal coil multiparametric magnetic resonance imaging.

Another limitation of this study was that the radiologists and pathologist were not blinded. This aspect seems more important for the imaging interpretation rather than for the pathology results. Indeed, in 44/60 patients (73%), 3TemMRI was performed after a positive biopsy, so the presence of prostate cancer was already ascertained. Although we acknowledge that this limitation could have affected the results, the calculated diagnostic accuracy of emMRI in the present study was not focused on the presence of disease, but rather on the presence of ECE.

Third, MRI spectroscopy was not used in our study. While it has been suggested that the addition of spectroscopic imaging to emMRI might improve local staging, these findings still need to be validated.[9]

Finally the retrospective design, the small sample size, and the presence of heterogeneity in the time between 3TemMRI and biopsy represent further limitations. Indeed, it has been postulated that artifacts from biopsies might alter emMRI accuracy in staging prostate cancer.[22] This aspect remains controversial. While Park and colleagues demonstrated that the time between biopsy and MRI did not significantly affect local staging accuracy, other studies have shown that post-biopsy hemorrhage can decrease the diagnostic accuracy.[23,24] To limit false positive findings related to post-biopsy artifacts, all patients undergoing 3TemMRI less than 3 weeks after biopsies were excluded (however, some experts have suggested 6 or more weeks).[25] Prospective, well-designed studies are needed to clarify this issue.

## Conclusions

Our study confirms that the use of 3TemMRI is useful to preoperatively detect ECE when locally advanced prostate cancer is suspected. Urologists should be aware of the complementary role of 3TemMRI in selecting appropriate management of patients with high-risk disease or when a nerve-sparing procedure may be planned. Prospective studies are needed to verify its usefulness in clinical practice and standardize its indications.

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This paper has been peer-reviewed.

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