ORIGINAL ARTICLE

Multiparametric magnetic resonance imaging for the assessment of extracapsular invasion and other staging parameters in patients with prostate cancer candidates for radical prostatectomy

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Abstract
Introduction: The proper evaluation of the extracapsular extension (ECE), the invasion of seminal vesicles and regional lymph nodes are necessary to plan the treatment of localized prostate cancer. A model that assesses the risk of ECE in the specimen considering the clinical, histological and imaging findings is defined.

Material and methods: Prospective study in 85 patients with prostate cancer treated with radical prostatectomy. Prostate biopsy was performed 4 weeks before multiparametric study (mpMRI). mpMRI included T2-weighted endorectal magnetic resonance imaging (T2W-MRI), diffusion-weighted magnetic resonance imaging (DW-MRI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). The apparent diffusion coefficient (ADC) was also measured. A study of consistency (k) was assessed comparing receiver operating characteristic (ROC) curve and area under the curve (AUC), which were obtained in each case (Z). Finally, a regression model was performed to predict ECE.

Results: The mean age was 63.7 ± 6.9 years and the mean value of PSA 12.6 ± 13.8. In 31.7% of cases, digital rectal examination was suspicious for malignancy. Prostatectomy specimen showed pT2a in 12 cases (14%), pT2b in 3 (3%), pT2c in 37 (43%), pT3a in 19 (22%) and pT3b 14 cases (17%). ECE was evidenced in 33 (39%) of the specimens, seminal vesicle invasion in 14 (16.5%) and pelvic node involvement in 5 patients (6%). The consistency in the

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Multiparametric magnetic resonance imaging for the assessment of extracapsular invasion in prostate cancer

PALABRAS CLAVE
Resonancia magnética nuclear;
Resonancia magnética nuclear multiparamétrica;
Valor coeficiente de difusión aparente;
Extensión extracapsular;
Gleason

evaluation of ECE (image and pathological studies) was .35 for MRI (sensitivity .33, specificity .96) and .62 for mpMRI (sensitivity .58, specificity .98). Mean value of ADC was .76 ± .2 in patients with ECE. This value was not associated with Gleason score (p = .2) or with PSA value (p = .6). AUC value as predictor of ECE was of 65% for MRI, 78% for mpMRI and 50% ADC (Z = .008). Univariate analysis demonstrated that ECE probability increases with each Gleason score point, whilst this probability increases 1.06 times with each PSA point, and decreases .3 times with each point of ADC. Multivariate analysis confirmed that ADC value is a slight protective factor against ECE (OR = .01; c1 95% .002-.14). The consistency in the evaluation of seminal vesicles was .43 for MRI and .67 for mpMRI. AUC was 69% and 82% respectively (Z = .02). The consistency in the evaluation of positive lymph nodes was .4 for MRI and .7 for mpMRI. AUC was 68% and 88% respectively (Z = .36).

Conclusions: Multiparametric study allows to carry out a more proper preoperative evaluation of ECE than conventional MRI. The most reliable predictors of ECE are DW-MRI combined with DCE-MRI, ADC coefficient and Gleason score. The superiority of mpMRI is also demonstrated for the detection of seminal vesicles invasion, but not for the evaluation of lymph nodes invasion.

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Evalúación de la invasión extracapsular y otros parámetros de estadificación mediante resonancia nuclear magnética multiparamétrica en pacientes con cáncer de próstata candidatos a prostatectomía radical

Resumen

Introducción: La correcta evaluación de la extensión extracapsular (EEC), la invasión de las vesículas seminales y de los ganglios linfáticos regionales es necesaria para planificar el tratamiento a seguir en el cáncer de próstata localizado. Se define un modelo que evalúa el riesgo de EEC en el espécimen considerando los hallazgos clínicos, histopatológicos y de imagen.

Material y métodos: Estudio prospectivo en 85 pacientes con cáncer de próstata tratados mediante prostatectomía radical. La biopsia de próstata se realizó 4 semanas antes del estudio multiparamétrico (mpMRI). Este incluyó resonancia magnética con antena endorrectal balanceada en T2 (MRI-T2W), secuencias balanceadas con difusión (MRI-DW) y secuencias balanceadas con perfusión (MRI-DCE). Se calculó también el coeficiente de difusión aparente (ADC). Se evaluó la consistencia de los estudios (k), comparándose las curvas de características receptor operador (ROC) y el área bajo la curva (ABC) obtenida en cada caso (Z). Finalmente se realizó un modelo de regresión para predecir EEC.

Resultados: La edad media fue 63,7 ± 6,9 años y el valor medio de PSA 12,6 ± 13,8. El tacto rectal resultó sospechoso de malignidad en el 31,7% de los casos. El espécimen de prostatectomía mostró pT2a en 12 (14%), pT2b 3 (3%), pT2c 37 (43%), pT3a 19 (22%) y pT3b 14 (17%) casos. Se evidenció EEC en 33 (39%) de los espécimen, invasión de vesículas seminales en 14 (16,5%) y afectación de ganglios pélvicos en 5 (6%). La consistencia en la evaluación de EEC entre imagen y anatomía patológica fue 0,35 en el caso de MRI (sensibilidad 0,33; especificidad 0,96) y 0,62 para mpMRI (sensibilidad 0,58; especificidad 0,98). El valor medio de ADC para los pacientes con EEC fue 0,76 ± 0,2. Este valor no se asoció con la puntuación de Gleason (p = 0,2) o con el valor de PSA (p = 0,6). El ABC para predecir EEC fue 65% para MRI, 78% para mpMRI y 50% para ADC (Z = 0,008). El análisis univariante mostró que por cada punto del valor de Gleason aumenta 5,1 veces la probabilidad de EEC, mientras que por cada unidad de PSA dicha probabilidad aumenta 1,06 veces y por cada punto de ADC la reduce 0,3 veces. El análisis multivariante confirmó que el valor ADC es un factor protector leve para EEC (OR = 0,01; IC 95%; 0,002-0,14), mientras que el índice Gleason aumenta abiertamente dicho riesgo (OR = 4,92; IC 95%; 2,1-11,4). La consistencia en la evaluación de la invasión de vesículas seminales fue 0,43 para MRI y 0,67 para mpMRI. El ABC respectivo fue 69 y 82% (Z = 0,02). La consistencia en la evaluación de ganglios positivos fue 0,4 para MRI y 0,7 para mpMRI, con un ABC respectivo de 68 y 88% (Z = 0,36).

Conclusiones: El estudio multiparamétrico permite llevar a cabo una mejor evaluación preoperatoria de EEC que MRI convencional. MRI-DW asociada a MRI-DCE, el coeficiente ADC y la puntuación de Gleason son los factores más fiables para predecir EEC. La superioridad de mpMRI también se demuestra a la hora de evaluar la invasión de las vesículas seminales, pero no para la evaluación de ganglios linfáticos.

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Introduction

Prostate cancer is the most frequent solid malignant neoplasm in male and is the second cause of cancer death. Accounts for 11.7% of new cases diagnosed worldwide, the figure rises to 19% in developed countries. Transrectal ultrasound guided prostate biopsy (TRUS) is necessary for confirmatory diagnosis revealing tumor differentiation grade (Gleason index) as prognostic factor in prostate cancer. However, many studies reveal infrastaging and overstaging of Gleason index and pathological stage comparing with the results obtained from pathological study of radical prostatectomy specimen. By the other side, the need of multiple prostatic biopsies on the same individual is not an isolate fact being indispensable to improve the disease diagnosis and staging strategies.

Certain risk groups of patients undergoing to radical prostatectomy show a high probability of extracapsular extension probability (ECE), invasion of seminal vesicles (SV), distant nodal disease and positive surgical margins. Gleason infra-staging may lead to misclassification of risk group and, in consequence, to a poor assessment after radical surgery regarding ECE, invasion of SV, lymphadenopathy and surgical margins. Imaging methods for a proper characterization of prostate tumors respect ECE, available until the moment, have shown a poor yield. Currently, nuclear magnetic resonance (NMR) is shown as the better imaging technique for local staging of prostate cancer, with an accuracy level between 64 and 91%. Diverse sequences applicable to conventional NMR have improved progressively the outcomes from prostatic imaging studies.

Diffusion-weighted magnetic resonance imaging (DW-MRI) allows to measure the motion of the water molecules in the tissue without the need of contrast media injection. These sequences would improve the outcomes of prostatic preoperative assessment regarding the use of conventional NMR. Motility quantifying is performed by apparent diffusion coefficient (ADC). This motility depends on cellular membrane integrity and is measured by 2 opposite diffusion gradients characterized by their b-values. The lower this b-value is the higher ADC value. Therefore, qualitative measurement of imaging obtained by DW-MRI with corresponding ADC map together with quantitative analysis of ADC values, allow us to assess the imaging study. Thanks to these imaging sequences it is possible the early identification of abnormal tissue. The use of other MRI sequences would make possible the assessment of metabolic features of tumor, improving neoplasm evaluation. Among them, the diffusion studies (DCE) or the spectroscopy could highlight.

The objective of our study is to assess the use of MRI with endorectal coil, using both T2W-MRI and multiparametric study (mpMRI: assess T2W-MRI in association with DW-MRI and DCE-MRI), in order to predict extracapsular extension risk and other characteristics related with the extension of tumor, previously to prostatic surgery. We also propose to carry out a model that allows assessing in our environment the ECE risk taking into account clinical, pathological and imaging findings.

Material and methods

Radical prostatectomy and systematic and complete histopathologic study of the specimen were carried out in 85 patients with prostate cancer (clinical stage T1c–T3a). The 2 main indications for endorectal MRI study were: (a) proximity of cancer to the neurovascular bundles in patients scheduled for nerve-sparing radical prostatectomy and (b) extension risk assessment in high-risk patients according to d’Amico-criteria in order to develop, if necessary, extended preoperative planification. Therefore, it is not surprising that this population shows criteria for locally advanced tumor in a significant proportion of cases. Lilo-obturator lymphadenectomy was performed in patients with PSA ≥ 10 ng/ml and/or Gleason ≥ 8 in TBP. ECE risk, SV infiltration and lymph node involvement were defined by radiologic, T2W-MRI, DW-MRI, DCE-MRI and ADC coefficient studies.

MRI imaging study was performed with a 1.5-T clinical magnetic resonance imaging system (Avanto, Siemens, Healthcare Solutions), endorectal coil (Medrad) with pelvic surface coil and parallel imaging acquisition (FoV 280 mm, iPAT 2). Protocol used is described as follows. Prostate morphology was obtained by T2W TSE sequence in three orthogonal planes parallel to the main prostate axis (TR9/TE/FA: 4000/95/139°, slice thickness 3 mm and matrix 460 × 152). EPI + fat sat (TR/TE/FA: 3400 ms/79 ms/90°, FoV 340 mm, PAT2, matrix 135 × 192 and b factor: 50/550/1000) was employed to obtain diffusion sequence (DW-MRI). Finally, a T1-w 3D-FLASH (TR/TE/FoV: 6.3 ms/2.5 ms/10°, FoV 430 mm, PAT2, matrix 106 × 192) was used for obtaining perfusion sequence (DCE-MRI).

Following characteristics were determined by the radiologist by T2W, diffusion (DW) and perfusion (DCE): tumor in contact with capsule, tumor extension into peri-prostatic fat, obliteration of recto-bladder angle, asymmetry of neurovascular bundle and seminal vesicles infiltration. Surgical sample was thoroughly studied by the pathologist: Indian ink staining, comprehensive assessment of prostatic specimen and lymph nodes in order to determine the possible presence of extraprostatic disease (> pT3R0-R1). In descriptive statistical analysis, sensitivity and specificity pattern, positive and negative predictive values (PPV and NPV) and predictive accuracy (PA) of the tests were calculated. Kappa coefficient was used to measure the consistency level in the risk assessment and the median of the ADC values; both isolated T2W-MRI and mpMRI (T2W-MRI with DW-MRI and DCE-MRI) were calculated. Receiver operating characteristic curve (ROC) analysis and area under the curve (AUC) comparisons were done with the statistic Z.

Results

Mean age of patients was 63.7 ± 6.9 years old (range 45–80). Mean PSA level was 12.7 + 13.8 (1–83.7) ng/ml. Digital rectal examination was suspicious for malignancy in 58 cases (68.2%). Patients’ classification according T and pT categories are showed in Table 1. The mean value of Gleason
score on prostate specimen was 7.12 ± 1.02,5-9 being 23 (27%) 6.39 (46%) 7.14 (16.5%) 8 and 9 (10.5%) 9, respectively. ECE was evidenced in 32 (37%), seminal vesicles infiltration in 16 (18.8%) and positive lymph nodes in 5 (5.9%) of prostate specimens.

According to T2W-MRI study, ECE was reported in 13 (15.3%) of patients. However, this figure rose to 20 (23.5%) of patients when mpMRI findings were taken into account. Thus, the consistency of assessment ECE, according with correlation coefficient, kappa, was: 0.35 (CI 95%: 0.15–0.53) for MRI (Sensitivity 0.33; Specificity 0.96; PPV 0.84; NPV 0.69; Ex 0.72) and 0.62 (0.45–0.69) for mpMRI (sensitivity 0.98; specificity 0.98; PPV 0.95; NPV 0.75; Ex 0.82). Patients with ECE showed a median of ADC of 0.76 (0.68–0.93). That value is not associated with Gleason (p = 0.2) neither with PSA (p = 0.6). The distribution of ADC value for total series according with ECE presence, Gleason and PSA distribution are showed in Table 2. The AUC for ECE were 0.65, 0.78 and 0.56 in T2W-MRI, mpMRI and ADC imaging assessments respectively (Z = 0.008) (Fig. 1).

According to T2W-MRI, SV infiltration was observed in 11 (12.9%) of patients. The figure rose up to 14 (16.5%) when DW-MRI and DCE-MRI were taken into account. The consistency of SV infiltration assessment was 0.43 (0.18–0.68) for MRI (sensitivity 0.5; specificity 0.94; PPV 0.66; NPV 0.89; Ex 0.86) and 0.67 (0.46–0.88) for mpMRI (sensitivity 0.75; specificity 0.96; PPV 0.80; NPV 0.94; Ex 0.92). The AUC regarding SV invasion was 0.69 for MRI and 0.82 for mpMRI (Z = 0.02) (Fig. 1). Finally, 4 (4.7%) of patients showed lymph node involvement in T2W-MRI study, whereas in mpMRI the figure was 6 (7.1%); being the consistency of lymph node involvement assessment 0.4 (0.02–0.82) for T2W-MRI (sensitivity 0.4; specificity 0.97; PPV 0.5; NPV 0.96; Ex 0.96) and 0.7 (0.38–1) for mpMRI (sensitivity 0.8; specificity 0.97; PPV 0.67; NPV 0.99; Ex 0.85). The AUC regarding lymph node infiltration was 0.68 for T2W-MRI and 0.88 for mpMRI (Z = 0.36) (Fig. 1).

A predictive model for ECE in the prostatectomy specimen has been investigated. ECE prediction is affected for the following variables (univariate analysis): PSA (likelihood of ECE increases 1.06 times with each PSA point); Gleason index (likelihood of ECE increases 5.1 times with each Gleason score point) and the ADC value (likelihood of ECE decreases 0.3 times with each point of ADC). In ECE prediction, the areas under the ROC curves were 0.65 for PSA, 0.38 for Gleason and 0.56 for ADC (Fig. 2). In multivariate analysis: PSA loses its predictive value; ADC maintains high values acting as protective factor against ECE (OR = 0.01; CI 95%: 0.002–0.14); and the highest Gleason values rose up strongly likelihood of ECE (OR = 4.92; CI 95%: 2.1–11.4).

### Discussion

The prostate cancer staging seeks to establish the prognostic of the disease and to select the more accurate treatment according to tumor extension. Thus, on the one hand the nomograms combining digital rectal examination, PSA and TRE along with, on the other hand, imaging techniques, allow us the more or less accurate preoperative assessment of the tumor extension.10-12

In patients with localized prostate cancer, radical prostatectomy appears like the most effective treatment tool, with the highest healing rates.7,13 However, around 30% of these tumors show ECE after surgical specimen analysis. The use of conventional MRI and CT as methods for the assessment of tumor extension entail low sensitivity and high economical cost,13 so then it is advised against routinely use. On the contrary, the use of different MRI sequences with endorectal coil have provided promising results, and therefore mpMRI is the choice technique for preoperative assessment of prostate cancer for many medical groups.14,15

The protocol of MRI staging of prostate cancer entails the assessment of whole prostate gland. In order to obtain a better image quality, to employ antiperistaltic drugs are necessary during the test. In our study, such a protocol includes T2W-MRI, DW-MRI and DCE-MRI sequences (in axial and sagittal cuts, 3 mm at 1.5 T and 3 T, image resolution of 0.3 × 0.3 mm to 0.7 × 0.7 mm for 1.5 T and of 0.3 mm × 0.3 mm to 0.5 mm × 0.5 mm for 3 T). Resulting from scarcity of conclusive data, the spectroscopy study is not included in the European Society of Urogenital Radiology’s recommendations.15 As not all patients are subsyndary of regional lymph node assessment, it is performed apart from prostate assessment16 (Fig. 3).

Among imaging tests, T2W-MRI imaging provides the best description of prostatic areas available, allowing both
cancer detection and location and staging. \cite{17,18} Their joint use with other available sequences has meant an increase in the test sensitivity and specificity, when is defined as multiparametric study (mpMRI). In T2W sequences, prostate cancer appears typically as foci having a weakly defined contour of low signal intensity (Figs. 3 and 4). ECE is suspected in those cases showing irregularities, neurovascular thickening and enhancement of the prostatic capsule. SSVV invasion is defined by low intensity in T2, obliteration of vesicle-prostate angle and peripheral enhancement.

Diffusion weighted sequences (DW-MRI) have shown promising outcomes regarding ECE assessment (pT3a) and seminal involvement (pT3b). \cite{17} The diffusion coefficient ADC turn allows quantitative and qualitative assessments of tumor aggressiveness, also showing correlation with Gleason score. \cite{15,16,19} That correlation is not reported in our study, although there are differences pointing to statistical significance. In this type of sequences tumors will show hyperintense signal with high b value and hypo-intensity in ADC map. \cite{14,15} Regarding ADC coefficient, the lowest values are the most characteristic of tumor within the gland. Although there is no consensus about higher probability of cancer cut-point, the published data shows that values in range 0.49–1.43 × 10^{-3}mm^{2}/seg. are suggestive of cancer. \cite{20,21}

It is known that combination of T2W, DW and DCE sequences improves significantly the outcomes obtained in cancer detection, showing better sensitivity a specificity than just T2W. \cite{21} Regarding ECE detection, the use of DW-MRI and DCE-MRI also improves the sensitivity a specificity.
with regard to T2W-MRI. According to our experience, the association between T2W-MRI, DW-MRI and DCE-MRI represents an improvement in the probability of correctly detecting the presence of ECE and SSVV invasion. These data are not corroborated in lymph node involvement, due probably to the scarcity of patients with this modality of disease. Moreover, ADC value together with Gleason total score is independent predictive value in the assessment of extraprostatic invasion. These findings are consistent with the recent experience of various research groups.

Dynamic contrast-enhanced sequences (DCE-MRI) employing the administration of gadolinium contrast, allow an excellent assessment of the tumor vascularization. The combination of DCE-MRI and T2W and DW-MRI (Figs. 3–6) shows high assessment accuracy of prostate gland than the obtained with each sequence. Even so, the clearest indication for DCE-MRI is probably its application in the evaluation of Gleason score.
of biochemical relapse after healing treatment.\textsuperscript{24,25} Finally, as consequence of the low spatial resolution, spectroscopy does not show a good assessment of tumor stage, because of the high-levels of choline and low-levels of citrates in diseased prostatic tissues regarding healthy ones. As spectroscopy shows a high risk of false positive, some studies do not take it into account as test of choice.\textsuperscript{13,14}

In conclusion, multiparametric study by T2W-MRI, DW-MRI and DCE-MRI sequences allows carrying out a more proper preoperative assessment of ECE (pT3a) and seminal vesicles involvement (pT3b) than tests available up to date. Diffusion sequences complementary to T2W sequences together with ADC coefficient assessment, allowing assessing the tumor aggressiveness, achieve promising outcomes in the preoperative study. However, it is necessary to carry out prospective, multicentric studies and with largest patient populations in order to achieve higher consensus regarding MRI use in prostate cancer assessment, especially of DW-MRI and DCE-MRI.

**Conflict of interests**

The authors declare that they have no conflict of interest.

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**References**


