ORIGINAL ARTICLE

Evaluation of risk of muscle invasion, perivesical and/or lymph node affectation by diffusion-weighted magnetic nuclear resonance in the patient who is a candidate for radical cystectomy

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KEYWORDS
Diffusion-weighted magnetic resonance; Bladder cancer; Cystectomy; Muscle invasion; Perivesical affectation; Lymph node invasion

Abstract

Introduction: Preoperative staging of bladder cancer using imaging methods has serious limitations. The accuracy of the abdominal diffusion-weighted magnetic resonance (DW-MRI) to predict residual muscle invasion, perivesical and/or lymph node affectation in the cystectomy specimen is evaluated.

Material and methods: A prospective study was performed on 20 patients with high grade muscle invasive bladder cancer who received transurethral resection of the bladder (TURB) in a period of <1 month. The DW-MRI was performed before the radical cystectomy and the radiologist predicted muscle invasion, extravesical affection and lymph node affection, being blind to the histopathological study. Sensitivity (S), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy (Ac) of the test were analyzed. The medians of the apparent diffusion coefficient (ADC) value (Mann-Whitney) were compared and the ROC curves study for DW-MRI and ADC was carried out.

Results: Distribution by categories was: pT0 1(5%), pT1 6(30%), pT2 2(10%), pT3 8(40%) and pT4 3(15%). There was an agreement in the T-pT assignment in 17(85%). In 7(35%) there was lymph node affectionation (pN1-2). Consistency of the DW-MRI for muscle affectionation was k = 0.89 (CI 0.67–1; S = 1.0, Sp = 0.86, PPV = 0.93, NPV = 1.0, Ac = 0.95), for perivesical fat affectionation k = 0.6 (CI 0.25–0.95; S = 0.8, Sp = 0.8, PPV = 0.8, NPV = 0.8, Ac = 0.8) and for lymph node affectionation k = 0.89 (CI 0.67–1; S = 0.86, Sp = 1.0, PPV = 1.0, NPV = 0.93, Ac = 0.95). Mean value of ADC was greater in G2 tumors (OMS1987) compared to G3 (p = 0.08). Evaluation of DW-MRI imaging

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and ADC numerical value showed equivalent areas under the curve for muscle (0.93 and 0.9; Z = 0.7), fat (0.8 and 0.91; Z = 0.31) and lymph node (0.93 and 0.97; Z = 0.36) affection, respectively.

Conclusions: DW-MRI allows for good pre-operative evaluation of the patient who is a candidate for cystectomy, especially for the prediction of muscle (<pT2 vs. ≥pT2) and/or lymph node (N0 vs. N1-2) affection. Both are key points to choose the therapeutic attitude after the bladder TURB. Furthermore, the ADC coefficient also predicts tumor differentiation grade.

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PALABRAS CLAVE
Resonancia magnética balanceada con difusión; Cáncer de vejiga; Cistectomía; Afectación muscular; Afectación perivesical; Afectación ganglionar

Evaluación del riesgo de invasión muscular, afectación perivesical y/o ganglionar mediante resonancia magnética nuclear balanceada con difusión en el paciente candidato a cistectomía radical

Resumen
Introducción: La estadificación preoperatoria del cáncer vesical por métodos de imagen presenta serias limitaciones. Se evalúa la exactitud de la resonancia magnética abdominal balanceada con difusión (MRI-DW) para predecir invasión muscular residual, afectación perivesical y/o ganglionar en el espécimen de cistectomía.

Material y métodos: Estudio prospectivo sobre 20 pacientes con cáncer de vejiga músculo-invasivo de alto grado que recibieron RTU vesical en un plazo menor de un mes. Se realizó MRI-DW antes de cistectomía radical y el radiólogo predijo invasión muscular, afectación extravesical y afectación ganglionar de manera ciega al estudio histopatológico. Se analizó sensibilidad (S), especificidad (E), valor predictivo positivo (VPP), valor predictivo negativo (VPN) y exactitud (Ex) de la prueba. Se compararon medias de valor ADC (Mann-Whitney) y se llevó a cabo estudio de curvas ROC para MRI-DW y ADC.

Resultados: La distribución por categorías fue: pT0 1(5%), pT1 6(30%), pT2 2(10%), y pT3 8(40%) y pT4 3(15%). Se realizó acuerdo en la asignación T-pT en 17 (85%). En 7 (35%) hubo afectación ganglionar (pN1-2). La consistencia de MRI-DW para afectación muscular fue k = 0.89 (IC 0.67-1; S = 1.0, E = 0.86, VPP = 0.93, VPN = 1.0, Ex = 0.95), para afectación de grasa perivesical k = 0.6 (IC 0.25-0.95; S = 0.8, E = 0.8, VPP = 0.8, VPN = 0.8, Ex = 0.8) y para afectación ganglionar k = 0.89 (IC 0.67-1; S = 0.86, E = 1.0, VPP = 1.0, VPN = 0.93, Ex = 0.95). La medición de valor de ADC fue mayor en tumores G2 (OMS 1987) frente a G3 (p = 0.08). La evaluación por imagen de MRI-DW y el valor numérico ADC mostraron áreas bajo la curva equivalentes para afectación muscular (0.93 y 0.9; Z = 0.7), grasa (0.8 y 0.91; Z = 0.31) y ganglionar (0.93 y 0.97; Z = 0.36), respectivamente.

Conclusiones: MRI-DW permite una buena evaluación preoperatoria del paciente candidato a cistectomía, especialmente para la predicción de afectación muscular (<pT2 vs ≥pT2) y/o ganglionar (N0 vs N1-2), ambos puntos clave para elegir la actitud terapéutica después de RTU vesical. Además, el coeficiente ADC predice también el grado de diferenciación tumoral.

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Introduction

Bladder cancer is the second most common malignancy of the genitourinary tract, and the fourth and eighth in terms of incidence in males and females, respectively. A key factor in the prognosis of bladder cancer is the presence of extravesical disease and/or regional lymph node infiltration. The survival rates of patients with extravesical disease provide data significantly worse than those with organ-confined disease, recurrence-free survival at 5 years being 89% in organ-confined ones, decreasing to 60, 50, and 35% for those with pT3, pT4, and N+ stages, respectively. For all this, the preoperative study of patients candidate for radical cystectomy due to muscle-invasive bladder cancer (MIBC) has a key role in assessing and predicting the prognosis of the disease. Various imaging tests have been used. Computed tomography (CT) shows a high accuracy for the diagnosis of bladder cancer, but on the other hand, it fails to achieve reliable results in assessing muscle invasion, extravesical disease, or presence of positive nodes. With up to 25% of patients with lymphatic disease (N+) in the cystectomy specimen which failed to be demonstrated preoperatively.

The use of magnetic resonance imaging (MRI) and, more specifically, of the diffusion-weighted magnetic resonance imaging (DW-MRI) have become more accurate in assessing the tumor stage, and thus, the possible presence of extravesical disease, eliminating in turn the possible effects of radiation associated with the use of CT. MRI involves the technique of choice in the preoperative evaluation of these patients by providing multiplanar images and better characterizing the soft tissues. Different papers published so far also suggest that the use of the apparent diffusion coefficient (ADC) improves the tumor grade characterization. Thus, the lowest ADC values correspond to higher grade tumor lesions associated with a high-intensity signal in
the diffusion-weighted magnetic resonance imaging (DW-MRI).  

We intend to evaluate the accuracy of abdominal DW-MRI to preoperatively predict residual muscle invasion, perivesical and/or lymph node involvement in the specimen of cystectomy in patients undergoing radical cystectomy for muscle-infiltrating bladder cancer.

**Material and methods**

We performed a prospective study with 20 consecutive patients diagnosed with high-grade muscle-invasive transitional cell carcinoma of the bladder (≥T2 G2-3) candidates to received radical cystectomy who have received transurethral resection of the bladder (TURB) within less than one month. The intervention included extended lymphadenectomy in all cases, with removal of all the lymph nodes included in the area defined by the aortic and iliac common bifurcation, the genitofemoral nerve, the circumflex vein, the Cloquet’s ganglion, and the hypogastric vessels. The lymph nodes were conveniently labeled according to the lymphatic stations established in: internal, external, and common presacral, obturator, and iliac.

In all cases we performed MRI 1.5 T (Avanto; Siemens Healthcare Solution, Germany). The protocol of imaging obtaining in sequences in T1 was 499 ms of repetition time (RT), 12 ms of echo time (ET), with matrix of 204 × 256 matrix, 40 cm of field of view, and 5 mm of slice thickness. The T2 images were obtained with 4000 ms of RT, 100 ms of ET, matrix of 256 × 256, 20 cm of field of view, 5 mm of slice thickness. Regarding the T2 images with diffusion, the parameters were: 4000 ms of RT, 107 ms of ET, matrix of 256 × 256, field of view of 40 cm, thickness of 5 mm of section, and in 3 orthogonal planes. Later, images were obtained in volumetric dynamic gradient in 3 dimensions (VIBE) with fat suppression (5.12 ms of RT, 2.41 of ET, 10° of angle of rotation, matrix of 116 × 256, 45 cm of field of view, 3 mm of slice thickness), all in an axial plane before and after injection of gadopentetate dimeglumine (MULTIHANCE). The images with that contrast were obtained with a delay of 20 s for the arterial phase followed by the venous phase at 70 s.  

All the MRI images were reviewed by experienced radiologists to predict muscle invasion, extravesical and lymph node involvement blindly to the histopathological study of the cystectomy specimen, which was considered the reference. The T tumor stage was evaluated independently by sequences in T2 initially, and T2 in combination with contrast subsequently. The tumors were presented as non-muscle invasive (Ta or T1) if the hypointense muscle layer was intact, T2 if the muscle layer was irregular or interrupted, T3 before tumor mass with extension to fat extravesical tissue and irregular margins, and T4 when invasion of adjacent pelvic organs was identified. Furthermore, lymph node involvement was defined by the presence of one or more lymph nodes suspicious of tumor involvement.

Descriptive analysis was performed of each case and the sensitivity (S), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and accuracy (Ac) of the test were subsequently analyzed. We evaluated the consistency in the assessment (kappa) and compared medians of the ADC value by means of Mann–Whitney U. Finally, a study of ROC curves was performed and comparing areas under the curve (Z) for the findings obtained by DW-MRI and the numerical value of the ADC quotient.

**Results**

The average age of the patients was 69 ± 10.3 years, with a male: female ratio 19:1. The radical cystectomy specimen showed the following distribution per categories: pT0 1 (5%), pT1 6 (30%), pT2 2 (10%), pT3 8 (40%), and pT4 3 (15%), which corresponds to 13 cases (65%) that showed muscle invasion (MIBC). The tumor grade was G2 in 4 (20%) and G3 in 16 (80%) cases (WHO 1987). It showed lymph nodes with tumor involvement (pN1-N2) in 7 cases (35%).

The preoperative study by DW-MRI defined: 1 (5%) T0, 5 (25%) T1, 5 (25%) T2, 6 (30%) T3, and 3 (15%) T4; 14 (70%) were N0, 5 (25%) N1, and one (5%) N2. That is, 14 (70%) were diagnosed as muscle-invasive tumors, of which 9 (45%) presented perivesical fat infiltration according to the imaging study (Fig. 1). There was agreement on the assignment of tumor stage and specimen (T-pT) in 17 cases (85%). Regarding the consistency of DW-MRI in the evaluation

![Figure 1](image-url) **Figure 1** MRI findings suggestive of bladder cancer. (A) ‘Worm sign’ in MRI-T2W, characteristic of non-muscle-invasive lesions. (B) Neoplasia with involvement of muscle layer without perivesical involvement (T2) in DW-MRI. (C) Bladder cancer with perivesical fat infiltration (T3) in DW-MRI. The lesions corresponding to (B) and (C) show low ADC, which corresponds to high-grade lesions.
of muscle involvement, the kappa coefficient was 0.89 (CI 0.67–1); S = 1.0, Sp = 0.86, PPV = 0.93, NPV = 1.0, and Acc = 0.95. In the assessment of perivesical fat involvement, the kappa value was 0.6 (CI 0.25–0.95); S = 0.8, Sp = 0.8, PPV = 0.8, NPV = 0.8, and Acc = 0.8. Finally, in the assessment of nodal involvement kappa was 0.89 (CI 0.67–1); S = 0.86, Sp = 1.0, PPV = 1.0, NPV = 0.93, and Acc = 0.95.

The average value of ADC in lesions was 1.06 (0.50–1.80). The ADC coefficient for G2 grade tumors, according to the 1987 WHO classification, was $1.4 \times 10^7$ mm$^2$/s (CI 0.73–2.02) and for G3 lesions $0.95 \times 10^7$ mm$^2$/s (CI 95 0.79–1.17), representing lower values for the most undifferentiated lesions (p = 0.08). Imaging evaluation of DW-MRI and the ADC numerical value showed equivalent areas under the curve both to detect the presence of muscle involvement (0.93 DW-MRI and 0.9 ADC; Z = 0.7), and fat involvement (0.8 DW-MRI and 0.91 ADC; Z = 0.31) or lymph node involvement (0.93 DW-MRI and 0.97 ADC; Z = 0.36) (Fig. 2).

**Discussion**

The treatment of bladder cancer is primarily dependent on the correct differentiation between superficial and invasive disease. Numerous studies have shown better results for MRI than for CT in the assessment of extravesical disease. This point is crucial in the prognosis of the disease, because patients with extravesical disease have a higher rate of recurrence and worse survival. However, CT is used routinely in the preoperative evaluation of bladder cancer, given its ready availability and cost-effectiveness; but it does not accurately determine the depth of tumor invasion into the bladder wall and its ability to detect the invasion to adjacent organs is limited, especially in the prostate, the seminal vesicles, and the bladder base.

Due primarily to the higher resolution provided by the MRI, its use has increased in recent years. On the other hand, the main problem of the use of MRI is its high rate of tumor overstaging. The use of diffusion-weighted magnetic resonance imaging (DW-MRI) shows better results, thus reducing that overstaging.

The overall accuracy of MRI for local staging of bladder cancer is 52–93%, according to the various published series, and the accuracy to differentiate MIBC is set at 75–92%. MRI provides high multiplanar resolution images non-invasively in the soft tissues, without associating high doses of radiation or ionizing nephrotoxic contrast agents, features that are especially important in elderly patients.

For proper bladder tumor staging by MRI, it is necessary to perform weighted sequences both in T1 (T1W) and in T2 (T2W). T1W provides images useful for gross extravesical infiltration and/or presence of nodal disease. The signal intensity (SI) of T1W in bladder tumors is similar to that provided by the healthy bladder muscle. This makes it difficult to achieve a correct differentiation of malignant lesions only in T1W sequences. Moreover, T2W images provide information about the depth of the tumor infiltration and the adjacent tissues. The healthy bladder wall shows in T2W low signal intensity and medium to high intensity in the case of tumor infiltration, making it possible to distinguish MIBC more precisely. The dynamic contrast sequences (MRI-DCE) add information on the injuries evaluated. The works published suggest that T1W, T2W, and MRI-DCE used together achieved a sensitivity, specificity, and accuracy of 95–97%, 55–67%, and 85%, respectively, to differentiate MIBC.

The use of DW-MRI improves the preoperative bladder study, increasing the differentiation ability of healthy and tumor tissues without need for added contrast. DW-MRI images are formed by measuring the quantification of water diffusion in the tissues, restricted in tumor tissues by the high cellularity and the limited extracellular space they present, which results in a relative increase in signal intensity. Patterns highly suggestive of invasion of the subepithelial connective, invasion of the muscularis propria, and perivesical fat invasion (Fig. 3) are established. A characteristic finding of this type of sequences is the 'worm sign' that appears in T1 bladder tumors, and showing a hypointense signal stalk, introduced in the hyperintense bladder tumor signal. This sign shows a PPV close to 100% for the diagnosis of T1 stage tumors, but with low Sp. El-Assmy et al. evaluated the accuracy to distinguish MIBC comparing the results obtained with T2W and DW-MRI, resulting 80% for T2W and 92% for DW-MRI, but with an over-staging of 76

**Figure 2** ROC curves corresponding to the comparison of results obtained in DW-MRI and ADC ratios with respect to: muscle infiltration (A), fatty infiltration (B), and lymph node involvement (C).
and 24.3%, respectively. In no case was there understaging in DW-MRI sequences.

Despite the limitation of a small number of cases, in this study, the diagnosis of muscle-invasive disease improves the data obtained in previous studies. Furthermore, the ADC ratio included in the DW-MRI study represents the degree of molecular water diffusion in the tissue evaluated. This ratio shows a pattern of restricted diffusion of water in biological tissues inversely proportional to the cellularity and integrity of the cell membranes of these tissues.21 Numerous studies show that the lowest values in this ratio correspond to lesions with high cellularity.7,24 In our study, the ADC ratio shows that the lower the values the higher the tumor grade. Since both the ADC and the histologic tumor grade are conditioned by other factors independent of the cell density assessed, this correlation should be considered with limitations. However, the ADC ratio may be useful in the preoperative study of bladder cancer candidate for cystectomy.25

The presence of extravesical disease is one of the most important factors in the evaluation of bladder cancer before cystectomy. Its confirmation entails the need for multimodal therapy with possible adjuvant chemotherapy. Routine CT reveals overall sensitivity of 89% and specificity of 95% in the diagnosis of extravesical disease.25 There are few studies comparing CT and MRI with respect to the ability of extravesical disease diagnosis.14,25 On the other hand, nodal disease is one of the most important prognostic factors that markedly decreases the survival expectancy.28,29 A node size greater than 10 mm in diameter is considered pathologic by consensus. However, the main problems lie in nodal metastases <10 mm and in distinguishing heterogeneous and tumor necrosis patterns.29 Our study has a number of limitations that should be considered. First, the small number of cases evaluated hinders the obtaining of definitive conclusions. Work needs to be done on a larger scale and with longer follow-up to reach definitive conclusions. Another limitation to consider is that not all patients diagnosed with MIBC after TURB are candidates for radical cystectomy. It is essential to consider that the findings related to inflammatory processes after TURB can alter the results of DW-MRI and the ADC values obtained. Finally, the experience of the radiologist can be critical when assessing the results obtained.

In conclusion, our experience confirms that the use of DW-MRI improves preoperative evaluation of the patient candidate for radical cystectomy. This fact is particularly important for the correct prediction of muscle and/or lymph node involvement. In addition, the ADC ratio also predicts the tumor grade of the injury and is useful for assessing the level of parietal invasion and the possibility of nodal involvement.

Conflict of interest

The authors declare that they have no conflict of interest.

References


