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The role of apparent diffusion coefficient values in detecting testicular intraepithelial neoplasia: Preliminary results

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ABSTRACT

Introduction: The aim of this study is to improve detection of testicular intraepithelial neoplasia (TIN) by measurement of apparent diffusion coefficient (ADC) values.
Materials and methods: Fifty-six MRI examinations of the scrotum, including 26 histologically proven testicular germ cell neoplasms were retrospectively evaluated. DWI was performed using a single shot, multi-slice spin-echo planar diffusion pulse sequence and *b*-values of 0 and 900 s mm^{-2}. ADC measurements were classified into three groups according to their location: group 1 ($n = 19$), non-tumoral part, adjacent to testicular carcinoma, where the possible location of TIN was; group 2 ($n = 26$), testicular carcinoma; and group 3 ($n = 60$), normal testicular parenchyma. Analysis of variance (ANOVA) followed by post hoc analysis (Dunnett T3) was used for statistical purposes.
Results: The mean ± s.d. of ADC values ($\times 10^{-3}$ mm^2/s) of different groups were: group 1, 1.08 ± 0.20; group 2, 0.72 ± 0.27; and group 3, 1.11 ± 0.14. ANOVA revealed differences of mean ADC between groups ($F = 38.859$, $P < 0.001$). Post hoc analysis showed differences between groups 2 and 3 ($P < 0.001$), groups 2 and 1 ($P < 0.001$), but not between groups 3 and 1 ($P = 0.87$).
Conclusions: Based on our preliminary results, ADC values do not provide a reliable differentiation between TIN and testicular carcinoma or normal testicular parenchyma.

1. Introduction

Testicular cancer represents between 1% and 1.5% of male neoplasms, but it is the commonest malignancy in men 20–40 years old [1]. Testicular germ cell neoplasms (TGCNs) constitute 90–95% of testicular tumors [1]. Testicular intraepithelial neoplasia (TIN) or intratubular germ cell neoplasia of unclassified type (ITGCNU) is considered the precursor of most TGCNs [2–7]. TIN is found in testicular tissue adjacent to TGCNs in about 90% of cases, and it is observed in all clinical groups known to be at high risk for testicular cancer, including contralateral testis of patients with TGCN, cryptorchidism, infertility and ambiguous genitalia. If TIN is left untreated, there is a 50% probability of progressing to frank TGCN within 5 years and a 70% probability of developing malignancy within 7 years [3–5,7,8].

International guidelines on diagnosis of TIN are inconsistent [4,8,9]. A contralateral testicular biopsy was previously advocated to all patients with TGCN, to prevent the development of bilateral carcinomas [6,8]. Although this was routine policy in some countries, the low incidence of TIN and contralateral metachronous TGCNs (up to 9% and 2.5%, respectively), the morbidity of TIN treatment, and the low stage of most metachronous tumors at presentation arise controversies regarding the recommendation of systematic contralateral surgical biopsy in all patients. According to the guidelines of the European Association of Urology (EAU), biopsy of the contralateral testis is indicated in high-risk patients

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for contralateral TIN, including men younger than 40 years old, men with an atrophic testis, a history of cryptorchidism, or poor spermatogenesis [1].

Surgical testicular biopsy detects TIN with a high rate of accuracy [2–6,8,9]. However, it is an invasive technique, associated with complications and false-negative biopsies [9–12]. A non-invasive method of identifying groups with a high risk of having TIN and therefore reducing the number of men referred for testicular biopsies would be useful. Old studies reported sonographic scanning for the diagnosis of early TGCN and MRI for the detection of TIN [13–17], although their use was not justified.

MRI of the scrotum has been proposed as a supplemental diagnostic tool in the investigation of scrotal pathology, especially recommended in cases of inconclusive sonographic findings [18–21]. The advantages of the technique are simultaneous imaging of both testicles, paratesticular spaces and spermatic cords, acquisition of adequate anatomic information and satisfactory soft tissue characterization. MRI has been proved useful in the differentiation between extratesticular from intratesticular mass lesions, in the preoperative characterization of the histologic nature of various scrotal masses and in the evaluation of the local extent of the disease in cases of testicular carcinomas [18–21].

Diffusion-weighted imaging (DWI), with measurement of the apparent diffusion coefficient (ADC) values is an evolving technique used to improve tissue characterization in MRI [22,23]. The ADC values of malignant neoplasms are reported lower than those of benign lesions or normal tissues and this was also proved for scrotal contents [22–24].

The purpose of this retrospective study was to improve detection of testicular intraepithelial neoplasia (TIN) by measurement of apparent diffusion coefficient (ADC) values.

2. Materials and methods

This was a retrospective study conducted at a single institution and included 26 men with histologically confirmed TGCNs (mean age: 34 years; age range: 19–58 years). Clinical indications were the following: painless scrotal enlargement and/or palpable mass ($n = 21$); testicular pain ($n = 3$); sonographically detected intratesticular mass lesion in an asymptomatic patient ($n = 1$) and sonographically detected hypoechoic testicular mass in a patient with supraclavicular lymphadenopathy ($n = 1$). All patients had radical orchiectomy. The time interval between MRI examinations and surgery was less than two weeks. During the same period, 30 healthy volunteers (mean age: 49 years; age range: 20–53 years) were also included in the analysis. These patients were referred to the urology department for a variety of clinical symptoms, including vague scrotal pain ($n = 20$), painless scrotal enlargement ($n = 7$), follow-up after surgery ($n = 2$, in one case after removal of a large paratesticular hematoma and in another patient for undescended testis) and partial thrombosis of corpus cavernosum ($n = 1$). The standard of reference included clinical and imaging follow-up, mainly sonographically.

Due to the retrospective nature of the study, the institutional review board did not require approval or patient's informed consent for the review of medical histories and MRI data.

All MRI examinations were performed on a 1.5 T Intera scanner (Philips Medical Systems, Cleveland, OH, USA), using a surface coil, a field of view of 240 mm × 270 mm and an acquisition matrix of 180 mm × 256 mm. The patients were examined in supine position, with the testes placed at a similar distance from the coil, by placing a towel beneath them, and the penis draped on the anterior abdominal wall. Transverse spin-echo T1-weighted images (TR/TE, 500–650/13–15 ms), transverse, sagittal and coronal fast spin-echo T2-weighted images (TR/TE, 4000/100–120 ms) were used for data analysis. DWI was performed along the axial plane, during quiet breathing using a single shot, multi-slice, spin-echo planar sequence with the following parameters: TR, 3900 ms; TE, 115 ms; number of signals averaged, 1; motion-probing gradient (MPG), 3; bandwith: 1, 5774 kHz/pixel; no parallel imaging; and water excitation with b-values of 0 and 900 s mm^{-2}. The total acquisition time was 29 s. The orientation and location of these slices were identical to the conventional transverse slices. Images were of 3–4 mm slice thickness, with a 0.5 intersection mm gap.

MRI data were interpreted by two radiologists in consensus (A.C.T., A.N.), both of whom were experienced in the field of urogenital imaging (a senior radiologist, with 9 years of experience and a junior radiologist, with 1 year of experience, respectively). Both reviewers were unaware of the final diagnosis or the histopathologic data. DW images were read in conjunction with the transverse T1 and T2-weighted images. The ADC maps were created on a workstation (Philips Medical Systems, Cleveland, OH, USA). Signal intensity mean ADC values of circular regions of interest (ROIs), defined by one radiologist (A.C.T.) to be as large as possible within the testicular carcinoma were recorded (Fig. 1). Special care was taken to exclude areas of hemorrhage and/or necrosis within the tumor, with the aid of the corresponding transverse T1- and T2-weighted images. Three measurements were obtained and averaged. Three smaller ROIs were placed in the non-tumor part of the testis, adjacent to testicular carcinoma, where the possible location of TIN was (Fig. 1b) and the measurements were averaged. Finally, five ROIs with a mean diameter of 65 mm^2 were placed in the middle of the normal testicular parenchyma and their measurements were averaged (Fig. 2). Care was taken to avoid partial-volume effects and subtraction artifacts. The mean and standard deviation of the ADC values were calculated.

For pathologic examination, tissue sections of testicular specimens were embedded in Bouin's fixative for two hours and then in alcohol 70° for 20 min. After that, specimens were put in labeled cassettes. They were then dehydrated by passing through multiple changes of dehydrating solvents. Tissue sections were cut and stained with the routine stain hematoxylin-eosin. Histologically, TIN consisted of large atypical cells, lining atrophic seminiferous tubules with a thickened basement membrane. These cells had clear cytoplasm, large nuclei and prominent nucleoli. Glycogen was detected in the cytoplasm by the Periodic acid-Schiff (PAS) stain. Positive staining for placental alkaline phosphatase (PLAP) was used to highlight the neoplastic cells (Fig. 1c–e).

The Kolmogorov–Smirnov test was used to assess normality of the data. ADC measurements were classified into three groups according to their location: group 1, non-tumoral part, adjacent to testicular carcinoma, indicating possible location of TIN; group 2, testicular carcinoma; and group 3, normal testicular parenchyma. One-way analysis of variance (ANOVA) was used to find whether mean ADC differs among groups. Post hoc analysis (Dunnett T3) was applied to reveal differences of ADC between groups. Statistical analysis was performed using IBM SPSS version 20.0. Statistical significance was set at P-value's of <0.05.

3. Results

Histologic examination disclosed the presence of 16 seminomas and ten nonseminomatous germ cell neoplasms. The diagnoses are presented in Table 1. Pathology showed the presence of TIN in the testicular tissue adjacent to the tumor in 18 (95%) out of 19 TGCNs. Excluded were seven tumors of large size, replacing almost all testicular parenchyma.

The mean ± s.d. of ADC values ($\times 10^{-3}$ mm^2/s) of testicular parenchyma in the non-tumoral part and the possible location of TIN (group 1, $n = 19$) were 1.08 ± 0.20 (Figs. 1–4). The mean ± s.d.