Use of 3D T2-Weighted MR Sequences for the Assessment of Neurovascular Bundle Changes after Nerve-Sparing Radical Retropubic Prostatectomy (RRP): A Potential Diagnostic Tool for Optimal Management of Erectile Dysfunction after RRP

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ABSTRACT

Introduction. Erectile dysfunction (ED) is one of the complications after radical retropubic prostatectomy (RRP), and recovery of erectile function is quantitatively related to the preservation of the neurovascular bundles (NVBs).
Aim. The aim of our study was to assess, in patients submitted to a nerve-sparing RRP, the capability of a dedicated 3D isotropic magnetic resonance imaging (MRI) T2-weighted sequence in the depiction of postsurgical changes of NVB formation.
Methods. Fifty-three consecutive patients underwent a bilateral nerve-sparing RRP. Two postoperative magnetic resonance (MR) examinations and International Index of Erectile Function Five-Item (IIEF-5) questionnaire were carried out at 6 and 12 months. Morphological imaging of the postprostatectomy fossa was performed by first acquiring turbo spin echo T2-weighted sequences in the axial and coronal planes and then with 3D T2-weighted isotropic sequence on axial plane. Image findings were scored using a relative 5-point classification (0 = normal; I = mild; II = mild to moderate; III = moderate; IV = severe alterations) and correlated with postoperative IIEF-5 score questionnaire.
Main Outcome Measures. The degree of association between the alteration score values obtained by postoperative MR morphologic evaluation for MR sequence and IIEF-5 score.
Results. Image interpretation was performed by two radiologists, that scoring MR alterations by the use of axial and multiplanar reconstruction 3D T2 isotropic sequence. The radiologists placed 43.30% of patients in class 0 (23/53 normal or quite normal), 32.00% in class I (17/53 mild), 11.40% in class II (6/53 mild to moderate), 7.50% in class III (4/53 moderate), and 5.70% in class IV (3/53 severe). In all cases, the correlation and regression analyses between the 3D T2 isotropic sequence and IIEF-5 score, resulted in higher coefficient values (rho = 0.45; $P = 0.0010$).
Conclusion. The MRI protocol and NVB change classification score proposed in this study would represent an additional tool in the postoperative phase of those patients with ED. **Sciarra A, Panebianco V, Salciccia S, Alfarone A, Gentilucci A, Lisi D, Passariello R, and Gentile V. Use of 3D T2-weighted MR sequences for the assessment of neurovascular bundle changes after nerve-sparing radical retropubic prostatectomy (RRP): A potential diagnostic tool for optimal management of erectile dysfunction after RRP. J Sex Med 2009;6:1430–1437.**

Key Words. Sexual Function; Prostate Neoplasm; Radical Prostatectomy

Introduction

Radical retropubic prostatectomy (RRP) is a standard treatment option for localized prostate cancer and provides excellent cancer control [1]. The incidence of prostate cancer has increased steadily in the last decade. This increase has been associated with decreased patients' age at diagnosis, resulting in a greater emphasis by patients on postoperative sexual dysfunction [2].

Erectile dysfunction (ED) is one of the complications after RRP, and recovery of erectile function is quantitatively related to the preservation of the neurovascular bundles (NVBs).

Probability of recovery of erections for satisfactory intercourse after radical prostatectomy is associated inversely with patient age and directly with extent and number of NVBs preserved [3,4]. Quality of preoperative erections should influence the probability of recovery, but this effect is less well documented [5].The determination of organ-confined tumors suitable for nerve-sparing procedures using preoperative nomograms and the simultaneous increase in experience in the surgical technique have led to an increase in nerve-sparing procedures [6]. Despite these improvements, many patients experience postoperative ED.

A nerve-sparing RRP performed in those patients with clearly noticeable bundle formation would have resulted in better erectile function compared with those with NVB anatomical variations. In a recent experience by Takenaka et al. [7], it has been suggested that anatomic variations exist regarding the definite formation of the NVB. If this is true, it is possible that nerve-sparing RRP performed in a traditional way would have resulted in better postoperative erectile function only in patients with definite bundle formation and also, this could be an explanation for the unsatisfactory recovery of erectile function observed after meticulously performed nerve-sparing RRP in some patients.

The introduction of nerve-sparing RRP [8] has improved postoperative results, but there is variation in published rates of preservation of nerves and recovery of erectile function. The discrepancy between the reported preservation of nerves and recovery of erectile function leads to several open questions. What is the mechanism for ED after RRP? Do we truly identify all of the nerves at the time of surgery? As the time course of recovery is consistent with nerve regeneration or repair, can something be done to enhance neural regeneration? Is there arterial injury? What is the benefit of penile rehabilitation after injury that occurs as a result of the surgery? If so, what kind, and when should it be started?

In this context, several diagnostic techniques were actually available for the assessment of post-surgery ED. A multidisciplinary approach was used, including International Index of Erectile Function (IIEF) and Self-rating Depression Scale questionnaires, and instrumental techniques such as polisomnographic recording of nocturnal erections [9–12]. Color doppler sonography is a diagnostic imaging technique usually employed in postoperative nomograms for the assessment of penile hemodynamics [13]. These diagnostic techniques give a probable distinction between vascular or neural lesions using clinical parameters and time of early penile spontaneous erections, but provide no morphologic data regarding NVB postoperative changes [14].

To our knowledge, the usefulness of a specific postoperative magnetic resonance imaging (MRI) protocol, with dedicated sequences, for the assessment of NVB integrity and anatomical course reorganization after nerve-sparing RRP procedure has not been previously evaluated.

For all these reasons, the aim of our study was to assess, in patients submitted to a nerve-sparing RRP, the capability of a dedicated 3D isotropic MRI T2-weighted sequence in the depiction of postsurgical changes in NVB formation, using the same method used for the study of other neurological diseases [15].

Furthermore, our aim was also to correlate a new magnetic resonance (MR) score scale of NVB alteration patterns viewed with postoperative potency modifications using the IIEF Five-Item (IIEF-5) questionnaire findings as the standard of reference [16].

Materials and Methods

This is a prospective single center study. Between January 2006 and January 2008, 53 consecutive patients underwent a bilateral nerve-sparing RRP by the same surgeon at our institution for clinically localized (Tlc-T2, NOMO) prostate adenocarcinoma.

Inclusion criteria for this study were: surgical pathological local stage pT2, negative surgical margins, post-RRP prostate-specific antigen (PSA) level <0.2 ng/mL (Hybritech method at 3, 6, 9, 12 months).

Exclusion criteria were: neoadjuvant hormonal or radiation treatments, and history of preoperative treatment for ED.

All patients completed the IIEF-5 questionnaire before RRP, as proposed by Rosen et al. [16].

No early penile rehabilitation regimens, such as phosphodiesterase type 5 inhibitor (PDE5) after RRP, were administered. Two postoperative MR examinations were carried out at 6 and 12 months after radical prostatectomy. At the same interval, patients' post-RRP potency status was assessed using the IIEF-5 questionnaire. The possible scores for the IIEF-5 range from 1 to 25 (one question has scores of 1–5). According to this

Table 1 Clinical and pathological characteristics of our population (number of cases; mean ± standard deviation [median]; range)

Number of cases	53
Age (years)	65.82 ± 5.43 (67) Range 50–71
pT_2N_0	53
Gleason score ≤7 (3 + 4)	38
Gleason score ≥7 (4 + 3)	15
Preoperative prostate-specific antigen ng/mL	7.48 ± 3.055 (7.05) Range 2.5–14.0
Preoperative score International Index of Erectile Function Five-Item	21.4 ± 2.3 (22) Range 14–25

scale, ED is classified into five categories based on IIEF-5 scores: severe (1–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25). Informed consent was obtained from all patients at the beginning of the study. Clinical and pathological characteristics of our population are reported in Table 1.

MR Imaging

All MRI examinations were performed on a commercially available 1.5-T system (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany; gradient strength 45 mT/m, slew rate 346 T/m/s, rise time 400 micro/s, featuring total imaging matrix-TIM® technology), equipped with surface phased-array (BodyMatrix, Siemens Medical Solutions) and endorectal coil (e-Coil, Medrad, Pittsburgh, PA, USA combined with Endo-Interface, Siemens Medical Solutions). Before MRI, a 20-mg butyl scopolamine (Buscopan, Boehringer Ingelheim, Ingelheim, Germany) was injected to suppress peristalsis. First, localizer images in the sagittal, axial, and coronal planes were obtained to ensure endorectal coil position and to select locations for the transverse images. Morphological imaging of the postprostatectomy fossa was performed, first acquiring turbo spin echo (TSE) T2-weighted (2D T2) sequences in the axial and coronal planes, and then with 3D T2-weighted isotropic sequence (3D T2 ISO) on the axial plane with parameters following: (time repetition: 5.64; echo time: 2.46; time acquisition: 4.30; flip angle: 56°; average: 2, thickness 0.7 × 0.7 × 0.7 mm; section gap: 0, matrix 512 × 512; field of view (FoV) read: 256 mm; FoV phase: 100; phase resolution: 100%, data acquisition time: 7.40 minutes). The choice of sequence parameters has been used to result in a better visualization of the NVB on the axial images. Other routine sequences, including 1H-spectroscopic analysis and dynamic contrast-enhanced imaging (during intravenous bolus injection of 0.1 mmol/kg of gadopentetate dimeglumine [Multihance, Bracco Spa, Milano, Italy]) on prostatic fossa, were performed sequentially in order to exclude post-RRP local cancer relapse [17]. The imaging protocol was generally completed in 40–45 minutes (mean 11 minutes for only morphologic sequences). Postprocessing phase was carried out on commercially available PACS software (Leonardo, Siemens Medical Solutions). Regarding 3D images, the readers initially determined if the NVBs were visible on at least one of the axial 3D sequences and if their signal intensity was normal (iso-hypointense) or hyperintense comparing two regions of interest (ROI) values respectively placed on NVBs and pelvic muscles. Then two coronal prostatic fossa multiplanar reconstructions (MPRs, left and right side) were performed for each NVBs' anatomical course evaluation. The reading time necessary for the postprocessing of the 3D MPR reconstruction required approximately 10 minutes per patient.

Imaging Interpretation and Data Analysis

Image interpretation sessions were retrospectively performed in two steps after the second MR protocol execution (12 months) by two radiologists (V. Panebianco and D. Lisi with 7 and 3 years' experience in prostate MR), who were unaware of the preoperative and postoperative clinical and ED status of the patients. The two readers independently interpreted 3D T2 ISO (axial and MPR) without no meaningful inter-observer variability. As previously described, they were asked to establish anatomical NVB course integrity and high signal intensity level (comparing an ROI placed on NVB with another ROI on the pelvic muscle) for each NVB using a relative 5-point classification. According to this scale, NVB chances are classified into five classes (Table 2).

In the classification, each category is scored on a point scale where higher values represent a higher grade of NVB alteration on MR images. These points were assigned on the basis of anatomical course delineation for each or both NVB, adding 0 points for low signal and 1 point when ROI analysis revealed higher NVB signal intensity.

Statistical Analysis

The degree of association between the alteration score values obtained by postoperative MR morphologic evaluation for MR sequence and IIEF-5

Table 2 Score to classify neurovascular bundle (NVB) changes in signal intensity and anatomical integrity after a bilateral nerve-sparing radical retropubic prostatectomy. In the classification, each category is scored on a point scale where higher values represent a higher grade of NVB alteration on magnetic resonance images. These points were assigned on the basis of anatomical course delineation for each or both NVBs, adding 0 points for low signal and 1 point when region of interest analysis revealed higher NVB signal intensity (when the NVB was identifiable on 3D-T2-ISO images)

0	Normal or quite (nearly) normal (0 to 2 points range): entire NVB anatomical course bilaterally evaluable (point = 0) ± high signal on T2w (point = 0 or 1 for each NVB)
I	Mild (3 to 5-point range): NVB anatomical course unilaterally partially evaluable (points = 3) ± high signal on T2w (points = 0 or 1) ± normal or quite normal controlateral NVB (0 or 1 points for high signal intensity)
II	Mild to moderate (6- to 8-point range): NVB anatomical course bilaterally partially evaluable (points = 6) ± high signal on T2w (points = 0 or 1 for each NVB)
III	Moderate (9 to 13 points range): NVB anatomical course unilaterally never evaluable, probable resection (points = 9) + 0 points for controlateral NVB entire anatomical course evaluable or 3 points for controlateral NVB anatomical course partially evaluable ± high signal on T2w (points = 0 or 1 for controlateral NVB)
IV	Severe: NVB anatomical course bilaterally never evaluable, probable resection (points = 14)

score was calculated using a rank correlation analysis with a Spearman correlation rho and Kendall's tau coefficient (*P* value and 95% confidence interval [CI] [with adjustment because of multiple observations per patient]). A correlation of +1 means that there is a perfect positive linear relationship between variables, while a correlation of –1 means that there is a perfect negative linear relationship between variables. A correlation of 0 means there is no linear relationship between the two variables. At the end, in order to find a further statistical validation of our MRI score, a Student's *t*-test was performed between preoperative and postoperative IIEF-5 values at 6 and 12 months (Table 3). For all statistical tests, a *P* value of less than 0.05 was considered significant.

Results

Forty-eight of the total 53 patients included in this study had normal potency preoperatively (five patients with 14–16 points), with a mean IIEF-5 score of 21.40 (95%CI for the mean = 20.7184 to 22.1872). At 6- and 12-month intervals between MRI and radical prostatectomy, the mean IIEF-5 score was 15.36, respectively (95%CI for the mean = 12.8421 to 16.4409), with a mean difference of –6.80 and statistical t of –7.59 ($P < 0.0001$; standard deviation [SD] 6.50; 95%CI –8.60 to –5.0) compared with preoperative values. The data showed a constant decrease in IIEF-5 that demonstrates a reduction in erectile function in all post-RRP patients (Figure 1). A further *t*-test between the two test scores obtained at 6 and 12 months after RRP was also carried out in order to exclude a statistical bias, and no meaningful differences were observed (mean difference: –0.3774; SD: 1.0782; 95%CI: –0.6746 to –0.0802; $t = -2.548$; $P = 0.0138$). Both radiologists, without meaningful inter-observer variability, scored MR alterations by the use of axial and MPR 3D T2 ISO images; the radiologists placed 43.3% of patients in class 0 (23/53 normal or quite normal), 32.0% in class I (17/53 mild), 11.40% in class II (6/53 mild to moderate), 7.50% in class III (4/53 moderate), and 5.70% in class IV (3/53 severe) (Table 1). The Spearman's rho coefficient among 3D T2 ISO and IIEF-5 scores was 0.457 ($P = 0.0010$; 95%CI = 0.213 to 0.647), while Kendall's tau coefficient resulted in 0.382 ($P = 0.0001$; 95%CI = 0.141 to 0.582) for 3D T2 ISO. The regression analysis of these data showed respectively a coefficient of determination R^2 of 0.2929 (slope coefficient 0.4792, SD 0.1043, $P < 0.0001$) for 3D T2 ISO images.

Discussion

A radical prostatectomy has been established as one of the standard management options for local-

Table 3 Magnetic resonance imaging (MRI) categories at 6- and 12-month intervals

	MRI category				
	0	1	2	3	4
Number of cases in 6 months (%)	23/53 (43.3)	17/53 (32)	6/53 (11.4)	4/53 (7.5)	3/53 (5.7)
Mean IIEF-5 score	16.95	15.88	14.17	5.0	1.33
Number of cases in 12 months (%)	27/53 (50.9)	14/53 (26.4)	5/53 (9.4)	4/53 (7.5)	3/53 (5.6)
Mean IIEF-5	16.35	16.0	14.0	5.25	1.0

IIEF-5 = International Index of Erectile Function Five-Item.

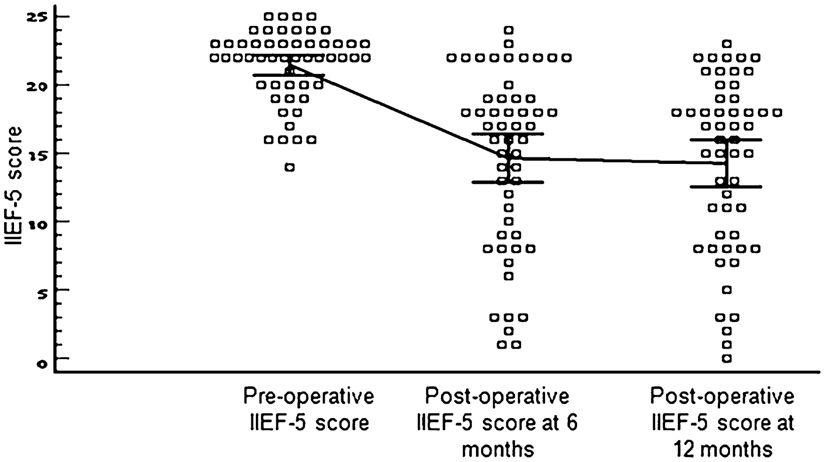

Figure 1 Chart with all International Index of Erectile Function Five-Item (IIEF-5) data points plotted for preoperative and postoperative (6 and 12 months) evaluations. Error bars represent a 95% confidence interval and a line connecting the mean of the three-time IIEF-5 score reported. The data demonstrate a constant decrease in patients' potency immediately after radical retropubic prostatectomy. At 6- and 12-month interviews, IIEF-5 scores did not reveal meaningful changes in erectile dysfunction status.

ized prostate cancer [18]. Despite recent improvements in detection and treatment, prostate cancer continues to be the most common malignancy and the third leading cause of cancer-related mortality in American men. The American Cancer Society estimated that in 2007, 218,890 new cases of prostate cancer would be diagnosed and approximately 27,050 men would die of the disease in the United States [19]. The face of prostate cancer is changing. The widespread use of PSA screening has led to diagnosis in younger age groups and a downstaging of prostate cancer [20]. Because men are being treated at a younger age, the long-term consequences of specific therapies merit increased consideration, as men may have to live with them for 20–30 years [21]. For these reasons, the thrust of cancer care in the new millennium is a risk-adjusted, patient-specific therapy designed to maximize cancer control while minimizing the risk of complications. If this is not possible, we must try to achieve optimal management of these complications. ED is a significant complication of RRP [22], in particular for patients who were sexually active before surgery. At this time, there is no consensus on the optimal management of ED after RRP. Although the clinical management of ED has been the subject of recent guidelines [23–25], no guideline has yet considered the specific case of RRP patients and this may partly be because of the fact that the diagnostic techniques currently available such as the color doppler sonography or polisomnographic recording of nocturnal erections provide no morphologic data regarding NVB postoperative changes. In the present study, the results obtained by the correlation analysis between MRI and IIEF-5 reveal a positive association between MRI changes and IIEF score. The availability of a morphologic assessment of NVB injuries and the possibility to discriminate cavernous artery hemodynamic changes from isolated cavernosal nerve modifications (comparing both Doppler and our MRI protocol results) may lead to an appropriate choice of pharmacotherapy for optimal recovery of erectile function after an RRP procedure. At present, PDE-5 inhibitor for vascular lesions [26,27] or new neurotrophic and neuroprotective agents for nerve alterations [28,29], or a combination of both, may be considered on the basis of the imaging and MRI classification score reported here. Our report proposes for the first time in the literature an MRI score to classify NVB changes in signal intensity and anatomical integrity after a bilateral nerve-sparing RRP. The choice of these two morphologic aspects reflects the end points of some authors that considered the probability of recovery of erections after RRP to be directly related with the extent and number of NVBs anatomical preservation and others that believe that although the cavernosal nerves are spared, the nerves are usually injured by direct trauma or by stretching during a nerve-sparing RRP. We believe that high signal intensity and bulging of NVBs on MR T2-weighted images may demonstrate earlier internervous fiber fluid (edema) because of blunt injuries to the cavernosal nerves; this may be considered as a recognizable morphological sign of "neuropraxia." For example, a patient with ED and clear noticeable mono or bilateral NVB on MRI after RRP (Figure 2) will probably benefit from a rehabilitation therapy with PDE-5 inhibitor. On the contrary, in a patient with moderate to severe alterations of NVB on MRI after RRP (Figure 3), the therapy with PDE-5 inhibitor may be ineffec-

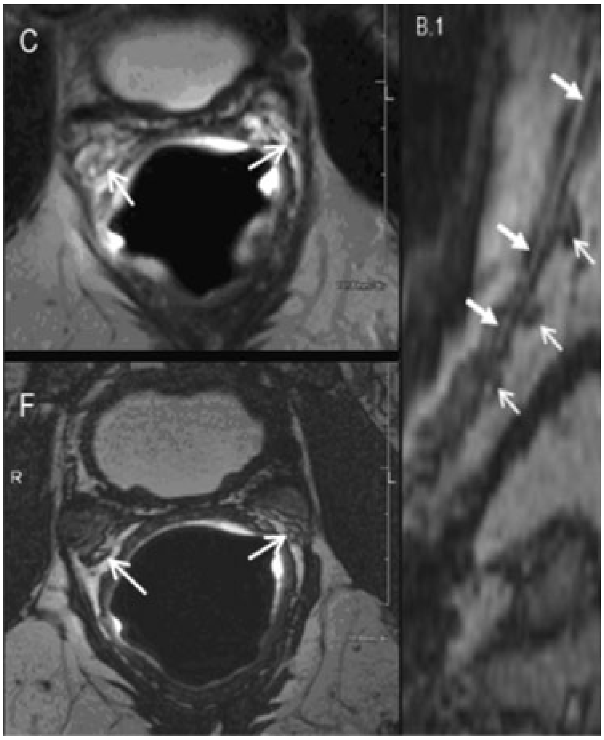

Figure 2 A 64-year-old man after radical retropubic prostatectomy (preoperative International Index of Erectile Function Five-Item [IIEF-5]: 22 points; postoperative IIEF-5 at 6 months: 8 points; postoperative IIEF-5 at 12 months: 9 points). C and F = axial sections at 6 months (C) and 12 months (F) after surgery obtained by 3D T2-weighted isotropic image at the level of prostatic fossa. The arrows indicate neurovascular bundle (NVB) location. Radiologists assessed bilateral low signal intensity on left and right NVBs at both times of examination. B.1 = left side coronal multiplanar reconstructions obtained by axial 3D sequence (6-month evaluation); NVB anatomical course is evaluable (arrows). NVB delineation results in good appearance (arrows). After evaluating this image, the radiologists assessed this patient as class 0 under the MRI classification score.

tive and inappropriate. Moreover, we believe that NVB evaluation can be performed in the preoperative phase of a nerve-sparing RRP in order to assess the NVB anatomical course, or after penile rehabilitation regimens in order to assess therapeutic improvements [30]. These could be two aspects for a future research in this field. In this first study, MRI of NVB was performed after RRP without the use of pharmacological rehabilitation to be directly related to surgical changes. In the future, we will try to analyze NVB changes during pharmacological rehabilitation, using the same study.

Some limitations of our study must be underlined. In this study, we perform MRI at 6 and 12 months after RRP whereas we have no data at earlier follow-up from RRP. In the design of the study, we used this timing for MRI to reduce the possibility that results were altered by processes of healing, swelling or bleeding, secondary to surgery. The aim of this study was not to outclass standard diagnostic procedures such as IIEF-5 that remain easy to manage, but rather to demonstrate that therapeutic benefit for patients with postoperative ED may be found in a correlation between clinical and morphologic MRI assessment, especially if PDE5 inhibitor and neurotrophic therapies continue to show promising results. Another limitation of our study is the lack of control group.

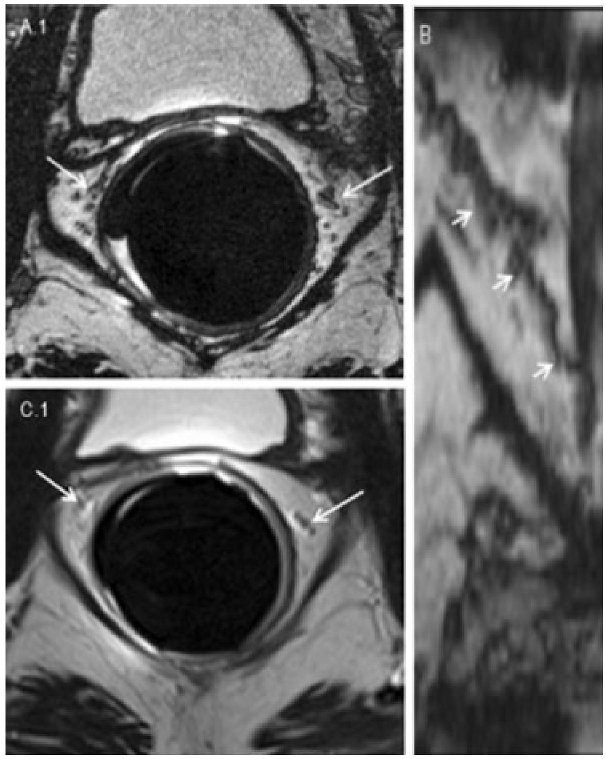

Figure 3 A 61-year-old man after radical retropubic prostatectomy (preoperative International Index of Erectile Function Five-Item [IIEF-5]: 21 points; postoperative IIEF-5 at 6 months: 5 points; postoperative IIEF-5 at 12 months: 6 points). A.1 and C.1 = axial sections at 6 months (A.1) and 12 months (C.1) after surgery obtained by 3D T2-weighted isotropic image at the level of prostatic fossa. The arrows indicate neurovascular bundles' (NVBs) location. Radiologists assessed bilateral high signal intensity on left and right NVBs. B = right side; coronal multiplanar reconstructions obtained by axial 3D sequence (12-month evaluation). Note that NVB on B image seems to be bulging and with an irregular course, according to interfiber fluid (edema). After evaluating this image, the radiologists assessed this patient as class III under the MRI classification score.

Conclusions

In conclusion, the imaging protocol and the NVB change classification score proposed in this study would provide an additional diagnostic tool in the postoperative phase of those patients with ED. The availability of a morphologic assessment of NVB injuries and the possibility to discriminate cavernous artery hemodynamic changes from isolated cavernosal nerve modifications (comparing both Doppler and our MRI protocol results) may lead to an appropriate choice of pharmacotherapy for optimal recovery of erectile function after an RRP procedure, especially if new PDE5 inhibitor and neurotrophic therapies continue to show promising results.

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