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ORIGINAL PAPER

Erectile dysfunction following hydrogel injection and hypofractionated radiotherapy for prostate cancer: Our experience in 56 cases

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Summary ***Introduction: The incidence of erectile dysfunction (ED) in men with organ-confined prostate cancer (PCa) submitted to hypofractionated radiotherapy (HRT) has been prospectively evaluated.***
Materials and methods: From April 2018 to September 2020, 56 patients (median age 70 years) with cT1c PCa were treated by HRT directed to the prostate and seminal vesicle. Median PSA was 8.3 ng/ml; 20 patients (35.7%) vs. 28 (50%) vs. 8 (22.3%) had a PCa Grade Group 1 vs. 2 vs. 3, respectively. All patients underwent hydrogel injection of Space OAR and intraprostatic fiducials before HRT. The prescription dose was 60 Gy in 20 fractions 5 days/week over 4 weeks. During the follow up, PSA, genitourinary (GU) and gastrointestinal (GI) toxicities were evaluated. The sexual function was evaluated by International Index of Erectile Function - 5 (IIEF-5) before, 6 and 18 months from HRT; 32/56 (57.1%) men referred a normal sexual activity before HRT (median IIEF-5 score: 22).
Results: Median PSA level at median follow up of 18 months was 0.92 ng/ml and none used adjuvant therapy. One man (1.8%) referred a tardive grade 1 GU complication. At a median follow up of 6 and 18 months, 20/32 (62.5%) kept pretreatment sexual potency (median IIEF-5 score: 21). The 12/32 men who worsened the sexual function following HRT had a median age higher than patients without ED (78 vs. 67 years).
Conclusions: The use of hydrogel injection and intraprostatic fiducials followed by HRT allowed to kept pretreatment sexual potency in 62.5% of the cases.

KEY WORDS: Prostate cancer; Erectile dysfunction; Hypofractionated radiotherapy; Intraprostatic fiducials; Hydrogel injection.

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INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed male malignancy and radical prostatectomy or *external radiotherapy* (RT) are currently recommended as definitive treatment alone or combination in men with a life expectancy greater than 10 years. Radiation damage to neural and vascular tissue, such as the *neurovascular bundles* (NVBs) and *internal pudendal arteries* (IPAs), during radiotherapy for PCa may cause *erectile dysfunction* (ED). The advances in physics, engineering and imaging have been channeled into the development of image-guided intensity-modulated radiotherapy that has shown that increasing dose improves biochemical disease-free survival with acceptable acute and long-term complications (1, 2). Recently, injection of a hydrogel spacer (*Space OAR*) between the rectum and the prostate and the use of intraprostatic fiducials have been suggested to reduce rectal toxicity and improve selective prostate radiation therapy (3-8) resulting particularly useful in men candidate to *hypofractionated radiotherapy* (HRT) (9-11). In this study, the incidence of ED in men with organ-confined PCa submitted to HRT has been prospectively evaluated.

MATERIALS AND METHODS

From April 2018 to September 2020, 56 patients (median age 70 years; range = 58-82) with organ-confined PCa (cT1c stage) were treated by HRT directed to the prostate and seminal vesicle. All the patients were previously submitted to multiparametric magnetic resonance imaging (mpMRI) (13) and transperineal prostate biopsy (14-15). The median PSA was 8.3 ng/ml (range = 4.5-23.1); 20 patients (35.7%) were at low risk (Grade Group 1/Gleason score 6), 28 (50%) at favorable intermediate risk (Grade Group 2/Gleason score 3 + 4) and only 8 (22.3%) at unfavorable intermediate risk (Grade Group 3/Gleason score 4 + 3) (6); moreover, all patients were without evidence of disease spread to the lymph nodes or the bones.
All patients were selected for a hydrogel injection Space OAR before HRT. The injection of hydrogel was performed under sedation by transrectal ultrasound guidance, furthermore, three gold fiducials were inserted transperineally at the prostate base and mid-gland (8). Patients were simulated 2 weeks after placement; CT simulation was obtained at 3 mm slice thickness using an immobilization device, extending from L1 to below the ischial tuberosities. CT-MRI image registration was accomplished using the MIM-software (*Maestro, version 7.0.5, MIM Software Inc., Cleveland, OH, USA*). The whole prostate and seminal vesicle were delineated as the *clinical target volume* (CTV). Non-uniform *planning target volume* (PTV) was defined by adding margins to CTV; the margin was 8 mm in the anterior, lateral, superior and inferior directions, while it was 4 mm in the posterior direction. The rectum, urinary bladder, bowel, femoral

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heads and penile bulb were contoured as organs at risk. The rectum was delineated from the rectosigmoid flexure to the anus; the treatment planning system was *Monaco-Elekta* (*Elekta AB, Stockholm, Sweden*). The prescription dose was 60 Gy in 20 fractions 5 days/week over 4 weeks, the CTV was planned to receive at least 100% of the prescription dose and the PTV at least 95% with maximum dose at CTV < 110% of the prescription dose. Dose-volume constraints were: dose given to 30% of rectal volume < 46 Gy, dose given to 50% of rectal volume < 37 Gy, dose given to 30% urinary bladder volume < 46 Gy, dose given to 30% urinary bladder volume < 37 Gy, dose given to 5% left/right femoral head volume < 43 Gy. Patients were treated with *volumetric modulated arc therapy* (VMAT) using the LINAC Sinergy Elekta and pretreatment verification of the prostate was conducted using a kilovoltage cone-beam CT during each treatment session. Patients were followed every 3 months for 2 years, and thereafter every 6 months. PSA relapse was determined according to the Phoenix consensus definition (nadir PSA value plus 2 ng/ml). *Genitourinary* (GU) and *gastrointestinal* (GI) toxicities were evaluated following RTOG/EORT score. Acute toxicity was defined as that occurred within 3 months after the initiation of radiotherapy, while late toxicity was observed after 3 months. The sexual function was evaluated by *International Index of Erectile Function-5* (IIEF-5) (12) before (baseline), 6 and 18 months from HRT. None of the patients used 5-phosphodiesterase inhibitors or prostaglandins to improve sexual activity.

The median prostate volume was 69.4 cm^2; clinical (comorbidities, drug therapy) and laboratory data collected before prostate biopsy are reported in Table 1. Thirty-two (57.1%) men referred a normal sexual activity before HRT (median IIEF-5 score: 22; range 20-25) and among them 12 (37.5%) *vs.* 18 (56.2%) *vs.* 2 (6.3%) men had a PCA Grade Group equal to 1 *vs.* 2 *vs.* 3, respectively.

Table 1.
Clinical findings and drugs therapy in the 56 patients submitted to hypofractionated radiotherapy.

Clinical findings Median age (years)	No (%) of patients 70 (range: 58-82)
PSA 4.1-10 ng/mL	43
PSA > 10 ng/mL	13
Abnormal DRE	-
LUTS	42
Q_{max}	12
IPSS (median)	11 (4-29)
Comorbidities:	35
Diabetes mellitus	9
Hypertension	23
Gastritis	12
Cardiovascular ischemic disease	6
Other	9
Drug therapy (overall):	495 (88.3)
Oral hypoglycemic	6
Antihypertensive	25
Antiplatelet agents	34
Diuretic	10
Proton pomp inhibitor	23
Alfa-blockers	50
Other	15

DRE: digital rectal examination; LUTS: lower urinary tract symptoms; IPSS: international prostate symptoms score.

Table 2.
International Index Erectile Function (IIEF-5) in 56 patients before (baseline) and after 6 and 18 months from hypofractionated radiotherapy.

IEFF-5 (score: 5-25) median age: 70 years	Baseline (%)	6 months (%)	18 months (%)
Absence of erectile dysfunction (ED) (22-25) median age: 67 years	32 (57.1)	20 (62.5)	20 (62.5)
Mild ED (17-21) median age: 72 years	4 (7.1)	3 (5.3)	2 (3.5)
Mild-moderate ED (12-16) median age	4 (7.1)	5 (8.9)	5 (8.9)
Moderate ED (8-11) median age: 76 years	4 (7.1)	3 (5.3)	2 (3.5)
Severe ED (5-7) median age: 78 years	12 (21.5)	13 (23.2)	14 (25)

Results

All patients tolerated well the injection of Space OAR plus intraprostatic fiducials and completed the HRT treatment. Median PSA level at median follow up of 18 months was 0.92 ng/ml (range: 0.01-3.6 ng/ml) and none used adjuvant therapy. Only one man (1.8%) referred a tardive grade 1 GU complication, the remain 55 (98.2%) had no tardive side effects.

Among the 32/56 (57.1%) men who had a normal sexual activity before HRT (median IIEF-5 score: 22; range 20-25), at a median follow up of 6 and 18 months, 20/32 (62.5%) kept pretreatment sexual potency (median IIEF-5 score: 21; range = 19-25) (Table 2). The 12/32 men who worsened the sexual function following HRT had a median age higher than patients without DE (78 *vs.* 67 years).

Discussion

However the advent of modern technology using advanced prostate targeting and penile-bulb sparing techniques, ED is a prevalent side effect of PCa treatment; *Hunt et al.* (16) in a recent systematic review of the literature reported in 2,714 patients at 2-year follow-up a median increase of ED equal to 17%, 26%, 23%, and 23%, in men who underwent three-dimensional conformal radiation therapy, intensity-modulated radiotherapy, low dose rate of brachytherapy, and stereotactic body radiation therapy, respectively. *Goy et al.* (17) reported in 1,503 men with intermediate risk PCa who underwent radical prostatectomy *vs.* external radiotherapy *vs.* brachytherapy a prevalence of ED at 10 years of follow up equal to 24.3%, 6.6%, 8.2%, respectively; in addition, ED was not significantly different in men submitted to standard dose radiation therapy (38.1%) *vs.* dose escalated radiation therapy (49.7%) (18). Recently, the introduction in clinical practice of the so-called precision medicin

decreased the risk of complications; in fact, neurovascular-sparing magnetic resonance-guided adaptive radiotherapy seems to reduce the risk of ED following external radiotherapy (19). At the same time, CT-MRI image registration using dedicated software, the use of intraprostatic fiducials and hydrogel spacer could help to better focalize radiation therapy into the prostate; therefore, these devices used before radiotherapy could better preserve neurovascular bundle reducing the risk of ED.

In our series, to our knowledge the first that evaluated ED following HRT in men submitted hydrogel spacer and intraprostatic fiducials injection, we reported among 32/56 (57.1%) men who had a normal sexual activity before HRT, at a median follow up 18 months, a restored pretreatment sexual potency in 20/32 (62.5%) (median IIEF-5 score: 21; range = 19-25). In addition, the 12/32 men who worsened the sexual function following HRT had a median age higher than patients without DE (78 *vs.* 67 years).

Regarding our results some considerations should be done. Firstly, the true sexual activity of the couple administering a sexual questionnaire to the partners was not investigated. Secondly, in the absence of a control group we don't know if the onset of ED was really given by HRT; at the same time, the role of hydrogel injection in preventing ED in comparison with HRT alone can not be established.

Finally, a greater number of patients should be evaluated.

In conclusion, in our preliminary experience, the use of hydrogel injection and intraprostatic fiducials followed by HRT allowed to kept pretreatment sexual potency in 62.5% of the cases.

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