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New Onset of Erectile Dysfunction in a Cohort of Patients Enrolled in Active Surveillance for Low Risk Prostate Cancer: A Preliminary Study to Evaluate Incidence and Prognostic Factors

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Abstract

Objective: Active Surveillance (AS) is a viable alternative to surgery or radiotherapy dedicated to selected patients suffering from low-risk prostate cancer. Aim of the study was to evaluate the onset of Erectile Dysfunction (ED) in patients underwent to AS option and identify potential factors associated to the onset of ED.

Methods: From January 2011 to May 2014 were prospectively assessed patients included in AS; we evaluated baseline comorbidity including Diabetes, Hypertension, Body Mass Index (BMI), International Prostate Symptoms Score (IPSS) and International Index of Erectile Function-5 (IIEF-5) score. Were excluded from the assessment patients with baseline ED, defined as an IIEF-5 score < 22 and patient with follow-up less than 24 months.

Results: Among the 28 patients underwent to AS aged between 48 and 67 years who meet the selection criteria, 16 (57%) developed new onset of ED with different degrees. At multivariate analysis, no comorbidity were statistically associated to ED even thought a correlation with the onset of E.D. and BMI, Diabetes, Hypertension and age were founded.

Conclusions: AS is associated to a high occurrence of ED; among the comorbidities, BMI, Diabetes and Hypertension showed a correlation to a new onset of ED; additional studies are needed to confirm this hypothesis.

Keywords: Active surveilllance; Erectile dysfunction; Prostate biopsy; Prostatic neoplasm

Abbreviations:

AS: Active Surveillance; ED: Erectile Dysfunction; BMI: Body Mass Index; PCa: Prostate Cancer; IPSS: International Prostate Symptoms Score; IIEF-5: International Index of Erectile Function-5 questions; PSA: Prostate Specific Antigen; LUTS: Lower Urinary Tract Symptoms; TRUS: Trans-Rectal Ultrasound

Introduction

After serum Prostate Specific Antigen (PSA) concentration was introduced as a screening test in prostate disease, prostate cancer has been increasingly detected at an early stage and grade [1]. PSA test leads to Prostate Cancer (PCa) over diagnosis and overtreatment [2].

To overcome overtreatment, low risk PCa patients are enrolled in AS in order to prevent overtreatment, delaying curative treatment according to neoplasm progression. The AS protocols were approved to delay radical treatment and spare treatment; however AS can influence quality of life related to health defined as "a physical, mental, and social well-being and not merely the absence of disease" [3]. In fact AS consists in repeating rectal examination, serial PSA evaluations and yearly repeated biopsies, that may be associated with side effects: haematuria, haemospermia, infection, [4-6], anxiety and Erectile Dysfunction (ED) [6].

Few data with conflicting opinions [7-9] have been reported in literature about the prevalence of ED in men under AS and about its correlations with comorbidity; aim of our study is to evaluate this evenience in our experience and to determine the variables that promote the onset of ED.

Methods

We prospectively evaluated patients enrolled in AS from January 2011 to May 2014. Exclusion Criteria was the preexistence of ED before the enrollment for AS, defined as International Index of Erectile Function - 5 questions (IIEF-5) score < 22, and patients with follow-up less than 24 months.

Once registrated in the study, we assessed the comorbidity, and among them Diabetes, Hypertension and Body Mass Index (BMI) and the presence of Lower Urinary Tract Symptoms (LUTS) before starting AS, valued with International Prostate Symptoms Score (IPSS), in order to find variables related to an higher risk of ED.

Every 12 months, for at least 24 months, were performed semi-structured interviews as follow-up. The questions regards the bother caused by the Trans-Rectal UltraSound (TRUS) guided prostate biopsy, the anxiety determined by the diagnosis of the disease, the loss of a regular sex life.

Regarding the procedure, TRUS guided biopsies were repeated every 12 months; number of cores varied from 12 to 22; every procedure was performed after local anesthesia, was done with a TruCut 18G needle, with the standard random technique [6].

The statistical analysis was led with Stata® 11.0; were performed a multivariate analysis in order to evaluate the presence of variables influencing the onset of ED. The variable Age was dichotomized into two groups 48-58 and 59-67 years.

The presence or absence of Diabetes and Hypertension was evaluated as dichotomous variable while the IPSS score pre A.S. and BMI were assessed as continuous variables. In multivariate analysis statistical significance was tested by t test; a p value < 0.05 was considered statistically significant; then were assessed a correlation table to complete the variables description.

Results

From January 2011 to May 2014, 28 patients aged between 48 and 67 years with diagnosis of low-risk Pca enrolled in AS met the selection criteria of the study; among them, after 24 months-follow up including 2 biopsies, 16 patients (57%) developed ED of different degrees, as showed in figure 1, absent at the time of enrollment.
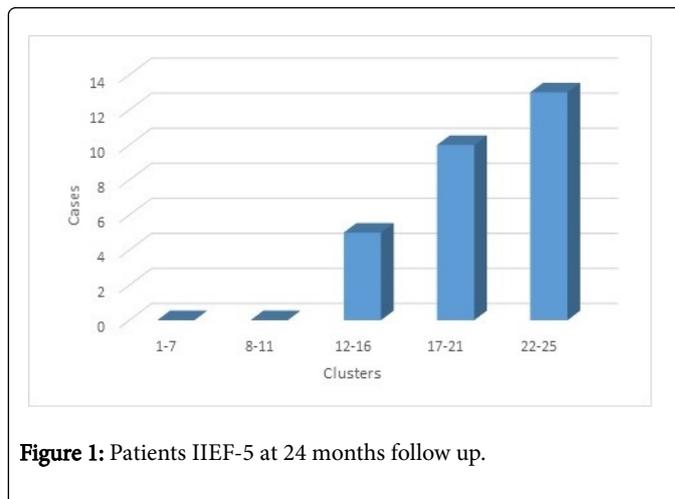

Figure 1: Patients IIEF-5 at 24 months follow up.

Table 1 reported IIEF-5 survey and the ED categories subdivided by IIEF-5 score.

Patients reported several conditions responsible of the onset of ED: we divided these causes into two categories, depending on the cause, in organic and psychogenic ED.

IIEF-5 Score	Erectile Function
25-22	Normal sexual activity
21-17	Mild ed
16-12	Mild to moderate ed
8-Nov	Moderate ed
1-Jul	Severe ed

Table 1: IIEF-5 survey and the ED categories subdivided by IIEF-5 score.

Among the first category, the main cause is revealed to be the bother caused by the repeated prostate biopsies, defined as an ED onset within 30 days after biopsy; on the other hand, the anxiety determined by the diagnosis of a prostate neoplasm, the loss of a normal sexual life, sometimes caused by the inadequate compliance of the partner, as stressed by the semi - structured interviews, resulted important causes of psychogenic ED.

At multivariate analysis, summarized in Table 2, strongly influenced by the low sample size, no comorbidity were statistically associated to ED even thought a correlation with the onset of ED and BMI, diabetes, hypertension and age were founded, as reported in Table 3. Prospective study with a larger cohort of patients is needed to verify our outcomes in term of incidence of ED and on variables related to its development.

Source	SS	df	MS			
Model	92.09656	5	18.41931	Number of obs = 28		
Residual	165.7606	22	7.534572	F(5,22) = 2.44		
Total	257.8571	27	9.550265	Prob > F = 0.0661		
				R-squared = 0.3572		
				Adj R-squared = 0.2111		
				Root MSE = 2.7449		
IIEF524 months	**Coef.**	**Std. Err.**	**t**	**p > |t|**	**[95% Conf. Interval]**	
IPSS pre	-0.27768	0.154079	-1.8	0.085	-0.59722	0.041864

Diabetes	-0.06646	1.828695	-0.04	0.971	-3.85894	3.726022
Ipertension	-1.42129	1.446301	-0.98	0.336	-4.42073	1.578156
BMI	-0.0403	0.280661	-0.14	0.887	-0.62236	0.541751
age_class_59_67	0.438526	1.565686	0.28	0.782	-2.80851	3.685559
_cons	23.63171	6.919747	3.42	0.002	9.281036	37.98239

Table 2: Multivariate analysis of features influencing onset of E.D.

Discussion

In literature, longitudinal studies on ED in men with PCa who underwent AS are few. In addition, there are no clear correlations between the onset of ED and specific demographics, clinical characteristics, and psychosocial parameters of patients. According to our work, however, the literature provides some examples of how the AS is not without consequences on male sexual function.

A recent study comprising 427 men on AS examine the impact of PB on erectile function. Median follow-up was 3.2 years from PCa diagnosis, 69% of patients had one prior biopsy, 16% had two biopsies, and the remainder had three or more. This study examined the association between PB and erectile function between men and longitudinally in the same patients. Neither erectile function nor sexual activity status was associated with number of PBs [10].

	IIEF524 Months	IPSS PRE	Diabetes	Ipertension	BMI	Age (59-67)
IIEF524 Months	1					
IPSS PRE	-0.5704	1				
Diabetes	-0.2365	0.3485	1			
Ipertension	-0.4213	0.4752	0.3333	1		
BMI	-0.4131	0.6647	0.2733	0.4229	1	
Age (59-67)	-0.4077	0.7128	0.3	0.5	0.5693	1

Table 3: Correlation table between features influencing onset of E.D.

In a longitudinal work of Sahane M. Pearce et al. [11] were evaluated 195 patients during the first 24 months of active surveillance, highlighting a decline in sexual function. Men experienced decreased sexual function and a decline in PCa anxiety over the first 24 months of enrollment on an AS protocol. Older age, time on AS, and diabetes were all associated with declining sexual function over time. Increased baseline PSA was associated with a more rapid decline in sexual function as well. Anxiety, other comorbid conditions, the number of cores, and the number of biopsies were not associated with declining sexual function in their study. Sexual function in men undergoing AS is multifactorial and is influenced by many factors including age, aging over time and comorbid conditions rather than increased biopsy exposure [11].

In an other study Fujita et al. [12] evaluated the erectile function of 152 men on an AS protocol with a mean follow-up of 3.2 years and mean number of biopsies of 2.3, they found that only the number of biopsies was independently associated with ED. Multivariable analysis also indicated that age, prostate volume and PSA had no association with ED; however, this study did not analyze the impact of ED-related comorbidities in their multivariable analysis. It must be noted that men who underwent more prostate biopsies were on AS longer; therefore, the observed reductions in erectile function must be interpreted with caution as it is well established that erectile function declines over time in men [12].

Braun et al. [7] performed a retrospective review of 342 patients enrolled on an AS protocol between 2000 and 2011. At each clinic visit, patients were asked to complete the Prostate Health-Related Quality of Life (PHRQoL), which includes six questions about erectile function similar to the International Index of Erectile Function (IIEF). The median age in this cohort was 64 years, median number of biopsies was 5, and the median follow-up was 3.5 years. During the first 4 years of AS, erectile function decreased by 1.0 point per year, and similar declines were seen when stratified by number of biopsies. Because their AS protocol mandated annual PB, analysis of the effect of multiple biopsies was limited, but their results suggest that number of biopsies does not have a large effect on erectile function [7]. In our previous study, we showed the incidence of ED in patients undergone to repeated TRUS biopsies for diagnosis of Atypical Small Acinar Proliferation (ASAP), an histological pattern that require repeated biopsies as follow up for its possible progression in neoplasm. Moreover, this study was useful to demonstrate ED after biopsies also in patients without diagnosis of prostate cancer, an important bias, and for showing a technique of led the prostate biopsies with echo color Doppler, in order to avoid neurovascular bundles and preserve erectile function [6].

This study has limitations, including the low sample size of patients valued and the follow up limited to 24 months; nevertheless it was underlined important correlations with comorbidity, as showed in chapter Results.

Conclusion

AS is a therapeutic option not devoid of side effects: especially in our preliminary experience, we have pointed up the high occurrence of ED, which may recognize physical and psychological causes. All the variable analized – age, BMI, hypertension and diabetes – resulted related to a high risk of develop DE, although not statistically significant; nevertheless, prospective study with a larger population is needed to verify our outcomes.

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