The Use of IIEF-5 for Reporting Erectile Dysfunction Following Nerve-Sparing Radical Retropubic Prostatectomy

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Abstract: *Introduction*: Increased detection of organ-confined prostate cancer has led to an increased demand for nerve-sparing surgery. Most studies of erectile dysfunction (ED) following nerve-sparing radical prostatectomy (RRP) use single-item assessment, and potency rates differ widely among various groups. We aimed to investigate the use of the IIEF-5, a validated questionnaire, for reporting ED following RRP.

Aims: To study the use of the IIEF-5 questionnaire in the evaluation of post-RRP ED, and to find possible variations in ED reporting when comparing IIEF-5 to single-item assessment.

Methods: At a minimum of 18 months post-surgery, patients completed a questionnaire on erectile function that included both single-item assessment and the IIEF-5. The study included sexually active patients who reported no pre-operative ED and who did not receive adjuvant or salvage therapy.

Main Outcome Measures: For the single-item assessment, potency was defined as "the ability to achieve erections firm enough for intercourse". For the IIEF-5 questionnaire, potency was defined as a score $\geq$22 (out of 25) points.

Results: Ninety-one patients were included in the study. The procedures consisted of bilateral nerve-sparing (55%) or unilateral or partial bilateral nerve-sparing surgery (45%). We found a striking difference in potency rates when using either IIEF-5 score or single-item assessment for reporting of potency after RRP. The results when using the IIEF-5 questionnaire indicated that 25.5% of all patients were potent. In contrast, single-item assessment indicated a potency rate of 53.8%.

Conclusions: Using the IIEF-5 questionnaire to evaluate ED following RRP results in a remarkably lower percentage of men being classified as having no ED. This might be the main reason IIEF-5 is not frequently used in the reporting of ED following radical prostatectomy. Literature search reveals that the IIEF-5 questionnaire is expected to have a higher level of validity, accuracy, and reliability, and may be more stable than single-item assessment. We think that the use of IIEF-5 in the reporting of ED following RRP enhances comparison of different series and of different treatment modalities. However, a prospective comparison between IIEF-5 and single-item assessment is needed to confirm this finding.

INTRODUCTION

Prostate cancer is a medical problem affecting many men. An estimated 301.500 new cases are diagnosed each year in the European Union, where prostate cancer constitutes about 24% of all male cancers [1]. At present, radical retropubic prostatectomy (RRP) is the treatment of choice in young men with clinically localized prostate cancer [1]. Increased screening using prostate-specific antigen has resulted in the detection of mostly clinically localized prostate cancer at earlier stages and in younger men; therefore, patients undergoing radical prostatectomy generally have good baseline erectile function and high expectations concerning the preservation of erectile function following the procedure. Since Walsh *et al*. published their insights into the etiology and prevention of impotence following RRP in 1982, their nerve-sparing technique has been widely employed to improve postoperative erectile function. The anatomical techniques used in RRP results in decreased blood loss and thus better visualization and safer dissection of the neurovascular bundles [2, 3]. Many studies on erectile dysfunction (ED) following nerve-sparing RRP have been published, revealing widely disparate potency rates (30-86%) among various groups in different studies [4-11]. This variation in potency rates may be due to patient selection, surgeon and hospital volume, and the proportion of nerve-sparing procedures [5, 12-14]. However, non-uniform data-collection, the assessment method, and the definition of potency also influence the reported erectile function outcome [15-17]. A single-item assessment is used in most studies, with potency defined as "having erections firm enough for intercourse." In concordance with the definition of ED introduced by the National Institutes of Health in 1992, ED is therefore the inability to attain and maintain erections firm enough for intercourse [18]. Although this single-item assessment has been used in many recent studies, the IIEF-5 may be a more standardized investigational technique for evaluating ED following RRP. Although it is widely accepted as a valid tool for evaluating ED, the IIEF-5 is used infrequently for the assessment of ED post-RRP [19-21]. We aimed to study the use of the IIEF-5 questionnaire in the evaluation of postoperative ED following nerve-sparing RRP and to compare the results to those obtained using single-item assessment. A questionnaire on the functional outcome of RRP was sent to 272 men who had undergone nerve-sparing RRP, and an extensive chart review was performed.

AIMS

The aims of this study were to evaluate the use of the IIEF-5 questionnaire for reporting ED following RRP, to

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find possible variations when comparing IIEF-5 to single-item assessment and to report the functional and oncological results of nerve-sparing RRP at our institution.

PATIENTS AND METHODS

Two-hundred-and-seventy-two patients underwent open nerve-sparing RRP: 45% were classified as unilateral- or partial bilateral nerve-sparing (UNS/PBNS) and 55% as bilateral nerve-sparing (BNS).

Clinical Staging

Local tumor staging was performed by digital rectal examination, transrectal ultrasound with biopsy, and, in some cases, MRI. Ten at random biopsies were taken from all patients and were scored according to the Gleason scoring system. A bone scan and CT of the pelvis and abdomen were performed to assess bone metastases and lymph node involvement when PSA was >10 ng/ml, when the clinical stage was T3 or when the Gleason score was $\geq$ 7.

Surgical Technique

Two surgeons (HVP, SJ) performed all procedures. Before performing the radical prostatectomy, all patients underwent a bilateral staging pelvic lymph node dissection without frozen section. The nerve-sparing technique was performed by a modified Walsh tehnique, [3, 22] with avoidance of use of clips and electrocautery near the neurovascular bundle, the accessory pudendal arteries, and the pudendal branch that innervates the extrinsic sphincter of the urethra (which runs dorsal to the sphincter complex).

Pathological Staging

The RRP specimens, including prostate, seminal vesicles, and bilateral pelvic lymph nodes, were examined microscopically after routine preparation. The prostate was weighed and cut as whole-mount 4-mm sections. All specimens were scored according to the Gleason grading system. Microscopic extension of malignant cells to the inked surface of the resected specimen was interpreted as a positive surgical margin. The pathological stages were recorded as pT2a, pT2b, pT2c, pT3a, pT3b, or pT4 and lymph node status was assigned according to the 2002 TNM classification [23].

Postoperative Care and Follow-Up

Patients had an indwelling silicone catheter for two weeks. Pelvic floor muscle exercises were started at catheter removal. Patients were evaluated at the outpatient clinic at 6 weeks, 3, 6, and 12 months after surgery, and every 6 months thereafter.

Data Collection

At a minimum follow-up of 18 months after surgery, a combined questionnaire was mailed to all 272 RRP patients (Appendix). Each patient was asked about pre- and postoperative potency (single-item assessment). Potency was scored as follows: 0: absence of tumescence or presence of erection not rigid enough for penetration (no recovery) or 1: erection that was rigid enough to allow penetration (full recovery). Patients also received an IIEF-5 questionnaire which is an abridged version of the validated International Index of Erectile Function questionnaire. The IIEF-5 consists of four questions derived from the erectile function domain and one question from the intercourse satisfaction domain of the IIEF. A cut-off score of $\geq$ 22 (out of 25) points was used as the definition of potency. All patients were also asked about their use of potency-enhancing medication or devices and about their ability to achieve orgasm.

Further, an extensive chart review was performed, and technical aspects of the procedure were noted. These aspects included the surgeon, blood loss, duration, and a score for the technical difficulty of the procedure as determined by the surgeon, ranging from 1 (easy) to 3 (difficult). If nerve preservation was attempted but complicated by bleeding, fibrosis, or other causes, it was noted as partially nerve-sparing on that side. Two categories of nerve-sparing surgery were noted, namely BNS or UNS/PBNS.

Inclusion and Exclusion Criteria

Patients who received adjuvant therapy and patients who reported an absence of erections rigid enough for intromission (using the single-item assessment) preoperatively were excluded. Using the IIEF-5, nonsexually active patients would be classified as having severe ED, since the score would be 0 for four of the five questions (Appendix). Therefore, for inclusion in the study, patients had to be sexually active.

Statistical Analysis

We used Cox univariate regression analysis for statistical analysis of the functional outcome predictors. The chi-square test was used for comparison of proportions when comparing outcomes with different definitions of ED. For all evaluations, the level of significance was set at $P = 0.05$. For statistical analysis, we used the software MedCalc® (version 8.1.1.0).

RESULTS

Using the IIEF-5 to Evaluate ED

A chart review was performed for the 272 patients in the study (Table **1**). The mean patient age was 58.2 $\pm$ 6.4 years (range: 45 to 70 years). Of the 272 patients who underwent RRP, 195 completed and returned the questionnaire; 15 of the 195 patients were excluded because they recieved adjuvant therapy, and 19 of the 195 patients were excluded because preoperatively they had no erections or erections not rigid enough for intromission. Of the remaining 161 patients, 70 were not sexually active when they filled out the questionnaire; thus, only 91 patients were included in the study. Of these 91 patients, 45% underwent UNS/PBNS; the remaining 55% had BNS surgery. ED was assessed regardless of whether potency-enhancing devices or medication were used.

We analyzed the influence of the questioning method on reporting of postoperative erectile function in 161 patients, and assessed potency rates in the subgroup of patients that reported being sexually active (n = 91). Using single-item assessment to assess whether erections sufficient for intromission were present, the overall full recovery rate was found to be 53.8%. However, of the patients that were sexually

active, only 25.5% had an IIEF-5 score of 22-25 points (i.e. no ED). This difference was statistically significant (P = 0.001). This difference in reported results between methods was present in all age groups (Fig. **2**) and in the UNS/PBNS as well as the BNS surgery group (Fig. **3**). The mean IIEF-5 score in all 91 sexually active patients was 16.27 points (95% CI: 14.97 to 17.58). At the time of the study, 31.2% of the 91 patients reported use of a PDE-5 inhibitor, 2.5% used intracavernous injection therapy, and one patient reported using a vacuum tumescence device. Univariate analysis of the predictors for erectile function showed that recovery of potency significantly correlated with perioperative blood loss, age, and prostate volume (Table **2**).

Table 1.

Variable		Number n = 272	(%)
Patient Characteristics			
Age	≤ 55	79	29,0
	56-64	123	45,2
	≥ 65	70	25,7
Surgical Characteristics			
Procedure	bilateral nerve-sparing	148	54,4
	Unilateral, or bilateral partial nerve-sparing	124	45,6
blood loss	Mean	684,8	
procedure time	Mean	90,0	
Tumor Characteristics			
PSA	< 4 ng/ml	31	11,7
	4-10 ng/ml	193	73,1
	>10 ng/ml	40	15,2
	Mean Range	7,0 0,50-26,0	
Clinical staging	cT1c	197	72,7
	cT2a-c	68	25,1
	cT3a	6	2,2
pathological staging	HPIN	3	1,1
	pT2	239	87,9
	pT3	30	11,0
Pathological Gleason score	Median Mean	7 6.55	
Positive section margins	Total	13	4,8
	T2a	1	
	T2b	2	
	T2c	2	
	T3a	6	
	T3b	2	

Table 2. Correlation of Variables with Erectile Function Outcome (IIEF-5 ≥ 22)

Variables		IIEF-5 Score p-Value
Surgical	Surgeon	0,707
	Surgical difficulty score	0,068
	Blood loss	**0,029**
	Duration	0,472
	Quality of nerve sparing	0,150
Patient	Age	**0,013**
	Prostate specimen volume	**0,008**
Tumor	Clinical stage	0,565
	Pathological stage	0,872
	Gleason score	0,818

Oncological Outcome

We used chart review to evaluate the oncological outcomes of all 272 patients who underwent nerve-sparing surgery.

Section Margins

Of all 272 surgical specimens that were examined 13 (4.8%) had microscopic extension of malignant cells to the inked surface. Of those 13, only 5 had positive section margins on the side were the nerve was spared. Eleven of those 13 patients underwent adjuvant radiation treatment. Two had salvage radiation therapy and hormonal treatment. The other 9 patients received only radiation therapy as adjuvant treatment. Most positive section margins were noted in stage pT3 tumors; 26.7% of pT3 tumors had positive section margins. In contrast, only 2.1% of the pT2 tumor specimens had positive section margins.

Biochemical Survival

When reviewing the charts of the 272 patients, only one patient had a PSA value above 0.2 ng/ml 18 months after surgery, and 4.6% of patients had detectable PSA.

Adjuvant Therapy

Postoperatively, radiotherapy was administered to 21 of the 272 patients. Salvage (> 3 months after surgery) radiotherapy was initiated in 10 patients because of rising PSA and adjuvant (started ≤ 3 months after surgery) radiotherapy was started in 11 patients because of positive section margins. In two patients who received radiotherapy because of positive section margins, hormonal therapy was added because of persisting elevated PSA.

None of the patients died in the first 18 months following surgery. One patient died during further follow-up from a non-cancer related cause.

DISCUSSION

The technique for nerve-sparing RRP used at our institution is also referred to as 'anatomical radical prostatectomy' [3,22]. This technique reduces blood loss, resulting in better visualization and identification of neurovascular bundles. These bundles arise from the pelvic plexus, and contain non-cholinergic non-adrenergic parasympathetic Nitric Oxide Synthase (NOS)-positive nerve fibres and hypogastric nerve fibers. Proximally, these neurovascular bundles lie in close contact with the tip of the seminal vesicles, and extend inferiorly and laterally to the prostate and the urethra to innervate the corpora cavernosa [24]. Even in nerve-sparing surgery, neuropraxia occurs, resulting in degeneration of the nerves and loss of NOS-positive nerve terminals in the corpus cavernosum [25]. This denervation causes neurogenic ED. Secondary to this neurogenic ED, structural changes occur in the corpus cavernosum, including fibrosis, apoptosis, and loss of subtunical smooth muscle mass. These structural changes possibly cause venous leak resulting in venogenic ED [26]. In our series, we found that the reduction in blood loss results in a better functional outcome for the patient. This is likely due to a better preservation of the neurovascular bundles because they are easier to locate, and thus easier to spare, during surgery. Although we strive to avoid the use of hemostatic clips and electrocautery near or on the neurovascular bundles, it is not always possible to avoid this. When blood loss increases, clips may be used to enhance visibility, resulting in damage to the bundles.

Concerning patient selection, we found that age correlated with recovery of erectile function (Fig. **2**) as well as with other functional outcome goals (continence and orgasm recovery). Younger patients are expected to have less vascular pathology and other comorbidities and have greater erectile capacity and neural regenerative ability than did older patients; this illustrates why patient selection can have a significant impact on the functional outcome of nerve-sparing radical prostatectomy. We found that approximately one-third of patients used medical aids to achieve and maintain erections, mostly PDE-5 inhibitors. Patients did not follow a standardized penile rehabilitation program. Single-item assessment showed higher erectile function recovery rates in sexually active patients (36.1% recovery for all 161 patients that returned the questionnaire, and 53.8% in sexually active patients), as was previously published by Geary *et al*. [27]. Recovery of erections sufficient for intromission in 53.8% of sexually active patients is similar to outcomes reported by others, taking into account that 45% of the patients in this group did not have BNS surgery.

Nerve-sparing surgery achieved satisfactory oncological results, with only 7.7% of all patients requiring adjuvant or salvage therapy. Of 13 (4.8%) patients with positive section margins, 8 were stage pT3 tumors; only 5 patients had positive margins at the nerve-sparing side.

The Use of the IIEF-5 Questionnaire to Evaluate Post-RRP ED

In 1999, the IIEF-5 was developed by Rosen *et al*. to assess the presence and severity of ED, and was stated to possess favorable properties for the detection and classification of ED. In that report, an IIEF-5 score of 21 was found to discriminate between ED versus no ED in the 1152 men that were studied [19]. In 2005, Karakiewicz *et al*. studied the reliability of remembered IIEF domain scores pre-RRP, and 6 and 12 months post-RRP, in 39 men with localized prostate cancer; they concluded that the remembered IIEF erectile function domain score (IIEF-EF) demonstrated high reliability with prospectively collected data [21]. The IIEF-5, which largely overlaps the IIEF-EF, thus seems a reliable instrument to use retrospectively for the analysis of ED in men who undergo nerve-sparing RRP. However, when reviewing studies performed since 1999 on post-RRP ED, we found that the IIEF-5 was used in only a minority of the (pro- and retrospective) studies. In most reports, the definition used for potency was: "having erections firm enough for intercourse", a definition that provides a 'black and white' measure of erectile function (single-item assessment). In contrast, the IIEF-5 score reflects not only penile function per se, but also measures patient satisfaction and confidence [19]. Furthermore, by evaluating erection maintenance frequency and maintenance ability after intromission, the IIEF-5 assesses penile function more thoroughly than does single-item assessment. In 2000, Cappelleri *et al*. found a moderate-to-high correlation between the IIEF erectile function domain score and patients' self-assessment of ED by single-item assessment, which we were able to reproduce in our series for the IIEF-5 (Fig. **1**) [20]. Cappelleri *et al*. stated that although a single-item assessment is likely to have a higher response rate, the IIEF erectile function domain score is expected to have a higher level of validity, accuracy, and reliability, and is a more stable measurement than the single-item self-assessment. In the current study, the difference in potency rate between age groups was more pronounced when using the IIEF-5 score than when using single-item assessment (Fig. **2**). However, because of the relatively small study population, we were not able to confirm this statistically. Concerning the difference in potency rates in the UNS/PBNS vs. the BNS group, we found the relative difference between the two groups to be 16% using the single-item assessment and 126% using the IIEF-5 (Fig. **3**). This fact seems to indicate a higher level of accuracy as was suggested by Cappelleri *et al.* [20].

We aimed to study the functional outcome of nerve-sparing RRP using the IIEF-5 as an instrument for evaluation compared to single-item assessment. In the group of 91 sexually active men at a minimum of 18 months postoperatively, we found that only 25.5% had no ED (i.e. an IIEF-5 score of 22-25). In the UNS/PBNS group, 15% had no ED vs. 34% in the BNS group. This illustrates an important discordance in reporting on erectile function outcome of nerve-sparing RRP when using different definitions for ED in the same patient population. This finding was also previously described by Krupski *et al*. [15]. In agreement with Walsh, we think that using such a scoring system confers minimal benefit to the patient; however, the introduction of the IIEF or IIEF-5 as a standard evaluation method for functional RRP outcome is likely to allow comparison of various series, and comparison of the outcomes of non-nerve-sparing, UNS, and BNS surgery [15, 28]. This discordance may be the main reason why IIEF-5 is not used frequently in studies of post-RRP ED. We assume that the differences in the percentages of reported ED are based on the fact that the IIEF-5 evaluates other parameters in addition to intromission. Noldus *et al*. found that in the group of patients that reported erections

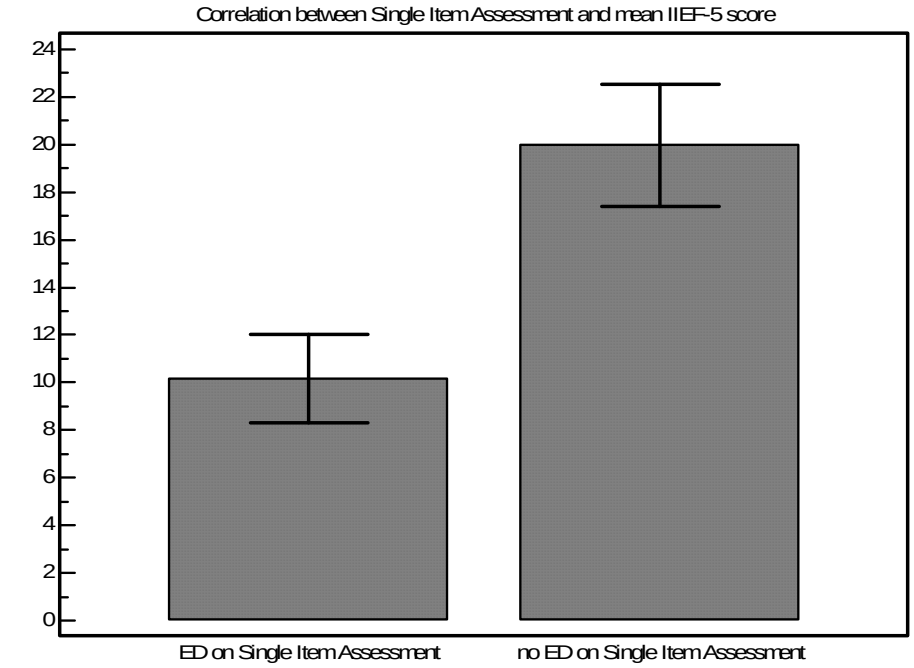

Fig. (1). There is a significant correlation between IEFF-5 and single-item assessment outcome scores. Note that the mean IIEF-5 score in the group with no ED on single-item assessment is only 20.44, indicating mild ED according to the scoring convention of Rosen *et al*.

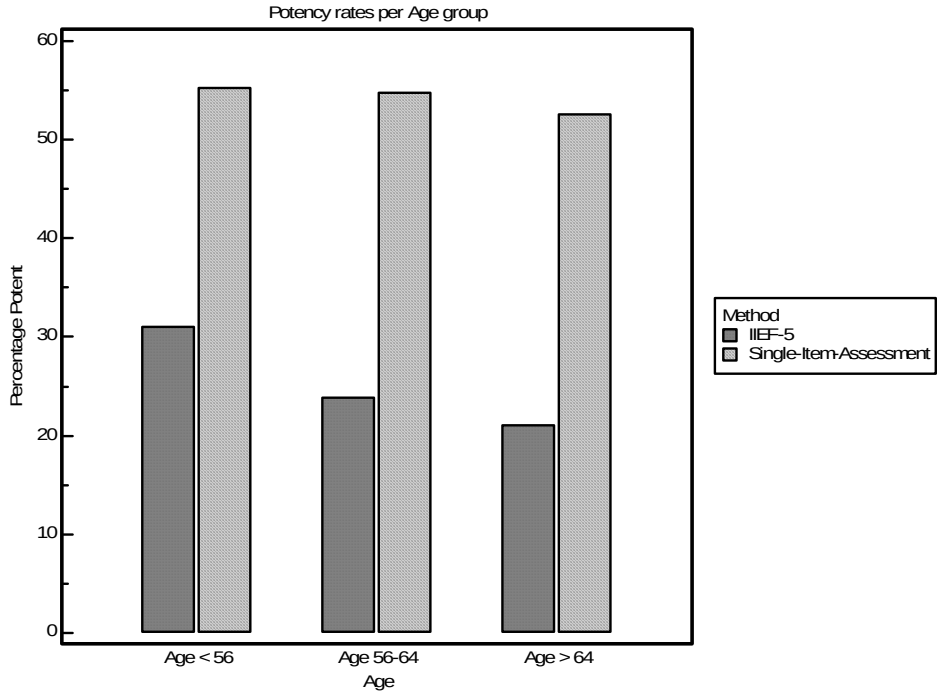

Fig. (2). There is a correlation between potency and age, and different definitions for potency result in different potency rates. The decline of potency rates in older age groups is more pronounced using the IIEF-5 definition versus the single-item assessment definition. This difference did not attain statistically significance because of the relatively small study population (n = 91).

rigid enough to be satisfactory for sexual intercourse using a single-item assessment, the average IIEF-5 score was 19.9, which indicates mild ED [8]. The lower average score using the IIEF-5 illustrates that the use of the IIEF-5 produces less optimistic results compared to the single-item assessment score. This is consistent with our findings: We found an average IIEF-5 score of 20.4 (mild ED) in the group that reported having erections sufficient for intromission on the single-item assessment score.

One major disadvantage of the IEFF-5 is that it can only be used to evaluate patients who are sexually active, since nonsexually active patients will be categorized as having severe ED, which is not always true. Patients who are temporarily nonsexually active can thus be classified as having severe ED while in fact they are perfectly capable of attaining and maintaining an erection sufficient for intromission. This is a concern when evaluating patients preoperatively, when they have only recently been diagnosed with cancer;

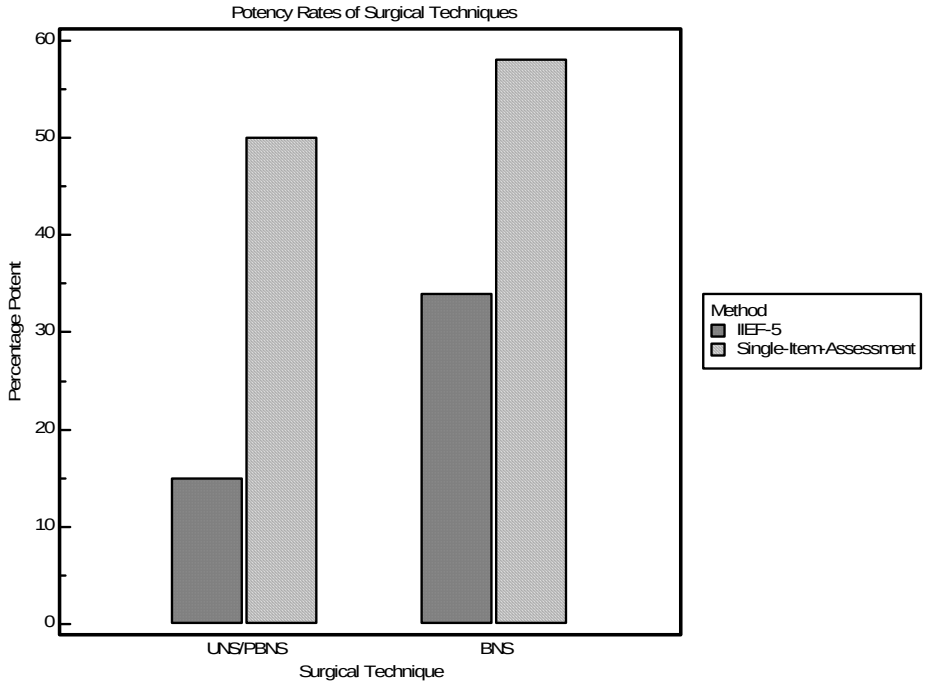

Fig. (3). Potency according to surgical technique (UNS/PBNS: unilateral- or partial nerve-sparing; BNS: bilateral nerve-sparing). There was a significant difference between the potency rates depending on the definition of potency (P = 0.001). There was a relative difference between the two groups of 16% using single-item assessment versus 126% using the IIEF-5 definition.

the diagnosis itself can result in loss of sexual interest and activity [29-33]. The present study has some limitations. Firstly, a retrospective study may not be optimal to address this topic. However, it is a good instrument to get an impression of the discordance between single-item assessment and IIEF-5 score. Secondly, the fact that pre-operative potency was evaluated by a remembered single-item assessment is also a major drawback. This could create considerable recall bias. To our knowledge, no data are currently available on remembered single-item assessment scores, however recent data indicates that remembered IIEF should not be used to assess SF in a real-life clinical setting in candidates for radical prostatectomy [33]. We assume this finding also could be true for the IIEF-5 score.

CONCLUSIONS

Increased detection of organ-confined prostate cancer has increased the demand for nerve-sparing surgery. In our institution, we found that nerve-sparing RRP resulted in satisfactory oncological and functional outcomes. We studied the use of the validated IIEF-5 questionnaire for reporting ED following nerve-sparing surgery, and found that a significantly lower percentage of men were classified as having no ED compared to single-item assessment. This may explain why the IIEF-5 is not used more frequently in studies of ED post-RRP. However, the IIEF-5 has a higher level of validity, accuracy, and reliability, and is more stable than the single-item assessment. We therefore think it is an excellent instrument for reporting on erectile function following radical prostatectomy. A prospective comparison between IIEF-5 and single-item assessment is needed to confirm this finding. It should be kept in mind that in comparing different studies, comparisons of patient selection, hospital and surgeon volume, and the overall proportion of nerve-sparing surgeries are as important as the questionnaire and definition of potency that are used.

APPENDIX: QUESTIONNAIRE

Sexual Function (Single-Item Assessment and Orgasm)

1a. Which of these statements fits best with your status before your prostate was excised?	**Score**
- I was not able to get an erection	0
- I was able to get an erection, but it was not rigid enough for penetration	0
- I was able to get an erection which was rigid enough for penetration	1
1b. Which of these statements fits best with your current status?	
- I am not able to get an erection	0
- I am able to get an erection, but it is not rigid enough for penetration	0
- I am able to get an erection which is rigid enough for penetration	1

(APPENDIX) contd….

2a. Were you able to have the sensation of orgasm before your prostate was excised?	
- No	0
- Yes	1
2b. Are you currently able to have the sensation of orgasm?	
- No	0
- Yes	1

Use of Potency-Enhancing Medication or Devices

1. Do you use aids to improve your potency?	
- Yes, Viagra® (Sildenafil)	
- Yes, Levitra® (Vardenafil)	
- Yes, Cialis® (Tadalafil)	
- Yes, injections in the base of the penis	
- Yes, a vacuum-device	
- No	

2. If you use oral medication to improve your potency, what is the dose you use?	
- Viagra® (Sildenafil)	25 mg. 50 mg. 100 mg.
- Levitra® (Vardenafil)	5 mg. 10 mg. 20 mg.
- Cialis® (Tadalafil)	10 mg. 20 mg.

IIEF-5

1. How do you rate your confidence that you could get and keep an erection?	**Score**
- Very low	1
- Low	2
- Moderate	3
- High	4
- Very High	5

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	
- I am currently not sexually active	0
- Never or almost never	1
- A few times (less than half of the attempts)	2
- Sometimes (approximately half of the attempts)	3
- Most times (more than half of the attempts)	4
- Always or almost always	5

(APPENDIX) contd….

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	
- I am currently not sexually active	0
- Never or almost never	1
- A few times (less than half of the attempts)	2
- Sometimes (approximately half of the attempts)	3
- Most times (more than half of the attempts)	4
- Always or almost always	5

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	
- I am currently not sexually active	0
- Extremely difficult	1
- Very difficult	2
- Difficult	3
- Slightly difficult	4
- Not difficult	5

5. When you attempted sexual intercourse, how often was it satisfactory for you?	
- I am currently not sexually active	0
- Never or almost never	1
- A few times (less than half of the attempts)	2
- Sometimes (approximately half of the attempts)	3
- Most times (more than half of the attempts)	4
- Always or almost always	5

Adjuvant Treatment

1 After your surgical treatment, did you receive any other form of treatment for prostate cancer?	
- No	
- Yes, radiation therapy	
- Yes, hormonal treatment	
- Yes, both I received both radiation therapy as hormonal treatment	

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