What’s known on the subject? and What does the study add?
Erectile dysfunction (ED) is a well known implication of radical prostatectomy (RP). Despite the search for technical improvement in the surgical procedure (e.g. nerve-sparing surgery, robot-assisted RP), many patients still suffer from an inability to achieve a satisfactory erection after surgery. In the last 20 years a great effort has been made to re-establish good sexual function in these patients. Many different approaches have been used, such as intracavernous prostaglandin E1 (PGE1), phosphodiesterase-5 inhibitors, vacuum devices and penile prostheses. Although many studies have addressed the main questions about efficacy of different approaches to ED, there is a lack of data about adherence to therapy and the main reasons why patients drop out of these treatment programmes. In the present study, a cohort of men treated with RP underwent a postoperative rehabilitation protocol with PGE1 intracavernous injections. During the follow-up period, we were able to assess a real-life practice pattern of adherence and dropout, evaluating the main causes of therapy discontinuation. This could be of help in the counselling of these patients during the path towards erection recovery.

OBJECTIVES
• To assess the rate of compliance in the first 6 months of a rehabilitation protocol that includes intracavernous alprostadil administration in patients undergoing radical retropubic prostatectomy.
• To determine the reasons for and timings of dropout from the protocol by the patients and their subsequent outcomes.

PATIENTS AND METHODS
• All patients undergoing radical prostatectomy (RP) at our institution between 1 January 2007 and 31 December 2009 were considered for a protocol of postoperative intracavernous sexual rehabilitation and were administered entry questionnaires to evaluate their preoperative sexual activity.
• Four weeks after surgery, the patients were invited to return for a first visit, where the aim of the protocol and possible risks and benefits were explained. For those who agreed to attend, subsequent visits to include assisted self-administration of increasing doses of intracavernous alprostadil and a period of autonomous sexual activity were planned.
• Patients were followed up at 3-month intervals, where data on functional outcomes, patient satisfaction, and the number of patients who dropped out and their reasons, were recorded by means of appropriate questionnaires.
• Statistical analysis was performed using Student’s t-test or a chi-squared test, where appropriate.

RESULTS
• Of 430 patients, 157 (36.5%) refused to undergo the protocol of rehabilitation and 18.6% of the patients who began the protocol dropped out over the first 6 months.
• Reasons for refusal were: patient’s lack of sexual interest (51.6%); lack of interest by the partner (30.2%); and presence of transitory incontinence (26.7%).
• Reasons for dropout were: disappointment with treatment efficacy (64.7%); injection pain (45%); and difficulties with or fear of performing the injection by themselves or by the partner (35.2%). No patient claimed the cost of the drug to be a cause for dropout.

CONCLUSIONS
• The protocol we used, involving intracavernous alprostadil injection, proved to be a safe and efficient way of achieving sexual rehabilitation in patients who have undergone RP. Nevertheless, high patient motivation and adherence to the protocol were required.
• Factors influencing patients refusal and early-to-medium time dropout were both patient- and partner-related. Appropriate information, counselling and support of the couple before the beginning and at all stages of the rehabilitation play a fundamental role in reducing the dropout rate.
• The situation regarding those patients who still need adjuvant therapy after surgery is less clear and further research on this is required.

KEYWORDS
radical prostatectomy, sexual, PGE1, alprostadil, rehabilitation, refusal, dropout
INTRODUCTION

Radical prostatectomy (RP) is a therapeutic option for patients with clinically localized prostate carcinoma and a life expectancy of at least 10 years [1]. Erectile dysfunction (ED) and urinary incontinence, its most common complications, severely affect patients’ health-related quality of life [2]. After the introduction of nerve-sparing RP by Walsh [3], increasingly less invasive approaches have been devised, including laparoscopic and robot-assisted RP; however, such methods involve similar disadvantages and limitations that result in considerable dropout rates. In addition, ~50% of patients refuse to undergo postoperative rehabilitation [6,7].

After the pioneering work of Montorsi et al. [5], early administration of erectile drugs to promote erection recovery after nerve-sparing RP, or satisfactory intercourse in patients who have undergone non-nerve-sparing RP, has become increasingly common. However, such drugs also have disadvantages and limitations that result in considerable dropout rates. In addition, ~50% of patients refuse to undergo postoperative rehabilitation [6,7].

We studied behaviour, after both nerve-sparing and non-nerve-sparing RP, in a series of Caucasian patients who have undergone non-nerve-sparing RP, has become increasingly common. However, such drugs also have disadvantages and limitations that result in considerable dropout rates. In addition, ~50% of patients refuse to undergo postoperative rehabilitation [6,7].

PATIENTS AND METHODS

All patients who underwent radical retropubic prostatectomy, either nerve-sparing or non-nerve-sparing, at a single academic institute from 1 January 2007 to 31 December 2009 were included in the study.

The day before surgery, after obtaining informed consent, we administered the abridged 5-item International Index of Erectile Function (IIEF-5) [8] to obtain information on each patient’s physiological and pathological history, together with a short semi-structured questionnaire (Form 1 [Appendix]) to gain information on his sexual habits.

At our institution all patients undergoing RP, whether nerve-sparing or non-nerve-sparing, are offered an ED rehabilitation programme with alprostadil (Caverject®, Pfizer Inc., New York, NY, USA). Approximately 4 weeks after the removal of the bladder catheter patients receive counselling through an interview aimed at evaluating the couple’s sexual habits and expectations with regard to the resumption of sexual activity. Patients are provided with information on the usefulness of rehabilitation, the potential complications of alprostadil use, which include ischaemic priapism, and the administration protocol. Those patients who agree to participate are seen once a week and taught the self-injection technique and how to achieve the correct dosage based on erection response, which takes place in 5–20 min. Administration begins with a starting dose of 2–3 mcg, and at the next visit, the patient is asked to report its effects so that dosage optimization can be achieved. The drug is stored at or below 25 °C. Patients are asked to report any pain. They are then seen again at 3-month intervals and administered a further questionnaire if they have decided to interrupt the treatment (Form 2 [Appendix]). After this stage they are prescribed an additional oral drug, a phosphodiesterase-5 (PDE-5) inhibitor.

The primary endpoint was the rate of compliance or dropout in the first 6 months; the secondary endpoints were the reasons for refusal or dropout. Patients were not divided into nerve-sparing and non-nerve-sparing RP groups, as we were interested in assessing their acceptance of a programme that is offered to all RP patients.

Data were analysed using Student’s t-test or the chi-squared test as appropriate. Significance was set at P < 0.05.

RESULTS

A total of 430 patients underwent RP at our institution; their mean (SD) age was 64.59 (6.5) years, and 66.7% had an IIEF-5 score ≥20 (Fig. 1). All patients reported being sexually active in the 6 months before the operation.

The ED rehabilitation programme was accepted by 273 patients and rejected by 157 (Table 1). Table 2 shows the PGE1 dose distribution. None of the patients who refused to participate eventually changed their minds. Refusal to participate was attributable to patient’s lack of sexual interest in 81 cases (51.6%) and lack of interest from the spouse/partner in 46 cases (30.2%) (Table 3). Patients who did not participate were significantly older than those who did and had a lower mean IIEF-5 score (<20 in 53.5% of patients). An additional 42 patients declined to participate because of urinary incontinence. The overall transitory urinary incontinence rate was 26.7%. The requirement for adjuvant
treatment (hormone and/or radiation therapy) significantly influenced the decision to adhere to the programme; the number of patients who refused or dropped out of the programme and needed adjuvant treatment was nearly four times the number of those who entered the programme.

Of the 273 patients who decided to participate, 212 (77.6%) had IIEF-5 scores ≥20. A total of 18.6% of patients dropped out over the first 6 months. In the majority of cases the reason was treatment ineffectiveness or disappointment with its effects, despite all attempts at adjusting the alprostadil dose. The second most frequent reason was injection pain. The difficulty of self-injection, often related to patient habits or to a fear of needles by the patient or his spouse/partner, and loss of spontaneity were responsible in a limited number of cases. Interestingly, the high cost of the drug was never stated as a reason. Numerical data are shown in Table 4.

**DISCUSSION**

To date, the long-term survival expectations of patients with prostate cancer who undergo RP have been favourable and any attempt to improve these patients’ quality of life, especially sexual life, is very important. Most of the studies performed to date have analysed the effectiveness of protocols and drugs in supporting and helping erectile function recovery, but few data are available on actual drug use patterns.

In our centre, we have adopted a rehabilitation protocol that is offered to all patients treated with RP, involving the use of intracavernous alprostadil in the first stage. The rationale for this treatment is the high, virtually immediate effectiveness of the drug in terms of erectile function and especially of hardness, a factor often considered critical to patient satisfaction. In fact, even after nerve-sparing RP, neuroapraxia involves a period of functional insufficiency of nerve fibres of up to 24 months, limiting the effectiveness of the use of PDE-5 inhibitors [11,12].

The results of the present study show that several factors contribute to sexual satisfaction after RP, including the quality of preoperative erection, the degree of disease control (because of the possible need for adjuvant treatment), the interest of the patient or his spouse/partner in sexual intercourse, and urinary incontinence. Notably, patients describing an unsatisfactory erectile function preoperatively also had a strong interest in penile rehabilitation. This observation was documented by substantially overlapping preoperative IIEF-5 scores among programme participants and non-participants, showing that preoperative function is not a critical factor in seeking help for postoperative ED. In addition, consistent intracavernous treatment did not correlate with the number of attempts at intercourse in a significant proportion of patients (data not shown). The vast majority of our patients had never sought medical help for their ED before the operation. The offer of a rehabilitation programme probably prompted them to seek assistance. However, a large problem with these patients, and one that in the present study accounted for the majority of dropouts, was unrealistic expectations, principally in relation to hardness even among subjects who underwent non-nerve-sparing surgery.

The present data highlight the role of spouses/partners, whose lack of interest in sexual intercourse was the underlying reason for ~30% of negative decisions. This surprising factor must be a focus of the postoperative management of what is, in effect, no longer a single patient, but a more complex entity, the couple. Indeed, in a recent survey of patients with prostate carcinoma treated with a variety of approaches, ~50% of the RP subset rated the problem of sexual intercourse as moderate or severe, as did a similar proportion of spouses/partners [13].

In the present study, sexual intercourse was the main quality-of-life domain for the spouse/partner.

Similarly to a previous investigation of the use of an oral ED medication in patients who underwent nerve-sparing RP, drug cost was never stated as the reason for dropout in the present study [7]. This fact is significant because the regional office of the Italian national health service in the Marches region does not refund the cost of ED drugs to patients who have undergone RP, unlike other regional offices. Although we have no data on patients’ income, cost did not affect their decision to join the rehabilitation programme, reflecting the deep motivation that prompts patients in these situations.

The implications of adjuvant treatment in these patients are still unclear. In the present study, the recommendation for radiation therapy discouraged some patients from undertaking ED rehabilitation, probably because they associated it with greater disease severity. The present data do not provide information on any effects of radiation or hormonal therapy in terms of reduction of the erectile function. This aspect is currently being investigated at our centre. Hormone therapy is known to affect quality of life by affecting erectile function and arousal. Analysis of the Prostate Cancer Outcomes Study data showed that 51% of patients who experienced some degree of sexual interest before the operation reported losing it afterwards, whereas 69% of those who previously had normal erections reported ED [14].

Pain was among the major reasons for patient dropout. The cause of this pain is unclear. It is well established that pain is particularly frequent and severe after RP, possibly reflecting a role for the surgical nerve injury in generating the nociceptive stimulus [15,16]. In the present study, the number of patients reporting pain was

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**TABLE 3 Reasons for patients refusing the rehabilitation programme (N = 157; 36.5%)**

<table>
<thead>
<tr>
<th>Reason, n (%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of sexual interest</td>
<td>81</td>
<td>(51.6)</td>
</tr>
<tr>
<td>Lack of sexual interest by the partner</td>
<td>46</td>
<td>(30.2)</td>
</tr>
<tr>
<td>Urinary incontinence (transitory)</td>
<td>42</td>
<td>(26.7)</td>
</tr>
</tbody>
</table>

**TABLE 4 Reasons for dropping out of penile rehabilitation programme (N = 51; 18.6%)**

<table>
<thead>
<tr>
<th>Reason for dropping out, n (%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of/disappointment with treatment efficacy</td>
<td>33</td>
<td>(64.7)</td>
</tr>
<tr>
<td>Injection pain</td>
<td>23</td>
<td>(45)</td>
</tr>
<tr>
<td>Problems with the injection (difficulty/fear)</td>
<td>18</td>
<td>(35.2)</td>
</tr>
</tbody>
</table>

[9,10]. In fact, even after nerve-sparing RP, neuroapraxia involves a period of functional insufficiency of nerve fibres of up to 24 months, limiting the effectiveness of the use of PDE-5 inhibitors [11,12].
significantly greater than the number dropping out because of it, indicating that in several cases the symptoms probably faded with treatment progress. Drug temperature was another critical factor in determining pain. By contrast, we found no significant correlation with drug dose, as was borne out by the fact that those patients who experienced intense pain reported it from the point of the first, low-dose injection.

Patient satisfaction with ED management and sexual intercourse was quite high (75% of patients reported to have recommenced their sexual life; among these, 60% reported satisfying intercourse). In a sample of patients treated with non-nerve-sparing RP, Gontero et al. [16] described an effectiveness of 70% among individuals undergoing early rehabilitation with a multistep treatment approach.

Our experience may be influenced by the counselling offered to patients and couples, who were given exhaustive information, instructions, and support and reassurance in case of failure (especially when injecting the lower doses).

In conclusion, most patients who underwent RP sought help to recover sexual potency, but the route to penile rehabilitation is demanding and frustrating; eventually nearly 20% of these patients dropped out of the rehabilitation programme. It is our opinion that early administration of injected drugs and careful counselling and support are required to motivate patients to pursue this goal after a traumatic procedure such as RP [17]. We also feel that the management of these subjects would benefit from a change of focus, from the patient to the couple viewed as a single and complex player.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Abbreviations: RP, radical prostatectomy; IIEF5, 5-item International Index of Erectile Function; ED, erectile dysfunction; PGE1, prostaglandin E1; PDE-5, phosphodiesterase-5.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

APPENDIX