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1 Use of a specific questionnaire and perineal electromyography to assess neuropathic pain after radical
2 retropubic prostatectomy

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9 Running title: Assessment of neuropathic pain after radical prostatectomy

10 Abstract:

11 Background: Prostate cancer is the most frequent cancer in men and radical retropubic prostatectomy (RRP) is
12 one of the first line treatment. However, RRP have some side effects and can lead to chronic perineal pain. The
13 objective of the study was to determine in patients suffering from perineal pain after RRP the possibility of a
14 neurogenic damage by means of a specific questionnaire dedicated to track down neuropathic pain.

15 Methods: Forty patients were explored by a specific and validated questionnaire, the Neuropathic Pain Symptom
16 Inventory (NPSI). Patients were divided into two groups: Group A with an NSPI score ≥ 4 was considered as
17 suffering from neuropathic pain and Group B was considered as a control group without neuropathic pain (NSPI
18 score < 4). All patients had a perineal electrophysiological testing to confirm the possibility of a neurogenic
19 damage.

20 Results: Group A was composed by 13 men and group B by 27 men, mean age 72.45 years and mean duration of
21 pain 2.7 years. In Group A, the most frequent symptoms were burning sensation, electrical shock and numbness.
22 Location of the pain was global perineal area (8/13), anus (10/13), , penis(5/13) and glans penis (2/13).
23 Electromyography (EMG) findings confirmed the presence of denervation and neurogenic damages compared
24 with controls ($p < 0.001$).

25 Conclusion: One third of the patients consulting for chronic pain following RRP had probably a neuropathic
26 lesion leading to a chronic perineal pain as suggested by an NSPI score ≥ 4 and EMG alterations.

27 Key words: Prostatectomy, neuropathic pain, specific questionnaire, perineal electromyography

28 Introduction

29 Prostate cancer is the most frequent cancer in men, with more than 240 000 patients newly diagnosed per year in
30 the United States alone (1). In these patients, retropubic radical prostatectomy (RRP) is the most common
31 technique for removing the prostate gland. Morbidity related to this procedure is quite low (2), however long-
32 lasting pain is not generally reported after RRP. Pelvic and perineal pain persisting more than 3 months after
33 surgery has been yet described (3), with a serious impact on patient's quality of life. It could be speculated that
34 some, or a part, the persistent pain occurring after RRP could be secondary to a neurogenic damage due to the
35 surgical procedure. Indeed, alterations of peripheral nervous system following RRP are well known (4-7) and
36 such neurogenic lesions (beside other consequences of neurogenic damage urinary incontinence, erectile

37 dysfunction) can lead to neuropathic pain. The aim of the study is to determine in patients underwent RRP and
38 suffering from perineal pain the possibility of a neurogenic damage by means of a specific questionnaire
39 dedicated to track down neuropathic pain, and then, to confirm neurogenic damage by a perineal
40 electromyographic (EMG) testing.

41

42 Patients and Methods

43 Forty patients admitted for perineal pain following RRP for prostate cancer were enrolled in the study. Pain was
44 at least persistent for 6 months postoperatively. They were all well informed about the project and gave their
45 written consent to participate. We have obtained the agreement of local ethics committee. (ID-RCB: 2015-
46 A00125-44). The patients had no neurological disorders and none had been treated by radiotherapy.

47 All the patients were referred to the Neuro-urology Department for EMG examination to track down a
48 neurologic cause related to their chronic pain, especially a pudendal nerve lesion. They underwent a full clinical
49 examination. Perineal skin sensation, anal and bulbo-cavernosus reflexes, voluntary contraction and tone of the
50 anal sphincter were examined in lithotomy position. For all patients, urinary incontinence was evaluated by a
51 specific questionnaire (Urinary Symptom Profile , USP) and erectile dysfunction by the International Index of
52 Erectile Function (IIEF-5).

53 EMG recordings were performed in all the patients. To demonstrate neurogenic changes, an EMG needle
54 electrode was inserted in the following perineal muscles: urethral sphincter, bulbocavernosus muscle and finally
55 external anal sphincter. Sacral reflex (bulbocavernosus reflex) was elicited by means of stimulations of the
56 dorsal nerve with a record of the motor potentials by means of a needle electrode inserted into the
57 bulbocavernosus muscle. Measurements of right and left latencies were performed at the onset of the motor
58 responses (normal latency < 44 ms). Cortical evoked responses following repetitive stimulation of the
59 pudendal nerve were recorded (normal latency < 44 ms). Finally, terminal motor latencies of the pudendal
60 nerve following intrarectal stimulations were recorded at the onset of motor potential of anal sphincter (normal
61 latency < 3.5 ms). Lesion of peripheral nervous system was defined as neuropathic changes in EMG
62 examination (increased rate of motor unit potentials $\geq 20/s$ presence of spontaneous fibrillation and/or positive
63 sharp waves) with at least alteration of sacral latencies and/or pudendal nerve terminal motor latencies and/or
64 cortical evoked potentials.

65 All the patients fulfilled a specific questionnaire, the Neuropathic Pain Symptom Inventory (NPSI). The NPSI is
66 a validated questionnaire (8) which allows to speculate a neurogenic cause of a chronic pain in case of a total
67 score ≥ 4 . (Supplement file). This cutoff has been used to determine two groups of patients. The first group
68 (Group A) included patients with NSPI score ≥ 4 defining patients with neuropathic pain. The second group
69 (Group B) included patients without neuropathic pain and so, with NSPI score < 4. All the results of EMG
70 findings were analyzed with a Fisher test and a *p* value less than 0.05 was considered as significant. All
71 statistical analyses were performed with the R-studio version 3.3.1

72 Results

73 The age of the 40 patients was 72.45 ± 7.45 years (mean \pm SD) and the duration of the chronic pain was $2.7 \pm$
74 2.2 years (mean \pm SD). They also had associated erectile dysfunction (*n*= 38/40) and urinary incontinence

75 ($n=9/40$). There were no statistical differences between the two groups. Thirteen patients were classified in
76 Group A (NSPI score ≥ 4) and considered as having neuropathic pain. Twenty-seven patients were classified in
77 Group B (NSPI score <4) and considered as without neuropathic pain.

78 The most frequent symptoms in Group A were burning sensation (10/13 vs 9/27 in Group B), electrical shock
79 (10/13), numbness (10/13) and paresthesia (10/13). Location of the pain was global perineal area (8/13), anus
80 (10/13), penis (5/13), glans penis (2/13), and scrotum (6/13).

81 EMG findings:

82 In group A, EMG findings confirmed the presence of a significant denervation in perineal muscles (13/13 vs
83 3/27 in Group B) ($p < 0.001$). Sacral latencies were delayed in 3/13 and pudendal nerve terminal latencies in
84 8/13 (vs 2/27 in Group B). Cortical evoked responses were altered in 2/13 patients in the neuropathic group and
85 2/27 in the non-neuropathic group (Table 1).

86 Discussion

87 This study is the first, to our knowledge, to demonstrate clinically a neurogenic cause of perineal pain following
88 RRP. Moreover, this neurogenic lesion is confirmed by specific neurogenic alterations of EMG testing. In this
89 study, one third of patients consulting for chronic pain following RRP had a neurogenic lesion leading to a
90 chronic perineal pain as suggested by an NSPI score ≥ 4 and EMG alterations.

91 The first limit of our study is that we could not obtain the overall data on surgical technique of prostatectomy for
92 all included patients, but the primary outcome of our study was to assess neuropathic pain and neurogenic
93 alterations in patients who underwent a radical prostatectomy (RP) regardless of the surgical technique that has
94 been used. Chronic pain following RRP is rarely reported (3, 9-11). Indeed, most of the studies are related to
95 evaluation and therapeutic strategies of the immediate pain occurring just after the surgery (12). Few studies
96 are devoted to the long-term post RRP painful syndrome [9,10]. However, this complication may seriously affect
97 the quality of life of these patients (13). Mirzapour et al. (14) have reported local pain after 12 months following
98 RRP in 28% of patients and 29% after perineal RP. In the same study, 6 months after RRP or perineal RP, one
99 third of the patients complained of their pain in sitting position. These data support firstly the hypothesis that the
100 pain does not depend on the surgical procedures and secondly that the pain is possibly due to a neurogenic cause
101 since it increases in sitting position suggesting a compression of the pudendal nerve against the ischial tuberosity
102 in this position. Data on local postoperative pain after RRP are available in a systematic review conducted by
103 Ficarra et al (15) in 2009 reporting nine studies. Seven studies compared pain after RRP or laparoscopic radical
104 prostatectomy (LRP) and the most used tool was a validated 10-point visual analogic scale (VAS). All these data
105 concerned acute postoperative pain.

106 The NSPI has been used to evaluate the type of pain in our 40 patients and suggest a neurogenic cause to this
107 chronic neuropathic pain, if the score was ≥ 4 . EMG was done to assess if these patients had also neurogenic
108 damages and to support the data found allowed by NSPI questionnaire. In 2012 Yiou et al (16) assessed the

109 penile cold and vibratory sensory thresholds to reflect the cavernous nerve damage after RP and found that some
110 surgical techniques had better results. Indeed, penile sensory threshold for warm and cold sensation increased
111 after Non-Nerve Sparing Radical Prostatectomy (NNSRP) but not after Nerve Sparing Radical Prostatectomy
112 (NSRP). Vibratory threshold only increased after transperineal NNSRP. With the same neurophysiological
113 evaluation, Lefaucheur et al (17) in 2000 demonstrated that the warm, cold and vibratory threshold was
114 significantly increased after trans urethral resection of the prostate (TURP) and supported the hypothesis of
115 neurogenic damage (penile small nerve fiber) as the primary cause of post-operative erectile dysfunction. Thus,
116 all these studies support the hypothesis of a neurogenic damage following RRP. Since then, it can be speculated
117 that these neurogenic lesions can lead not only to urinary incontinence and/or impotence, but also to a
118 neuropathic pain since acute or chronic nerve lesions can determine chronic neurogenic pain syndrome.

119 Nevertheless, even if changes and neurologic damages could be part of the explanations of a neuropathic pain,
120 other causes could be discussed.

121 Gerbershagen et al (10) in 2009 have evaluated the preoperative pain status and its influence on the occurrence
122 of chronic post-surgical pain (CPSP). Mental and physical health regarding CPSP development were analyzed.
123 From 72 patients evaluated after RP, 12 had CPSP and all the patients suffered from preoperative pain
124 ($p=0,003$). In this study only one patient suffered from chronic pain at the 6 months follow-up. A systematic
125 review conducted in 2015 by Boogaard et al (18) assessed pain and tried to find predictive factors. The main
126 factors leading to post-surgical pain were psychological distress, pain at day 2 (VAS >3) or a higher body mass
127 index. In 2012, the European Association of Urology (19) proposed guidelines on prostate cancer pain
128 management. Pain can be precisely caused by the cancer (77%) or by cancer treatment (19%). Furthermore, the
129 overall incidence of chronic pain in prostate cancer patients was found about 30% to 50% (19).

130 Another key point is the clinical evaluation of cancer pain. VAS usually used to quantify chronic pain is not only
131 inadequate in term of diagnosis, but also imperfect for a complete evaluation since pains that impact the
132 psychological, mental and physical health status are not strictly taken into account with this tool. The use of a
133 specific questionnaire as the McGill Pain Questionnaire (20,21) seems to be better to evaluate such chronic pain.
134 Furthermore, the interest of a specific questionnaire as the NPSI (8) is major, since it can give strong arguments
135 for a neurogenic pain. It characterizes with great accuracy the neurogenic etiology using specific words as
136 “burning” or “electrical shock” or “numbness”, all words largely reported by patients suffering from neuropathic
137 pain (22). The knowledge of such an etiology, e.g. neuropathic pain, is important in terms of therapeutic
138 strategies (12).

139 Conclusion

140 A neurogenic cause of perineal pain following RRP is possible. This can be clinically confirmed by using a
141 specific questionnaire like NSPI and eventually by perineal EMG. The knowledge of such an etiology can be
142 taken into account in adjusting the therapeutic strategies.

143

144 Compliance with Ethical Standards:

145

146 All procedures performed in studies involving human participants were in accordance with the ethical standards
147 of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later
148 amendments or comparable ethical standards.

149 Informed consent was obtained from all individual participants included in the study.

150

151 Conflicts of interests: zzzzzzzThe authors declare no conflict of interest.

152

153

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- 207

Q1. Does your pain feel like burning?

No burning	0	1	2	3	4	5	6	7	8	9	10	Worst burning imaginable
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Q2. Does your pain feel like squeezing?

No squeezing	0	1	2	3	4	5	6	7	8	9	10	Worst squeezing imaginable
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Q3. Does your pain feel like pressure?

No pressure	0	1	2	3	4	5	6	7	8	9	10	Worst pressure imaginable
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Q4. During the past 24 h, your spontaneous pain has been present:
Select the response that best describes your case

Permanently	/	/
Between 8 and 12 h	/	/
Between 4 and 7 h	/	/
Between 1 and 3 h	/	/
Less than 1 h	/	/

We wish to know if you have brief attacks of pain. For each of the following questions, please select the number that best describes the average severity of your painful attacks during the past 24 h. Select the number 0 if you have not felt such pain (circle one number only).

Q5. Does your pain feel like electric shocks?

No electric shocks	0	1	2	3	4	5	6	7	8	9	10	Worst electric shocks imaginable
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Q6. Does your pain feel like stabbing?

No stabbing	0	1	2	3	4	5	6	7	8	9	10	Worst stabbing imaginable
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Q7. During the past 24 h, how many of these pain attacks have you had?
Select the response that best describes your case

More than 20	/	/
Between 11 and 20	/	/
Between 6 and 10	/	/
Between 1 and 5	/	/
No pain attack	/	/

Q8. Is your pain provoked or increased by brushing on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable
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Q9. Is your pain provoked or increased by pressure on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable
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Q10. Is your pain provoked or increased by contact with something cold on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable
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We wish to know if you feel abnormal sensations in the painful area. For each of the following questions, please select the number that best describes the average severity of your abnormal sensations during the past 24 h. Select the number 0 if you have not felt such sensation (circle one number only).

Q11. Do you feel pins and needles?

No pins and needles	0	1	2	3	4	5	6	7	8	9	10	Worst pins and needles imaginable
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Q12. Do you feel tingling?

No tingling	0	1	2	3	4	5	6	7	8	9	10	Worst tingling imaginable
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RESULTS

Total intensity score	Subscores	
	Burning (superficial) spontaneous pain:	
1. Q1 =	Q1 =	/10
	Pressing (deep) spontaneous pain:	
2. (Q2 + Q3) =	(Q2 + Q3)/2 =	/10
	Paroxysmal pain:	
3. (Q5 + Q6) =	(Q5 + Q6)/2 =	/10
	Evoked pain:	
4. (Q8 + Q9 + Q10) =	(Q8 + Q9 + Q10)/3 =	/10
	Paresthesia/dysesthesia:	
5. (Q11 + Q12) =	(Q11 + Q12)/2 =	/10
(1 + 2 + 3 + 4 + 5) =	/100	

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209
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211

Supplement file. NSPI questionnaire

212 Table1. Results of EMG testing and clinical complications on a population of 40 men who underwent RRP.

Patient characteristics	Group A (NSPI \geq 4) (n = 13)	Group B (NSPI < 4) (n = 27)	p value
EMG findings			
Delayed sacral latencies	3/13 (23%)	2/27 (7%)	0.3
Delayed pudendal nerve terminal latencies	8/13 (62%)	2/27 (7%)	<0.001*
Delayed cortical evoked responses	2/13 (15%)	2/27 (7%)	0.58
Perineal muscles denervation	13/13 (100%)	3/27 (11%)	<0.001*
Urinary incontinence	2/13 (15%)	7/27 (26%)	0.69
Erectile dysfunction	12/13 (92%)	26/27 (96%)	1.00

213 NPSI , Neuropathic Pain Symptom Inventory (a neurogenic cause of a chronic pain is speculated in case of a
 214 total score \geq 4).

215

216