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Keywords: urinary incontinence, prostatic cancer, electromyography, pelvic floor, rehabilitation, urodynamics, robotic surgery.

ABSTRACT

Background: Stress Urinary Incontinence (UI) is the most common presentation following Robot-Assisted Radical Prostatectomy (RARP), but a post-operative non-invasive and objective test is still lacking. To assess pelvic floor integrity after RARP, we recently proposed Uroflow Stop Test (UST) with surface Electromyography (EMG).

Aims: Here we provide two new clinical parameters: the Neurologic Latency Time (NLT) and the Urologic Latency Time (ULT) derived from UST-EMG test. Principal outcome was to evaluate their variation during one year follow-up and ULT ability to predict post-RARP UI.

Design: Observational and longitudinal study.

Setting: Interdivisional Urology Clinic (Perugia-Terni)

Population: Patients with prostate cancer treated with a full nerve-sparing RARP who underwent post-operative Pelvic Floor Muscles Training (PFMT): a diurnal functional home program and a weekly hospital program with the use of biofeedback, between 1 and 3 months post-operatively.

Methods: All patients consecutively performed a UST-EMG test at one, three, six, and twelve months after surgery. At each follow-up visit we collected NLT values, ULT values, 5-item 26-Expanded Prostate Cancer Index (EPIC), Incontinence Developed on Incontinence Questionnaire (ICIQ-UI) Short Form and International Prostate Symptom Score (IPSS). We analysed statistically significant differences in NLT and ULT between continent and incontinent patients and we evaluate the diagnostic ability of 1-month post-surgery ULT value to diagnose the presence of post-operative UI.

Results: Sixty patients were enrolled. The mean time to PFMT was 31.08 (range: 30-35) days. Overall IPSS, NLT and ULT had similar trends: progressive decrease until the six months after surgery (1-month vs 3 months vs 6 months, $p<0.05$) to plateau thereafter. When considering the two group of patients, IPSS and NLT were significantly higher in the incontinent group only one month after surgery, while ULT became similar between the two groups at 6 months after surgery. The best cut-off of 1-month ULT values that maximized the Youden function at 12-months resulted 3.13 second.

Conclusions: NLT and ULT may respectively account for the nerve and the urethral closure system integrity post-RARP. In the first month after RARP, both NLT and ULT differs between incontinent vs continent patients. NLT become similar between two group after one month, confirming the recovery from neuropraxia, but ULT remains statistically significant different until 3 month post-operatively. The value of 1-month ULT resulted a valid tool to predict incontinence status at 12 months.

Clinical rehabilitation impact: ULT and NLT may be also useful tools to monitor the continence progressive recovery after RARP and they may help rehabilitation specialists to evaluate the ongoing results during post-operative follow-up.

Introduction:

The widespread use of Robot-Assisted Radical Prostatectomy (RARP) to treat localized Prostate Cancer (PCa) reduced the incidence of treatment-related bothersome adverse effects, however, the rate of male Stress Urinary Incontinence (UI) after RARP still remains elevated.[1] In the meantime, cancer detection rate improves, thanks to new imaging diagnostic tools, lowering the median age at diagnosis.[2] Thus, the continence recovery becomes a critical step to return to regular daily activities in these patients with a long-expected lifetime. Although the UI demonstrates a high spontaneous resolution rate, in some patients it may persist for 1–2 years. The UI, defined as no need of daily pad, was identified, in 20% patients at 90 days and in 4-31% at 12 months, after RARP.[3]

The long-lasting impact of UI profoundly impairs patients' quality of life and rate to recovery are essentially managed with Pelvic Floor Muscle Training (PFMT).[4] The absence of an objective and non-invasive tool able to measure the severy of UI, currently based only on patient's perceptions, does not allow to make a standard classification among incontinent patients particularly regarding the sphincteric efficiency. Moreover, it would be necessary a quick recognition of UI to adapt the best supportive program.[5]

El-Hakim et al. proposed the Uroflow Stop Test (UST) to predict the risk of UI after RARP. Thanks to its neurophysiological implications, Alenizi et al. proposed UST as a surrogate for the pelvic floor integrity.[5, 6] Although this test is easily applicable into the clinical practice, it was neither measured pre-operatively nor standardized. We recently combined the UST with the simultaneous measurement of superficial perineal Electromyography (EMG). In this way, it was possible to determine the Latency Time (LT) as the time lapsing between the stop command and the interruption in urinary flow. We validated the test in patients who underwent RARP taking as reference the preoperative latency time of each patient.[7]

During RARP two surgical steps reduced the natural urinary continence system: the prostatic urethra is resected and a new urethrovesical anastomosis connected the bladder neck with the membranous urethra. Thus, the continence system after RARP is based on external urethral sphincter integrity and function and on the membranous urethra, supported by surrounding structures as pelvic diaphragm and supporting fascial network. All this can produce weakening of the membranous urethra, hypermobility of the bladder and the displacement of the posterior support.[8-10]

Indirect lesions of the external urethral sphincter during RARP are not uncommon, so that urinary continence regularly depends on the elastic tension of the urethra, on the watertight seal of soft tissues and on the Pelvic Floor Muscles (PFMs) complex efficiency. All these structures are highly interdependent but it is not completely clear how they cooperate and the relative contribution of each element.[10] Beside of the anatomical integrity of the PFMs, the persistence of neuro-vascular support

to these anatomical structures seems to be decisive in strengthening the continence mechanism. For this reason, PFMT is the first postoperative recommended treatment.[11]

We aimed to provide more information about this complex system by splitting the previously introduced global index of latency time into two more specific components: the Neurologic Latency Time (NLT) and the Urologic Latency Time (ULT). It was possibile to identify these new parameters by analyzing the beginning of EMG signal activation during UST-EMG test. The principal outcome was to evaluate if and how these parameters change according to post-surgical UI. Secondary outcome was to verify if these new parameters can predict post-surgical urinary incontinence reported by the patient.

MATERIAL AND METHODS

Subjects

We conduct a prospective observational study in a high-volume tertiary care institute starting from January 2018 until January 2020 on patients with clinically localized Prostate Cancer (PCa) underwent full nerve sparing RARP, according to our previously described extraperitoneal full-nerve sparing PERUSIA technique,[12] with a minimum follow-up time of 12 months. We obtained written informed consent from every participant before enrolment and surgery, according to our protocol, approved by the institutional medical research ethics committee (n. 12393/18/AV).[7] All patients underwent a 3-T prostatic MRI based cognitive fusion biopsy as previously described.[13] ASA (American Society of Anaesthesiology) and Charlson Comorbidity Index were used to classify performance status and comorbidity, respectively. Every patient completed the International Prostatic Symptoms Score (IPSS) pre-operatively. We recorded positive surgical margins status and postoperative complications (according to Clavien-Dindo classification). All patients performed PFMT within the first and the third month after surgery. They completed two questionnaire at 1-, 3-, 6- and 12-months after surgery: 5-item of the EPIC-26 questionnaire,[14] and the International Consultation on Incontinence Questionnaire-Urinary Incontinence short form (ICIQ-UI Short Form), comprising a question about everyday QoL.[15]

Exclusion criteria

Exclusion criteria were: non-organ confined PCa or high-risk disease; non-nerve sparing procedure; preoperative radiotherapy; previous prostatic surgery; neurological or diabetic diseases; prostate volume > 70 ml; positive-cores at biopsy in the anterior zone (preservation of dorsal venous complex not applicable); preoperative incontinence; preoperative maximum flow rate < 15 ml/s at uroflowmetry; evidence of anastomotic leakage at cystography and use of oral anticholinergics for post-operative UI; patients unable to correctly contract pelvic floor muscles a first post-operative evaluation.

Surgical procedure

The same skilled surgeon, who was not blinded on patients' characteristics and on study results, performed the PERUSIA technique in the same high volume interdivisional institute to reduce the impact of the treatment on the results [11]. We showed complete preservation of neuro-vascular bundles in all patients.

Uroflow Stop Test with EMG record of PFMs activity

All patients underwent UST - EMG (Mediwatch®, Northpoint Parkway, West Palm Beach, FL, USA) at 1-, 3-, 6- and 12-months after surgery, as previously described [7]. The device produced the stimulus tone (stop command) for 1 second during practice trials and for 0.2 seconds during testing. Participants had to respond to the auditory stimuli by interrupting the urine as quickly as possible. Appropriate response reaction time was set > 150 ms, with lower time representing an anticipatory response [17, 18]. The test was accepted if patient achieved voluntary interruption of the urine flow for at least 3 seconds. A maximum flow rate $\geq$ 15 mL/s ensured a non-obstructed normal flow [19].

The raw EMG signals were visually controlled for artefacts. The filtered EMG signal and the urinary flow signal were exported into an Excel® 2018 (Microsoft Corporation). Two landmarks were identified on the filtered EMG signal corresponding to the onset of PFMs activity and to zero urinary flow. The onset of PFMs activity was defined as the value equal to twice the resting value at the beginning of the test. We normalized the average to the peak value obtained within the same window, according to the Surface Electromyography Non-Invasive Assessment of Muscles (SENIAM) recommendations [16]. The time between the stop command and the onset of PFMs activity was defined as Neurological Latency Time (NLT); the time between the onset of PFMs activity and the achievement of a zero urinary flow value as Urological Latency Time (ULT). The sum of the two values was called NeuroUrology Latency Time (NuLT).

Figure 1 graphically shows the exact calculation method of the three latency times.

Rehabilitation Protocol

During the pre-operative visit the patient was educated about the anatomy of the genital area and its modifications after surgery. Patient's goals and impact of UI on his lifestyle were defined and the patient was fully advised about the benefits of PFMT. During this visit the patient was instructed on the exercise of "stop the urinary flow".

One day after catheter removal, the patient was trained by a resident physician on PFMT by using the "Kegel" exercises maintaining visual feedback by the "shorten the penis" technique.

After the first post-operative month, all patients went to the hospital once a week to discuss about their bladder diaries and for sexual rehabilitation. Moreover, a urologist assessed patient's PFMs performances under anal digital examination, estimating muscles activation. If the patient was unable to contract the pelvic floor muscles correctly, he was referred to a pelvic health physiotherapist. At 1 month evaluation we also performed the UST-EMG and we considered ULT as a marker of contraction ability of the patient, using it to encourage contractions during functional tasks and to tailor program on every single patient.

The PFMT program was organized in two parts: a home program without use of biofeedback and a hospital program with use of biofeedback.

The first included five exercises sequences during diurnal functional activities. In the home program the patients were invited to initially perform 3 seconds maximal contractions in sitting (6 contractions) and standing (6 contractions) five times daily (60 contractions per day), with 5 seconds of rest and relaxations after each contraction. Each patient was instructed on expiration (contractions) and inspiration (rest) phases. The duration of the contractions was increased until 6 seconds over time. Every patient received a pelvic floor exercises leaflet, in which was encouraged to perform these exercises at home five times a day. At every hospital meeting during rehabilitation the patient was instructed to implement PFMT program at home with new dynamic functional tasks: in supine position elevating hip, walking, lifting and squatting.

In the hospital PFMT program, leaded by physician, the patients were invited to attend eight one-to-one sessions held by the same continence- specialized urology nurse over two months. A combination of different types of exercises including PFMs contraction – targeting both slow and fast-twitch muscle fibres was performed. During this hospital training we used biofeedback tool to educate patients to perform an effective and graded pelvic muscle contraction. Surface intra - anal probes were used to provide visual or auditory feedback about the pelvic floor muscle strength and contractions. Patient was instructed to graphically display PFMs performances. At every evaluation the patient was progressively invited to focus the attention from the anal activating focus on the urethral focus, through the "short the penis" task: subjective feeling of squeezing and lifting of the muscular-fascial planes of the pelvic area.

PFMT was continued as long as any degree of UI persisted and patients were controlled for adherence to the home exercises.[20]

Statistical analysis

At each visit after surgery, patients were split into two groups according to urinary continence assessed through the 5-item of the 26-EPIC questionnaire. Patients were classified continent if they answered "*no pads*"; incontinent if they answered "*1 pad per day*", "*2 pads per day*" or "*3 or more pads per day*". Because the normality test failed, the Friedman Repeated Measures Analysis of Variance on Ranks was applied to investigate the evolution with time (set as independent variable) of NuLT, NLT, ULT and IPSS. The Kruskal-Wallis One Way Analysis of Variance on Ranks was used at each visit to investigate if and how these parameters differed between continent and incontinent patients. Finally, to evaluate the diagnostic ability of 1-month post-surgery ULT to diagnose the presence of post-

operative UI, we examined the ROC curve and the Area Under Curve together with the optimal cut-off values were computed. The Area Under Curve is the chance that the model will be able to distinguish between positive class and negative class. The optimal cut-off points were determined as the values at which the Youden's index (i.e.: sensitivity + specificity −1) was maximized. We set a *p*-value of 0.05 to determine the statistical significance of both intra- and inter-group. We used SigmaStat® software for statistical analysis.

RESULTS

One-hundred and nine patients were enrolled. Forty-nine patients did not meet the inclusion criteria and they were therefore excluded from our analysis. We finally evaluated 60 patients. Pre- and peri-operative characteristics of both groups of patients are shown in *Table 1*. Before surgery, all patients were unobstructed with a minimum flow rate of 17 ml/sec and moderate lower urinary tract symptoms as specified by IPSS mean score. Positive Surgical Margins were all < 1mm and notified in 10 patients (16.7%). No biochemical recurrence detected in the entire follow-up period. Complications occurred in 6.7% of the patient, all of Clavien-Dindo grade I-II. No major complications occurred. The mean time between the time of surgery and the beginning of PFMs rehabilitation was 31.08 (30-35) days.

Incontinence severity (ICIQ-UI Short Form), ULT and NLT values before and after PFMT program

Incontinence was reported by 36 patients (60%) in the first month after surgery, by almost half patients (32) after three months and then incontinence stabilized around 40% (25 patients after six and 24 after 12 months).

Overall IPSS, NLT and ULT had similar trends: progressive decrease until the six months after surgery to plateau thereafter. More in detail, IPSS progressively passed from moderately to mildly symptomatic (figure 3). In spite of the statistical significance, NLT changes were not clinically relevant before and after surgery. On the other hand, post-operative ULT were systematically higher than pre-operative values (figure 4).

When considering the two group of patients, IPSS and NLT were significantly higher in the incontinent group only one month after surgery (figure 3 and 4), while ULT became similar between the two groups 6 months after surgery (figure 4).

Urologic Latency Time (ULT) cut-off for diagnosis of incontinence after surgery

ULT values at 1-month (before rehabilitation program) was implemented in a ROC curve (figure 5) analysis to identify its ability to predict incontinence at 1-, 3-, 6- and 12 months' post-surgery.

The best cut-off of 1-month ULT values that maximized the Youden function at 1-month after surgery resulted 3.3 second corresponding to 0.95 of sensitivity and 0.83 of specificity. The Area Under Curve was 0.88.

The best cut-off of 1-month ULT values that maximized the Youden function 3-months after surgery resulted 3.02 second corresponding to 0.46 of sensitivity and 0.87 of specificity. The Area Under Curve was 0.67.

The best cut-off of 1-month ULT values that maximized the Youden function at 6-months after surgery resulted 3.07 second corresponding to 0.48 of sensitivity and 0.96 of specificity. The Area Under Curve was 0.72.

The best cut-off of 1-month ULT values that maximized the Youden function at 12-months after surgery resulted 3.13 second corresponding to 0.50 of sensitivity and 0.91 of specificity. The Area Under Curve was 0.70.

Discussion

Urinary continence mechanism is physiologically regulated by an involuntary autonomic nervous system controlling the internal urethral sphincter and by a voluntary somatic nervous system controlling the external urethral sphincter. The principal pathophysiologic mechanism underlying UI is an urethral closure pressure lower than the bladder one in which play a role both nerves and muscles integrity.[22]

During RARP the internal urinary sphincter is surgically removed, inducing modifications on the urinary continence mechanisms, that are still not completely understood.[3] We can describe three principal factors ensuring an urinary continence after prostatectomy: 1) integrity of the external urethral sphincter, 2) integrity of the pelvic floor mucles, strongly connected with the external urethral sphincter 3) integrity of the neurovascular supply of these muscles. Therefore, even if after a prostatectomy can be observed a notable decrease in both maximum urethral closure pressure and functional urethral profile length,[22] a urinary continence mechanism is still possibile if the three factors mentioned above are preserved.

If in the past a direct surgically-induced damage of the external urethral sphincter was considered a principal mechanism of the post-prostatectomy UI, the introduction of robotic surgery have moved the attention on these fine muscles' neurovascular supply as a main mechanism underlying the urinary continence.[23,24] Indeed, the clinical use of the UST-EMG arises from the need to identify and evaluate the complex phenomenon of post-RARP UI.

Historically, the diagnosis of stress UI was primarily based only on patients' self-reported symptoms, and a suitable objective test to be employed in clinical practice, lacked for long time[25]. The clinical use of the Uroflow Stop Test (UST) after radical prostatectomy was suggested in 2015 and then it was demonstrated to be a strong predictor of urinary continence post-RARP when applied at time of catheter removal.[5] However, this test took into account only the capacity to obtain flow interruption (positive or negative UST) without distinguishing between the time necessary to obtain flow interruption or the neurological reaction from the muscular contribution.

In order to overcome these limits, we have recently introduced in this clinical field the UST-EMG.[6] The EMG perineal tracing allows to distinguish the time of the neurological response (i.e.: the time from the stop command necessary to the PFMs response) from the urethral closure system response (i.e: the time from the muscular activation to the effective urine flow interruption, *Figure 1*).

In this study, we have introduced for the first time two new parameters derived from UST -EMG test: NLT and ULT, that can be respectively used to discriminate the nervous and the urethral closure system efficiency. In fact, NLT can be considered as "neurological" reaction time, defined as the time (in the order of several hundred milliseconds) necessary for the nervous system to get the contraction

command to the striated muscle structures, according to reaction-time methodology described by Fozard and colleagues.[18] Thus, NLT may account for the nerve integrity. Conversely, ULT, defined as the time between the onset of PFMs activity necessary to achieve a zero urinary flow value, may help to clinically assess urethral closure system (assuming that the external urethral sphincter contraction is contemporary with the contraction of the pelvic floor mucles).

In our cohort of patients, both ULT and NLT values resulted significantly longer than their pre-operative values. The ULT showed a significant increase after the first month, later it decreased gradually reaching a plateau at six months after surgery; in a similar way NLT reaches a plateau at 3 months.

However, NLT resulted significantly longer in incontinent group only in the first month after surgery, instead ULT resulted significantly longer in incontinent group until 3-months. Since all patients underwent a full neuro-vascular bundles preservation, NLT values' trend can be explained with an early recovery from neuropraxia after surgery;[11] conversely the more gradually improvement of ULT can be associated with the functional adaptation of the remaining urethral closure system consisting of external urethral sphincter and pelvic floor muscles.[23]

About this functional adaptation after RARP, supporting literature focused on the conservative surgical strategy of the endopelvic fascia, a stable interface between pelvic floor and the external urinary sphincter.[24, 26, 27] The permanence of this fascial envelopment of the peri-prostatic neuro-vascular structures plays an important role in the continence recovery, overcoming the historical concept of bundle-like anatomy in favour to a postero-lateral and anterior spray-like arrangement.[28, 29]

Based on the hypothesis that a reduction of ULT is associated with a full recovery of the neuro-vascular function of PFMs and external urethral sphincter, we evaluated ULT at 1-month (before PFMT) as a predictive tool of 12 months' UI. In particular, the use of the value of 3.13 seconds at 1-month as a cut-off value, may help rehabilitation specialists in selecting patients who will need a more intensive rehabilitation program.

Several studies well demonstrated the positive impact of PFMT on UI recovery after-prostatectomy[17, 26]. Post-operative PFMT improves urethral closure pressure, enhanced the urethral stability and downward movements are minimized[24]. Literature suggests that skill acquisition in PFMs contraction is perhaps more important than their morphological changes[26,30].

A strenght of PFMT protocol used in this study was the biofeedback provided to the patients. Patients' perception of the active recruitment of PFMs is not easily trainable and biofeedback is a valuable tool in order to optimize this rehabilitative goal (*Figure 2*).[20] The biofeedback assistance allowed real-time monitoring of the ability to recruit and deactivate PFMs upon command, the speed of returning to

baseline after contraction, to isolate them from accessory muscles, to repeat PFMs contractions and to record the amplitude of the contraction.[21]

The lack of a control group without PFMT is a limit of this study and did not allow to evaluate its potential effects on ULT values. The use of surface EMG allows the therapist to identify the patient's progress both on muscular contraction amplitude and on the urethral closure system efficacy. Latency times (NLT and ULT) derived from UST-EMG test are objective, noninvasive and easily measurable parameters to use during the rehabilitation protocol. They may represent a useful tool guiding the physicians to evaluate the efficacy of rehabilitation program. Furthermore, the patient could have the possibility to verify his progress with an objective tool. The simple application of UST-EMG test made the related parameters to be easily applied also during PFMT programs for female patients with pure stress UI.

It is important to highlight that the single centre experience and the small sample represents the main limitations of our study, together with the need of an external validation. Single surgeon's experience could be considered a strong point in reducing variability when functional results has been analyzed after surgery (different surgical skills and experience, such as several tecniques can impact on functional outcomes after surgery), although this may limit the ability to generalize results to patients who undergoing RARP performed with others tecnique.

Conclusion:

Established evidence in efficacy and safety of PFMT program after-RARP prompted the need of a objective tool to assess continence status and PFMs performance during PFMT. UST with EMG confirms to represent an excellent test to globally assess continence status and to potentially individualize neuro-rehabilitation program. ULT and NLT may be useful tools to monitor the continence progressive recovery after RARP and they may help physician to evaluate the global rehabilitation efficacy during follow-up. Moreover, in a clinical setting, a ULT value > 3,13 sec at 1-month after RARP can predict 1- year continence and it may be used in counselling with patient, to intensify PFMT program or to improve patient's motivation.

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Table 1. Peri-operative characteristics

	Sample (n = 60)
Age, years – mean (min - max)	65.3 (49 - ~~63~~69)
BMI, kg/m2 – mean (min - max)	26.5 (22.5 - 36.2)
ASA score – median (IQR)	2 (1 - 4)
Charlson Comorbidity Index – median (IQR)	5 (3–8)
Gleason Score ≥ 7 - no. of pts (%)	32 (53.5%)
Prostate volume, ml – mean (min-max)	51,4 (27 - 74)
IPSS – mean (min-max)	12.2 (3 - 18)
QoL - median (min-max)	3 (2 - 5)
Maximum flow rate – mean (min-max)	18.4 (17–22)
PSMs - no. of pts (%)	10 (16.7%)
Post-operative complication - no. of pts (%)	4 (6.7%)

BMI: Body Mass Index; ASA: American Society of Anaesthesiology; IPSS: International Prostatic Symptoms Score, QoL: Quality of Life (from IPSS); PSM: Positive Surgical Margins

Figure legend

Figure 1: Example of Uroflow Stop Test with EMG with the calculation method of Urologic and Neurologic Latency Time

NLT: Neurologic Latency Time; ULT: Urologic Latency Time; NuLT: Neuro-Urologic Latency Time; Vura: Total Volume of Urine (ml), Qura: Average Urine Flow (ml/s)

Figure 2: – EMG trace during PFMT program. Observing the surface electromyographic trace is possible to promptly differentiate the recruitment of the abdominal muscles (blue line) from the active contraction of the pelvic floor muscles (green line).

Figure 3: Box-and-whisker plot representing the median (line within the box), the interquartile range (length of the box), the 90th and the 10th percentiles (whiskers above and below the box) of the International Prostate Symptom Score (IPSS) in all patients at 1-, 3-, 6- and 12 months' post-surgery. The grey area represents the interquartile range before surgery (*pre*). The dashed grey line represents the median before surgery. The median and the interquartile range of continent (blue symbols) and incontinent (red symbols) patients are also overlapped.
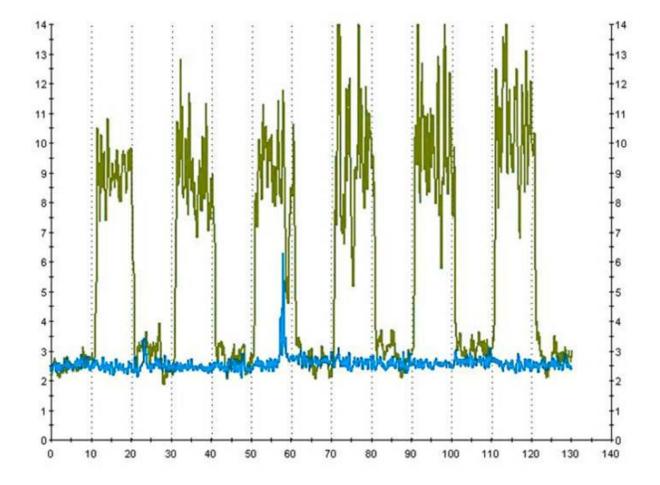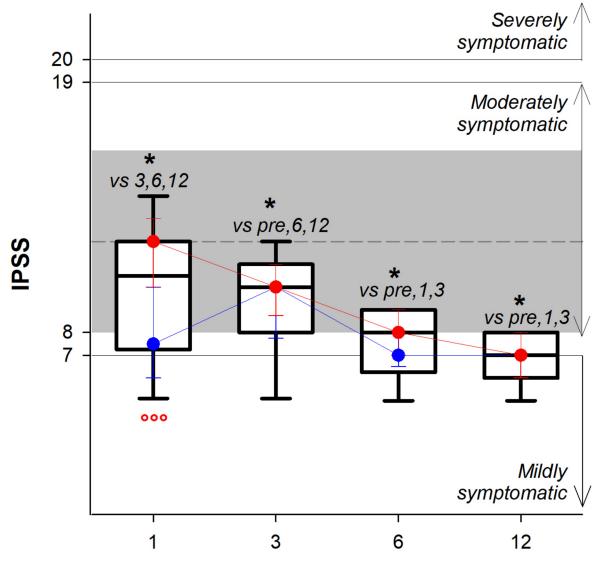
*: $p < 0.05$; °°, °°°: $p < 0.01, 0.001$ continent vs incontinent patients

Figure 4: Box-and-whisker plot representing the median (line within the box), the interquartile range (length of the box), the 90th and the 10th percentiles (whiskers above and below the box) of the Neurologic Latency Time (NLT, left panel) and the Urologic Latency Time (ULT, right panel) in all patients at 1-, 3-, 6- and 12 months' post-surgery. The grey area represents the interquartile range before surgery (*pre*). The dashed grey line represents the median before surgery. The median and the interquartile range of continent (blue symbols) and incontinent (red symbols) patients are also overlapped.

*: $p < 0.05$; °°, °°°: $p < 0.01, 0.001$ continent vs incontinent patients

Figure 5: Receiver Operating Characteristic (ROC) curve of ULT values at 1 month post-surgery to descriminate post-surgery incontinence after 1 (red); 3 (green); 6 (yellow) and 12 (blue) months after surgery. Y-axis: sensitivity (true-positive rate); x-axis: 1-specificity (false-positive rate) for various cut-offs.