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Founded in 1924
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Urological and Andrological Sciences

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SCRIPTA MANENT EDIZIONI

Società Italiana di Urologia Oncologica

La SIUrO, Società Italiana di Urologia Oncologica, nasce nel 1990 grazie all'iniziativa di un gruppo di medici specialisti, composto da Urologi, Oncologi Medici e Radioterapisti accomunati dall'interesse verso le neoplasie urologiche e dalla volontà di istituzionalizzare l'approccio multidisciplinare al paziente uro-oncologico. Oggi fanno parte dell'Associazione anche Anatomo-Patologi e Ricercatori di Base.

La SIUrO offre agli specialisti interessati alle problematiche dell'Urologia e dell'Oncologia occasioni per confrontare le proprie conoscenze e la propria esperienza professionale favorendo lo sviluppo di un patrimonio culturale comune che supera i "gap" attitudinali e operativi che si frappongono, spesso artificiosamente, fra le diverse discipline e figure professionali cointeressate alla gestione dei pazienti uro-oncologici.

XV Congresso Nazionale SIUrO

Giardini Naxos (Taormina) 3-6 novembre 2005
Centro Congressi - Hotel Ramada

Main topic:
I tumori della vescica

PRESIDENTI DEL CONGRESSO:
Prof. Darwin Melloni
Prof. Mario Motta
PRESIDENTE ONORARIO:
Prof. Francesco Micali

XIV Congresso Nazionale SIUrO

Lo scorso 12 dicembre si è concluso a Trieste il XIV Congresso Nazionale SIUrO. La giornata di giovedì 9, è stata dedicata alla memoria del Prof. Luciano Giuliani, a dieci anni dalla sua scomparsa e ha visto coinvolti, per la prima volta, tutti insieme i suoi allievi. Oltre ad una seduta di chirurgia in diretta sono stati trattati gli argomenti più cari al Prof. Giuliani che hanno caratterizzato la scuola "genovese": la chirurgia oncologica, la chirurgia laparoscopica, la chirurgia ricostruttiva, l'andrologia, l'endourologia, l'iperparatiroidismo, ecc. Alla cerimonia inaugurale erano presenti anche la Signora Giuliani e la figlia Francesca. Il congresso, accreditato per giornata, secondo le norme ECM, ha visto la presenza di oltre 400 persone per ogni giorno. Sono stati presentati più di 200 contributi scientifici tra comunicazioni poster e video. Sono intervenuti 120 relatori di cui circa il 25% non urologi (tra patologi, oncologi, radioterapisti e ricercatori di base) e numerosi ospiti stranieri.
Durante la assemblea dei soci dell'11 dicembre u.s., tenutasi nell'ambito del congresso, sono stati assegnati i 4 premi SIUrO alle migliori comunicazioni selezionate per le quattro aree: terapia chirurgica, terapia medica, terapia radiante, ricerca di base. Ed è stata inoltre eletta, come sede del congresso nazionale 2006 la città di Genova sotto la presidenza del Prof. Francesco Boccardo - Direttore della Oncologia Medica Universitaria dell'Istituto Nazionale per la Ricerca sul Cancro di Genova.

Chi intende iscriversi alla SIUrO trova le istruzioni ed i moduli necessari sul sito internet **www.siuro.it** - La quota associativa annuale è pari a:
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News SIUrO

La SIUrO ha presentato domanda di iscrizione alla FISM (Federazione delle Società Medico Scientifiche Italiane)

Il 12 febbraio 2005 la SIUrO organizza a Bologna la prima Consensus Conference Nazionale sulle linee guida per la biopsia prostatica.
Il documento di "consenso", redatto dopo anni di attento lavoro, dal Gruppo Italiano Biopsia Prostatica, costituito da esperti di diverse discipline, con la supervisione di alcuni metodologi, verrà discusso ed approvato da una giuria "esterna" di 12 membri.
Il documento finale rappresenterà un punto di riferimento essenziale per definire l'approccio diagnostico alla neoplasia prostatica su un tema così controverso come la biopsia.

La SIUrO organizzerà un corso residenziale a Erice dal 6 al 10 aprile 2006.

Per ottenere ulteriori informazioni è possibile contattare la segreteria SIUrO c/o Clinica Urologica, Alma Mater Studiorum Università di Bologna, Policlinico S. Orsola Malpighi, Padiglione Palagi, via P. Palagi, 9 - 40138 Bologna
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Archivio Italiano di Urologia e Andrologia

GENERAL INFORMATION

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ORIGINAL PAPER

A novel spectral ultrasonic differentiation method for marking regions of interest in biological tissue: *in vitro* results for prostate.

Roberto Ponchietti[1], Giuseppe Martorana[2], Filippo Di Loro[3], Alessandro Bertaccini[2], Gabriella Nesi[4], Walter Franco Grigioni[5], Simona Granchi[6], Luca Breschi[6], Elena Biagi[6], Leonardo Masotti[6]

[1]Department of Urology University of Siena, Italy; [2]Department of Urology University of Bologna, Italy; [3]Department of Urology University of Florence, Italy; [4]Department of Pathology University of Florence, Italy; [5]Pathology Division F. Addarii Institute, University of Bologna, Italy; [6]Department of Electronic Engineering University of Florence, Italy

Summary

Objective: *The aim of the present study was to evaluate the effectiveness of a new method of spectral analysis of the radiofrequency (RF) ultrasonic echo signal in discriminating neoplastic from non-neoplastic tissue of the prostate gland.*

Material and Methods: *The proposed method was previously set up on ten prostatic glands where cancer had been detected by histology in order to correlate the tumour areas with specific spectral parameters. In the present study sixty prostate specimens of patients undergoing radical retropubic prostatectomy for clinically localized prostate cancer were examined. The surgically removed prostate glands were scanned using an echo signal acquisition apparatus and the spectral parameters were obtained by the wavelet transform The echographic scans of all cases were then compared with the whole-mount histological sections of the prostate in order to evaluate sensitivity and specificity of the proposed method.*

Results: *The sensitivity and specificity for cancer detection were 93% and 91%, respectively. The specificity was invalidated by the fact that in some of the cases studied, the tumour was located in areas of benign prostatic hyperplasia (BPH). As for the sensitivity, of the three false negative cases two were due to the coexistence of cancer foci and BPH.*

Conclusions: *Our proposed method, named WAMBLE (Wavelet Analysis Multi Band Local Estimator), is accurate in detecting prostate cancer. Further in vivo studies are warranted to confirm the clinical value of this technique.*

KEY WORDS: *Prostate cancer; Imaging of prostate cancer; Radiofrequency echo signal processing.*

INTRODUCTION

Currently, prostate cancer is the most commonly diagnosed malignancy in men and, with the aging population, the incidence of prostate cancer is on the increase. In an attempt to decrease mortality of prostate cancer, much effort has been directed toward its early detection. The diagnostic tools for the detection of prostate cancer are the serum prostate-specific antigen (PSA) levels, digital rectal examination (DRE) and transrectal ultrasonography (TRUS). Each method has limitations and at present ultrasound-guided biopsy is mandatory for the diagnosis. The main limitation of TRUS in detecting prostate cancer is that the conventional grey-scale ultrasound is not specific for the diagnosis of prostate cancer. Indeed, there is overlap in the ultrasound findings indicating carcinoma, benign prostatic hyperplasia (BPH), prostatic infarct or inflammatory disorders that may affect the gland. In order to improve the specificity and sensitivity of ultrasound imaging of prostate cancer, several techniques (3D ultrasound, Doppler, contrast-enhanced power Doppler, intermittent, harmonic and pulse inversion techniques) have been introduced but their results are still unsatisfactory.

For these reasons new ultrasound techniques for detecting prostate cancer are still developing. One of the most

Figure 1.
Diagram of Measurement Setup.

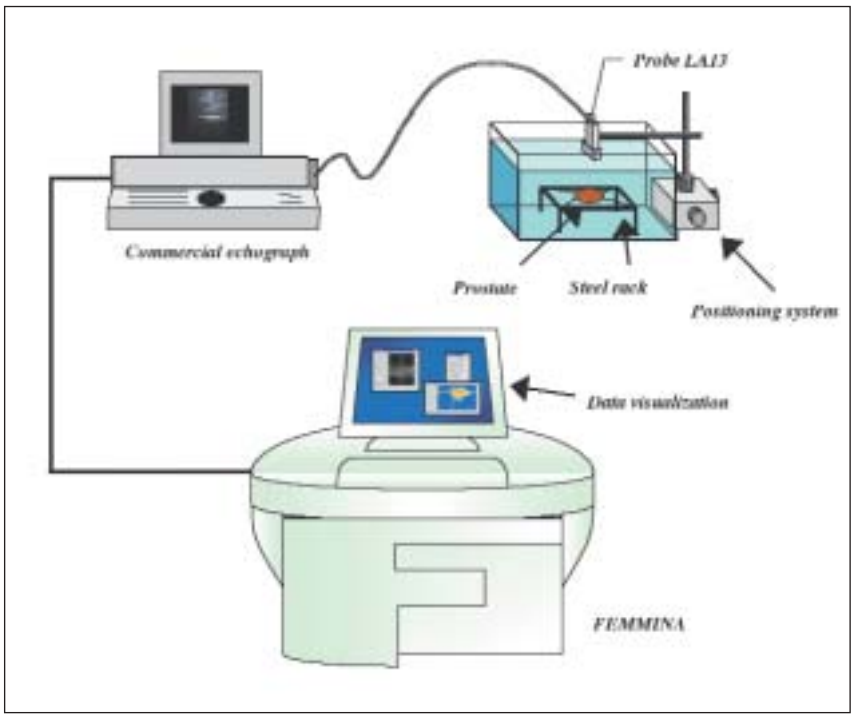
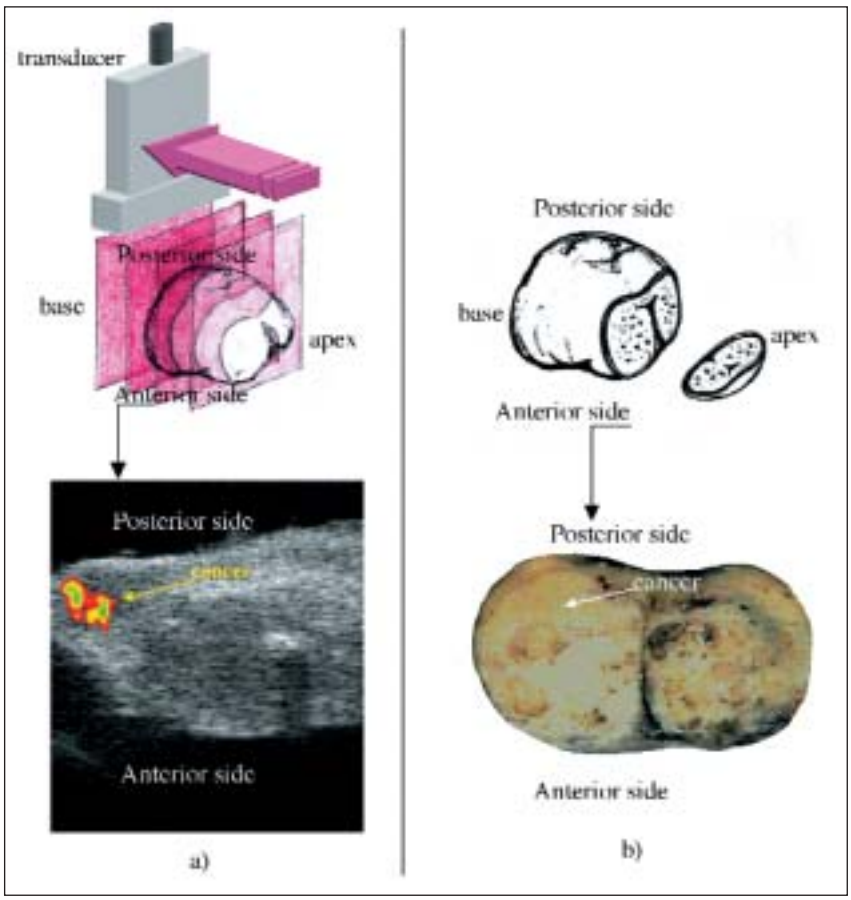


Figure 2.
Image of a transverse scan plane (a) compared with a transverse whole –mount section of the radical prostatectomy specimen (b).



promising techniques seems to be ultrasonic radiofrequency (RF) signal processing for extracting local spectral information (1). Various methods have been proposed to interpret the information contained in the ultrasonic RF signal. Many of the proposed methods have high computation load procedures and are hard to implement for real-time applications.

We have developed a local spectral analysis method of the RF signal (1-4) which allows a simple and rapid representation of the results.

The purpose of the present study was to compare in vitro the spectral ultrasound parameters with the histopathological findings of the radical prostatectomy specimens, evaluating the validity of the proposed method in discriminating neoplastic from non-neoplastic tissue.

Material and methods

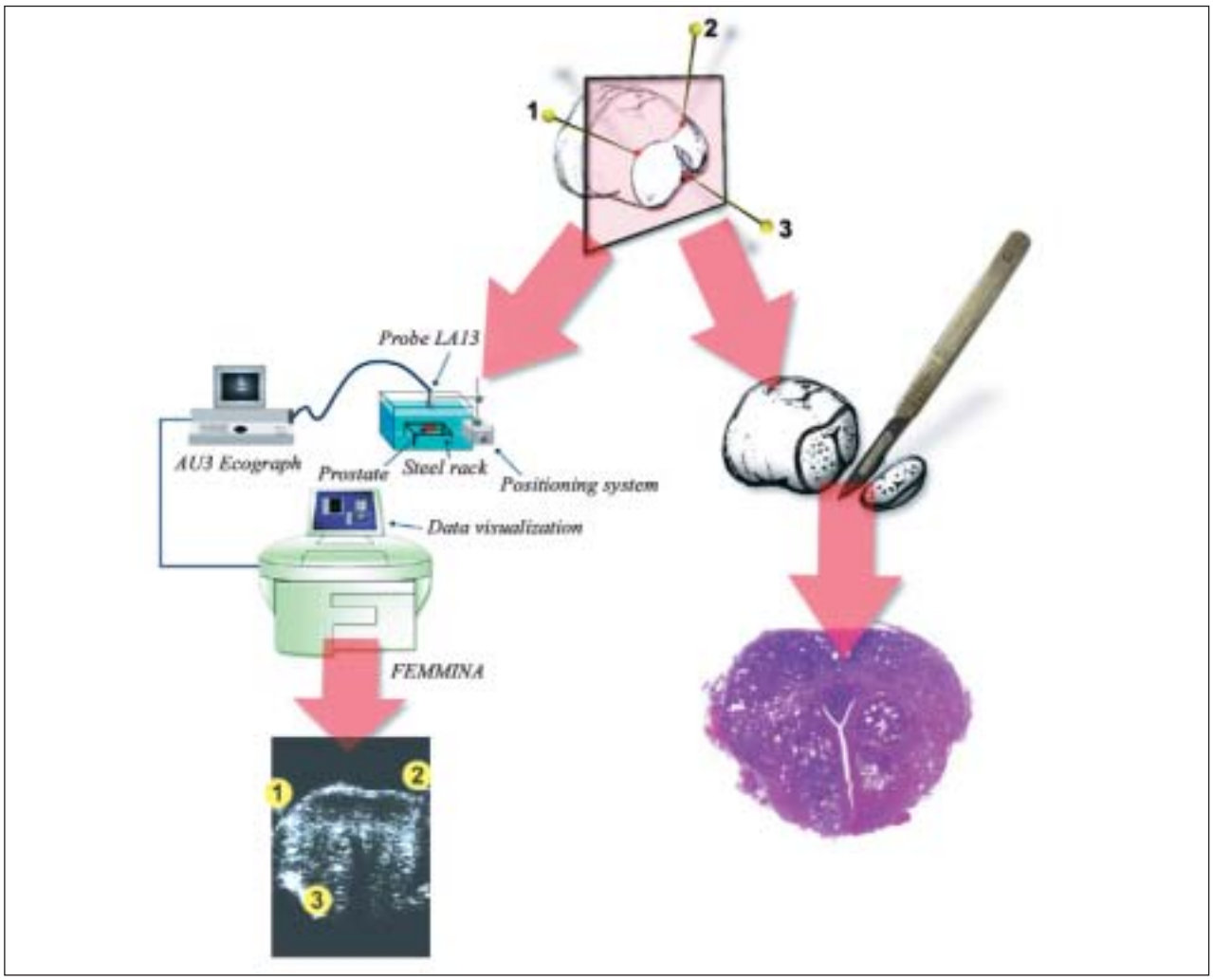
The study was performed on 60 prostate glands of patients who had undergone radical retropubic prostatectomy for clinically localized prostate cancer.

After the prostate was surgically removed, it was scanned in vitro using the FEMMINA (Fast Echographic Multiparametric Multi Image Novel Apparatus) platform (5,6), with a commercial echograph modified to give RF signal output (AU3 Esaote). A 7.5 MHz linear array probe was employed. The FEMMINA platform allows echo signal acquisition and processing with a multi-image data representation. The scan procedure was repeated several times in different measurement conditions in order to verify the reproducibility and reliability of results. Radical prostatectomy specimens were placed in a tank filled with physiological saline and held in the correct position by means of threads. The prostate was ultrasonically scanned from the apex to the base at 2 mm intervals by moving the probe with a mechanical system (Figure 1).

Surgical specimens were fixed in 10% neutral buffered formalin and then serially sectioned at 4 mm intervals from the apex to the base depending on the preoperative

Figure 3.

Marking of reference section in order to preserve the correct anatomical orientation for comparison with RF acquired frames.



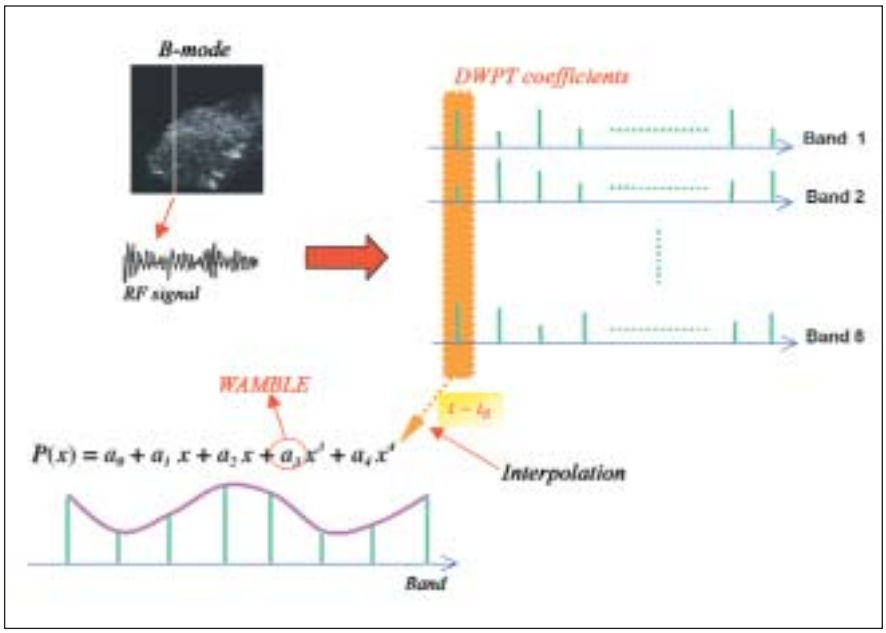
echographic acquired section. Special care was taken to preserve the correct anatomical orientation for comparison with RF acquired frames: three pins were inserted into the gland in order to mark the same starting section for echographic acquisition and histological slicing (Figures 2 and 3). Each section was microscopically examined and the tumour areas were demarcated with an ink line and transferred onto paper to make a histological map. For each radical prostatectomy specimen three areas showing prostatic cancer, BPH and normal tissue were compared.

In order to preserve local information and to obtain spectral images, time frequency transform is required. The system of wavelet transform was chosen for its noise immunity, its capability to recover the signal and its balanced compromise between time and frequency resolution (7). In particular, the results reported here were obtained by Discrete Wavelet Packet Transform (DWPT) For each sight line of a B-mode image, we considered the RF signal, which is decomposed by DWPT into eight different spectral bands, and consequently eight series of wavelet coefficients were calculated preserving the space or time reference. For every space location, or else for every time instant, the wavelet coefficients were collected and the best-fitting fourth degree polynomial curve was calculated.

The considered area was 3x50 points and it consisted of 150 polynomials. The histogram of coefficients of the area under study was evaluated. The third degree coefficient, named LE (Local Estimator), was extracted from each polynomial belonging to the area under consideration (Figure 4).

The histogram was processed over a range with lower and upper bounds of, respectively, minimum and maximum values obtained from processing the entire gland, and it was subdivided into 400 classes. From this histogram, the most representative subset of values was extracted and mapped on a conventional B-mode through a chromatic code (Figure 5). The study consisted in two stages: the first step, carried out on ten sections referring to ten radical prostatectomy specimens where cancer had previously been diagnosed by histology, to set up the procedure for correlating the different spectral parameter distribution to the three different areas previously identified by the pathologist; the second step, performed on all echographic sections (375 scans) acquired before histological evalua-

Figure 4.
Method for spectral parameter evaluation.



tion, was finalized to assess the sensitivity and specificity for cancer detection.

Results

After having processed all the prostatic glands under study, a range of values from 4957.7 to 5080 was obtained. We divided this range into 400 classes to attain a good compromise between statistical representation of each class and discrimination among values belonging to different classes. The classes referring to neoplastic areas exhibited different distribution compared to non-neoplastic areas. Indeed, it was noted that the tumour and BPH areas exhibited Gaussian statistics, while normal tissue had a nearly uniform distribution throughout all classes (Figure 6).

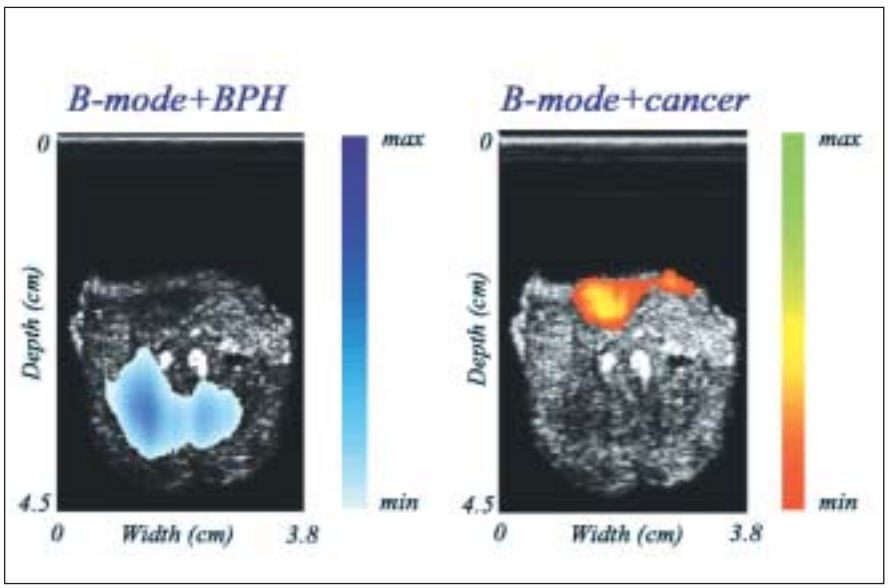
Thus, it was possible to differentiate normal from pathological tissue (BPH and cancer).

From the analysis of the histograms concerning BPH and tumour areas, it could be assumed that a range of classes exists which is mostly representative of the two pathologies. The selection was made over classes whose population ranges from 75% to 100% of maximum values. Spectral analysis carried out in the tumour areas generally gave values within classes 130-135.

In order to evaluate the accuracy of the class range associated with cancers, we processed all echographic scans of the sample studied. The results were visualized by a B-mode echographic image in which the area of interest was shown by means of a selectable chromatic scale, the colour levels of which were proportional to the population intensity of the classes researched (Figure 7).

Comparing the images obtained through the histological maps, we observed a specificity of 91% and a sensitivity of 93%. The specificity was invalidated by the fact that, in some of the cases studied, the tumour classes overlapped with those of BPH (Figure 8). As for the sensitivity, we obtained three false negatives: two were due to the presence of cancer foci in BPH sites for which different class ranges were found.

Figure 5.
Representation of two different pathological areas by means of two different pseudocolour scales.



Discussion

Prostate cancer is one of the most common malignancies in men and the second leading cause of cancer death after lung cancer in the USA and many European countries. This rise in incidence has been related to improvements in diagnostic procedures (PSA levels, TRUS) and increasing life expectancy.

Although hypoechoic areas on TRUS are more than twice as likely to contain cancer as isoechoic areas, 25% to 50% of cancer could be missed if only hypoechoic areas were biopsied. The variable appearance of prostate cancer on conventional ultrasonography requires targeted and

Figure 6.
Different Wamble distribution for three different areas.

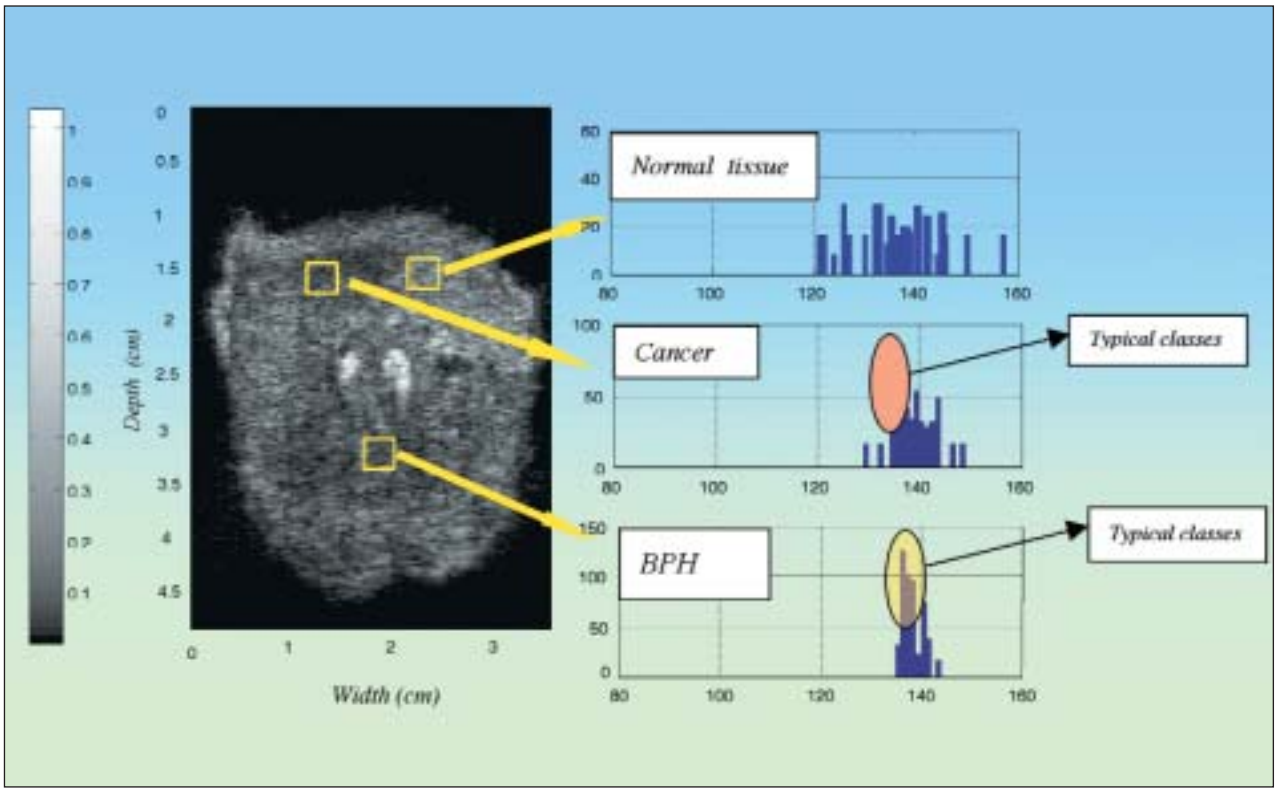
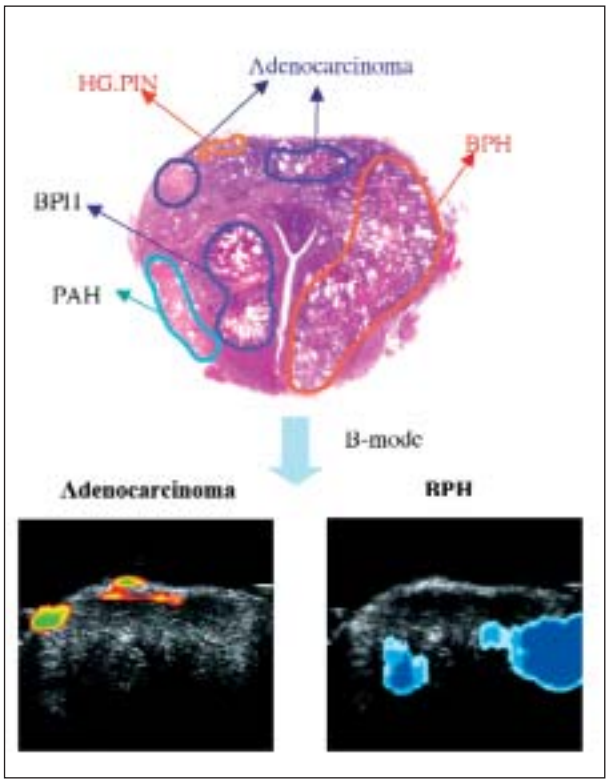


Figure 7.
Comparing between histological characterization and processed images of one reference section, marked with repere points.



random biopsies in order to achieve the correct diagnosis, with a significant increase in morbidity and costs.
Since the imaging of prostate cancer is currently limited by the poor accuracy of systematic conventional grey-scale ultrasonography, in recent years research has focused on software developments to improve the existing ultrasound technology, such as three-dimensional imaging, colour Doppler (with or without ultrasound contrast agents), power Doppler and combined techniques (three-dimensional contrast-enhanced power Doppler ultrasonography) (8-13).
Garg et al. (14) in a study on 3D-US imaging observed that specificity and sensitivity for cancer detection were similar to those of 2D-TRUS.
However, the addition of 3D transrectal ultrasonography resulted in a 22% increase in overall staging accuracy (94%) compared with conventional ultrasonography (72%). In a small series of patients *Hamper et al.* (15) documented that 3D-US may allow better depiction of tumours and extraglandular extension than the 2D technique. In contrast, *Sedelaar et al.* (16) stated that comparison between 3D-US and 2D-US did not bring in significant clinical improvement in the detection and staging of prostate cancer.
Over the last 20 years, many researchers (17-21) have proposed processing techniques to extract information about biological tissue microstructure or material properties that are not yet conveyed in conventional echographic B-mode images. All these techniques use radiofrequency echo signals to preserve information that is otherwise lost (Figure 9).

Figure 8.
Histogram referring to all 375 scans analysed in order to evaluate sensitivity and specificity of the proposed method.

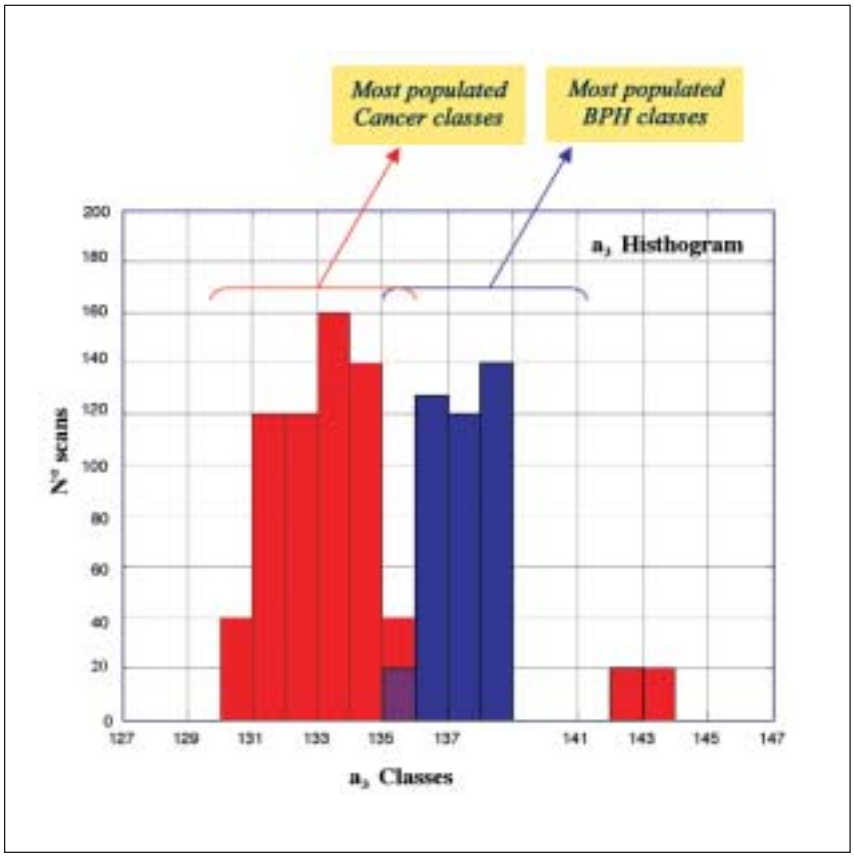
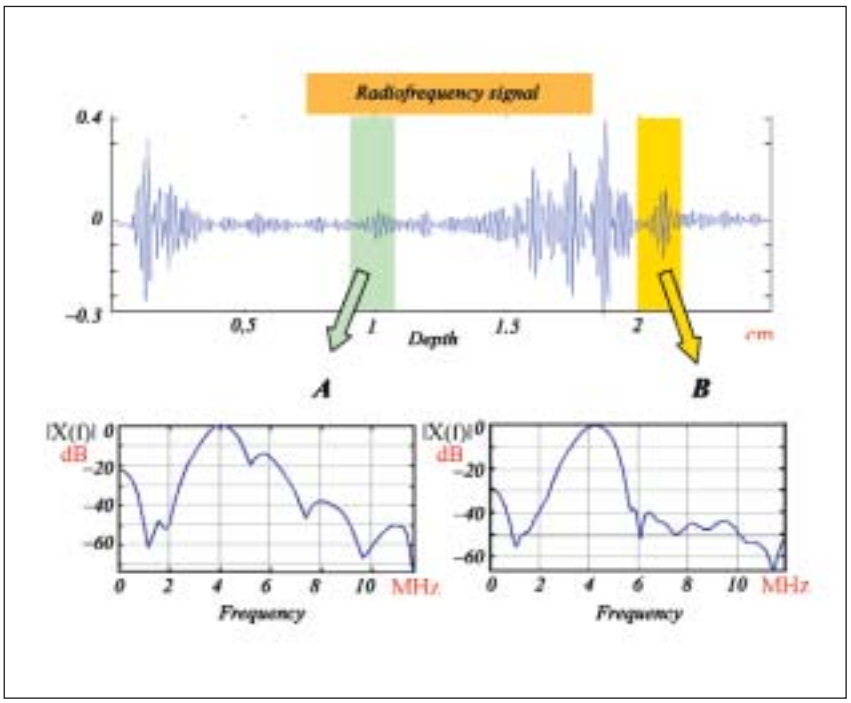


Figure 9.
Radiofrequency signal with two spectrum (A e B) related to two different signal portions. Two different local spectral shapes can be noted.



Current generation echographs utilize signal envelope (i.e., the A-Mode, B-Mode and M-Mode representations are based on the enveloped signal). By adopting this solution, the information contained in the RF signal is completely lost. Only recently, echographic systems, such as the General Electric System FIVE and Vivid VII, equipped with an ultrasonic RF output for research purposes, have been put on the general market. Previously, only a few academic research groups had access to vendor supplied engineering mode interfaces adapted for modified commercial systems.
One example of this type of interface was the General Electric Extend option for GE Logiq700 that permitted access to raw beamformed line data. Some fluency in relatively low level programming languages was required to use these earlier interfaces.
In order to preserve local information and to obtain spectral images, time frequency transform is needed. The wavelet transform has been chosen for its noise immunity, its capability to recover the signal and its balanced compromise between time and frequency resolution.
In particular, the results reported here were obtained by Discrete Wavelet Packet Transform (DWPT) and the final spectral parameters were determined. The statistical distribution of these parameters seems to be typical of prostate cancer, BPH and normal prostatic tissue which are characterized by specific class values.

Conclusions

Our proposed method is based on RF echo signal processing to extract local spectral parameters characterizing microstructural tissue organization to allow a rapid diagnosis by the physician.
In this study, spectral signal processing produces a final image where the tumour area is shown up by means of a chromatic code superposed on the B-mode representation.
The in vitro study was performed on 60 radical prostatectomy specimens, pertaining to patients who underwent surgery for clinically

localized prostate cancer, and these preliminary results provided an encouraging confirmation with the histological findings.
At present, a correlation between the Gleason score and the range of classes does not seem possible. As the aim of this study was to determine the presence of cancer, the minimum cost parameter was selected with the consequence being an incorrect evaluation of tumour volume. This is possibly due to the fact that a single portion alone of all the information was considered: only a third order coefficient was taken into account and the whole tumour structure was probably not represented.
Further in vivo studies are warranted to confirm the clinical utility of this promising technique in detecting prostate cancer.

REFERENCES

1. Masotti L, Biagi E, Granchi S, Breschi L. Metodo e dispositivo per l'analisi spettrale di un segnale ecografico. FI2002A 000034, 27 Febbraio 2002. European Patent No. 03425118.1, February 25, 2003. US Patent, February 25, 2003

2. Masotti L, Biagi E, Cerofolini M, Bertini A, Calzolai M, Bigagli A, Galardi L, Giovannucci C. Method for enhancing the diagnostic power of ultrasonic scanning system by using real time spectral maps, and device operating by said method. US Patent 6 066 098, May 23, 2000

3. Masotti L, Biagi E, Acquafresca A, Breschi L, Calzolai M, Facchini R, Giombetti A, Granchi S, Ricci A, Scabia M. Ultrasonic images of tissue local power spectrum by means of wavelet packets for prostate cancer detection. In Proc 26th Int Symp Acoust Imaging, 2001; 97

4. Biagi E, Calzolai M, Granchi S, Masotti L, Scabia M. Real-time processing of the radiofrequency ultrasonic echo signal for on-line spectral maps. In Proc 24th Int Symp Acoust Imaging, 2000; 95

5. Scabia M, Biagi E, Masotti L. Hardware and software platform for real-time processing and visualization of echographic radiofrequency signals. IEEE Trans Ultrason Ferroelect Freq Contr 2002; 49:1444

6. Biagi E, Calzolai M, Capineri L, Granchi S, Masotti L, Scabia M. FEMMINA: a fast echographic multiparametric multi-imaging novel apparatus. In Proc IEEE Ultrason Symp, 1999; 739

7. Georgiou G, Cohen FS. Tissue characterization using the continuous wavelet transform. Part I: Decomposition method. IEEE Trans Ultrason Ferroelect Freq Contr 2001; 48:355

8. Watanabe H, Igari D, Tanahasi Y, Harada K, Saito M. Development and application of new equipment for transrectal ultrasonography. J Clin Ultrasound 1974; 2:91

9. Sedelaar JP, Vijverberg PL, De Reijke TM, de la Rosette JJ, Kil PJ, Braeckman JG, Hendrikx JM. Transrectal ultrasound in the diagnosis of prostate cancer: state of the art and perspectives. Eur Urol 2001; 40:275

10. Bogers HA, Sedelaar JP, Beerlage HP, de la Rosette JJ, Debruyne FM, Wijkstra H, Aarnink RG. Contrast-enhanced three-dimensional power Doppler angiography of the human prostate: correlation with biopsy outcome. Urology 1999; 54:97

11. Shigeno K, Igawa M, Shiina H, Wada H, Yoneda T. The role of colour Doppler ultrasonography in detecting prostate cancer. BJU Int 2000; 86:229

12. Unal D, Sedelaar JP, Aarnink RG, van Leenders GJ, Wijkstra H, Debruyne FM, de la Rosette JJ. Three-dimensional contrast-enhanced power Doppler ultrasonography and conventional examination methods: the value of diagnostic predictors of prostate cancer. BJU Int 2000; 86:58

13. Takahashi S, Yamada Y, Homma Y, Horie S, Hosaka Y, Kitamura T. Power Doppler ultrasonography-directed prostate biopsy in men with elevated serum PSA levels: an evaluation of the clinical utility and limitations. Urology 2002; 60:248

14. Garg S, Fortling B, Chadwick D, Robinson MC, Hamdy FC. Staging of prostate cancer using 3-dimensional transrectal ultrasound images: a pilot study. J Urol 1999; 162:1318

15. Hamper UM, Trapanotto V, DeJong MR, Sheth S, Caskey CI. Three-dimensional US of the prostate: early experience. Radiology 1999; 212:719

16. Sedelaar JP, van Roermund JG, van Leenders GL, Hulsbergen-van de Kaa CA, Wijkstra H, de la Rosette JJ. Three-dimensional grayscale ultrasound: evaluation of prostate cancer compared with benign prostatic hyperplasia. Urology 2001; 57:914

17. Lorenz A, Pesavento A, Scheipers U, Ermert H, Garcia-Schürmann M, Sommerfeld HJ, Senge T, Philippou S. Ultrasonic tissue characterization-assessment of prostate tissue malignancy in vivo using a conventional classifier based tissue classification approach and Elastographic Imaging, IEEE Ultrasonic Symposium 2000

18. Scheipers U, Lorenz A, Pesavento A, Ermert H, Sommerfeld HJ, Garcia-Schürmann M, Kühne K, Senge T, Philippou S. Ultrasonic multifeature tissue characterization for the early detection of prostate cancer, IEEE Ultrasonic Symposium 2001

19. Schmitz G, Ermert H, Senge T, Tissue-characterization of the prostate using radio frequency ultrasonic signals. IEEE Trans Ultrason Ferroelect Freq Contr 1999; 46:126

20. Lizzi FL, Feleppa EJ, Astor M, Kalisz A. Statistics of ultrasonic spectral parameters for prostate and liver examinations. IEEE Trans Ultrason Ferroelect Freq Contr 1997; 44:935

21. Feleppa EJ, Kalisz A, Sokil-Melgar JB, Lizzi FL, Liu T, Rosado AL, Shao MC, Fair WR, Wang Y, Cookson MS, Reuter VE, Heston WD. Typing of prostate tissue by ultrasonic spectrum analysis. IEEE Trans Ultrason Ferroelect Freq Contr 1996; 43:609

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ORIGINAL PAPER

PSA decrease after levofloxacin therapy in patients with histological prostatitis.

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Summary

Objective: To evaluate the effect of levofloxacin (LVX) oral therapy on total serum prostate specific antigen (PSA) values in patients with histological prostatitis. Materials and Methods: All consecutive outpatients with histological evidence of chronic prostatitis, total PSA > 4ng/ml, normal DRE and urinalysis and treated once daily with LVX 500 mg per os for 20 days were retrospectively evaluated for total serum PSA reduction. A decrease of PSA value > 5% was considered correlated with the antibiotic therapy. Results: A total of 26 outpatients were evaluated (median age = 65 years). Median total serum PSA concentrations, before and after LVX therapy, were 7,1 ng/ml (range 4,1-15 ng/ml) and 5,8 ng/ml (2-15 ng/ml), respectively (p= n.s). The median reduction of total PSA was 16,6% (range 5,7 – 63,6%). A statistically significant decrease of median total PSA was observed in 15 out of 26 patients (57,6%): 7,2 ng/ml and 4,2 ng/ml before and after LVX therapy, respectively (p=0.002); the marker normalized in 7 out of 15 patients (46.7%). In all the remaining patients prostate biopsy was repeated: prostate cancer (Pca) was detected in 1 out of 8 patients with significant reduction of total PSA and in 4 out of 11 patients with no significant marker decrease. The incidence of Pca in second prostate biopsies raised from 19% (5 cases out of 26) to 26% (5 cases out of 19). Conclusions: treatment with LVX significantly reduced PSA values in over half of the patients with asymptomatic prostatitis, elevated total PSA and normal DRE and urinalysis. This approach could be applied in the ambulatory setting in order to increase the specificity of total PSA testing, reducing the number of negative, unnecessary, prostate biopsies.

KEY WORDS: *Prostate; Prostatitis; Prostate-specific antigen; Biopsy; Antibiotics; Levofloxacin.*

INTRODUCTION

Prostate specific antigen (PSA) testing has brought innovation in the diagnosis and treatment of Prostate carcinoma (Pca) in clinical practice. Both the American Cancer Society and the American Urologic Asssociation have recommended to start annual total serum PSA determination in combination with digital-rectal examination (DRE) in male subjects (50 years old) presenting for Pca prevention and to perform prostatic biopsy when total PSA serum concentration is above 4 ng/ml and DRE is normal (1, 2).

However, elevated serum concentrations of PSA are founded both in patients with benign prostate hyperplasia (BPH) and in patients with prostatitis, and, finally, in patients with Pca. Total serum PSA concentration is above the cutoff in about 15-47% of BPH subjects and up to 70% of patients with clinical evidence of acute prostatitis (3). Furthermore, a diagnosis of Pca, after trans-rectal prostatic biopsy, is reported in 34% of patients older than 50 years and PSA > 4 ng/ml (4). It is worth noting that in the range of PSA between 4,0 ng/ml and 10 ng/ml the specificity of the marker is very low, thus the vast majority of the prostatic biopsies, performed in this range, are negative for Pca (5-7).

On this basis many authors tried to increase the specificity of PSA testing. Particularly, there is still controversy regarding the use of a unique cutoff of 4 ng/ml or 2.5

ng/ml, mainly in the younger age class (50-59 years), and research is now focusing on total PSA derivatives or precursors (5,8).
Total PSA serum concentration may be influenced by acute prostatic flogosis, while the influence of subclinical inflammatory foci on elevation of the marker is still on debate. Noteworthy, is the study of Nadler and coll that compared prostatic biopsies of 148 patients with PSA > 4ng/ml and normal DRE, with those of 64 patients, with suspected DRE and PSA < 4ng/ml, being both groups asymptomatic for prostatitis (9). Histologic acute or chronic inflammation was prevalent in patients with elevated PSA: 63% versus 27%, p=0.0001 and 99% versus 77%, p=0.0001, respectively (9).
In order to avoid negative biopsies in patients with acute or chronic prostatitis, PSA > 4ng/ml and normal DRE, recent studies evaluated, the effect of antibiotic therapy on the marker. A controlled, randomized, open-label study evaluated in a cohort of 90 patients with PSA > 4ng/ml, normal DRE, a history of urinary tract infection (UTI) and with no clinical evidence of prostatitis the serum variations of total PSA caused by a 3 weeks administration of ofloxacin (OFX, 200 mg *per os bis in die*) comparing them with the biological variations in untreated patients (10). Significant variations of mean PSA have been reported in this study only in patients treated with antibiotics (6.9 ng/ml vs 5.8 ng/ml, p =0.001). Another prospective, no controlled, open-labelled study, conducted in 51 patients with diagnosis of subclinical prostatitis, normal DRE and urinalysis, and with elevated total PSA (mean = 9.5 ng/ml) studied the effect on the marker of 4 weeks of therapy with ciprofloxacin (CPX, 500 mg *per os, bis in die*): in 42% of cases total PSA normalized (mean = 2.9 ng/ml) and these subjects avoided prostatic biopsy (11). Finally, an Italian longitudinal study evaluating the effect on total PSA of 3 weeks of therapy with CPX in 58 patients asymptomatic for prostatitis, with normal DRE and total PSA between 4 and 20 ng/ml, reported a 30% reduction of mean total PSA in 58,6% of patients (12).
A recent subset analysis from a multicenter double-blind active control clinical trial that compared levofloxacin (LVX) at a daily oral dosage of 500 mg for 28 days, with CPX, administered orally twice daily at a dosage of 500 mg for 28 days, in the treatment of chronic bacterial prostatitis reported a decrease up to more than 30% in both treated groups and approximately half of these patients had a post-therapy PSA level below 4 ng/ml (13).
LVX is a recent fluorochinolone with activity on Gram positive, Gram negative, atypical bacteria and anaerobes and with an oral bioavailability of 100% (14). LVX accumulates into the prostate, achieving concentrations between 1.23 and 20.8 µg/g (mean 12.37 µg/g), values higher from 10 to 50 times the MIC of the most frequent uropathogens (i.e. E. coli) and administered orally once daily at a dosage of 500 mg for 28 days shows comparable efficacy and tolerability as CPX administered orally twice daily at a dosage of 500 mg for 28 days in the treatment of chronic bacterial prostatitis (15).
Recently LVX has been approved in USA for the treatment of prostatitis and thus may represent an interesting option in the management of patients with subclinical prostate inflammation.
Aim of this study was to evaluate the effect of LVX on total PSA, administered orally once a day in ambulatory patients with PSA > 4ng/ml, normal DRE and urinanalysis and histological prostatitis.

Materials and Methods

All consecutive outpatients patients with total PSA > 4 ng/ml, normal DRE and urinalysis, an histological evidence of chronic prostatitis (Figures 1-3) and treated once daily with LVX 500 mg per os for 20 days were retrospectively identified in a 3 month time frame (January – March 2003) and evaluated for total serum PSA response two weeks after the end of antibiotic therapy.

Figure 1.
Follicolar chronic prostatitis
(x 200; haematoxylin and eosin staining).

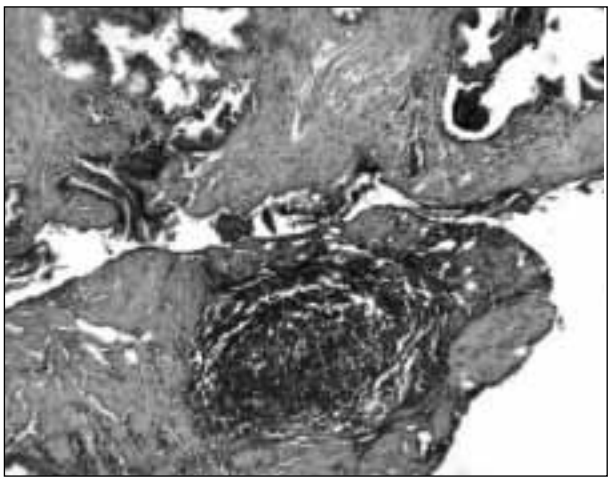


Figure 2.
Interstitial chronic prostatitis
(x 200; haematoxylin and eosin staining).

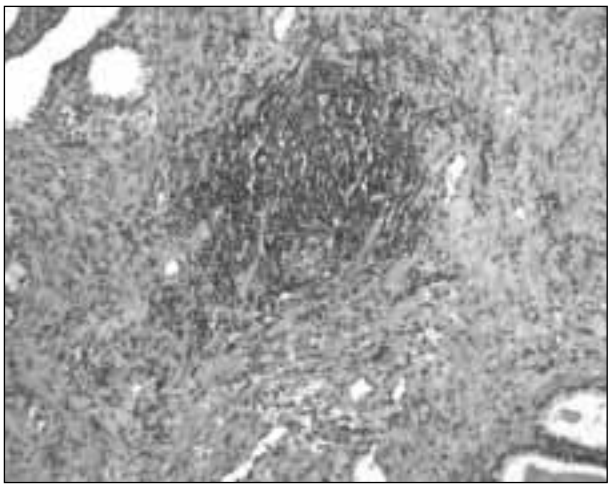


Figure 3.
Chronic prostatitis with peri-tubular inflammatory infiltration (x 200; haematoxylin and eosin staining).

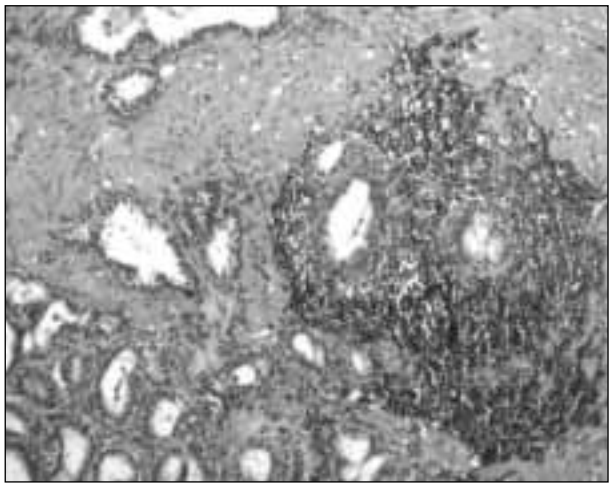
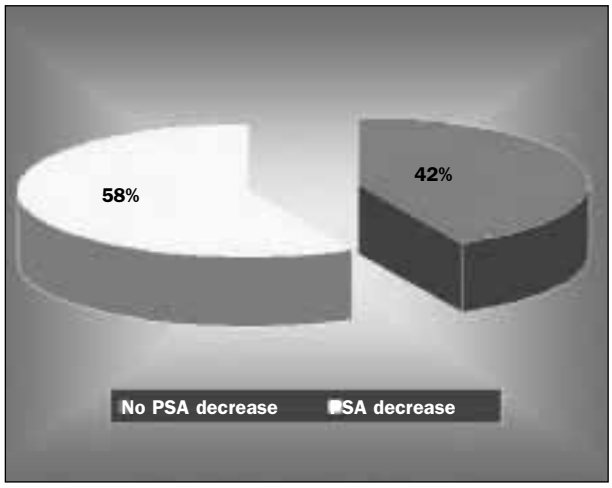


Figure 4.
Proportion of patients with significant decrease of PSA after therapy with levofloxacin 500 mg per os once a day.



All patients were asymptomatic for prostatic flogosis. Chronic prostatitis was detected by 8 core prostate biopsy performed at the Universitary Division of Urology at "San Luigi Gonzaga" Hospital of Orbassano, Italy.
The values of total PSA, pre-biosy and after 2 week treatment with LVX, were compared: a decrease of more than 5% was considered correlated with the antibiotic therapy, that is above the current laboratory error, estimated between 3-4% (7).
Descriptive analysis was used for demography and clinical characteristics. The non parametric Mann-Witney U test was performed for the comparison. Two-tailed test were used for all comparisons and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistica for Windows software 5.1.

Results

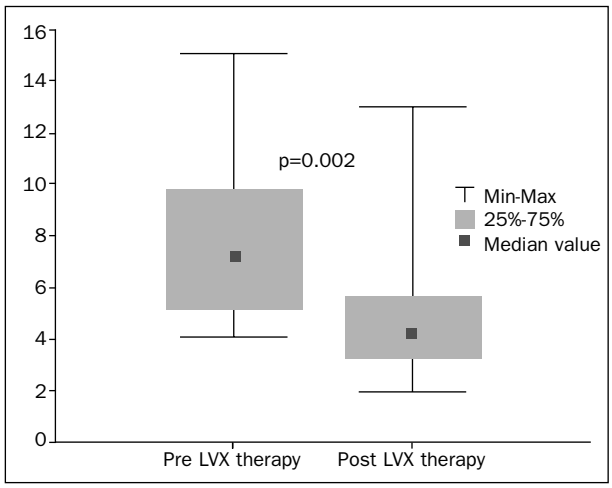
A total of 26 consecutive, outpatients patients were identified for this study (median age = 65 years; range 58-75 years).
Median total PSA serum concentrations, before prostate biopsy and after LVX therapy, were 7,1 ng/ml (range 4,1-15 ng/ml) and 5,8 ng/ml (2-15 ng/ml) respectively (p= n.s). The median reduction of total PSA was 16,6% (range 5,7 – 63,6%).
A significant decrease of median total PSA was observed in 15 out of 26 patients (57,6%): median PSA, before biopsy and after antibiotic therapy, in these patients, was 7,2 ng/ml and 4,2 ng/ml respectively (p=0.002; Figures 4 and 5). Total PSA serum concentration normalized in 7 out of 15 patients (46.7%). The remaining 8 patients (53.3%) with a decrease of total serum PSA, but without normalization, underwent a second prostate biopsy with 12 cores: in one case an histological diagnosis of Pca was established (12.5%).
No significant difference in age or baseline total PSA values (pre-biopsy) was founded between patients with normalization of the marker and patients without.

The remaining 11 patients (42.3%) with no significant decrease in total PSA concentration, or with a rise of the marker after antibiotic therapy, were biopsed again and 4 of them (36%) had a diagnosis of Pca.
The incidence of positive second prostate biopsies raised from 19% (5 cases out of 26) to 26% (5 cases out of 19).

Discussion

Since its discovery total PSA still remain the most important marker for Pca. However it is well known that other prostate diseases, such as BPH and prostatitis, or aggressive procedures on the prostate itself, may increase the serum levels of the prostatic antigen.
Particularly, when DRE is normal and total PSA is between 4,1 ng/ml and 10 ng/ml, the so called "grey zone", Pca can be found in only 15-22% of biopsies (5-7). Negative prostate biopsies for Pca often show presence

Figure 5.
PSA value before and after therapy with levofloxacin (LVX) 500 mg per os once daily in patients with significant reduction of the marker.



of flogosis, that can be responsible for the elevation of PSA, even in the absence of symptoms of prostatitis. This findings are particularly important if we consider the economic burden due to prostatic biopsy and its possible, although infrequent, sequelae, and the physical and psychological discomfort for patients.
In order to reduce the number of negative biopsies, different authors explored the effects of 3 or 4 week antibiotic therapy with fluoroquinolones on total PSA in patients with clinical evidence of acute or chronic prostatitis, elevated PSA and normal DRE, showing a mean decrease of the marker up to more than 30% in the treated cases (10-13, 15). However, if symptomatic prostatitis, either acute or chronic, represent a definite clinical condition whose role in increasing total PSA is now well recognized, studies on the influence of chronic asymptomatic prostate inflammations on variations in PSA values are still few. Men with chronic prostatitis frequently show perineal pain and lower urinary tract symptoms but many are asymptomatic and may have negative urinanalysis and/or urocoltures.
We report here the results of the effect on total PSA of 3 weeks of levofloxacin 500 mg administered per os once daily in 26 consecutive outpatients with PSA > 4 ng/ml, normal DRE and urinalysis and with an hystological diagnosis of chronic prostatitis. In our data 57,6% of treated patients reported a significant reduction of total PSA (> 5%) and in 46% of them PSA normalized (< 4 ng/ml), figures that are consistent with the results of similar studies (10-13,15). Thus this therapeutic approach avoided 27% of new biopsies, achieving an incidence of positive second biopsies for prostate adenocarcinoma from 19% to 26%.
Asymptomatic patients for prostatitis or urinary tract infections, with normal DRE and urynanalisis, represent a group of patients of special interest because frequently may present abnormal levels of total PSA, whose causes are difficult to understand and suspected presence of inflammatory foci may be one of these.
Our study has to be considered explorative and, in agreement with previous studies on this subject, show that also subclinical chronic prostatitis may have a role in rising total PSA and its treatment with fluoroquinolones may decrease and normalize the plasma level of the marker.
The individual, although not frequent, biological variation that may influence the mean levels of the PSA up to 10-15% should also to be taken in consideration, at least in large sample size cohort studies. A controlled, randomized, open-label study analized the biological variations of serum concentrations of total PSA comparing them with the variations caused by three weeks with OFX (200 mg per os bis in die) in a cohort of 90 patients, with PSA > 4 ng/ml, normal DRE, negative urocoltures and a history of UTI and without clinical evidence of prostatitis. Significant variations of mean total serum PSA have been reported only in patients treated with antibiotics (6.9 ng/ml vs 5.8 ng/ml, p =0.001), showing that biochemical criteria for prostatic biopsy, can be modified by antibiotics in the patients with no evidence of prostatitis and with history of UTI.

Conclusions

We believe that the therapeutic approach investigated in this pilot study could improve the specificity of total PSA testing in patients asymptomatic for prostatitis, with PSA > 4 ng/ml, both normal DRE and urinalysis, and with histological signs of prostatic inflammation, reducing the number of negative, unnecessary, prostate biopsies.
Cost-effectiveness analysis of routine screening for subclinical chronic prostatitis (i.e. the Meares-Stamey Test), subsequent treatment with antibiotics, before recommending ultrasound guided prostatic biopsy, are still lacking. Prospective, well designed studies are awaited in order to clarify if a therapeutic protocol including fluoroquinolones, is cost efficacious and well tolerated in patients with normal DRE and elevated PSA compared with procedures that include prostate biopsies or monitoring of the individual biological variations of total PSA.

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References

1. Mettlin C, Jones GW, Avarette H, Gusberg SB, Murphy GP. Defining and updating the American Cancer Society guidelines for the cancer-related checkup: Prostate and endometrial cancer. Cancer 1993; 43:42

2. AUA: American Urological Association policy statement: early detection of prostate cancer and use of transrectal ultrasound. Baltimore: 1991

3. Catalona WJ, Richie JP, Ahman FR et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6630 men. J Urol 1994; 151:1283

4. Keetch DW, Catalona WJ, Smith DS. Serial prostatic biopsies in men with persistently elevated serum PSA values. J Urol 1994, 151:1571

5. Brawer MK. Prostate specific antigen: current Status. CA: a Cancer Journal for Clinicians 1999; 49:264

6. Gion M. Il PSA: parametro chiave nel trattamento del cancro prostatico. In Intramed, Il carcinoma della prostata. Diagnosi. Milano: 2000:34

7. Brawer MK. Prostate Specific Antigen. New York: Marcel Dekker Inc., 2001

8. Punglia RS, D'Amico AV, Catalona WJ, Rohel KA, Kuntz KM. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. N Engl J Med 2003; 349:335

9. Nadler RB, Humphrey PA, Smith DS, Catalona WJ, Ratliff TL. Effect of inflammation and benign prostatic hyperplasia on elevated PSA serum prostate-specific antigen. J Urol; 154:407

10. Lorente JA, Arabgo O, Bielsa R, Cortadellas, Gelabert-Mas A. Effect of antibiotic treatment on serum PSA and percent free PSA lev-

els in patients with biochemical criteria for prostate biopsy and previous lower urinary tract infections. Intern J Biol Markers 2002; 17:84

11. Potts JM. Prospective identification of national institutes of health category IV prostatitis in men with elevated prostate specific antigen. J Urol 2000; 164:1550

12. Ascoli R, Galuffo A, Lupo A, Di Gregorio L, Allegro R, Serretta V, Messina G, Pavone Macaluso M. Modificazioni del PSA dopo terapia antibiotica in pazienti candidati alla biopsia prostatica. 77° Congresso Nazionale Società Italiana di Urologia: Poster C151; abstract book pg.118

13. Schaeffer AJ, Wu S-C, Tennenberg AM, Zadeikis N. Levofloxacin and ciprofloxacin in the treatment of chornic bacterial prostatitis lower serum prostate specific antigen. J Urol 2004; 171(4 Suppl):62 Abs No 237

14. Langtry HD and Lamb HM. Levofloxacin. Its use in infection of the respiratory tract, skin, soft tissue and urinary tract. Drugs 1998; 56:487

15. Bundrick W, Heron SP, Ray P et al. Levofloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis: a randomized double-blind multicenter study. Urol 2003; 62:537

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ORIGINAL PAPER

Out-of-focus shockwaves: a new tissue-protecting therapy?

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Summary

Introduction: It seems that vasoconstriction induced by 12 Kv shock waves reduces kidney lesions caused by subsequent application of 24 Kv shock waves. The lowest shock wave voltage to induce this protective effect is not known yet and may be lower than the common energy setting of commercial lithotripters. Because of this we propose the application of shock waves as a tissue protecting method. Materials and methods. Preliminary pressure measurements were performed on an experimental umnodified HM3 lithotripter (at 12 and 24 Kv), using a 20 ns rise time needle hydrophone connected to a 100 MHz digital oscilloscope. Ten pressure records were obtained at different aging of the spark plug. A new spark plug was used for each voltage. Pressure measurement were also performed on a Tripter compact lithotripter at 6 positions along the focal axis, starting at F2 and moving away from the reflector, using maximum voltage and capacitance (22 Kv, HI-2). The position on the focal axis of the Tripter Compact with the same pressure as measured at 12 Kv on the HM3 at F2 was chosen as the prophylactic treatment spot (PTS). In vivo pressure measurement were done on the Tripter Compact placing the needle hydrophone inside the lower pole of the right kidney of an anesthetized healthy 25 kg female pig. Measurements were done at the same positions mentioned above, without moving the hydrophone, inside the pig. For both in vitro and in vivo measurements, the radiopaque hydrophone was aligned with the focal axis, using the fluoroscopy system of the lithotripter. Results: The mean positive pressure peak at the second focus of the HM3 lithotripter was 64 and 153 mV, at 12 Kv, respectively. Coefficients of variations were 0.28 and 0.13. No significant pressure differences were detected below 700 and 2220 discharges with the HM3 and the Tripter compact, respectively. The difference peak amplitudes are all significant (p<0.01 in a one tailed test) with the exception of F2 and F2+1 Ohm. Conclusions: Prophylactic administrations of out-of-focus shock waves may reduce tissue damage during SWL. Experiments in vivo are underway in order to prove this hypothesis.

KEY WORDS: ESWL; Lithotripsy; Stones.

INTRODUCTION

Extracorporeal shock wave lithotripsy (SWL) has been a reliable procedure for patients with renal and ureteral calculi for more than twenty years (1). Nevertheless, intrarenal and subcapsular hematoma have been found (2-5) after SWL in a high percentage of cases examined. Organs adjacent to the kidney are usually unaffected. The size of the injury increases with increasing shock wave energy and number of shock waves. Research is still necessary to define techniques that minimize tissue damage.

The first systematic assessment of the acute effects of SWL on renal hemodynamics in the minipig was published in 1996, showing that shock waves reduce both glomerular filtration rate (GFR) and renal plasma flow (RPF) in pigs (6).

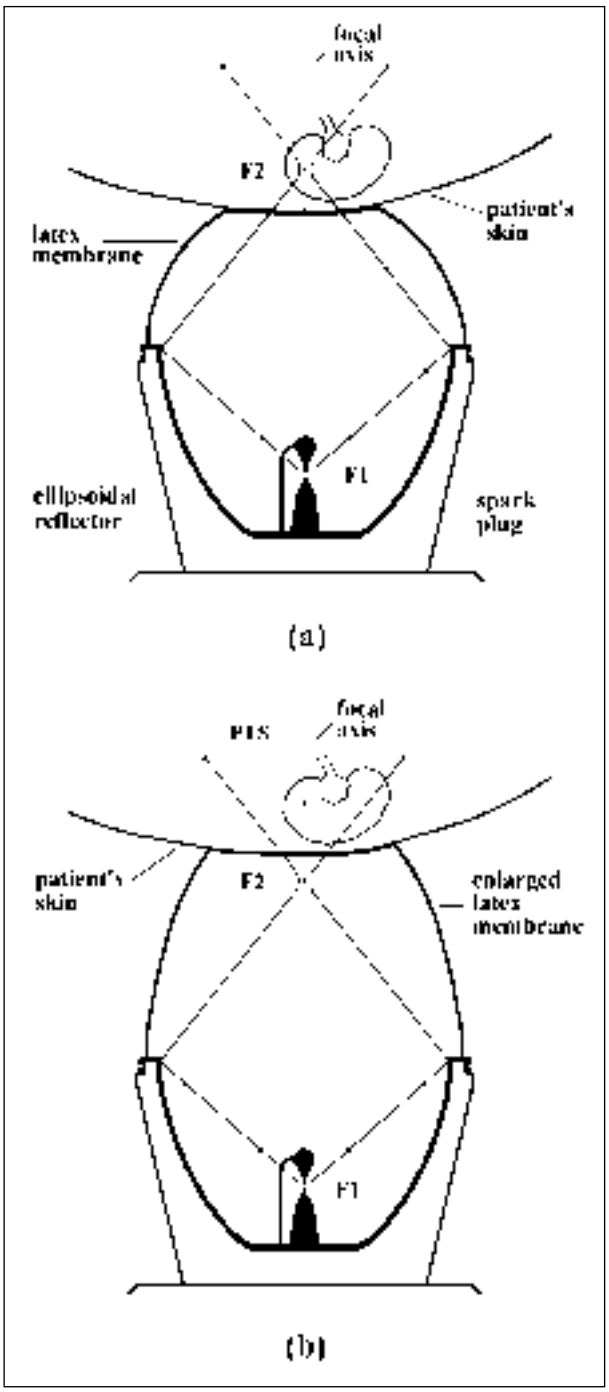
A few years later, *Willis et al.* (7) reported that using an unmodified HM3 (*Dornier Medizintechnik GmbH, Germering, Germany*) lithotripter, RPF appeared to be independent of the voltage between 12 and 24 kV.

Two thousand shock waves (12 kV) applied to one renal

pole (Figure 1a) did not cause hemorrhagic lesions but induced vasoconstriction. They also examined lesions in upper and lower poles of kidneys after 2000 shock waves at 12 kV to one pole, followed by the same amount of shock waves at 24 kV to the other pole. Massive hemorrhagic injury occurred in kidneys treated only in one pole at 24 kV. Kidneys previously treated with 2000 shock waves at 12 kV showed little to no hemorrhagic tissue damage. It seems that vasoconstriction induced by the application of 12 kV shock waves reduced bleeding and lesion development caused by subsequent application of 24 kV shock waves. The lowest shockwave energy level (voltage) to induce this protective effect is not known yet and may be lower than the minimum energy commercial lithotripters. Because of this, we propose the out-of-focus application of shock waves as a tissue-protecting method.

Figura 1.

(a) Prophylactic treatment with shockwaves focused at the lower pole. (b) Prophylactic out-of-focus treatment with shockwaves focused outside the kidney. At the prophylactic treatment spot (PTS) the pressure, generated on a Direx Tripter Compact lithotripter at maximum energy, is equivalent to the pressure generated at F2 on an unmodified Dornier HM3 lithotripter at 12 kV.



BRIEF THEORETICAL BACKGROUND

Conventional extracorporeal shockwave lithotripsy

We decided to test the out-of-focus technique on an electrohydraulic device because the first experiments on the protecting effect of low energy shock waves were performed on an HM3 lithotripter. Nevertheless, our group will also test the methods described here on a piezoelectric lithotripter. Electrohydraulic lithotripters induce shock waves by electrical breakdown of water between two electrodes, located at the focus (FI) closest to a rigid para-ellipsoidal reflector (Fig. 1a).

Shock waves are reflected off the reflector and concentrated at the second focus (F2). A water-filled cushion couples the shock waves into the patient's body. Several hundred shock waves are needed to completely disintegrate the stone. At F2, shock waves consist of a high-pressure pulse (up to 150 MPa) with a rapid rise time (less than 10 ns), followed by a "*negative*" phase of up to about -20 MPa. Frequencies range from a few hundred kHz to a few hundred MHz. The -6 dB focal zone (volume in which, at any point, the pressure has more than 50% of the maximum amplitude) of the electrohydraulic lithotripter used in this study is a cigar-shaped volume, having a length of about 40 mm and a diameter of 10 mm.

Application of out-of-focus shock waves

Application of out-of-focus shock waves is based on the fact that the protective effect of low energy shock waves may be enhanced if a larger volume of the kidney is treated with these prophylactic waves. Our technique may also open the possibility to treat the kidney at energies lower than the energy obtained at F2 using the lowest voltage setting of commercial lithotripters. As shown in Figure 1b, during out-of-focus prophylactic treatment the lower pole is located at the focal axis, a few centimeters away from F2. Because of this, F2 is outside the patient's body.

MATERIALS AND METHODS

Preliminary pressure measurements were performed on an experimental unmodified HM3 lithotripter (8) (at 12 and 24 kV), using a 20 ns rise time needle hydrophone (*Imotec GmbH, D-5102 Wùrselen, Germany*) connected to a 100 MHz digital oscilloscope (*Tektronix, Inc., Beaverton, Oregon, USA, model 2430A*). Ten pressure records were obtained at different aging of the spark

Table 1.

Mean amplitude of the positive pressure peak (p+) obtained with a needle hydrophone placed at different positions along the focal axis of a Direx Tripter Compact lithotripter.

Position*	P+ (mV)**	Coefficient of variation
F2	95.0	0.22
F2 + 10 mm	127.5	0.33
F2 + 20 mm	42.0	0.38
F2 + 30 mm	61.8	0.21
F2 + 40 mm	43.6	0.30
F2 + 50 mm	30.1	0.19

*Pressure was measured at 6 positions along the focal axis, starting at F2 and moving the hydrophone away from the reflector;
**Peak amplitudes are expressed in mV as obtained from the screen of the oscilloscope.

plug. A new spark plug was used for each voltage. Pressure measurements were also performed on a Tripter Compact (*Direx Medical Systems Ltd., Petach Tikva, Israel*) lithotripter at 6 positions along the focal axis, starting at F2 and moving away from the reflector, using maximum voltage and capacitance (22 kV, HI-2). The hydrophone was fastened inside a specially designed (40 x 36 x 35 cm) Lucite test tank. One side of the tank had a rubber membrane, used as an acoustic window by placing it in contact with the latex membrane of the lithotripter. Due to the rubber membrane, a pressure attenuation of about 10% was registered. The position on the focal axis of the Tripter Compact with the same pressure as measured at 12 kV on the HM3 at F2 (Figure 1b) was chosen as the prophylactic treatment spot (PTS).

In vivo pressure measurements were done on the Tripter Compact placing the needle hydrophone inside the lower pole of the right kidney of an anesthetized healthy 25 kg, female pig. Measurements were done at the same positions mentioned above, without moving the hydrophone inside the pig. For both *in vitro* and *in vivo* measurements, the radiopaque hydrophone was aligned with the focal axis, using the fluoroscopy system of the lithotripter.

Results

The mean positive pressure peak (voltage measured on the screen of the oscilloscope) at the second focus of the HM3 lithotripter was 64 and 153 mV, at 12 and 24 kV, respectively. Coefficients of variation (standard deviation divided by average) were 0.28 and 0.13.

Results obtained with the Tripter Compact are shown in Table 1 (*in vitro*) and Table 2 (*in vivo*).

No significant pressure differences were detected below 700 and 2220 discharges with the HM3 and the Tripter Compact, respectively. The difference between peak amplitudes shown in Table 1 and 2 are all significant ($p \leq 0.01$ in a one tailed test) with exception of data reported in Table 2 for F2 and F2 + 10 mm.

Discussion

The pressure measured on the HM3 lithotripter at F2 using 12 kV turned out to be equivalent to the pressure generated by the Tripter Compact at its maximum energy, 30 mm away from F2. This position was defined as the PTS. Coefficients of variation of *in vivo* measurements at F2 + 10 mm and F2 + 40 mm were relatively high (Table 2). This may be due to cavitation generated inside the body, along the shockwave path.

Table 2.

Mean amplitude of the positive pressure peak (p+) obtained with a needle hydrophone placed inside the lower pole of a pig's kidney.

Position*	P+ (mV)**	Coefficient of variation
F2	130.3	0.34
F2 + 10 mm	105.2	0.56
F2 + 20 mm	54.6	0.37
F2 + 30 mm	36.0	0.29
F2 + 40 mm	16.7	0.47
F2 + 50 mm	10.9	0.31

*Pressure was measured at six positions along the focal axis, starting at F2 and moving the hydrophone away from the reflector;
**Peak amplitudes are expressed in mV as obtained from the screen of the oscilloscope.

In vivo experiments with three groups of healthy 10-week-old female pigs are being performed to compare the protecting therapy reported by other authors with our out-of-focus therapy. Pigs from group 1 are treated with 6000 shock waves (22 kV), focused on the lower pole of one kidney. A second group of pigs is receiving the same treatment but is previously treated with 3000 prophylactic, shock waves generated at 22 kV, positioning the lower pole of the kidney at the PTS (Figure 1b). A third group of pigs is used as shams. Treated and non-treated kídneys are being removed at the end of the experiment to evaluate histological damage.

Conclusions

Prophylactic administration of out-of-focus shock waves may reduce tissue damage during SWL. Experiments are underway in order to prove this hypothesis.

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References

1. Chaussy C, Schmiedt E, Jocham D, et al. First clinical experience, with extracorporeally induced destruction of kidney stones by shock waves. J Urol 1982;127: 417

2. Coleman M, Saunders JE. A review of the physical properties and biological effects of the high amplitude acoustic fields used in extracorporeal lithotripsy. Ultrasonics 1993; 31:75

3. Delius M. Medical applications and bioeffects of extracorporeal shock waves. Shock Waves 1994; 4:55

4. Evan AP, Willis LR, Connors BA, et al, Shock wave lithotripsy-induced renal injury. Am J Kidney Dis 1991; 17:445

5. Evan AP, Willis LR, Lingeman JE, et al. Renal trauma and the risk of long term complications in shock wave lithotripsy. Nephron 1998; 78,1

6. Willis LR, Evan AP, Connors BA, et al. Effects of extracorporeal shock wave lithotripsy to one kidney on bilateral glomerular filtration rate and PAH clerance in minipigs. J Urol 1996; 156:15

7. Willis LR, Evan AP, Connors BA, et al. The application of low-energy shock waves to one renal pole prevents hemorrhagic injury induced by high-energy shock waves in the other pole. In: Bettucci A (Ed), Proceedings of the 17th International Congress on Acoustics, vol. IV, Rome, Italy 2001. ISBN 88-88387-03-X.

8. Locke AM, Méndez A, Fernández F, et al. Conversion of an HM3 lithotripter into a research device. J Endourol 2003

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ORIGINAL PAPER

Randomized placebo-controlled study of periprostatic local anaesthetic for transrectal ultrasound-guided prostate biopsy.

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Summary

Objectives: To determine the efficacy of injectable periprostatic anaesthesia with 1% lidocaine to reduce pain and complications experienced by patients undergoing transrectal ultrasound (TRUS) guided prostate biopsy.
Materials and Methods: We investigated 126 consecutive asymptomatic men, mean age 64.5 years, SD 6.7, suspected of having prostate cancer. Each patient was planned to undergo transrectal ultrasound-guided systematic (8 step scheme) and hypoechoic lesion directed biopsies. We randomly assigned 71 patients to receive a periprostatic 10 ml injection of 1% lidocaine (5 ml per side) and 55 without anesthesia. Immediately at the conclusion of the procedure and a week later, patients completed ten 10-point visual analogue scale scores (VAS) about the pain and morbidity.
Results: Patients who received local anaesthesia had a lower VAS score compared with the group without lidocaine during the biopsy regarding pain during and after biopsy and on the duration of pain. At day 7-follow-up differences of VAS scores resulted similar.
Lidocaine injection caused no local or systemic adverse effects.
Conclusions: The periprostatic anaesthesia represent a simple, safe, rapid and easy to implement procedure and significantly reduces pain and morbidity associated with prostate biopsy. Therefore it is recommended in patients at higher risk of prostate cancer who require a re-biopsy during lifetime.

KEY WORDS: *Local anaesthesia; Pain; Transrectal ultrasound; Periprostatic plexus block.*

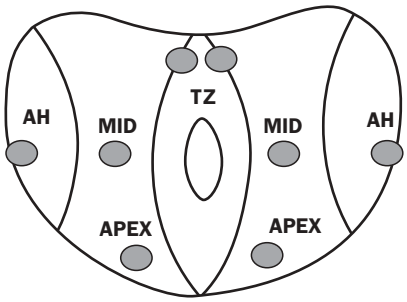
INTRODUCTION

Transrectal ultrasound (TRUS) systematic guided biopsy is the standard procedure for diagnosing prostate cancer. Pain related to the procedure result be significant and related to needle puncture of the prostatic capsule and to positioning and maintaining the probe in the rectum (1).
Generally the prostate biopsy is a well tolerated office procedure without anaesthesia, but, as increasing the number of cores enhances cancer detection, presently more extensive bioptic scheme are applied in practice (2) and increasing the number of cores taken during biopsy, pain and discomfort associated with this procedure results more intense (3,4). Aim of our study is to determine the efficacy of injectable periprostatic anaesthesia with 1% lidocaine to reduce pain and complications experienced by patients undergoing transrectal ultrasound guided prostate biopsy.

MATERIALS AND METHODS

126 patients, mean age 64.5 years, SD 6.7 , with abnormal digital rectal examination (EDR) and/or elevated prostate specific antigen (PSA), were submitted to a transrectal ultrasound evaluation followed by guided systematic (8 step scheme) and hypoechoic lesion directed biopsies (5) (Figure 1).
We randomly assigned patients in two groups, submitted to periprostatic injection of 5 ml lidocaine 1% for each side (71 patients) or no anaesthesia (55 patients) before biopsy procedure.

Figure 1.
Systematic 8 cores bioptic scheme.



8 step biopsy scheme

TZ: transition zone toward base
MID: midlobar parasaggital plane at midgland
APEX: midlobar parasaggital plane at apex
AX: peripherial zone lateral border at mdgland (anterior horn)

All patients were informed regarding procedure and related complications, and each received 5 doses of 500 mg ciprofloxacin the day before, on the morning of, and three days after biopsy, and a fleet enema two hour before biopsy.
Anticoagulation or aspirin therapy were stopped 1 week before biopsy.
The TRUS was performed in the left lateral decubitus or lithotomic position using a 7.5 MHz multiplan end-fire probe.
Periprostatic infiltration was performed using a 22-gauge needle through the biopsy guide and positioned on each side basero-laterally between the base of the prostate and seminal vesicles.
The position of the needle was confirmed by the lack of resistance while injecting and by visual confirmation of fluid on ultrasound scanning.
Lidocaine 1% was injected in 5 ml each side during needle withdrawal toward prostate apex.
No epinephrine was mixed with lidocaine. At the end of the procedure, the ultrasound probe was withdrawaled for a mean time of 10 minutes, and then re-positioned for prostate biopsy with the use of an automated gun with a 18 gauge 22 mm core Tru-Cut needle.

At the end of the procedure and seven days following procedure, pain and discomfort were evaluated using a questionnaire with a visual analogue score (VAS) scale for pain characteristics and complications (6). Patients were informed regarding the use of anaesthetic only after questionnaire compilation. Results were analyzed using an unpaired t-test and statistical software (Student' t test).

Results

Both groups resulted similar regarding age (67.4 SD 4.1 vs 62.5 SD 5.6 years), PSA value (11.6 SD 4.7 vs 16.7 SD 3.4 ng/ml) and prostate size (47.5 SD 13.5 g vs 56.4 SD 10.5 g). A lower VAS score during (mean VAS 2.7 vs 4.6, p value 0.03) and after bioptic procedure (mean VAS 2.3 vs 3.8 p value 0.04) and a lower duration of pain (mean VAS 1.9 vs 2.5, p value 0.05) has been reported at the end of the procedure in patients submitted to periprostatic lidocaine infiltration. Similar differences were recorded after seven days from procedure (pain during biopsy mean VAS 2.6 vs 3.9, p value 0.05; pain after biopsy mean VAS 2.3 vs 3.9, p value 0.03; pain duration mean VAS 2 vs 2.7, p value 0.04) (Table 1).
Lidocaine injection caused no adverse local or systemic effects in this group of patients before and /or after bioptic procedure. Complications related to biopsy following procedure and a week later resulted similar between intervals and comparable in both groups (Table 2).

Discussion

Prostate biopsies are usually performed as an office procedure and without anaesthesia. Anyway, in our experience and in several studies many patients reported pain during procedure, specially with extensive bioptic schemes (1, 2, 5). Crundwell (7) reported mild to moderate pain in 24% of patients undergoing transrectal prostate biopsy.
Among patients evaluated by Irani (8), 16% reported a pain VAS scores > 5 and 19% refused to undergo repeat prostatic biopsy without anaesthesia. So a significant number of patients experienced pain during prostate biopsy and anaesthesia resulted helpful to them.
Several anaesthetic procedures has been described, and among them periprostatic nervous block, as reported first by Nash (1) and adopted in this study, results a safe, simple and easy to perform procedure.

Table 1.
Pain VAS score between anaesthesia or not groups (P-value).

	Following biopsy		A week later	
Visual analogue score (vas)	**lidocaine**	**no**	**lidocaine**	**no**
Pain during probe insertion	0.8	0.7	0.5	0.6
Pain during biopsy	2.7	4.6 (p value 0.03)	2.6	3.9 (p value 0.05)
Pain following biopsy	2.3	3.8 (p value 0.04)	2.3	3.9 (p value 0.03)
Pain duration	1.9	2.5 (p value 0.05)	2	2.7 (p value 0.04)

Table 2.

Complications VAS score between anaesthesia or not groups (P-value).

	Following biopsy		A week later	
Visual analogue score (vas)	**lidocaine**	**no**	**lidocaine**	**no**
Hematuria	3.4	3.2	3.1	3.2
Rectal bleeding	2.8	2.6	3	2.8
Urethral bleeding	2.7	2.8	2.9	3
Voiding difficulties	2.5	2.4	2.6	2.5
Pain during voiding	1.9	2.3	2	2.1
Chills and fever	1.6	1.7	1.8	1.6

Anaesthetic effect is caused by the block of transmission of nociceptive impulses along periprostatic plexus nerves, in which are included sensitive fibres that travel within endopelvic fascia, laterally to the prostate and reach inferior hypogastric plexus and pelvic plexus and then sacral and toracolombar spinal centres.
Local anaesthetic is injected, under TRUS guidance, at the prostate base at the junction between the prostate and seminal vesicles along the neurovascular bundle (9).
Soloway (10) described a modified version of the periprostatic nerve block, involving instilling local anaesthetic agent into the periprostatic nerve with a bilateral injection at the junction of the base of the prostate and seminal vesicles and also in two additional points, one beside the apex and one in between the apex and the base.
The rationale of this approach should be the detection of a more intense pain when bioptic cores are taken at the level of prostate apex (11,12). In a randomized controlled trial, Schostak (13) reported that infiltration at the apex gave the lowest pain score.
The use of lidocaine is related to its characteristics, as the rapid onset and the duration (1-3 h) useful for bioptic procedure (14, 15). No epinephrine was mixed to the lidocaine to prolong the anaesthetic effect.
Pain during probe insertion and related to probe positioning in rectum has not ever been evaluated in previous studies, even if the TRUS is itself considered cause of patient discomfort.
Our study showed a lower pain score related to probe insertion and positioning in rectum with no significant statistical difference between patients submitted or not to anaesthesia

Conclusions

Periprostatic anaesthesia during prostate biopsy represent a simple, safe and easy to perform procedure and our data report a significant reduction of pain. The use of small volumes of lidocaine 1% allows an effective nociceptive and sensorial anaesthesia, reducing pain related to the bioptic procedure.
No patient presented complications related to the use of anaesthesia and all referred to repeat the procedure without hesitancy, if necessary. Complications resulted similar and comparable among different patients groups. Periprostatic anaesthesia results indicated in patients with abnormal PSA value, EDR and/or atypical findings (high grade prostate epithelial neoplasia – PIN) who require a repeat biopsy during lifetime.

References

1. Nash PA, Bruce JE, Indudhara R, Shinohara K. Transrectal ultrasound guided prostatic nerve blockade eases systematic needle biopsy of the prostate. J Urol 1996; 155: 607

2. Eskew LA, Bare RL, McCullough DL. Systematic five region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. J Urol 1997; 157:199

3. Stewart CS, Leibovich BC, Weaver AL et al. Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. J Urol 2001; 166:86

4. Stirling BN, Shockley KF, Carothers GC, Maatman TJ. Pain perception during transrectal ultrasound guided prostate needle biopsy: an objective analysis of local anesthesia use. Prostate Cancer Prostatic Dis, 2002; 5:209

5. Damiano R, Oliva A, Esposito C, Cantiello F, Sacco R, D'Armiento M. Are re extended biopsies necessary to improve prostate cancer detection? Prostate Cancer Prostatic Dis. 2003; 6:250

6. Damiano R, Oliva A, Cantiello F, Esposito C, Perdona' S, De Sio M, Bitonti M, Sacco R, D'Armiento M. Questionnaire based evaluation of prostate biopsy complications comparing different bioptic schemes".Arch Ital Urol Androl 2003; 75:40

7. Crundwell MC, Cooke PW, Wallace DM. Patients' tolerance of transrectal ultrasound-guided prostatic biopsy: an audit of 104 cases. Br J Urol 1999; 83:792

8. Irani J, Fourier F, Bon D et al. Patient tolerance of transrectal ultrasound-guided biopsy of the prostate. Br J Urol 1997; 79:608

9. Hollabaugh RS, Dmochowski RR, Steiner MS et al. Neuroanatomy of the male rhabdosphincter. Urology 1997; 49:426

10. Soloway MS, Obek C. Periprostatic local anesthesia before ultrasound guided prostate biopsy. J Urol 2000; 163:172

11. Kaven I, Mabjeesh NJ, Matzkin H. Randomized prospective study of periprostatic local anesthesia during transrectal ultrasound guided biopsy. Urology 2002; 59:405

12. Jones JS, Ulchaker JC, Nelson D, Kursh ED, Kitay R, Angie S, Horvat M, Klein EA, Zippe CD. Periprostatic local anesthesia eliminates pain of office-based transrectal prostate biopsy. Prostate Cancer Prostatic Dis 2003; 6:53

13. Schostak M, Panick M, Goessl C, Chistoph F, Miller K. Optimizing local anesthesia for systematic tenfold prostatic biopsy. J Urol 2001; 165

14. Lynn NNK, Collins GN, Brown SCW, O'Reilly. Periprostatic nerve block gives better analgesia for prostatic biopsy. Br J Urol 2002; 90:424

15. Leibovici D, Zisman A, Seigel YJ, Sella A, Kleinmann J, Lindner A. Local anestesia for prostate biopsy by periprostatic lidocaine injection: a double–blind placebo controlled study. J Urol 2002; 167:563

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ORIGINAL PAPER

Clinical staging accuracy of renal tumors.

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Summary

Objective: To evaluate the reliability of measurements obtained using standard imaging techniques (ultrasound and CT scan) vs pathological measurements and the relationship between clinical staging and the choice of the type of surgery. We also analyzed the relationship between cancer parameters (size, site, type of surgery) and prognosis. Materials and Methods: A retrospective analysis was conducted to examine a series of 140 patients with kidney cancer, all of whom underwent preoperative staging with abdominal ultrasound scan US and CT scan. To assess agreement between US and CT measurements and the pathologic size of renal tumors, we calculated the mean difference between the techniques, Pearson's correlation coefficient and Bland-Altman test. Results: The comparison between imaging and pathological findings revealed a good classification of tumor dimensions between the two imaging methods and pathologic size (correlation coefficients all over 0.8), and with limits of agreement of ± 2.2 cm for US measurement and of ± 2.3 cm for CT measure. We observed that the range in which the measurement error is lowest is over 6 cm: in other words, when smaller lesions are present there is a greater likelihood of committing measurement errors. As expected, logistic regression analysis shows that the size of the tumors significantly influenced the surgical approach and survival at five years follow-up. Conclusions: The imaging methods used in clinical staging of renal tumors currently allow us to select the most appropriate surgical option with a certain amount of confidence. Tumor size continues to be one of the most important factors in prognosis and it can influence both the surgical approach and cancer-specific survival.

KEY WORDS: *Renal tumors; Clinical staging; Surgical approach.*

INTRODUCTION

The use of ultrasound and CT scan in clinical practice and their continuous development (helical CT, 3D-CT) (1) has modified preoperative staging, affecting the choice of surgical approach. Radical nephrectomy continues to be the treatment of choice for renal tumors, although there is increasingly frequent reliance on nephron sparing surgery, elective or mandatory, particularly for smaller tumors (< 4 cm) (2).

The choice between radical or conservative surgery is inseparably linked to preoperative staging. The objective of this study is to evaluate the reliability of the measurements obtained using imaging techniques and if they have impact on the choice of surgery; and finally if site, tumor size and type of surgery affect cancer-specific survival.

MATERIALS AND METHODS

A retrospective analysis was conducted to examine a series of 140 patients with kidney cancer (January 1990 - January 2000), with a mean age of 60 years (range 18-82 years).

All of them underwent preoperative staging including abdominal ultrasound scan and CT scan, with measurement of major diameter; regardless CT scan, width of CT slides were identical in all patients, and we chose the largest diameter reported by the radiologist.

According to clinical staging and intra-operative pattern, ninety patients underwent radical nephrectomy, while conservative surgery was performed on fifty.

Nephron sparing surgery were performed for absolute indication in 10 patients (3 cases of single kidney, 3 cases of bilateral involvement and 1 case with a contralateral upper urinary tract tumor; however, considering only tumor size, all these patients were suitable for an elective nephron-sparing surgery) or for elective indication in tumor less than 5 cm (not involving upper urinary tract) with a normal controlateral kidney (in 40 patients), after a carefull evaluation of correct indica-

Table 1.

Comparison between imaging methods and pathologic results expressed as the mean of the differences, Pearson's correlation coefficient and limits of agreement.

	PS – US	PS – CT
Mean of differences (cm)	-0.3	-0.4
Correlation coefficient	0.906	0.899
Limits of agreement (cm)	2.22	2.32

PS-US: pathological-size-ultrasound; PS-CT: pathological-size-CT

tions and counter-indications (age, performance status, co-morbidities, renal function), and after an informed consensus.

During conservative surgery we avoided the use of vascular occlusion (we used it only in cases in which is helpful during haemostasis).

After surgery, we measured tumor's diameter prior to formalin fixation after a coronally transection of the neoplasia, valuing its largest diameter.

Statistical analysis

To assess agreement between US and CT clinical measurements and pathologic size PS of renal tumors, we calculated the mean difference of measures between techniques, Pearson's correlation coefficient and Bland-Altman test (3). In this case, the correlation coefficient indicates only the correct reclassification of tumor size. We used the Bland-Altman test that provides for the limits of agreement of imaging techniques; the limits of agreement represent the maximum discrepancy that may be below or above the pathologic size. Chi-square test instead was used to compare the frequencies of localization of renal tumors.

To determine if and to what extent the size of the tumor measured with the three techniques and the site affect the surgical option, a model of multiple logistic regression was produced.

Nephrectomy was used as a binary dependent variable (partial=0; radical=1) and as independent predictor variables we used tumor location (upper, mesorenal, inferior); the tumor sizes evaluated with the three techniques were used one at a time in separate analyses.

Lastly, we also analyzed how the variables of site, diameter and type of surgery influenced patient survival by adopting a successive multiple logistic regression model in which the dependent variable was survival (not survival=0; survival=1) and the independent variables were age, site, tumor size measured with the two imaging techniques and the histological examination, and the type of surgery performed. Using this model, through the regression coefficients we determined the survival odds ratios at 2 and 5 years of follow-up.

All statistical analyses were carried out with SPSS v 6.1.3, SPSS Inc., Chicago, USA, with the exception of the Bland-Altman test, which was performed using a program developed by a member of our group.

RESULTS

All patients were reassessed according to 1997 TNM staging.

Clinical staging showed 118 pts with T1 disease (84.2%), 8 pts with T2 disease (5.7%), 13 pts with T3a disease (9.2%) and only 1 case of T4 disease (0.9%); all patients were N0 and M0.

Mean US diameter was 4.7 cm (median value 4 cm, SD ± 2.68 cm); mean CT diameter was 4.8 cm (median value 4.5 cm, SD ± 2.65 cm).

In 28% of cases the tumor was located in the upper pole, in 38% in the mesorenal area, and in the lower pole in 34%; in 79 patients (56%) the right kidney was involved while in 61 the left kidney was involved. There are no significant differences with regard to either the frequency of tumor location in the three sites (upper pole, mesorenal, lower pole) or the side involved.

Pathological staging was pT1 in 103 patients (74%), pT2 in 12 patients (8.5%), pT3 in 24 patients (17%) and pT4 in only one patient (0.5%).

Histological examination revealed 102 cases of clear cell carcinoma, 21 cases of granular cell carcinoma, 6 cases of papillary adenocarcinoma, 2 cases of sarcomatoid carcinoma and 9 cases of oncocytoma.

Mean specimens diameter was 4.7 cm (median value 4 cm, SD ± 3.55 cm).

The comparison between the clinical measurements and the pathologic findings regardless of site or size showed a moderate mean of differences (less than 0.5 cm) with all the differences in measurement lying between the two standard deviations, as envisaged by the Bland-

Table 2.

Comparison between imaging methods and pathologic results expressed as the mean of the differences, limits of agreement and Pearson's correlation coefficient divided according to the site of the lesion.

	Superior pole		Mesorenal		Inferior pole	
	PS–US	PS-CT	PS–US	PS-CT	PS–US	PS-CT
Mean of differences (cm)	-0.6	-0.6	-0.2	-0.3	-0.2	-0.3
Correlation coefficient	0.908	0.902	0.854	0.882	0.940	0.903
Limits of agreement (cm)	2.83	2.90	2.00	2.02	1.79	2.07

PS-US: pathological-size-ultrasound; PS-CT: pathological-size-CT

Table 3.

Percentage and absolute values of limits of agreement subdivided according to tumor size.

	percentage value		absolute value (cm)	
Tumor size (cm)	**PS – US**	**PS – CT**	**PS-US**	**PS-CT**
≤2.5	52.13	56.52	0.96	1.03
>2.5 - ≤4	53.23	45.40	1.84	1.83
>4 - ≤6	59.82	65.08	2.57	2.56
>6	39.37	41.23	3.24	3.49

PS-US: pathological-size-ultrasound; PS-CT: pathological-size-CT

Altman test. A good classification was also noted in terms of tumor size between the two imaging methods and pathologic size, with correlation coefficients that all exceeded 0.8 and limits of agreement of ± 2.2 cm in the comparison between pathologic size and US measurement and of ± 2.3 cm between pathologic size and CT measurement (Table 1).

Table 2 lists the same statistics divided according to tumor location. The worst results were observed with regard to the staging of the upper pole.

With regard to the evaluation of the limits of agreement alone, divided according to tumor size (Table 3), the best values were noted with lesions with a diameter of more than 6 cm (both for PS-US and PS-CT).

The site of the tumor is not correlated with the type of surgery, while size showed a positive significant correlation for the US evaluation (r=0.392; p<0.0001), CT study (r=0.396; p<0.0001) and pathological measurement (r=0.412; p<0.0001).

The same type of analysis was applied to the model using survival as a dependent variable and age, site, tumor size and type of surgery as independent variables. The results showed that only tumor size was negatively and significantly correlated with survival at both two and five years of follow-up.

Discussion

The statistical analysis shows that ultrasound measurement and CT scan diameters compared with the pathological diameters respectively showed a mean of differences equivalent to 0.3 and 0.4 cm with limits of agreement of ± 2.2 cm and ± 2.3 cm.

These figures reflect the ones reported in the most recent literature, in which the variations in differences in diameters diagnosed with CT varied from 0.3 to 0.6 cm, with ranges of error that were also higher (± 3 - 4 cm) (4-5).

Similar results were obtained by repeating the test for each tumor localization site (upper pole, mesorenal and lower pole); in this case, the worst limits of agreement were noted for the upper site (approximately ± 3 cm) and this could be explained by the fact that the radiographic margins of the upper pole are often masked by adrenal gland, diaphragm, liver and spleen (5). These results are not confirmed by other authors as Irani (4).

Statistical analysis of error of measurement showed that this error is distributed over the entire range of the measurements with a trend in the value of the limits of agreement proportional to the size of the lesions. This interpretation of numeric data is commonly used in most of the case studies reported in the literature (4-6): however, according to our experience, the range in which the measurement error was lowest is for lesions over 6 cm (39.4% for PS-US and 41.2% for PS-CT). This means that for smaller lesions there is a greater possibility of committing measurement errors.

With regard to choice of the type of surgery – radical or conservative – logistic regression analysis shows that the location of the tumor does not significantly affect this choice. Indeed, the size of the tumors, evaluated with different diagnostic methods and compared with pathological findings, significantly influenced the surgical approach (PS (p<0.0001), US (p<0.0001) and CT (p<0.0001)).

In terms of cancer-specific survival, the results clearly show that only tumor size (clinical or pathological measurements) were negatively and significantly correlated with outcome, at both the two- and five-year follow-up. We adopted a probability approach to the study of survival with respect to the retrospective one commonly used, because it yields a more fine-tuned evaluation of the impact of tumor size on outcome (7, 8). While the statistical approach was different, our data yielded the same results: tumor size is the most important prognostic factor for patient survival.

Conclusions

The imaging techniques commonly used in the clinical staging of kidney cancer do not currently offer more accurate information on the cancer. Nevertheless the indications that can be drawn from these studies allow us to choose the most appropriate surgical option with a certain amount of confidence, even if there is a good correlation between clinical and pathological size.

Naturally, the introduction of new diagnostic imaging methods such as the helical CT and the 3D-CT may offer additional information thanks to the accuracy of the anatomic details that are displayed. As a result, this may offer better indications for the choice of conservative surgery.

Tumor size continues to be one of the most important factors in prognosis.
This can affect both the surgical approach and the long-term results evaluated as cancer-specific survival.

REFERENCES

1. Teigen EL, Newhouse H. Imaging renal masses. Curr Opin Urol 2000; 10:421

2. Uzzo RG, Novick A. Nephron sparing surgery for renal tumors: indications, techniques and outcomes. J Urol 2001; 166:6

3. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measure. Lancet 1986; I, 307

4. Irani J, Humbert M, Lecocq B, Pires C, Lefèbvre O, Dorè B. Renal tumor size: Comparison between Computed Tomography and surgical Measurements. Eur Urol 2001; 39:300

5. Herr HW. Radiographic vs surgical size of renal tumors after partial nephrectomy. BJU International 2000; 85:19

6. Herr HW, Lee CT, Sharma S Hilton S. Radiographic versus pathologic size of renal tumors: implications for partial nephrectomy. Urology 2001; 58: 157

7. Fergany AMR F, Hafez KS, Novick A. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10 years of follow-sup. J Urol 2000; 163:442

8. Kinouchi T, Saiki S, Meguro N, et. al. Impact of tumor size on the clinical outcomes of patients with Robson stage I renal cell carcinoma. Cancer 1999; 85:689

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CASE REPORT

Radical prostatectomy as unique chance for huge prostatic stones.

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Summary

Prostatic calculi occur very often in men, but exceptionally they cause an almost total destruction of the prostatic parenchyma. Preferred treatment in order to obtain complete resolution is either transurethral resection or suprapubic simple prostatectomy. We report for the first time a radical prostatectomy as a unique chance for huge prostatic stones in a 56-years old man with severe urinary symptoms. We perform a retropubic radical prostatectomy using a nerve sparing technique. There were no intraoperative or postoperative complications. Though radical prostatectomy is an invasive approach to treat a young man affected by prostatic stones and without prostate cancer, we chose to perform it because of the impossibility to obtain complete recovery with transurethral or suprapubic simple prostatectomy.

KEY WORDS: *Prostatic stones; Prostatitis; Prostatism; Radical prostatectomy.*

INTRODUCTION

Prostatic calculi are caused by acinar obstruction. Treatment is either transurethral resection or suprapubic prostatectomy. Radical prostatectomy for diffuse prostatic calcifications has never been reported.

CASE REPORT

A 56 years-old male patient presented in August 2000 with fever, dysuria, painful micturition, decreased stream and perineal pain. He was unable to sit down. The years earlier the patient had undergone meatoplasty for meatal urethral stenosis. Before surgery he had several episodes of prostatitis with perineal pain and fever; prostatic ultrasound scans had shown gross calcifications in both prostatic lobes and around the bladder neck; the capsule was normal. At the cystourethrometrogram voiding time, several vacuolated dilations filled with calcified formations, had been observed. Three years later the patient had suffered episodes of dysuria, perineal pain and fever, that often cleared up after spontaneous purulent urethrorrea. Antibiotic therapy had failed. On admission to our Unit the perineum was oedematous and indured; digitorectal exam revealed a gritty prostate with areas of palpable induration. The patient's temperature was 38,5 °C. Blood tests and urinalysis were normal; urine colture was negative. Total PSA was 0,28 ng/ml. Prostatic ultrasound scans showed diffuse hyperechogenic spots in the parenchyma indicating calculi; hypoechogenic areas were also detected. NMR showed a reduced prostatic parenchyma with three vacuolated formations 5, 4 and 3 cm in diameter; two contained a corpuscolate fluid with calcified formations and the third one three large stones. The prostatic capsule was thinned and partially calcified at NMR. Lymph nodes were normal; the bladder wall was thickened. As the entire prostate was almost destroyed and calcified we opted for a radical retropubic prostatectomy using a nerve sparing technique. Transurethral resection of the prostate or suprapubic simple prostatectomy were unlikely to be successful. At prostate dissection 38 calculi of 25 g total weight were found. Histology reported chronic phlogosis. The postoperative period was uneventful and four months later transrectal ultrasound confirmed no stones were present.

DISCUSSION

Prostatic calculi may be solitary but usually occur in clusters (1). Symptoms include poor urinary stream and prostatism. Complications such as prostatic and perineal abscess, prostatic induration, urethral obstruction have been reported (2). Prostatic calculi may be formed by corpora amylacea calcification and prostatic fluid precipitation. An inflammatory reaction may contribute to their growth, or they may arise secondary to another pathology

Figure 1.
NMR shows poor residual prostatic parenchyma and the cavities inside of the prostate containing corpuscolate fluid and large stones.

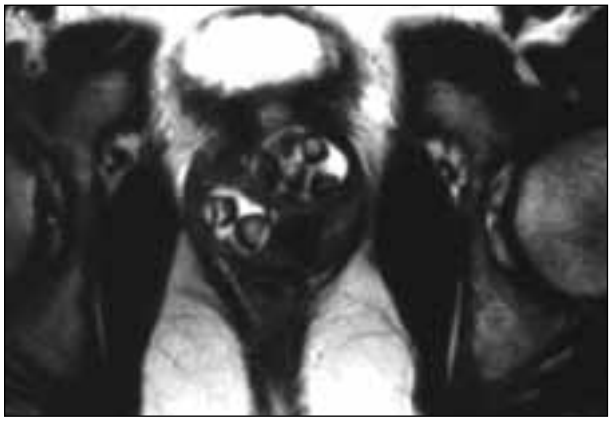

Figure 2.
The prostate has been dissected radically. Both prostatic cavities and stones can be seen.

such as urethral or meatal stenosis, as in our case, which obstructs the acina (3). In our opinion urethra and prostatic duct dilation caused prostatic fluid stasis and infection which led over the years to almost total calcification of the prostate. We performed a radical prostatectomy as the whole prostate was occupied and destroyed by stones and could not be saved. The unusual therapeutic choice has never been reported elsewhere.

References

1. Klimas R, Bennet B, Gardner WA Jr. Prostatic calculi: a review. Prostate 1985; 7:91

2. Kamai T, Toma T, Kano H. Urethral obstruction due to protruding prostatic calculi. J Urol 1999; 162:163

3. Fox M. Gross calcification within the prostate gland. Br J Urol 1998; 82:461

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CASE REPORT

Acupunctural reflexotherapy as anaesthesia in day-surgery cases. Our experience in left internal vein ligature for symptomatic varicocele and in circumcision.

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Summary

Acupunctural reflexotherapy has been performed in patients during minimally invasive treatments for benign prostatic hyperplasia and in patients with lower urinary tract symptoms. We report two cases of left internal spermatic vein ligature for varicocele and a case of circumcision using acupunctural reflexotherapy, a procedure, to our knowledge, never applied before in open surgery. A 38 and a 24 years old male patients came to our observation for a 2nd degree symptomatic left varicocele and a 40 years old patient came to have a circumcision; mthey requested alternative anaesthesia for the operation and acupunctural reflexotherapy has been performed. This technique for analgesia can be useful and can be applied in selected cases, i.e. minor surgery in patients who do not wish or cannot have a general anaesthesia; it can be associated to other techniques of anaesthesia as peri - and post - operative analgesia. No contraindications nor collateral effects exist. The limits of this methods are represented by the length of time required for preparation of the patient and the existence of patients non - responder to electrostimulation.

KEY WORDS: *Acupunctural reflexotherapy; Varicocele; Left spermatic internal vein ligature; Circumcision.*

INTRODUCTION

Acupunctural reflexotherapy has been performed in patients during minimally invasive treatments for benign prostatic hyperplasia (1); the good results obtained with this method drove us to use it in patients with lower urinary tract symptoms (LUTS) (2).

We report two cases of left internal spermatic vein ligature for varicocele and a case of circumcision using acupunctural reflexotherapy, a procedure, to our knowledge, never applied before in open surgery.

CASES PRESENTATION AND MANAGEMENT

A 38- and a 24-years old male patients came to our observation for a 2nd degree symptomatic left varicocele; they objected formally to assumption of any kind of medications for the operation and on purpose requested alternative anaesthesia.

The patients gave the informed consent, although being aware that acupunctural reflexotherapy was never applied before in open surgery.

Steel needles 15 – 40 mm in length were used, connected to an electrostimulator with 7 lines, each with possibility of selective regulation.

For stimulation during acupunctural reflexotherapy the following points have been used:

a) Somatic points

- 4GI bilaterally, between the 1st and the 2nd finger, stimulated at low frequency (5 Hz) and high intensity (below the pain threshold);
- 36St bilaterally, in the leg below the knee, stimulated at low frequency (5 Hz) and high intensity (below the pain threshold);
- 6 subcuticular needles, inserted tangentially around the skin incision, stimulated at high frequency and high intensity;

b) Auricular points
• Shenmen: conch of the outer ear, bilaterally, stimulated at low frequency and high intensity;
• "Valium": near the temporo-mandibular joint, bilaterally, stimulated at low frequency and high intensity;
• Point zero: at the center of the outer ear, bilaterally, stimulated at low frequency and high intensity.
The stimulation began 90 minutes before and lasted during all surgery.
Intraoperative monitoring was performed in both patients as during standard surgery; no medications were administered before, during and after surgery.
Twenty minutes after stimulation the patients manifested a moderate well-being, hilarity and laughter; a light burning was reported during skin incision, but no other discomfort during the procedure of left spermatic vein ligature.
The procedure lasted 30 minutes and during monitoring vital parameters remained unchanged.
At the end of surgery the patients stood up by their own, reached the stretcher and fed two hours later.
The post operative analgesia lasted 12 hours.
The patients were discharged in the evening.
Two years later a Doppler ultrasound of the pampiniformis plexus was performed, that did not show varicocele bilaterally.

A 40-years old patient came to our observation to have a circumcision; he requested alternative anaesthesia for his operation, therefore acupunctural reflexotherapy was proposed.
Also in this case steel needles 15-40 mm in length were used, connected to an electrostimulator with 7 lines, each with possibility of selective regulation. The following points were used for stimulation:
a) Somatic points
• "pudendal", bilaterally, above the pubis symphisis, stimulated at high frequency and intensity;
• "penile", bilaterally, on the ventral penile surface, tangentially, stimulated at high frequency and intensity;
• 4GI bilaterally, between the 1st and the 2nd finger, stimulated at low frequency (5 Hz) and high intensity (below the pain threshold);
• 36S+ bilaterally, on the outer part of the leg, close to the knee.
b) Auricular points
• Shenmen: conch of the outer ear, bilaterally, stimulated at low frequency and high intensity;
• "Valium": near the temporo-mandibular joint, bilaterally, stimulated at low frequency and high intensity.

Discussion

The techniques described by us implies both the nociceptive afferences blockade (by needles inserted beneath the skin incision) and the stimulation of neuromodulators production - endorfins, serotonine, dopamine (by stimulation of trigeminal nerve - auricular points - and of spinal cord - somatic points); the neuromodulators are able to inhibit the perception of painful sensations in the central nervous system (posterior horn of the spinal cord and periacqueductal grey substance) (3).
This technique for analgesia can be useful and can be applied in selected cases, i.e. minor surgery in patients who do not wish or cannot have a general anaesthesia; it can be associated to other techniques of anaesthesia as peri- and post operative analgesia.
No contraindications nor collateral effects exist.
Unfortunately, the limits of this method are represented by the length of time required for preparation of the patient and the existence of patients non-responder to electrostimulation.

References

1. Ricci L. Anestesia con elettroagopuntura nella resezione prostatica per via endoscopica con laser. G It Riflessot Agopunt 1997; 9:1

2. Ricci L, Minardi D, Romoli M, Galosi AB, Muzzonigro G. Acupunctural reflexotherapy in the treatment of sensory urgency that persists after transurethral resection of the prostate. A preliminary report. Neurourol Urodynam 2004; 23:58

3. Oleson T, Kroening R, Bresler D. An experimental evaluation of auricular diagnosis: the somatotropic mapping of musculoskeletal pain at ear acupuncture points. Pain 1980; 8:217

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CASE REPORT

Gastrointestinal stromal tumor presenting as a large abdominal mass.

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Summary

Objective: We report on a male patient operated on for a mesenchymal tumor of the digestive tract presenting a mega cyst-like abdominal mass. Material and Methods: The size of the lesion was magnum, the mass presented as unilocular, the wall thickness was not uniform (0,1 to 1 cm) with hemorragic areas, the lesions were multiple measuring 3x2 cm and less, the mitotic index was borderline. The diagnosis was histologically defined as GIST borderline (low mitotic count and tumor size < 5 cm). The ultrasonography and TAC were unable to diagnostic information. Conclusion: The GIST presents no specific signs and the most frequent symptoms are abdominal pain and abdominal mass, the CT scan and ultrasonography are sensitive in the evaluation of location, size, invasion of adjacent organs but not for diagnosis. Prognostic predictions are on the basis of mitotic index and tumor size (1). The precise cellular origin of GIST (2) has recently been proposed to be the interstitial cell of Cajal, an intestinal pacemaker cell. The gain-of function mutation of c-kit (receptor tyrosine kinase – KIT positive tumor) proto-oncogene has been detected in GIST and its role in molecular pathogenesis has been established. The treatment of unresectable and metastatic lesion is Imatinib mesylate, inhibitor of tyrosine-kinase activity (Gleevec, Novartis).

KEY WORDS: *GIST (Gastrointestinal Stromal Tumor); Abdominal mass.*

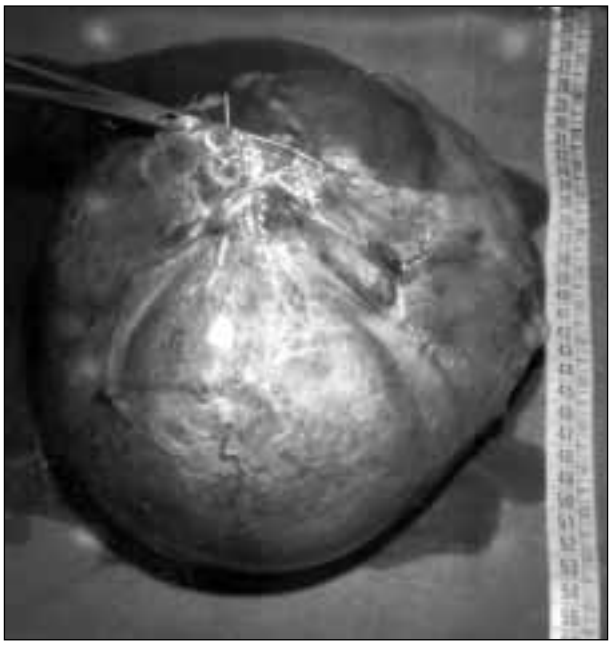
INTRODUCTION

GIST is an uncommon mesenchimal visceral tumor arising from the gastrointestinal tract whose malignancy is often difficult to predict. It may be found anywhere in the GI tract from the lower esofagus to the anus (1). We report a patient who was admitted to treatment for a suspected-supposed great cyst of the urachus and was scheduled for surgery.

CASE REPORT

A 63-years old patient came to our observation with the following symptoms: feeling of epigastric tension, rapid increase of abdominal girth due to a quickly expanding mass, pollachiuria. His anamnestic records did not reveal any major disease. Abdominal echography evidenced a large pelvic cyst (size 20x15x9 cm) arising from the top of the bladder and expanding towards the upper abdomen, suggesting a differential diagnosis with an enormous bladder diverticulum. Computed tomography scan of the abdomen confirmed the hypothesis of an abdominal cyst. In addition, neither the administration of i.v. contrast nor a cystoscopy could detect a communication between the bladder and the supposed cyst. A Meckel diverticulum or an urachal neoformation where therefore suspected. The patient was proposed for surgical exploration. A great intraperitoneal cyst was easily isolated from the bladder wall but presented a strong adherence to a portion of the ileus. A sample of fluid obtained from the cyst was searched for malignant tumor cells but showed only erythrocytes and isolated histiocytes. The operation was then successfully carried out after complete resection of the cyst and of a small ileal tract (Figure 1). A latero-lateral anasthomosis was performed. An accurate exploration of the abdominal cavity did not show any other lesion. Seven days after surgery the patient was dismissed from the hospital. First observations showed a cyst containing about 5 litres of brownish fluid; wall thickness measured between 0.1 and 1 cm, its surface was smooth and presented multiple hemorragic spots, the biggest rising from the resected ileus tract. Histopathologic investigation showed a GIST 3x2 cm. with a borderline smooth muscle differentiation. Mitotic rate was 1 per 50 HPF. More small GIST areas were detected within the hemorragic lesions of the cyst wall.

Figure 1.
Excised mass of a 5 litres volume.



This report deserves a particular attention as a cyst of such magnitude enclosing a GIST constitutes a clinical observation that was never described in literature before. Three years after the operation, the patient is still well up. Tumor markers (CEA, CA 125, Alfafetoprotein etc.) are within the normal range.

Discussion

GIST is an uncommon tumor mainly described in adult population (> 40 years) of both sexes. GIST is most commonly seen in the stomach (60%) and ileus (30%), whereas it is rarely observed in esophagus, colon and rectum (2). Size and mitotic rate are considered predictive of malignancy (3-6). It can therefore be considered benign a mitotic rate around 0 and size > 5 cm, borderline a mitotic rate 1-10 per 50 HPF and a size of 5-10 cm, malignant a mitotic rate > 10 per 50 HPF and a size > 10 cm. This classification is associated to a 100% survival rate for benign tumors, a 69% survival rate for borderline and 14% survival rate for malignant tumors. Surgery has been recognized as the only effective therapy. Adjuvant therapy as chemotherapy and radiation therapy did not prove to be satisfactory (1). Recently patients with diffuse metastases or with tumors considered to be unresectable were proposed for treatment with a tyrosine-kinase inhibitor such as Imatinib mesylate (Gleeven, Novartis). GIST may spread in the abdominal cavity and can exceptionally metastatize at extraadbominal sites.

Conclusion

We report on a 63-years old patient with gastrointestinal neoplasm. Diagnosis was possible only after hystopathologic investigation, since neither clinical findings nor surgical exploration could clearly detect neoplastic lesions. Even intraoperative analysis of some fluid contained in the cyst was negative for malignant tumors cells. Abdominal echography and computed tomography with i.v. contrast were able to localize site and size of the mass but were not useful for a more accurate diagnosis. The neoplasm resembled a big cyst, whose proximity to the bladder suggested a possible origin from the urinary tract. Significant predictors of survival are mitotic rate, recurrence and above all size of tumor (which is considered significant if greater than 10 cm (1). Three years after surgery our patient is still in good health and there is no clinical evidence of recurrence of metastases. Patients with unresectable and metastatic tumor may be treated with Imatinib mesylate, a KIT-selective Tyrosine-kinase inhibitor.

References

1. DeMatteo R, Lewis J, Leung D, Mudan S, Woodruff J, Brennan M. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231:51

2. Miettinen M, Lasota J. Gastrointestinal stromal tumours; definition, occurrence, pathology, differential diagnosis and molecular genetics. Pol J Pathol 2003; 54:3

3. Moral MG, Gil PF, Velasco OA, Seco GJ, Galindo M, Garcia S. Stromal tumors of the digestive tract. Prognostic value of mitotic index. Rev Esp Enferm Dig 1998; 90:335

4. Ballarini C, Intra M, Ceretti A, Prestipino F, Bianchi FM, Sparaccio F, Berti E, Perrone S, Silva F. Gastrointestinal stromal tumors: a "benign" tumor with hepatic metastasis after 11 years. Tumori 1998; 84:78

5. Pidhorecky I,Cheney RT, Kraybill WG, Gibbs JF. Gastrointestinal stromal tumors: current diagnosis, biologic behaviour, and management. Ann Surg Oncol 2000; 7:705

6. Fletcher CD, Berman JJ, Corless F, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Int J Surg Path 2002; 10:81

7. Zighelboim I, Henao G, Kunda A, Gutierrez C, Edwards C. Gastrointestinal stromal tumor presenting as a pelvic mass. Gynecol Oncol 2003; 91:630

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A case of tumor of the penis: interstitial brachitherapy after conservative surgical therapy.

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Summary

The neoplasms of the penis are extremely rare and have an incidence of 1400 new cases for year in the United States (1). Higher is the percentage of incidence in Africa and Asia (10-20 %) and in some areas of Brasil where the cancer of the penis constitutes 17 % of all the male tumors (2). In Israel this neoplasm is rare, less than 0.1/100000 men for year, because in Jewish population men are circumcised prematurely (1). Recently it has been placed attention to the possible aetiologic role of human papillomavirus (HPV-16 and HPV-18) in penis carcinoma. In fact, in the tumoral cells, DNA of this virus has been found with a percentage that varies from the 30 to 82%. Traditional surgical approach is total or partial penis resection basing on the extension of the disease. This procedure is associated to remarkable psycosessuals problems that greatly affect the quality of life (1). We bring back a case with organ sparing conservative treatment.

KEY WORDS: Brachitherapy; Hypodermic needles; Iridium wires.

CASE REPORT

A patient of 65 years reaches our attention with diagnosis of unlocked fimosis with balanopostitis and sclero-atrophic lichen of the prepuce with coronal hardening suspicious for espansive lesion. The patient underwent circumcision and resection of two papillary lesions of the prepuce (2,5 cm of greater axis) and the glandis (3,2 cm of greater axis).

The histological examination of this lesions has evidenced the presence, in the prepuce, of a well differentiated verrucous epidermoid carcinoma, ulcerated and infiltrating to all thickness the sub-epithelial connective up to the fibrovascular tissue; the neoplasm infiltrates the surgical margins marked with china. In the glandis was diagnosed an ulcerated, moderately differentiated epidermoid carcinoma, with verrucous aspects, infiltrating the sub-epithelial connective tissue up to the fibrovascular one, associated to lichen and chronic balanopostitis. Margins of deep resection were free from disease while in the glandis the pathological process was found in proximity of a lateral margin. Basing on this last medical report the patient underwent brachitherapy. Moreover before the radiotherapic sitting the patient executed an abdominal-pelvic computerized tomography that revealed the absence of pathological finds. At the palpation of the inguinal region no adenopathies were found.

The patient was treated by interstitial implantation using iridium wire after loading technique. This technique has been previously described in literature (3). Hypodermic needles (length of 8 cm) were used as vectors for the iridium wires. Three needles were placed beyond the inferior region of the

Figure 1.
Five sources of Ir-192 were loaded into the needles.

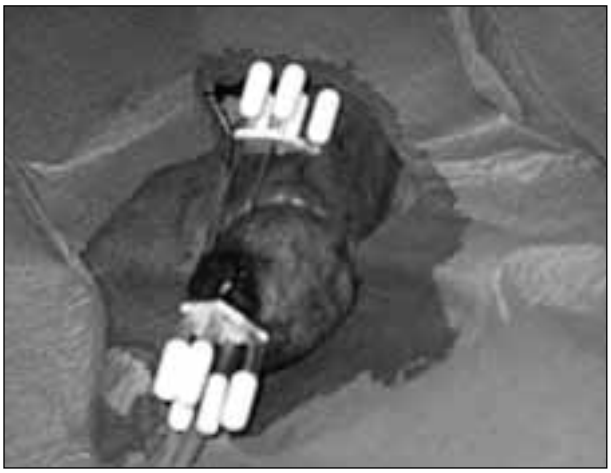

Figure 2.
Plan frontal oblique.
The activity of the Ir-192 sources order to provide a minimum peripheral dose-rate of 50.1cGy/hr. Total dose 6000cGy, total time 122.37hr.

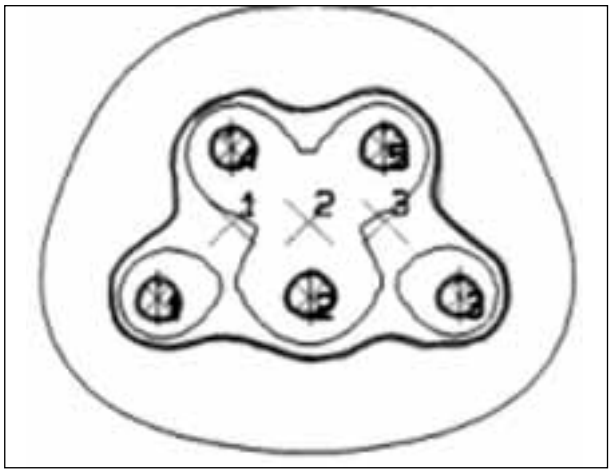

Table 1.
Interstitial brachitherapy data.

Radioactive length	50 mm
Distance between lines	10 mm
Reference isodose	100 %
Reference dose	50.1 cGy/hr
Dose	6000 cGy
Linear activity	28.6 MBq/cm
Time	122.37 hr

target volume and the separation between the needles was 1.0 cm. The other two needles were disposed to the superior limit of the target volume passing through the tumor lesion. Two rigid templates (plexiglass plates) were used and their advantage is to precise geometrical source distributions and to maintain parallelism between sources. Five sources of Ir-192 were loaded into the needles (*Figures 1 and 2*). Low dose rate was used. The mean value of the parameters with regard to the distance between lines, the reference isodose, the dose and the linear activity are in agreement with Paris system recommendations (*Table 1*). The patient brought bladder catheter during the brachitherapy and for fifteen days after interstitial treatment to avoid urethral stenosis.
The follow-up consisted of physical examination every three months for the first three years.
Moreover the patient was also eudcated to perform physical self-examination regularly.
At 39 months follow-up the patient is disease free.

Discussion

The tumors of the penis hit in 48 % of the cases the glandis, in 21% the prepuce, glandis and prepuce in 9 % of the cases and the coronal furrow in 6 %. The lymphonodals involvement is present at diagnosis in 58 % of the cases with a range that varies from 20 to 96 % as brought back from many authors (4). Penis tumors can originate from the connective tissue, the urethra, the epithelium or can be metastasis of other tumors and in this case, the lesion usually hits the cavernous bodies. The small tumors of the penis limited to the prepuce could be treated only with circoncision when the surgical margins turn out negative; in cases of small and superficial tumors the Nd:YAG or CO2 Laser can also be used. Subsequently for the local control of the disease, conformational or interstitial adiuvant radiotherapy could be used. The tumors of the penis involving the glandis and the pars distalis are usually treated with the partial penectomy while in case of tumors that involve the base of the penis the treatment consists on penis amputation and urethrectomy. The presence of inguinal lymphadenopaties demands the inguinal lymphadenectomy that has a morbility percentage of 30 - 50 % (necrosis of the cutaneous border). Because of this high morbility various techniques has been proposed in order to carry out this procedure. In literature many cases of interstitial brachitherapy associated or no to surgical resection are described with a disease control in 65 % of cases. Recently the conservative approach is usually preferred because of the psychological sequele that an amputation of the penis can determine on the patients quality of life (5). The complication rates of the external-radiotherapy and Brachitherapy are the following: urethral stenosis 30-45% of cases, necrosis of penis 15 % in the Brachitherapy while in the conformational radiotherapy occur in 5-8% of cases. Approximately the half of the patients with penis necrosis underwent amputation of the penis. In agreement with other authors (1) and basing on our experience we can reasonably propose a conservative treatment in T1 tumors smaller than 4 cm and localized in the end part of the penis as well as in cases where is not possible to carry out the surgical resection and in well differentiated tumors. In this cases radiotherapy could be sufficient for disease control even if this type of approach goes against to the classics parameters of oncologic surgery that need the fixed margins free from disease for 2 cm of length.

References

1. Opyordsmoen S. et al. Quality of life in patients treated for penile cancer. A follow-up study. Br J Urol 1994; 74:652

2. Russo P, Gaudino P. Carcinoma of the penis. Diagnosis and saging. Cont Urol 2000; 4:12

3. Crook et al. Interstitial brachyterapy for penile carcinoma: an alternative to amputation. J Urol 2002; 167:506

4. Mobilio G, Ficarra V. Genital treatment of penile carcinoma. Curr Opin Urol 2001; 11:299

5. Zouhair et al. Radiation therapy alone or combinated surgery and radiation therapy in squamous-cell carcinoma of penis? Eur J Cancer 2001; 37:198

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CASE REPORT

Non Hodgkin lymphoma of the ureter: a rare disease.

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Summary

Non urotelial malignant neoplasm of the ureter has been rarely described, usually arising from muscular, vascular and nervous tissue. Primary lymphoma of the ureter is an uncommon finding; we report a case of primary Non Hodgkin Lymphoma of the ureter in young woman.

KEY WORDS: *Urinary tumors; Non Hodgkin lymphoma; Flank pain.*

INTRODUCTION

Upper excretory way tumours represent between 2 and 5% of all urinary cancers. A quarter of them are placed in the ureter. Most of the ureteral neoplasms are located in the lowest portion of the ureteral wall. Transitional cancer is the most common histological type. Squamous cell carcinoma, adenocarcinoma, and other primitive malignant neoplasm of muscular, vascular and nervous origin have also been described (1). Plasmocytoma and lymphoma of the ureter are found very rarely.

CASE REPORT

A 22-years old woman was admitted to the hospital because of a left flank pain together with an episode of urosepsis. A similar episode of flank pain was referred by the patient one month before during a trip abroad. On that occasion pain was associated with gross haematuria. Ultrasound abdominal examination was carried out and showed a 0.5 cm ureteral stone with a slight omolateral hydronefrosis. Medical emergency therapy with analgesic, removed all the symptoms. When the patient came back to Italy she was still feeling something lying heavy on her flank. This sensation became soon a sharp, irrepressible pain and was associated with gross haematuria and a chill fever. Ultrasound and IVP showed a left hydronephrosis but did not demonstrate the presence of stones inside the excretory way (Figure 1). CT scan confirmed the hydronephrosis but it was not able to show any cause of obstruction. Retrograde pielography demonstrated an ureteral stricture which appeared so severe that ureteroscopy was judged impos-

Figure 1.
The IVP showed a left hydronephrosis but did not demonstrate the presence of stones inside the excretory way.

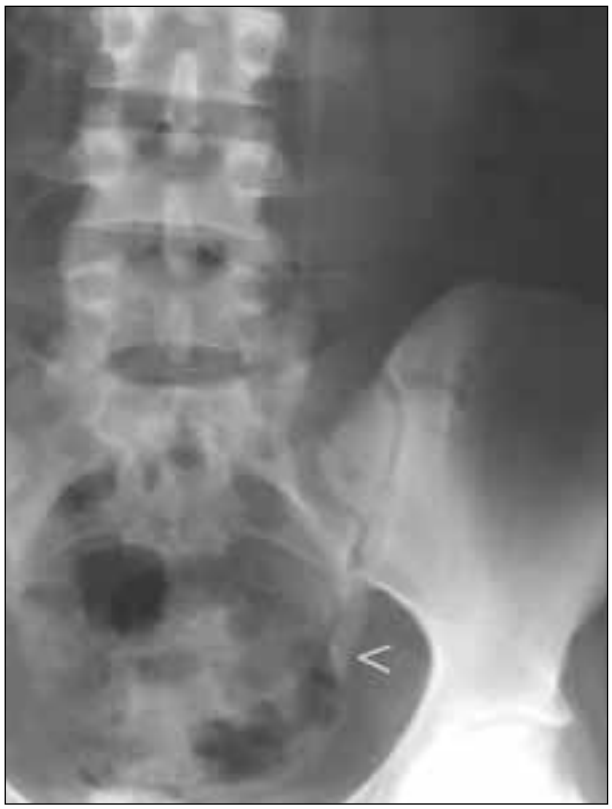
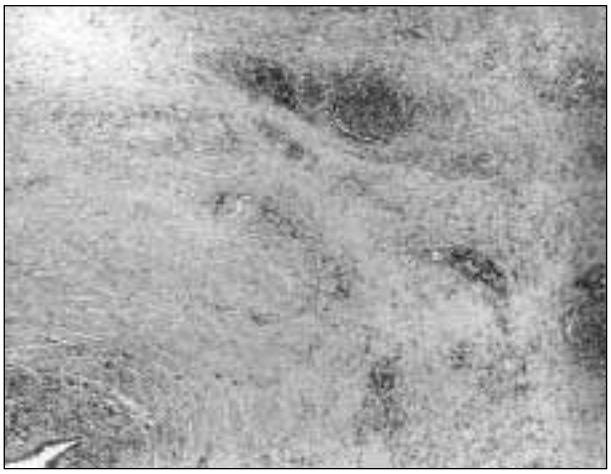


Figura 2.
Histological examination shows submucosal infiltrating lymphoma cells. H & E, reduced from 40.



sible. Explorative operation demonstrated that the distal ureter was narrowed by a fibrotic tissue completely involving the ureteral wall for 4-5 cm. This portion of the ureter was completely removed and a new implant of the ureter inside the bladder was performed by means of a "psoas hitch" technique. Histological examination of the specimen diagnosed a primitive non Hodgkin lymphoma of the ureter (Figure 2). Two years after the operation the patient is tumour free.

Discussion

Non Hodgkin lymphoma of the ureter is a very rare disease and only five cases have been described in the literature (2). Neoplastic involvement of the ureteral wall produces a stenosis which, in turn, causes hydronephrosis and an acute flank pain similar to that commonly described in the renal colic. Sometimes the retroperitoneal lymph nodes involvement is the main cause of bilateral hydronephrosis. Symptoms may be scanty and the patient describes only a little flank pain associated with microscopic haematuria. For that reason , all the cases that we found in the literature were in a pathological stage of the disease which was more advanced and all the patients were submitted to post-operative chemotherapy or radiotherapy. When the disease is still at the initial stage, surgery is generally therapeutic and the patient could be followed-up every 6 months by means of a total body CT scan and an X-Ray of the chest. In our patient the check was carried out 2 years after the operation and she was judged tumour free.

References

1. Messing EM, Catalona W. Urothelial tumors of the renal pelvis and ureter In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ (Eds), Campbell's Urology, Vol. 3, 7th edn. Philadelphia, WB Saunders, 1998; p 2383

2. Hashimoto H., Tsugawa M., Tsushima T., Kumon H. Primary non-Hodgkin of the ureter. Br J Urol Intern 1999; 83:148

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REVIEW

Premature ejaculation.
1. Definition and etiology.

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Summary

There is no general agreement on the definition of premature ejaculation, therefore scientific studies often reach discordant results depending on whether they assess the increase in ejaculatory latency or the couple's sexual satisfaction. Etiological theories can be divided into psycho-sexual (anxiety-related, behavioral) and biological (pelvic floor alteration, hypersensitivity of the glans penis, accelerated conduction and cortical amplification of the genital stimuli), both sharing the neurobiological assumption of serotonergic mediation. Premature ejaculation can be iatrogenic (amphetamine, cocaine, dopaminergic drugs) or secondary to urological diseases (prostatovesiculitis, frenulum breve) or to neurological diseases (multiple sclerosis, peripheral neuropathies, medullary expansion processes).

KEY WORDS: *Premature ejaculation; Pelvic floor; Hypersensitivity of the glans penis; Serotonin, Dopamine; Prostatitis, Neuropathies.*

INTRODUCTION

If from a practical point of view what is meant by premature ejaculation (PE) is perfectly clear, from a scientific point of view it is still undefined and open to question. Some argue that it should not even be considered a pathology or dysfunction, since it is "naturally" present in many animal species and, after all, has little or no impact on the survival and selection of the species (1). This thesis may be rejected, since cases of interference with reproduction (e.g. in ante moenia ejaculation) and with sexuality in general are well documented in andrological clinical practice.

DEFINITION

There is no universally accepted definition, and it is perhaps impossible to provide an exact definition of "premature ejaculation" (2, 3). It undoubtely concerns the couple since it is strongly connected with the orgasmic response of the female partner and is influenced by a great number of parameters (age, novelty and/or attitude of partner or situation, frequency of sexual activity, etc.).

Using the numeric factor "ejaculatory latency time", ejaculation is considered premature when it takes place within 15 seconds or 15 thrusts (4, 5). This definition has the advantage of being objective and therefore reproducible in clinical trials (perhaps also in conjunction with staged classification such as item PE of the Vis Libido Rating Scale) (6, 7), but it has the drawback of being of scarce significance for practical purposes, since a numerical improvement may very well not correspond to a subjectively satisfying clinical situation (for instance, a transition from 5 to 15 coital thrusts does not necessarily imply the achievement of coital satisfaction).

If the subjective factor "satisfaction deriving from the sexual act" is considered instead, various definitions have been proposed:

a) Masters & Johnson (1970): inability of a man to delay ejaculation long enough to allow his partner to achieve orgasm in 50% of their attempts at intercourse (8).
b) Kaplan (1974): absence of control of the ejaculatory reflex in most acts of intercourse (9).
c) DSM III R (1987): persistent or recurrent ejaculation with minimal sexual stimulation before, upon or shortly after penetration, and before the person wishes it to occur (10).
d) DSM IV (1995): Persistent or recurrent ejaculation with minimum sexual stimulation before, on, or shortly after penetration and before the person wishes it, taking into account age, partner novelty, situational component and sexual frequency (11).

These definitions, which describe the situation well, have the drawback of being difficult to reproduce objectively in clinical trials (1).
An attempt to unify these two criteria is represented by the definition given by Gruppo Italiano di Studio sull'Impotenza (12): "a situation where, in an adequate sexual relationship, one of the partners achieves orgasm before the other at least 50% of the times and/or, in any case, within 2 minutes from the beginning of interaction" (13), but this seems to combine the drawbacks rather than the advantages of the two kinds of definitions.
The lack of an appropriate definition makes it very difficult to analyze and compare international literature, due to the use of diverse approaches, different criteria and therefore to the presence of contradictory information. A common language must be established along with a diagnostic and therapeutic flowchart (14).

Frequency

Although from clinical experience one gains the impression that the frequency of this sexual dysfunction (40% of men) (15) is very high, which brings many men to andrology clinics (214 visits for PE out of 1458 [14.67%] at a new Urological Andrology facility) (16), no precise data are found in the literature, and this is also an obvious consequence of the lack of a precise definition.
For instance, one question in the SIMONA study (Italian System of Andrological Monitoring) questionnaire about the ability to control ejaculation as desired resulted in 24.2% of answers indicating PE. However, out of the same sample, only 9.2% indicated PE regarding the ability to ejaculate over 15 seconds after penetration, though at the same time the rate of people who did not answer rose from 3.9% for the previous question to 12% (1).
As proof of the extreme variability of the data provided in literature, while some Authors (17), on the basis of a questionnaire for urological patients, reported PE in 22% of the cases, others (18) found results of 31% for PE with a questionnaire meant for the general population. These results concur with another study (19) that revealed PE in 30% of the general male population and a loss of desire in 30% of the general female population. Scarcely reliable due to the exiguity of the sample is a 2001 study (20) in which a questionnaire sent to 43 families showed that 93% of the couples who had answered it (20 = 43% of the questionnaires sent), indicated they had one sexual dysfunction at least and that in 66% of the cases was represented by PE (thus representing 30.6% of the questionnaires sent). On the other hand, a study conducted in England (21) by means of a questionnaire sent by mail to 4,000 subjects and to which 789 males and 979 women answered, showed 88 cases of PE (11.15%).
A 2001 review (22) of 52 works published over 10 years on this topic sets PE around 4-5%, while a similar review by the same group (23) on works dating back to the previous decade reported a frequency of 36-38%, a sign of the evolution of the criteria adopted over the years.
Quite obviously the adoption of a descriptive type of definition, especially if it tends to be too broad in the attempt to encompass every circumstance that may determine PE, runs the risk of an improper amplification of actual frequency (24).

Neurophysiology of ejaculation

Ejaculation, an act of the male sexual function which takes place in the 3rd phase (orgasmic phase) of the sexual response cycle (8), is normally divided into emission (the seminal fluid is deposited into the prostatic urethra) and ejaculation in the strict sense of the word, also called ejection (semen is expelled from the urethra by contractions of the pelvic floor, especially of the bulbocavernosus muscles) which is followed by the orgasmic sensation (12, 25-27).
The whole process "emission – ejaculation – orgasm" represents the final event in the male sexual activity and is called "ejaculatory reflex": it has an important cerebral component and is the result of a complex integration of central serotonergic, oxytocinergic and dopaminergic neurons (28).
The afferent tracts of the ejaculatory reflex consist of fibers which originate in Krause's end bulbs principally of the glans and, to a lesser extent, of the penile skin, scrotum and perineum, and reach the medullary centers through both somatic (dorsal nerve of the penis, towards S4) and autonomic pathways (hypogastric plexus, sympathetic ganglions).
At the cerebral level, the ejaculatory response is modulated by the paraventricular nucleus (PVN) of the hypothalamus and by the medial preoptic area (MPOA), which are closely interconnected (therefore involving anterior hypothalamus, limbic system and amygdala): impulses activating ejaculation originating from the MPOA are thought to reach the spinal cord through the periaqueductal gray. Descending oxytocinergic and dopaminergic fibers coming from the PVN have an activating effect, while serotonergic fibers spread from the paragigantocellular nucleus inhibiting the ejaculatory reflex (and sexual reflexes in general). Activities on the sexual function are mediated mainly by dopaminergic D2-activating receptors (29) and by serotonergic 5HT1A and 5HT2C inhibitors (30). Leptin is believed to have an activating effect on ejaculation; leptin is produced by adipocytes and interferes on the hypothalamus with suppression of appetite, weight control and control of sexual behavior: high levels of serum leptin are observed in patients suffering from PE (31) and diminish with the improvement of intra-vaginal ejaculatory latency time pharmacologically induced with serotonergic drugs (32).

Efferent tracts

Efferent tracts influencing emission are mainly composed of α-adrenergic fibers of the lateral columns of the thoracolumbar gray matter: they originate from T12-L2 to form the lumbar sympathetic ganglions

first, then the hypogastric plexus and the pelvic plexus, where the postganglionic neurons originate, which spread to the vasa deferentia, seminal vesicles and prostate.
The vas deferens receives α-adrenergic nervous fibers from the sympathetic nervous system (coming from the pelvic plexus through the presacral nerve) and from the parasympathetic nervous system, while cholinergic contribution is of secondary importance (33).
Innervation of the seminal vesicles comes from the pelvic nerve and from the hypogastric plexus which supplies adrenergic and cholinergic fibers. Cholinergic fibers are found only in the mucous membrane and are stimulants of the vesicular secretory activity, while their presence is not proved in the tunica muscularis (35).
Adrenergic innervation appears to be the most represented in all three deferential muscle layers; in the vesicle musculature it is α_1 adrenergic type, with different responses in longitudinal and circular layers induced by noradrenaline and other α-adrenergic agents (36).
Receptors for neuropeptide Y, tyrosinhydrolase and VIP (37) have been identified, but their role is still unclear.
In the deferential and vesicular tunica adventitia, nerve endings showed positivity for heme oxygenase-2 (which synthesizes carbon monoxide - CO) and neuronal nitric oxide synthase (nNOS) while in the tunica mucosa and muscolaris only nNOS activity is present, well represented especially in the musculature of the seminal vesicles (38). These remarks open the way to studies on the role of CO and NO on the control of the vas deferens and of seminal vesicles: on this subject a 1994 article 39 put forward the hypothesis that nitric oxide inhibits emission in rats, thus playing an important role in ejaculatory prematurity.
The inhibitory action of NO on the norepinephrine-induced contractility of seminal vesicles in men has been recently proved in vitro, hypothesizing the use of NO donors (S-nitrosothiols such as S-nitrose-glutathione and S-nitrose-N-acetylcysteine) in premature ejaculation (40).
Other studies (35) have confirmed the presence of Neuropeptide Y and NOS in the distal seminal tracts in the absence of acetylcholine (observed with VAChT – Vesicular Acetylcholine Transporter), while the latter is well represented in the lower urinary tract.
An extremely interesting observation is the detection of D1 and D2 dopaminergic receptors in the vesicular smooth musculature of mice and men (41): this could be proof of interference of dopamine on the emission – ejaculation mechanism, peripherally as well as centrally.
Another interesting work (42) underlines a possible role of seminal Magnesium in determining PE: the levels of Mg^{++} have been found to be constantly low in 9 patients suffering from primary PE, contrary to findings in a normospermic group (15 patients) and a dyspermic group (15 patients), assuming a physiopathogenic cascade of local vasoconstriction with an increase of thromboxane, an increase of intracellular Ca^{++}, and a fall in the level of NO with consequent facilitation of emission and thus of ejaculation. In rats the different potency of inhibiting action on the Ca^{++} channels in the vas deferens would explain the different lengthening times of ejaculatory latencies obtained by thioridazine, chlomipramine and fluoxetine (43).
Ejaculation in the strict sense of the word is controlled, on the contrary, by somatic fibers that originate in Onuf's nucleus (S2-S4) and unite to form the pudendal nerve's motor component, which innervates the striated muscles of the pelvic floor: in particular, the rhythmic contractions of the bulbocavernosus and ischiocavernosus muscles cause the expulsion of the semen from the urethra.

Etiology

None of the many etiological theories are scientifically validated (24, 44): some of them were actually advanced using criteria based on therapeutic responses.
There is agreement on the distinction between primary PE (PPE), which appears during the first sexual experiences and persists, and secondary PE (SPE), which develops after a period, whether long or short, of adequate control (45, 46); this distinction merely considers the chronological aspects of the onset of PE, and does not indicate that the dysfunction is a consequence of a verified organic pathology or iatrogenic cause, in which case the term symptomatic PE is used (47).
Obviously SPE can be "symptomatic" of a developing organic pathology, generally urological (48) or neurological (49).
Etiological theories for PPE fall into three main groups (24, 44):

- psychoanalytical and psycho-sexual theories: anxiety-related models and behavioral models;
- theory of inadequate pre-orgasmic perception;
- biological theories: constitutional models.

Psychoanalytical and psycho-sexual theories

Anxiety-related models

These are based on the hypothesis that anxiety can induce a lowering of the ejaculatory threshold. Anxiety-causing elements can be represented by an unresolved fear of the vagina, hostility against woman, and castration anxiety (intrapsychic causes), while elements that in the psycho-sexual interpretation of the genesis of anxiety relate to interpersonal conflicts with the partner, fear of letting her down, fear of being misunderstood or rejected, and of not appearing sufficiently virile, represent relationship causes (50-54).
The above-stated causes then combine with immediate causes, such as ignorance of sex organs and their functions, inability of the couple to discuss fears and a situation of perceptory and intellectual defense against erotic sensations in which the patient takes on a spectator's point of view ("spectatoring") (8), thus losing contact with the feelings of pleasure and arousal (54).
While some authors describe a lack of correlation between PPE and anxiety (55), others stress the association between PPE and anxiety, whereas in the female

population anxiety and depression are more often associated with sexual dysfunctions (56).

Behavioral models
These are based on case histories with first intercourse experiences that had been hurried, for whatever reason, and come to represent an imprinting that results in PE (8, 57).
Once this conditioning has arisen, it is believed to represent an anxiety-causing element which further induces PE (58). The role of various social and religious cultural backgrounds in the onset of PPE is also suggested by these models (59).
A recent work recognizes in social phobias and panic attacks the neglected causes of male sexual dysfunctions, primarily premature ejaculation (60).

Theory of inadequate pre-orgasmic perception
According to this theory patients suffering from PPE are incapable of recognizing the premonitory signs of orgasm and therefore of activating the ejaculatory control mechanisms: this theory was advanced by *Kaplan* (9, 61), who compares this control to what takes place in the process of learning micturition control. This theory proposes to define PE as a "syndrome of ejaculatory incontinence" and ejaculatory dysfunctions in general as a "syndrome of ejaculatory incompetence" (62). Anxiety could however be at the origin of the phenomenon, interfering on the central neuromodulation of sensory signals with an alteration of perceptions at the moment of emission (24).

Biological theories: constitutional models
These theories are based on the biological mechanisms most likely to determine PPE:
- pelvic floor dysfunctions (63, 64);
- penile hypersensitivity due to low threshold of penile proprioceptors (65-68);
- excessively rapid ejaculatory reflex (4, 9, 69, 70);
- augmented sensitivity to genital stimulation or decrease in the threshold of genital sensitivity (71):
- larger cortical representation in the genital area (72, 73).

The theory of pelvic floor dysfunction is based on the hypothesis that inability to manage the muscles may trigger a failure to learn the techniques of ejaculatory control. Perineal dysfunctions may arise from hypotonia of the levator ani muscles or from a functional sphincter-perineal neuromotor disorder (24). Functional dyskinesias arise when, during perineal contraction, agonist muscles (gluteal muscles, adductors) or antagonist muscles (abdominal, diaphragm muscles) are activated, determining in the latter case a reversal of the action requested, since the subject "pushes" instead of "squeezing": this is the so-called "reversal of command" which can often be observed with an objective examination, while agonist contractions are often less evident. Perineal dyskinesias are believed to be an expression of poor neuron recruitment and may derive from a dysfunction, congenital or maturational, in learning sphincter-perineal automatisms (74).

Etiological theories for PPE based on endocrinopathies do not currently have much support: one author (75), though reporting a decrease in the levels of testosterone, free testosterone, LH and FSH in 12 patients with PPE and high levels of PRL in 4 of them, admits that many studies in literature rule out the association with hypogonadotropic hypogonadism (6, 7), and the same author subsequently suggests that the increase in testosterone, obtained with an effective fenfluramine treatment in patients affected by PPE and hypogonadotropic hypogonadism, is probably linked to a serotonergic neuromodulatory activity (76). The recent hypothesis of the existence of a bihormonal modulation (testosterone/estrogens) of the sympathetic and parasympathetic activity on sexual arousal (77, 78), could revive studies on hormonal etiology and treatment of PPE.
For the sake of completeness and for the opportunities they offer to future research, we are here mentioning again the hypotheses previously described in the paragraph on neurophysiology, regarding the low levels of NO (39, 40) and of seminal Mg^{++} (42) and the proposed correlation with serum leptin (31, 32).
The analysis of related literature shows that, while works of the last century (mainly proposing psychological causes) are not scientifically unexceptionable, current works are much more significant and tend to consider PPE a neurobiological phenomenon related to central serotonergic neurotransmission, probably influenced by hereditary factors (79).
The history of a secondary PE (excluding "symptomatic" forms) often includes a short- or long-term interruption of a stable relationship (illness, separation, widowerhood, etc.), often implying a change of part-

Table 1.
Symptomatic premature ejaculation. from (47) modified.

Urological diseases	Urethro-prostato-vesicular diseases Frenulum breve
Neurological diseases	Multiple sclerosis Peripheral alcoholic neuropathy Medullary expansion processes
Systemic diseases	Diabetes mellitus Atherosclerosis
Iatrogenic forms	Drugs - Narcotics Amphetamine Cocaine Naloxone Yohimbine Dopaminergic drugs: Bromocriptine, L-Dopa, Apomorphine

ner: a psycho-dynamic anxiety-related situation is created which comes close to what is reported in the primary forms (47).
Another form of SPE may develop after a period of erectile dysfunction, especially of erectile maintenance dysfunction: once again we have an anxiety-related but also behavioral model, since the patient tends to ejaculate before detumescence takes place.
Erectile instability itself often develops after a period of sexual inactivity (a typical example is the "widower's syndrome"), attributable to the previously described model (61).
As for diseases that can cause symptomatic PE (Table 1) (47). Inflammatory prostato-vesiculitis is the most frequent cause: it is present in 56.5% of patients suffering from PE (80).
The population of dialysis patients has a very high prevalence of PE, revealed by the IIEF questionnaire (81).

References

1. La Pera G, Gentile V. Eiaculazione precoce o sindrome dell'incontinenza eiaculatoria: dati epidemiologici. Giorn It Androl 2000; 7:106

2. Mirone V, Soli M. L'eiaculazione precoce. Abstract 68° congr. Soc It Urol 1995; 33

3. Piediferro G, Russo A, Crimi A, Luciano G. Eiaculazione precoce: nostra esperienza. Urologia 1996; 63:254

4. Colpi GM, Fanciullacci F, Beretta G, Negri L, Zanollo A. Evoked sacral potentials in subjects with true premature ejaculation. Andrologia 1986; 18:583

5. Seagraves RT, Saran A, Maguire E. Clomipramine versus placebo in the treatment of premature ejaculation. J Sex Marital Ther 1993; 19:198

6. Piediferro G. Trattamento dell'ejaculatio precox con metoclopramide. In: G D'ottavio, D Pozza eds. Acta Medica Edizioni & Congressi, Rome, Progressi in andrologia chirurgica, 1987; p 285

7. Piediferro G, Vanacore M, Sorrentino F .Terapia dell'ejaculatio precox. (atti 60° congr. Soc. It. Urol. Palermo, 1987) – Acta Urol Ital 1988; 1:361

8. Masters VH, Johnson VE. Human sexual inadequacy. Little, Brown & Co, Boston, 1970

9. Kaplan HS. The new sex therapy. Brunner-Mazel, New York, 1974

10. American psychiatric association. Diagnostic and statistical manual of mental disorders, 3rd edition, 1987

11. American psychiatric association. Diagnostic and statistical manual of mental disorders, 4th edition, 1995

12. G.I.S.I. I disturbi dell'eiaculazione. E Belgrano, G Breda, G Carmignani, P Giannotti, A Maver, V Mirone, M Soli (Eds), Edimes, Pavia, 1995

13. Mirone V, Imbimbo C, Sessa G, Longo N. I disturbi dell'eiaculazione. In: Andrologia. Fisiopatologia e clinica, Molinatti GM, Fontana D (Eds), Rome, Verduci, 1997

14. Rowland DL, Cooper SE, Schneider M. Defining premature ejaculation for experimental and clinical investigations. Arch Sex Behav 2001; 30:235

15. Epperly TD, Moore KE. Health issues in men: part I: Common genitourinary disorders. Am Fam Physician 2000; 61:3657

16. Piediferro G. Attività del Centro di Andrologia Urologica dell'Ospedale San Leonardo di Castellammare di Stabia. Comunicazione 1° Incontro Andrologico Stabiese (Sez. Campano-Calabra della Soc. It. Androl.). Prevenzione in Andrologia. Progetto uomo… per età., Castellammare di Stabia (NA), 25/01/1997

17. Goldmeier D, Keane FE, Carter P, Hessman A, Harris JR, Renton A. Prevalence of sexual dysfunction in heterosexual patients attending a Central London Genitourinary Medicine Clinic. Int J Std Aids 1997; 8:303

18. Read S, King M, Watson J. Sexual dysfunction in primary medical care: prevalence, characteristics and detection by the general practitioner. J Public Health Med 1997; 19:387

19. Rosen RC. Prevalence and risk factor of sexual dysfunction in men and women. Curr Psychiatry Rep 2000; 2:189

20. Aschka C, Himmel W, Ittner E, Kochen MM. Sexual problems of male patients in family practice. J Fam Pract 2001; 50:773

21. Dunn KM, Croft PR, Hackett GI. Sexual problems: a study of the prevalence and need for health care in the general population. Fam pract 1998; 15:519

22. Simons JS, Carey MP. Prevalence of sexual dysfunctions: results from a decade of research. Arch Sex Behav 2001; 30:177

23. Spector IP, Carey MP. Incidence and prevalence of the sexual dysfunction: a critical review of the literature. Arch Sex Behav 1990; 9:389

24. Pirozzi Farina F, Curreli A, Deriu M, Pischedda A, Aiello I, Bercovich E. L'eiaculazione prematura primitiva: nostri criteri di inquadramento e definizione diagnostica. Giorn It Androl 1998; 5:84

25. Buch JP. Anomalie dell'eiaculazione. In: L'impotenza, Bennett AH (ed), Verduci, Rome, 1995; p 199

26. Jannini EA, D'Armiento M. Patologia dell'eiaculazione. Federazione Medica 1995; 105-114

27. Maver A. Fisiologia dell'eiaculazione. Abstract 68° Congr Soc It Urol 32, 1995

28. Mc Mahon CG. Neuroanatomy and neurophysiology of orgasm and ejaculation. Gior It Androl 2000; 7:109

29. Ferrari F, Giuliani D. The selective D2 dopamine receptor antagonist eticlopride counteracts the ejaculation praecox induced by selective D2 dopamine agonist SND 919 in the rate. Life Sci 1994; 55:1155

30. Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. Behav Brain Res 1998; 92:111

31. Atmaca M, Kuloglu M, Tezcan E, Semercioz A, Ustundag B, Ayar A. Serum leptin levels in patients with premature ejaculation. Arch Androl 2002;48:345

32. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Semercioz A. Serum leptin levels in patients with premature ejaculation before and after citalopram treatment. BJU Int 2003; 91:352

33. Schlegel PN, Chang TSK. Fisiologia della riproduzione maschile: testicolo, epididimo e deferente. In: Walsh PC, Retik AB, Vaughan AD jr, Wein AJ (eds), Verduci, Rome, Urologia di Campbell 1999; p 1265

34. Mawhinney MG. Male accessory sex organs and androgen action. In: Infertility of the male, 2nd ed, LI lipshultz, SS howards Eds, New York, Churchill Livingstone, 1992; p 124

35. Dixon JS, Jen PY, Gosling JA. The distribution of vesicular acetylcholine transporter in the human male genitourinary organs and its co-localization with neuropeptide Y and nitric oxide synthase. Neurol Urodyn 2000; 19:185

36. Amobi N, Smith CH. The human vas deferens: correlation of response pattern to noradrenaline and histological structure. Eur J Pharmacol 1995; 273:25

37. Tainio H. Peptidergic innervation of the human prostate, seminal vesicle and vas deferens. Acta Histochem 1995; 97:341

38. Grozdanovic Z, Goessl C. Comparative localization of heme oxygenase-2 and nitric oxide synthase in the autonomic innervation to the ductus deferens and seminal vesicle. J Urol 1999; 162:2156

39. Hull Em, Lumley LA, Matuszewich L, Dominguez J, Moses J, Lorrain DS. The roles of nitric oxide in sexual function of male rats. Neuropharmacology 1994; 33:1499

40. Machtens S, Ckert S, Stief CG, Tsikas D, Frlich JC, Jonas U. Effects of various nitric oxide-donating drugs on adrenergic tension of human seminal vesicles in vitro. Urology 2003; 61:479

41. Hyun JS, Baig MR, Yang DY. Localization of peripheral dopamine d1 and d2 receptors in rat and human seminal vesicles. J Androl 2002; 23:114

42. Omu AE, Al-Bader AA, Dashti H, Oriowo MA. Magnesium in human semen: possible role in premature ejaculation. Arch Androl 2001; 46:59

43. Mousavizadeh K, Ghafourifar P, Sadeghi-Nejad H. Calcium channel blocking activity of thioridazine, clomipramine and fluoxetine in isolated rat vas deferens: a relative potency measurement study. J Uurol 2002; 168:2716

44. Piediferro G, Nerva F, Contalbi GF, Colpi EM. L'ejaculazione precoce. In: Deficit erettivo. F. Menchini-Fabris (Ed), Pisa, Felici Editore, 2002; p 36

45. Godpodinoff ML. Premature ejaculation: clinical subgroups and etiology. Psychosom Res 1984; 28:331

46. Cooper AJ, Cernovsky ZZ, Colussi K. Some clinical and psychometric characteristics of primary and secondary premature ejaculators. J Sex Marital Ther 1993; 19:276

47. Mirone V, Imbimbo C. Eiaculazione precoce secondaria. Giorn It Androl 2000; 7:123

48. Williams W. Secondary premature ejaculation. Aust N Z J Psychol Chol 1984; 18:333

49. Kurh CS, Heiman J, Cardenas D, Bradley W, Berger RE. Premature emission after spinal cord injury. J Urol 1995; 153:429

50. Lo Piccolo J, Lo Piccolo L. Handbook of sex therapy. New York Plenum, 1978

51. Mayer JK, Schmidt CW, Wise TN. Clinical management of sexual disorders. Bbaltimore, Williams & Wilkins, 1983

52. Schmidt CW, Cowie D. Common male sexual disorders: impotence and premature ejaculation. In: Mayer JK, Schmidt CW, Wise TN (Eds). clinical management of sexual disorders. Baltimore Williams & Wilkins, 1983; p 173

53. Crepault C. Dal seme di eva. Milan, Franco Angeli, 1989

54. Simonelli C, Rossi R. Patogenesi psicosessuologica e comportamentale dell'eiaculazione precoce. Giorn It Androl 2000; 7:114

55. Cooper AJ, Magnus RV. A clinical trial of beta blocker propanolol in premature ejaculation. J Psychos Res 1984; 28:331

56. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological and physical problems in men and women: a cross sectional population survey. J Epidemiol Community Health 1999; 53:144

57. St Lawrence JS, Madakasira S. Evaluation and treatment of premature ejaculation. Int J Psychiatry Med 1992; 22:77

58. Althof SE. Pharmacologic treatment of premature ejaculation. Psychiatr Clin North Am 1995; 18:85

59. Faber B, Christensen HB, Bjorner JB. Premature ejaculation results of treatment of men of 2 different cultural backgrounds. Ugeskr Laeger 1992; 154:1638

60. Figueira I, Possidente E, Marques S, Hayes K. Sexual dysfunction: a neglected complication of panic disorder and social phobia. Arch Sex Behav 2001; 30:369

61. Kaplan HS. How to overcome premature ejaculation. New York, Brunner Mazel, 1989

62. Turchi P, Bertozzi MA, Chiechi A, Benelli R, Menchini Fabris F. i disturbi da incompetenza eiaculatoria. Giorn It Androl 2000; 7:149

63. Zilberged B. Male sexuality. Toronto, Bartam, 1978

64. Siegel LM. A guide to natural orgasm for women and men: the function of the anal sphincter muscle on vaginal orgasm and premature ejaculation. New York, Vantage Press, 1993

65. Damvar F. Premature ejaculation: use to ethyl amino benzoate to prolong coitus. J Urol 1963; 89:936

66. Xin ZC, Chung WS, Choi YD, Seong DH, Choi YG, Choi HK. Penile sensitivity in patients with primary premature ejaculation. J Urol 1996; 156:979

67. Xin ZC, Chung WS, Choi YD, Rha KA, Choi HK. Somatosensory evoked potentials in patients with primary premature ejaculation. J Urol 1997; 158:451

68. Paick JS, Jeong H, Park MS. Penile sensitivity in men with premature ejaculation. Int J Impot Res 1998; 10:247

69. Semans JH. Premature ejaculation: a new approach. South Med J 1956; 49:353

70. Vignoli GC. Premature ejaculation: a new electrophysiologic approach. Urology 1987; 11:81

71. Strassberg DS, Mahoney JM, Schaugaard M, hale VE. The role of anxiety in premature ejaculation; a psychophysiological model. Arch Sex Behav 1990; 19:251

72. Fanciullacci F, Colpi GM, Beretta G, Zanollo A. Cortical evoked potentials in subject with true premature ejaculation. Andrologia 1988; 20:326

73. Salinas Casado J, Virseda Chamorro M, Samblas Garcia R, Esteban Fuertes M, Aristizabal Agudelo JM, delgado Martin JA, Blazquez Izquirdoj, Resel Estevez L. Neurobiology of ejaculation and orgasm disorders. Arch Esp Urol 1998; 51:265

74. Di Benedetto P. Riabilitazione uro-ginecologica. Minerva Medica, Turin 1995

75. Cohen PG. The association of premature ejaculation and hypogonadotropic hypogonadism. J Sex Marital Ther 1997; 23:208

76. Cohen PG, Holbrook JM. Effects of fenfluramine on ejaculatory function, luteinizing hormone and testosterone levels in men with hypogonadotropic hypogonadism and premature ejaculation. int clin psychopharmacol 1999; 14:91

77. Motofei IG. A bihormonal model of normal sexual stimulation; the etiology of premature ejaculation. Med Hypotheses 2001; 57:93

78. Motofei IG. The etiology of premature ejaculation starting from a bihormonal model of normal sexual stimulation. Int J Imp Res 2001; 13:49

79. Waldinger MD. The neurobiological approach to premature ejaculation. J Urol 2002; 168:2359

80. Screponi E, Carosa E, Di Stasi SM, Pepe M, Carruba G, Jannini EA. Prevalence of chronic prostatitis in men with premature ejaculation. Urology 58, 19

81. Aslan G, Arslan D, Cavdar C, Sifil A, Esen AA, Camsari T. Analysis of premature ejaculation in hemodialysis patients using the international index of erectile function Urol Int 2003; 70:59

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REVIEW

Premature ejaculation. 2. Classification and diagnosis.

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Summary

A classification of premature ejaculation must distinguish between hyper-orgasmic or hypo-orgasmic, between situational or global; furthermore, it must define whether it occurs during vaginal penetration only or also in masturbation, and must study its latency periods and its relationships to the erectile dysfunction, with which it is often associated. Tests with local anesthetics, biothesiometry and penile vibrotactile stimulation, integrated with a thorough study of the general and psycho-sexual history, provide a good diagnostic classification that makes the therapeutic approach appropriate.

KEY WORDS: Premature ejaculation; Local anesthetics; Penile biothesiometry; Penile vibrotactile stimulation.

CLINICAL CLASSIFICATION

Personal clinical experience and international literature indicate that there are various forms of Primary Premature Ejaculation (PPE), with etiological causes pointing to various theories (1, 2) (and therefore to different therapeutic approaches).

The first distinction that should be made is between hyper-orgasmic PE and hypo-orgasmic PE (1-3).

Hyper-orgasmic PE is a "premature orgasm" that, despite its short latency, is experienced by the patient as intense and gratifying. Generally the patient has a good level of libido with medium to short refractory periods, both erectile and orgasmic: the patient's sexual history often shows that, for a certain period of time, he compensated for the rapidity of the performance with repetition after a brief interval.

In these conditions PE is a consequence of difficulty in controlling orgasm (a central event as a state of awareness), which always determines ejaculation (a peripheral event), even in case of lack of emission: a "quick orgasm", therefore, rather than a premature ejaculation.

In hypo-orgasmic PE, on the contrary, rapid ejaculation is the primary cause and is accompanied by a low-intensity orgasm, endured, rather than experienced, by the patient, with scant pleasure, since the ejaculatory reflex takes place before the orgasmic event has "matured". In this case patients normally have low libido, both physical and mental, with longer mean erective and orgasmic periods: they are neither capable of nor interested in repeating intercourse.

These represent the psycho-sexual signs that mainly characterize secondary PE (4), especially if the primary origin is a dysfunction in erectile maintenance, which in time can induce a symptomatic secondary PE, since the patient tends to anticipate the ejaculatory reflex before the possible intravaginal detumescence that he knows will take place.

These forms are indeed often associated with organic erectile dysfunctions, especially dysfunctions regarding erectile maintenance (4), although some authors (1) refuse to consider this fact because they have also encountered the hypo-orgasmic form in PPE, evidenced by a nocturnal penile tumescence test and intracavernosal injection of vasoactive drug test: it is however possible that a hypo-orgasmic PPE may in time cause a psychogenic ED, determined by performance anxiety, sometimes also linked to depressive aspects of psychiatric nature.

Apart from the classification of a PPE as hyper- or hypo-orgasmic, patients can be divided into three types (1, 3):

- Type I: Ejaculatory prematurity only occurs in penetrative intercourse;
- Type II: It also occurs in non-penetrative sexuality in the presence of the partner, but not in masturbation;
- Type III: It is present in masturbation as well.

In type III patients the most likely etiological hypothesis is of biological origin, since a psycho-sexual cause is highly unlikely in a PPE that occurs in solitary masturbation (5); here careful assessment of the entire reflex arc from receptors to perineal muscles is necessary (1).

Psycho-sexual aspects certainly play a role in type II, where the partner's presence affects the ejaculatory

response, both in penetrative and non-penetrative intercourse (1); however, poor control of the ejaculatory reflex can also be due to a biological cause.
In type III and, to a lesser extent, in type II, insufficient epispinal control of the emission and ejaculation centers should by hypothesized.
Instead type I represents a typical anxiety-related model, well represented by ejaculation before penetration. In these cases a psycho-sexual assessment is necessary in order to discover the meaning that the penetrative act assumes for the patient (6), but a neurosensory cause should not be completely ruled out, based on the theories of low threshold levels of penile proprioceptors or of their excessive cortical representation (1, 3).
A chronological classification based on ejaculatory latency time, such as the old subdivision of the Vis Libido Rating Scale (VLRS) (7) can be useful to monitor the progress of a therapy:
- ejaculation before penetration (ante-moenia);
- ejaculation upon penetration;
- ejaculation within 1' from penetration;
- ejaculation between 1' and 2' from penetration.

Diagnosis

The foregoing implies the absolute necessity of a correct general and psycho-sexual clinical history in order to classify the PE in question into one of the above-described types, so that causes can be researched. A questionnaire may prove useful for this purpose (to this date there is no validated questionnaire for PE, though isolated proposals can be found in literature).
At this point in the evaluation of the patient's history, besides distinguishing a) between primary and secondary PE (and whether PE is symptomatic, with investigation of pathologies or drugs that may generate it) without neglecting the data on abstinence (!!!), b) between hyper-orgasmic and hypo-orgasmic forms, c) between the three types in relation to non-intercourse sexuality or in solitary masturbation, and d) between the phases based on ejaculatory latencies, it should be ascertained e) whether PE is global, i.e. it always occurs, in any situation and with any partner, or situational, i.e. it occurs in certain situations, with particular kinds of stimulation and particular partners (8). Of equal importance is the assessment of the patient's partner, in order both to ascertain whether she has hyporgasmia, in which case the male would be "premature" anyway, and to evaluate what situation of conflict exists in the couple. Five phases can be recognized (9) in this conflict: 1) Self-accusatory phase (the woman thinks she is responsible for the sexual failure); 2) Aggressiveness (she becomes impatient and insists on finding a solution); 3) Resignation (disappointed, she gives up, mingling feelings of tenderness and contempt for her partner); 4) Adultery (she considers her partner incapable of giving her pleasure and recovery is considered unlikely); 5) Break-up (she feels repulsion for any contact with her partner).
In the clinical examination particular attention should be paid to the andro-urological examination (congested prostate and presence of prostatorrhoea, signs of acute or chronic orchiepididymitis, short frenulum, penis curvature, etc.), and to cremasteric and especially bulbocavernosus reflexes, with particular attention to the anal sphincter and to whether there are signs of reversal of command (patient "pushes" contracting the recti abdominis muscles in response to the functionally opposite invitation to contract his anus). The clinical examination may reveal extremely evident hypersensitivity of the glans penis if the patient feels awkwardness and discomfort, to the point of feeling local pain sometimes, and in this case an inflammatory pathology (balanitis, balanoposthitis) should be assessed.
Clinical diagnosis includes tests aimed at identifying the pathologies or constitutional models that cause PE.
It is always advisable to check for the presence of an urethro-prostato-vesicular inflammatory process, even in the absence of clear micturition symptoms. A cytological assessment of expressed prostatic secretion (10) must be therefore always carried out, since it is an excellent screening test for identifying inflammation (11) and is to be integrated, if necessary, with the bacteriological research of the etiological agent using the Meares-Stamey test or its modified versions (7) and urethral swabs.
Transrectal prostato-vesicular-ejaculatory duct ultrasonography, besides corroborating the diagnosis of inflammation (12), may reveal organic and functional alterations in voiding of the distal seminal tract, especially if a pre- and post-ejaculatory assessment is made (13, 14).
The presence of glans or penile hypersensitivity can be detected using biothesiometry, which evaluates the threshold of perception of vibratory stimuli (pallesthesia) at a constant frequency (100 Hz) and the integrity of the conduction pathways running along the posterior spinal cord (15-19). This test shows subjective responses and proves operator-dependent: therefore some changes have been proposed for its standardization, i.e. a floor stand with articulated arms and micrometric adjustment gear (20). The threshold values obtained from the different glans and penile points (and from the tips of index fingers as reference points) are interpreted using a nomogram (21).
In our experience this test is able to qualitatively reveal the presence of glans or penile hypersensitivity that could require a therapeutic approach, while simultaneously collecting information on the afferent medullary pathway of pallesthesia. In our experience the lowest threshold of pallesthesia was found in the dorsal area of the balanopreputial sulcus in 53.3% of cases and in the frenular area in 30%, while in 16.7% the thresholds were overlapping.
A very useful test to study the threshold values of glans proprioceptors is the home test (which becomes a therapeutic approach, as well), based on the prolongation of ejaculatory latency after topical application of anesthetics (22, 23). An anesthetic cream is applied on the glans and on the internal layer of the prepuce 15'-20' prior to intercourse, and subsequently removed by washing: a qualitative assessment is made after at least three attempts. The patient must be informed that anesthesia of the glans may cause a temporary erectile dysfunction due to reduced sensitivity and thus lack of sexual pleasure.
Responders are considered to be suffering from PE due to hypersensitivity of the glans, while etiology for non-responders may be found in psychological causes (generally type I PE) or in the constitutional model of congenital short latency of the ejaculatory reflex (type 3 PE) (3).
Ejaculatory reflex latency may be studied with the penile

vibrotactile stimulation (PVS) technique, drawn from a therapeutic principle used in anejaculating spinal cord injured patients, in whom it induces ejaculation in 52-59% of cases 24 within 3-6 minutes (25), since the tactile stimuli can be processed in the spinal cord without central mediation (26). PVS is able to evoke an ejaculatory reflex even in non spinal cord injured patients, for whom the range of 3-6 minutes can be adopted as standard latency of PVS-induced ejaculation, taking into account that the absence of a spinal lesion will make it possible to inhibit or disinhibit the reflex both voluntarily and involuntarily (1, 3), while other stimulations, such as visual stimulation, do not seem to have a determining influence on the ejaculatory reflex (27). The test is performed by applying a vibrator on the frenular portion of the glans at a frequency of 70-80 Hz and an amplitude of 2.5-3 mm and by timing induced ejaculation latencies. The application of this test to PE diagnosis can give three kinds of results: 1) the patient controls ejaculation indefinitely in time (genesis of PE is almost certainly of psycho-sexual origin, although PVS neglects the role of penile proprioceptor stimulation during intravaginal penetration); 2) the patient ejaculates in a time < 3 min, being unable to control the reflex in any way (genesis is probably of biological nature); 3) the patient ejaculates within a time > 3 min but < 6 min (genesis has a biological basis with overlapping psycho-sexual motivations). Combining the results of the local anesthetic test with that of the PVS test leads to obtain a fairly precise idea of the role of psychogenic etiology and of the biological constitutional models (hypersensitivity of the glans penis, low receptor threshold of the genital area, rapid spinal reflex).

Other neurophysiological tests have been used, and often still prove useful in the diagnosis of PE. One of these is the study of Somatosensory Evoked Potentials of the pudendal nerve, which analyses morphology and latency of the potentials found in the cortex after electrical stimulation of the area innervated by the pudendum (28). These have a two-phase morphology with two positive peaks (P1 and P2) separated by a negative peak (N1), that present latencies of 36-46 msec for P1, 47-58 msec for N1 and 55-74 msec for P2,with an amplitude of the P1-N1 complex of 0,6-5,4 mV (29).

This neurophysiological analysis may reveal a larger amplitude of SEPs, indicating a larger cortical representation of the genital stimuli (30, 31) or a reduction in latencies that encourages the hypothesis of an excessive rapidity of the ejaculatory reflex (32).

In patients affected by PE, only potentials resulting from stimulation of the genital area were found to be altered, while those resulting from other stimulation such as auditory stimulation resulted normal (33).

Although the study of cutaneous sympathetic response has a rationale, since it assesses the neurovegetative pathway, which is certainly involved, along with the somatic pathway, in sexual dysfunctions, it is not commonly used in clinical practice.

More common is the assessment of pelvic floor muscle tone with electromyography, aimed at finding abdominal-perineal dyskinesias, particularly those poorly evident in clinical examination. It may be associated with PVS for a dynamic electromyographic analysis of the ejaculatory reflex (1).

Premature ejaculation and erectile dysfunction

A particular aspect is the frequent combination of PE with erectile dysfunction (34, 35). Erectile dysfunction (ED) due to an altered veno-occlusive mechanism is found in 22.7% of PPE cases and in 39.1% of Secondary PE (SPE) cases, while ED due to an arterial dysfunction is found in 9% of PPEs and 8.6% of SPEs (36).

Quite often, finding out the primary origin of this complex sexual dysfunction is rather difficult.

A dysfunction in erectile maintenance can cause a secondary symptomatic PE, since the patient tends to anticipate the ejaculatory reflex before the possible intravaginal detumescence that he knows will occur, but it is also true that PPE may gradually determine a psychogenic-induced ED, caused by performance anxiety.

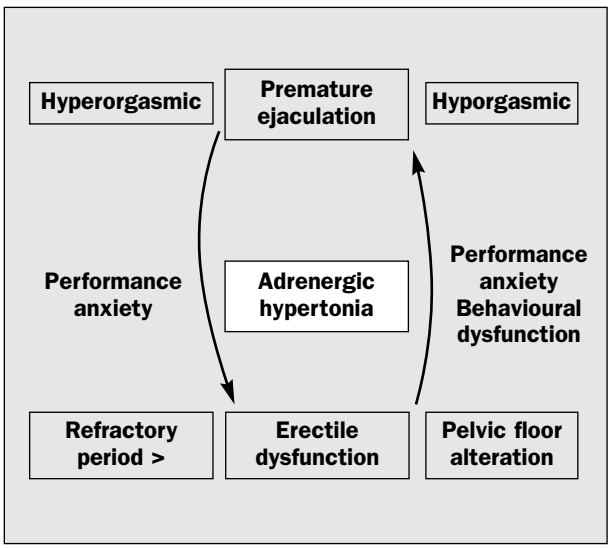
Even in hyper-orgasmic forms, if the patient has troubles in repeating coitus owing to a physiological (or pathological) lengthening of the refractory period, this fact may lead him to loss of self-esteem, performance anxiety, and behavioral alterations in everyday life, in relations with others and particularly with his female partner, and to loss of libido.

Biological causes are commonly the root of these anxiety-related or behavioral models: adrenergic hypertonia (with consequent functional alteration of the veno-occlusive mechanism) and alteration of the pelvic floor muscles (with the loss of the "squeeze" mechanism of the crura, important for maintaining erection) are common mechanisms that need to be further investigated (35).

In the diagnostic phase it is necessary to integrate ED tests such as nocturnal penile tumescence (NPT), which may provide information on the psychogenic genesis of the erectile dysfunction, and, if appropriate, a dynamic penile color Doppler ultrasonography, with the limits involved by the adrenergic hypertonia.

Obviously, the sexological study of the patient's case history plays a very important and delicate role here, since it must ascertain the starting point of the sexual problem and its predominant condition.

Figure 1.
PE and erectile dysfunction



REFERENCES

1. Pirozzi Farina F, Curreli A, Deriu M, Pischedda A, Aiello I, Bercovich E. L'eiaculazione prematura primitiva: nostri criteri di inquadramento e definizione diagnostica. Giorn It Androl 1998; 5:84

2. Piediferro G, Nerva F, Contalbi GF, Colpi EM. L'ejaculazione precoce. In: F. Menchini-Fabris (Ed), Deficit erettivo, Pisa, Felici Editore, 2002; p 36

3. Curreli A, Pirozzi Farina F. Le patogenesi biologiche dell'eiaculazione prematura primitiva. Gior It Androl 2000; 7:118

4. Cooper AJ, Cernovsky ZZ, Colussi K. Some clinical and psychometric characteristics of primary and secondary premature ejaculators. J Sex Marital Ther 1993; 19:276

5. Kockott G, Feil W, Ferstl R, Aldenhoff J, Besinger U. Psycho-physiological aspects of male sexual inadequacy: results of an experimental study. Arch Sex Behav 1980; 9:477

6. Tignol J. I disturbi della sessualità maschile. Milan, Masson, 1994

7. Piediferro G. Terapie integrate nell'ejaculatio precox. In: Società Italiana Andrologia, XI Congresso Nazionale, Di Silverio F, Gentile V (Eds), Bologna, Monduzzi, 1997; p 223

8. Simonelli C, Rossi R. Patogenesi psicosessuologica e comportamentale dell'eiaculazione precoce. Giorn It Androl 2000; 7:114

9. Tordjam G. La couple, realites et problemes. Hachette, Paris, 1982

10. Weidner W, Ludwig M. Diagnostic management in chronic prostatitis. In: Prostatitis. Weidner W, Madsen PS, Schiefer HG (Eds). Etiopathology, diagnosis and therapy. Berlin Heidelberg, New York Springer, 1994; pp 49

11. Colpi GM, Piediferro G, Scroppo FI, Nerva F. Il trattamento delle patologie delle ghiandole accessorie. In: Foresta C, Scandellari C (Eds), La medicina della riproduzione: aspetti clinici e terapeutici", Padova, Cleup, 2002; p 163

12. Christiansen E, Tollefsrud A, Purvis K. Sperm quality in men with chronic abacterial prostatovesiculitis. Urology 1991; 38:545

13. Colpi GM, Negri L, Nappi RE, Chinea B. Is transrectal ultrasonography a reliable diagnostic approach in ejaculatory duct subobstruction? Hum Reprod 1997; 12:2186

14. Scroppo FI, Benaglia R. Ecografia prostato-vescicolare transrettale. In:. Colpi GM (Ed), L'infertilità maschile oggi, 2001; 1:27

15. Padma-Natan H, Goldstein I, Krane RJ. Evaluation of the impotent patient. Semin Urol 1986; 4:225

16. Rowland DL, Haensel SM, Blom JH, Slob AK. Penile sensitivity in men with premature ejaculation and erectile dysfunction. J Sex Marital Ther 1993; 19:189

17. Rowland DL, Den Ouden AH, Slob AK. The use of vibrotactile stimulation for determining sexual potency in the laboratory in men with erectile problems: methodological consideration. Int J Impot Res 1994; 6:153

18. Xin ZC, Chung WS, Choi YD, Seong DH, Choi YG, Choi HK. Penile sensitivity in patients with primary premature ejaculation. J Urol 1996; 156:979

19. Paick JS, Jeong H, Park MS. Penile sensitivity in men with premature ejaculation. Int J Impot Res 1998; 10:247

20. Pirozzi Farina F, Curreli A, Moretti M, Spano G, Poddighe S, Belgrano E. L'impiego della biotesiometria peniena con metodica standardizzata nello studio dei pazienti affetti da eiaculazione precoce primitiva. atti III giornate andrologiche italiane, Bologna, Monduzzi, 1994; p 213

21. Breda G, Xausa D, Giunta A, Tamai A, Silvestre P, Gherardi l. nomogram for penile biothesiometry. Urol 1991; 20:67

22. Pirozzi Farina F, Curreli A, Moretti M, Spano G, Poddighe S, Belgrano E. L'anestesia di superficie con lidocaina nella diagnosi e nel trattamento dell' eiaculazione precoce primitiva. atti iii giornate andrologiche italiane, Bologna, Monduzzi 1994; p 219

23. Bercovitch M, Keresteci AG, Koren G. Efficacy of prilocaine-lidocaine cream in the treatment of premature ejaculation. J Urol 1995; 154:1360

24. Brindley GS. The fertility of men with spinal injuries. Paraplegia 1984; 22:337

25. Oates RD, Stakin DR, Krane RJ. Penile vibratory stimulation in the spinal cord injured male to induce ejaculation. J Urol 1990; 143:344

26. Buch JP. Anomalie dell'eiaculazione. In: Bennett AH. L'impotenza (Ed) Rome, Verduci, 1995; p199

27. Rowland DL, Strassberg DS, De Gouveia Brazao CA, Slob AK. Ejaculatory latency and control in men with premature ejaculation: An analysis across sexual activities using multiple sources of information. J Psychosom Res 2000; 48:69

28. G.I.S.I. E Belgrano, G Breda, G Carmignani, P Giannotti, A Maver, V Mirone, M Soli (Eds) I disturbi dell'eiaculazione Edimes, Pavia 1995

29. Tackman W, Porst H, Van Ahlen H. Bulbocavernous reflex latencies and somatosensory evoked potentials after pudendal nerve stimulation in the diagnosis of impotence. J Neurology 1988; 235:219

30. Fanciullacci F, Colpi GM, Beretta G, Zanollo A. Cortical evoked potentials in subject with true premature ejaculation. Andrologia 1988; 20:326

31. Salinas Casado J, Virseda Chamorro M, Samblas Garcia R, Esteban Fuertes M, Aristizabal Agudelo JM, Delgado Martin JA, Blazquez Izquirdoj, Resel Estevez L. Neurobiology of ejaculation and orgasm disorders. Arch Esp Urol 1998; 51:265

32. Colpi GM, Fanciullacci F, Beretta G, Negri L, Zanollo A. Evoked sacral potentials in subjects with true premature ejaculation. Andrologia 1986; 18:583

33. Ozcan C, Ozbek E, Soylu A, Yilmaz U, Guzelipek M, Balbay MD. Auditory event-related potentials in patients with premature ejaculation. Urology 2001; 58:1025

34. Rowland DL, Den Ouden AH, Slob AK. The use of vibrotactile stimulation for determining sexual potency in the laboratory in men with erectile problems: methodological consideration. Int J Impot Res 1994; 6:153

35. Catuogno C. Fisiopatologia, diagnosi e terapia dell'eiaculazione precoce associata o correlata a disfunzione erettiva. Giorn It Androl 2000; 7:130

36. Ozturk B, Cetinkaya M, Saglam H, Adsan O, Akin O, Memis A. Erectile dysfunction in premature ejaculation. Arch Ital Urol Androl 1997; 69:133

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REVIEW

Premature ejaculation. 3. Therapy.

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Summary

Serotonergic drugs (SSRIs) are the most commonly used, but they are characterized by relapse some time after medication interruption as well as by sexual side effects. The efficacy of phosphodiesterase-5 inhibitors seems excellent, but the risk of tachyphylaxis has been reported. The former (fluoxetine, paroxetine, sertraline, clomipramine) should be used in young patients with hyper-orgasmic forms, while the latter (sildenafil, tadalafil, vardenafil) should be used in hypo-orgasmic forms, in old age or when PE is associated with erectile dysfunction. Topical anesthetics provide satisfactory results in premature ejaculation due to hypersensitivity of the glans, and physiotherapy of the pelvic floor muscles proves successful in cases associated with pelvic floor dysfunction. Therapeutic associations and psycho-sexual therapy techniques may improve results, particularly in the long term.

KEY WORDS: *Premature ejaculation; Pelvic floor muscle physiotherapy; Local anesthetics; SSRIs; Phosphodiesterase-5 inhibitors.*

INTRODUCTION

Since etiology varies and is multifaceted (1), the therapeutic approach must necessarily vary, adjusting itself to the various conditions discovered or hypothesized during the diagnostic phase: integrated multimodal schemes of therapy (2-6) are now deemed essential when a symptomatic Premature Ejaculation (PE) has been ruled out, which would require a specific therapy (for instance in PE due to prostatitis, very satisfactorily treated with ciprofloxacin) (7).

PSYCHO-SEXUAL THERAPY

Since psychological motivations are constantly present, both in the first and the second instance, a psycho-sexual approach, for which we refer to specialized literature, is always necessary. We will just mention the behavioral techniques that are most widespread in use even among more "organicist" physicians, such as the well known Stop/Start and Squeeze techniques and those of coital positions, that are considered essential in the therapeutic approach to PE (2) although, as a monotherapy, they prove less effective than pharmacological treatment (3, 8). Futuristic therapeutic possibilities are to be found in psychodynamic approaches of psychotherapy integrated with virtual reality (9, 10).

REHABILITATION OF THE PELVIC FLOOR

Rehabilitation of the pelvic floor both with Kegel's exercises (3, 11) (Table 1), and with electrotherapy and biofeedback (12, 13), though not universally recognized as being effective in its etiological intent, does prove useful as an approach that allows patients to become more familiar with their own body and as a relaxation technique useful in psychodynamic therapy (5, 6, 14): so it has an important role in PE multimodal integrated therapy (1, 3).

TOPICAL THERAPY

The use of topical anesthetics has a rationale in case of hypersensitivity of the glans penis and is also used as a diagnostic test.With 2 cm of lidocaine + prilocaine cream applied on the glans for 20' for a diagnostic test, Primary PE (PPE) disappeared in 37% of patients (15). These test responders were subsequently treated with a progressively reduced application of the cream, passing from a situation of glans anesthesia (sometimes uncomfortable) to that of a hypoesthesia sufficient not to give rise to ejaculatory prematurity, in an attempt to "desensitize" to the point of reaching a time 0 of application: this was reached in 55% of test responders, while 39%

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Table 1.

Exercises for the rehabilitation of the pelvic floor.

Basic exercises (to be carried out on a regular basis during the day)

- Sitting down or standing, contract the pelvic floor muscles, especially the area between the testicles and the anal sphincter. Repeat the exercise 10 times and repeat it every hour without interrupting normal daily activities (contract anal sphincter).
- During micturition repeatedly interrupt the urine flow.

Exercises for strengthening the pelvic floor muscles

(to be performed daily in the morning and in the evening for 10-15 minutes resting between each exercise)

- Lie on your back with a pillow under your head, arms resting straight at your sides, legs bent and knees together. Contracting the pelvic floor muscles and breathing in slowly, lift pelvis a few inches off the ground. Then, breathing out slowly, return to the starting position, relaxing the perineum.
- Lie on your back with legs open and knees bent, and placing a large ball against the internal face of the thighs, try to close the knees squeezing the ball.
- Standing up, with feet rotated outwards, place a large ball between the ankles and try to pull the ankles together straining against the ball

had to maintain personalized cream application time and 6% left treatment (15).

An application time of 20 minutes prior to intercourse was shown to yield the best results with the least undesired effects (16).

We use the same cream with an inverse technique: application for 15'-20' and removal before intercourse of increasing amounts of cream on progressively larger areas of the glans, starting from those in which biothesiometry showed a lower pallesthesic threshold (generally the dorsal area of the balanopreputial sulcus) and searching for a personalized dosage.

Responder patients who choose to cooperate are invited to apply the cream daily, regardless of intercourse, on the whole glans, creating complete anesthesia (provided that it does neither create discomfort nor generate Erectile Dysfunction – ED), often achieving a desensitization that makes treatment unnecessary at the moment of intercourse. Inferior results (27.5%) are obtained using lidocaine alone (17).

Korean studies show the topical efficacy of SS-cream which contains extracts from nine oriental plants. SS-cream produced dose-dependent improvements in Sensory Evoked Potential (SEP) parameters (18) and in biothesiometric threshold values (19), and yielded excellent clinical results, indicating a prolongation of ejaculatory latency > 2' in 79.81% of patients treated (compared to 15.09% of the placebo group) with treatment satisfaction obtained in 82.19% (compared to 19.81% of the placebo group), with only limited side effects such as a mild burning sensation in 14% (20, 21).

Oral drug therapy

Neurophysiological knowledge about the pro-ejaculatory effect of dopamine (22) and the inhibiting effect of serotonin (23) have led to the use of anti-dopaminergic and serotonergic drugs in PPE therapy. Similarly, proofs of the α_2-adrenergic presynaptic inhibiting action, of the α_1-adrenergic postsynaptic stimulating action (24, 25) and of nNOS mediated α1-adrenergic innervation of the vas deferens and of the seminal vesicles (26-28), have led to the use of α_1-lytics. Literature is extremely rich in clinical experience with the above-mentioned drugs, but quite often it is impossible to compare and reproduce these studies owing to the limitations cited in the introduction.

As already stated in a previous review of oral pharmacotherapy for PE (29), the mechanisms of action of the various drugs are often neither clear nor univocal, and rather often more than one activity is present, as for instance in the case of many tricyclic antidepressants that combine in different proportions the serotonergic serotonin reuptake inhibiting action with an α-lytic action, so that in literature they have often been considered in either category (e.g.: clomipramine, sertraline). For reasons of simplicity we have subdivided the drugs as shown in Table 2.

The last two categories (α_2-adrenergic = clonidine; anticholinergic = oxybutynin) do not have much credit in literature, because of both their severe side effects and their extremely limited efficacy.

The rationale for the use of anxiolytic drugs lies both in their hyperprolactinemizing action, mediated by an antidopaminergic activity, and in a no further identified alphalytic activity. The anxiolytic effect as such is beneficial for the psychogenic aspect. Besides lorazepam, which has proved of scarce (episodic) efficacy (30), the administration of alprazolam - 1 h prior to intercourse at a dosage of 0.25 – 0.50 mg receives a certain support, with positive results in about 30-40% of cases (31-33).

The use of antidopaminergic drugs was quite popular in the '80s; it was not supported by clinical results that

Table 2.

Drugs used in PE.

Central	Peripheral
Anxiolytic drugs	α_1-lytic drugs
Anti-dopaminergic drugs	α_2-adrenergic drugs
Serotonergic drugs	Anticholinergic drugs

would justify its use (34), but some initial study was published even recently (levosulpiride) (35).
Metoclopramide was the antidopaminergic drug most used in the past, both at a dosage of 10-15 mg 1-2 h prior to intercourse (acute therapy) and in chronic administration of 10 mg x 2 daily for 3 months (36, 37). Our experience with this drug yielded positive results in 26% with acute therapy and 28% (patients who did not respond to acute therapy) with chronic treatment, 54% in all (3, 38, 39). Literature too records poor results (40), so, on average, we can assess that pharmacological response to metoclopramide ranges around 35%.
The class of serotonergic drugs is the most supported in literature. Their mechanism of action consists of inhibition of presynaptic reuptake of serotonin (SSRI).
The most frequently described drug, particularly in Italian scientific literature, is paroxetine (41-54), used in various trials at dosages of 10–20 mg/d for 1–6 months, with positive results between 50 and 100%, with an average of 85%. The results are dose-dependent and linked to the length of treatment (50), while therapeutic efficacy of "on demand" treatment appears to be scarce (51, 52). Data on side effects and drop-out are discordant (drop-out percentages vary from 4 to 50% depending on statistics).
Another SSRI used is fluoxetine, administered at 5-20 mg/d dosages for 2–6 months with positive results ranging between 62% and 68% (3, 55-58). Fluoxetine is also recommended in erectile dysfunction (ED) associated with PE, for the beneficial effects on the sexual function (59). It increases amplitude and latency of SEPs, intravaginal ejaculatory latencies and penile sensitivity threshold (60). Therapeutic response and side effects (nausea, tachycardia, insomnia) are dose-dependent (61, 62).
Citalopram, which in addition to its SSRI action also inhibits the neuronal 5HT1a receptor, has caused an improvement in PE in 98-100% of cases at a dosage of 10–20 mg/d for 4–6 months in some trials (63-65), with results considered subjectively very satisfactory in 69.3% vs. 7.7% of the placebo group (66) and linked to serum leptin levels (67).
Clomipramine has been used at a dosage of 25–50 mg/d for 2 months, obtaining positive results in 35-58% of patients with a drop-out of about 20% due to side effects, consisting mainly of xerostomia (86%) and somnolence (76%) (46, 68, 69). It has been proved to induce prolongation of ejaculatory latency, increase of SEPs (68, 70), but also inhibition of nocturnal penile tumescence: therefore it is not indicated for patients with PE combined with ED (71). Some Authors recommend the use of a daily dosage of 20-30 mg up to 12 weeks in case of failure of the "on demand" therapy with dosages of 25 mg (72).
Sertraline has been used at a 50 mg/d (25-100) dosage for 2-6 weeks with positive results (about 68%) and dose-dependent side effects (anorexia, dyspepsia, gastrointestinal disorders). Only at a 100 mg dosage it caused anxiety and erectile dysfunction (73-76), while at low doses there was no drop-out, though prolongation of ejaculatory latency was maintained (77). An "on demand" administration prior to intercourse also seems to yield positive responses, considering that the blood peak is reached between 4 and 8 hours from oral administration (78).
Comparative studies between different SSRIs and/or their therapeutic combination have revealed that:

- clomipramine is 100 times more powerful than fluoxetine, sertraline and paroxetine on inhibiting norepinephrine-induced contraction of the distal seminal tract muscles (79);
- clinical efficacy in the treatment of premature ejaculation with sertraline or fluoxetine is comparable: disappearance 38.7% vs. 30.8%, improvement 32.3% vs. 42.3, failure 29% vs. 26.9% (80);
- clinical results obtained with fluoxetine (54%), paroxetine (50%), sertraline (51%) and fluvoxamine (60%) are similar, and the same applies to the increase in ejaculatory latency time and side effects (81);
- paroxetine seems to have higher efficacy than citalopram (positive results in 24/32 vs. 19/32 [chi-square test: p=0.3472, non significant, Editor's Note]) with similar side effects (82);
- the association of oral fluoxetine + topical lidocaine is more effective than the treatment with oral fluoxetine alone: disappearance in 52.9% vs. 30.8% of cases, improvement in 23% vs. 42.2%, failure in 17.6% vs. 26.9% (83);
- the association of various therapeutic principles improves results: metoclopramide (MCP) + Stop/Start and Squeeze (SSS) 61.11% vs. MCP 54.35%; fluoxetine (FLX) + SSS + rehabilitation of pelvic floor muscles 86.36% vs. FLX + SSS 74.19% vs. FLX 61.54% (3);
- lengthening of ejaculatory latency time is of 1-3 minutes with sertraline (as with stop/start and squeeze techniques), of 1-4 minutes with clomipramine and paroxetine, whereas it reaches up to 15 minutes with sildenafil 8;
- the association of paroxetine + sildenafil obtains better clinical results than paroxetine alone 84,85, and the same applies to sertraline +/- sildenafil (86).

The use of SSRIs is characterized by reappearance of symptoms some time after withdrawal from therapy: the resort to multimodal therapeutic schemes seems to diminish the frequency of relapse (3).
Therapy with SSRIs, on the other hand, cannot be continued indefinitely, because it causes sexual function disorders such as loss of libido and erectile dysfunction due to hyperprolactinemia, to its anticholinergic effects, to inhibition of nitric oxyde synthase that arises with drug accumulation (87). Various strategies are suggested in order to avert this limitation, such as progressive reduction in dosages up to an "on demand" administration, cyclic administration, association with α-lytics and phosphodiesterase-5 inhibitors. According to a multicenter, prospective trial, paroxetine induces a higher decrease in sexual activity and erectile dysfunction compared to fluoxetine, fluvoxamine and sertraline (88), and furthermore in treatment with fluoxetine, no major difference on sexuality between acute treatment (20 mg/d for 13 weeks) and chronic treatment (90 mg/week for 25 weeks) has been observed, and this provides a positive flexibility (89).
Among the α_1-blockers used, quite a few studies select

Phenoxybenzamine ($\alpha_{1\text{-}2}$–blocker), which showed results at about 53% (90-93); its use is opposed by the frequency of side effects (>30%) and by its reported carcinogenicity (94).
Other studies have used alfuzosine and terazosine obtaining positive results in 46% and 54% of cases respectively, with scarce side effects that led to a drop-out rate of 4% (40) only.
Phosphodiesterase-5 inhibitors such as sildenafil have been mainly used for therapy of erectile dysfunctions due to the use of antidepressant SSRIs and therefore proposed in association with them in treatment of PE (17, 84, 86, 95-99).
In clinical practice, as a confirmation of the data found in literature, the efficacy of sildenafil (which has replaced the use of the intracavernous prostaglandin E_1 used in the pre-Viagra era) is constantly being observed in the treatment of the PE symptom. Efficacy goes beyond the simple reduction in the refractory period (100), which favors repetition of intercourse and gratification of the couple. It may be hypothesized that the strengthening of sildenafil-induced no activity has a direct influence on the inhibition of the ejaculatory reflex (27, 28), perhaps through adrenergic neuromodulation of the distal seminal tracts (26, 28). A further consideration must be made from an anatomical point of view: the muscular coat of the ejaculatory ducti, of limited thickness, is formed by smooth muscle cells and in the caudal segment it has more fibroelastic tissue and a cavernosus-like venous plexus (101) that responds to sildenafil causing difficulty at emission.
A limitation of the use of sildenafil for single-drug treatment of PPE not associated with ED can be represented by the risk of tachyphylaxis which has been described in literature (102).

Surgical therapy

It is commonly thought that frenuloplasty can induce a reduction in the ejaculatory stimulus, but no scientific proof is recorded in literature. We prefer to resort to surgery only after biothesiometry has shown a low threshold of frenular sensitivity and/or a test with EMLA on the frenular area alone has proved of beneficial effect for frenulum anesthesia, in partial agreement with other Authors (103).
Sensitivity alterations which sometimes cause non-gratification in intra-vaginal intercourse (104) and the report of a more frequent presence of PE in circumcised men compared to non-circumcised ones (105) rule out circumcision as a therapeutic weapon in PE, and the same applies to selective neurectomy of the distal crura of the dorsal nerve of the penis, which can cause extremely severe sensitivity damage up to anorgasmia and which was reported only once in literature (106).

Premature ejaculation and erectile dysfunction

In case of ascertained hyper-orgasmic PPE with secondary ED, medical therapy (necessarily associated to psycho-sexual therapy) can benefit from the use of SSRIs (obviously preferring those with the least risk of decline in sexuality such as fluoxetine and sertraline), if necessary in association with sildenafil for a particularly serious ED. In such conditions the Authors prefer to use sildenafil only when absolutely necessary, considering the risk of tachyphylaxis described in literature (102).
Association with local anesthetics must be carefully evaluated in order not to overdo in the reduction of glans sensitivity, thus causing loss of pleasure in a patient who already has ED, but in these conditions it can have a rationale, especially in type I PPE.
In case of hypo-orgasmic PE (generally secondary, symptomatic of ED) the therapy to be preferred is that specific for ED, using sildenafil (not apomorphine, which would worsen ejaculatory prematurity though improving the state of arousal) or intracavernous PGE_1 as the case may be, while it is advisable to avoid SSRIs and local anesthetics.
A hormonal assay is useful here to detect the presence of hypogonadism, and an androgen therapy could turn out to be useful for observations on the bihormonal model of the sexual and ejaculatory function with modulating function carried out by androgens (107, 108).
Rehabilitation of the pelvic floor may also play a role in this situation, since the dysfunction in erectile maintenance can benefit by improved bulbo- and ischiocavernosus muscle tone, with increased contraction of the crura.
Finally, if they are tolerated for their hypotensive effects, α-lytic drugs (or anxiolytics with intrinsic α-lytic activity such as alprazolam) concur in fighting the adrenergic hypertonia which the two sexual alterations share.

References

1. Piediferro G, Nerva F, Contalbi GF, Colpi EM. L'ejaculazione precoce. In: Menchini-Fabris F (Ed), Deficit erettivo, Pisa, Felici Editore, 2002; p 36

2. Lee BO. Treating premature ejaculation in the multi-modal therapeutic framework: a single case study. Ann Acad Med Singapore 1995; 24:668

3. Piediferro G. Terapie integrate nell'ejaculatio precox. In: Società italiana andrologia, XI Congresso Nazionale, Di Silverio F, Gentile V, (Eds), Bologna, Monduzzi, 1997; p 223

4. Rosso C, Rolle L, Fontana D, Furlan PM. Le terapie dell'eiaculazione precoce: prassi e fondamenti teorici. Gior It Androl 1998; 5:39

5. Simonelli C, Rossi R. Il trattamento psicosessuologico dell'eiaculazione precoce. Gior It Androl 2000; 7:134

6. Metz ME, Pryor JL. Premature ejaculation: a psychophysiological approach for assessment and management. J Sex Marital Ther 2000; 26:293

7. Brown AJ. Ciprofloxacin as cure of premature ejaculation. J Sex Marital Ther 2000; 26:351

8. Abdel-Hamid IA, El Naggar EA, El Gilany AH. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. Int J Impot Res 2001; 13:41

9. Optale G, Munari A, Nasta A, Pianon C, Verde JB, Viggiano G. A VR based therapy for the treatment of impotence and premature ejaculation. Stud Health Technol Inform 1998; 58:136

10. Riva G, Alcaniz M, Anolli L, Bacchetta M, Banos R, Beltrame F, Botella C, Galimberti C, Gamberini L, Gaggioli A, Molinari E, Mantovani G, Nugues P, Optale G, Orsi G, Perpina C, Troiani R. The vepsy updated project: virtual reality in clinical psychology. Cyberpsychol Behav 2001; 4:449

11. Beretta G. Disfunzioni sessuali maschili. Milan, Del Cerro, 1994

12. La Pera G, Nicastro A. A new treatment for premature ejaculation: the rehabilitation of the pelvic floor. J Sex Marital Ther 1996; 22:22

13. La Pera G. Eiaculazione precoce, possibilità terapeutiche. Abstract 2a Giornata Andrologica. Disturbi dell'Erezione e dell'Eiaculazione, Torre del Greco 28/3/1998 – Prevenzione uomo (SIA Campano-Calabra) 1998

14. Curreli A. Pirozzi Farina F. Le patogenesi biologiche dell'eiaculazione prematura primitiva. Gior It Androl 2000; 7:118

15. Pirozzi Farina F. Gli anestetici di contatto nel trattamento dell'eiaculazione prematura primitiva. Gior It Androl 2000; 7:141

16. Atikeler MK, Gecit I, Senol FA. Optimun usage of prilocaine-lidocaine cream in premature ejaculation. Andrologia 2002; 34:356

17. Chen J, Mabjeesh NJ, Matzkin H, Greenstein A.. Efficacy of sildenafil as adjuvant therapy to selective seroton reuptake inhibitor in alleviating premature ejaculation. Urology 2003; 61:197

18. Xin ZC, Choi YD, Seong DH, Choi HK. Sensory evoked potential and effect of SS-cream in premature ejaculation. Yonsei Med J 1995; 36:397

19. Xin ZC, Choi YD, Lee WH, Choi YJ, Yang WJ, Choi HK, Kim DK. Penile vibratory threshold changes with various doses of ss-cream in patients with primary premature ejaculation. Yonsei Med J 2000; 41:29

20. Choi HK, Xin ZC, Choi YD, LeE WH, Mah SY, Kim DK. Safety and efficacy study with various doses of SS-cream in patients with premature ejaculation in a double-blind, randomised, placebo controlled clinical study. Int J Impot Res 1999; 11:261

21. Choi HK, Jung GW, Moon KH, Xin ZC, Choi YD, Lee WH, Rha KH, Choi YJ, Kim DK. Clinical study of ss-cream in patients with lifelong premature ejaculation. Urology 2000; 55:257

22. Ferrari F, Giuliani D. The selective D2 dopamine receptor antagonist eticlopride counteracts the ejaculation praecox induced by selective D2 dopamine agonist SND 919 in the rate. Life Sciences 1994; 55:1155

23. Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. Behav Brain Res 1998; 92:111

24. Brown GM, Mc Grath JC, Summers RS. The effect of alpha-adrenoreceptors agonist and antagonist on response of transmurally stimulated prostatic and epididymal portion of the isolated vas deferens of the rat. BR J Pharmacol 1979; 66:553

25. Clark JT, Smith ER, Davidson JM. Evidence for the modulation of sexual behaviour by alpha-adrenoceptors in male rats. Neuroendocrinology 1985; 41:36

26. Grozdanovic Z, Goessl C. Comparative localization of heme oxygenase-2 and nitric oxide synthase in the autonomic innervation to the ductus deferens and seminal vesicle. J Urol 1999; 162:2156

27. Hull EM, Lumley LA, Matuszewich L, Dominguez J, Moses J, Lorrain DS. The roles of nitric oxide in sexual function of male rats. Neuropharmacology 1994; 33:1499

28. Machtens S, Ckert S, Stief CG, Tsikas D, Frlich JC, Jonas U. Effects of various nitric oxide-donating drugs on adrenergic tension of human seminal vesicles in vitro. Urology 2003; 61:479

29. Piediferro G. Eiaculazione precoce oggi: terapie farmacologiche ad azione sul sistema nervoso centrale. Risultati clinici. Gior It Androl 1998; 5:47

30. Seagraves RT. Treatment of premature ejaculation with lorazepam. Am J Psychiatry 1987; 144:1240

31. G.I.S.I. Belgrano E, Breda G, Carmignani G, Giannotti P, Maver A, Mirone V, Soli M. I disturbi dell'eiaculazione (Eds), Edimes, Pavia, 1995

32. Kimura Y, Kisakin N, Sarvrada S, Tadano T. On the brain monoaminergic system relating to ejaculation. Brain dopamine and ejaculation. Andrologia 1976; 8:313

33. Mirone V, Imbimbo C, Sessa G, Longo N. I disturbi dell'eiaculazione. In: Andrologia. Fisiopatologia e clinica, Molinatti GM, Fontana D (Eds), Rome, Verduci, 1997

34. Giammusso B. La terapia medica sistemica dell'EP: farmaci attivi sul sistema nervoso centrale e periferico e sull'erezione. Gior It Androl 2000; 7:138

35. Greco E, Polonio-Balbi P, Speranza JC. Levosulpiride: A new solution for premature ejaculation?. Int J Impot Res 2002; 14:308

36. Rocco A, Falaschi P, Pompei M, Frajese G, Gessa GL . Ruolo del sistema dopaminergico nel controllo della eiaculazione. J Endocrinol Invest 1980; 3:14

37. Falaschi P, Fraiese G, Rocco A, Pompei G, Gessa GL. Role of brain dopamine in the regulation of male sexual behaviour. In: The menopause: clinical, endocrinological and pathophysiological aspects, Fioretti A (Ed), London, Academic Press, 1980

38. Piediferro G. Trattamento dell'ejaculatio precox con metoclopramide. In: D'ottavio G, Pozza D (eds), Progressi in andrologia chirurgica, Rome, Acta Medica Edizioni, Congressi, 1987; p 285

39. Piediferro G, Vanacore M, Sorrentino F. Terapia dell'ejaculatio precox. (atti 60° congr. Soc. It. Urol. Palermo, 1987), Acta Urol Ital 1988; 1:361

40. Cavallini G. Alpha1-blockade pharmacotherapy in primitive psychogenic premature ejaculation resistant to psychotherapy. Eur Urol 1995; 28:126

41. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomised, placebo-controlled study. Am J Psychiatry 1994; 151:1377

42. Waldinger MD, Hengeveld MW, Zwinderman AH. Ejaculation-retarding properties of paroxetine in patients with primary premature ejaculation: a double-blind, randomised, dose-response study. Br J Urol 1997; 79:592

43. Ludovico GM, Corvasce A, Cirillo Marucco E, Curatolo C, Pagliarulo G, Paglarulo A. La paroxetina nel trattamento dell'eiaculazione precoce: risultati preliminari. Urologia Oggi Suicmi 1995; 3:263

44. Ludovico GM, Corvasce A, Pagliarulo G, Cirillo Marucco E, Marano A, Pagliarulo A. Paroxetine in the treatment of premature ejaculation. Br J Urol 1996; 77:881

45. Di Lena S, Saponaro P, Verriello V, Ludovico GM, Corvasce A, Pagliarulo A. Paroxetina vs terapia intracavernosa con PGE1 nel trattamento della eiaculazione precoce psicogena. Atti X Congr. Soc. It. Andrologia, Menchini Fabris F (Ed), Bologna, Monduzzi, 1996; 797

46. Corvasce A, Ludovico GM, Cirillo Marucco E, Pagliarulo A. Paroxetina vs clomipramina nella terapia della eiaculazione precoce. Atti X Congr. Soc. It. Andrologia, Menchini Fabris F (Ed), Bologna, Monduzzi, 1996; 793

47. Giammusso B, Morgia G, Spampinato A, Motta M. La paroxetina nel trattamento dell'eiaculazione precoce. Arch It Urol 1997; 69:11

48. Pagani G, Silvani M . Paroxetina vs PGE1 intracavernosa nella terapia della eiaculatio precox. Abstracts 70° Congr. Soc It Urol P221, 1997

49. Gattuccio F, D'Alia A, Musotto S, Di Trapani D, Terrana M, Motta M, Morgia G, Giammusso B. La paroxetina nel trattamento dell'eiaculazione precoce. Atti XI Congr Soc It Andrologia, F Di Silverio, Gentile V (Eds), Bologna, Monduzzi, 1997; p 229

50. Paulis G, Nupieri P. Impiego della paroxetina nel trattamento medico della eiaculazione precoce. In: Atti XI Congr Società Italiana di andrologia, Di Silverio F, Gentile V (Eds), Bologna, Monduzzi, 1997; p 235

51. Mcmahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. J Urol 1999; 161:1826

52. Mcmahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride. Int J Impot Res 1999; 11:241

53. Delle Rose A, Stomaci N, Mazzilli T, Posti A, Raugei A, Mondaini N, Salaris C, Tazzioli S. Uso della paroxetina nel trattamento dell'eiaculazione precoce. Giorn It Androl 2000; 7:11

54. Qiu YC, Wang XK, Cui ZB, Lin SH, Chen M. Effects of seroxat on premature ejaculation: a clinical trial. Zhonghua Nan Ke Xue 2002; 8:117

55. Piediferro G, Russo A, Crimi A, Luciano G. Eiaculazione precoce: nostra esperienza. Urologia 1996; 63:254

56. Kindler S, Dolberg OT, Cohen H, Hirschmann S, Kotler M. The treatment of comorbid premature ejaculation and panic disorder with fluoxetine. Clin Neuropharmacol 1997; 20:466

57. Pecoraro G, Grosso G, Sidoti O. Trattamento dell'eiaculazione precoce idiopatica: nostra esperienza. Gior It Androl 1997; 2:91

58. Haensel SM, Klem TM, Hop WC, Slob AK. Fluoxetine and premature ejaculation: a double-blind, crossover, placebo-controlled study. J Clin Psychopharmacol 1998; 18:72

59. Power-Smith P. Beneficial sexual side-effects from fluoxetine. Br J Psychiatry 1994; 164:249

60. Yilmaz U, Tatlisen A, Turan H, Arman F, Ekmekcioglu O. The effects of fluoxetine on several neurophysiological variables in patients with premature ejaculation. J Urol 1999; 161:107

61. Kara H, Aydin S, Yucel M, Agargun MY, Odabas O, Yilmaz Y. The efficacy of fluoxetine in the treatment of premature ejaculation: a double-blind placebo controlled study. J Urol 1996; 156:1631

62. Lee HS, Song DH, Kim CH, Choi HK. An open clinical trial fluoxetine in the treatment of premature ejaculation. J Clin Psychopharmacol 1996; 16:379

63. Andriani E, Contini L. Impiego del citalopram nell'eiaculazione precoce. Gior It Andrologia 1997; 1:36

64. Piediferro G. Terapie integrate nell'eiaculatio precox: 13 anni di esperienza. Abstract 2a giornata andrologica. Disturbi dell'erezione e dell'eiaculazione. Torre del Greco 28/3/1998, prevenzione uomo (sia Campano-Calabra) 1998

65. Piediferro G. Citalopram nell'eiaculazione precoce primitiva. Abstracts XII Congr. Soc It Andr, Giorn It Andr 1999; 6:26

66. Atmaca M, Kuloglu M, Tezcan E, Semercioz A. The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study. Int J Impot Res 2002; 14:502

67. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Semercioz A. Serum leptin levels in patients with premature ejaculation before and after citalopram treatment. BJU Int 2003; 91:352

68. Colpi GM, Fanciullacci F, Aydos K, Grugnetti C. Effectiveness mechanism of chlomipramine by neurophysiological tests in subjects with premature ejaculation. Andrologia 1991; 23:45

69. Montorsi F, Guazzoni G, Trimboli F, Rigatti P, Pizzini G, Miani A. Clomipramine for premature ejaculation: a randomized, double blind, placebo controlled study. Acta Urol Ital 1995; 1:5

70. Strassberg DA, De Gouveia Brazao CA, Rowland DL, Tan P, Slob AK. Clomipramine in the treatment of rapid (premature) ejaculation. J Sex Marital Ther 1999; 25:89

71. Haensel SM, Rowland DL, Kallan KT. Clomipramine and sexual function in men with premature ejaculation and controls. J Urol 1996; 156:1310

72. Rowland DL, De Gouveia Brazao CA, Slob AK. Effective daily treatment with clomipramine in men with premature ejaculation when 25mg (as required) is ineffective. BJU Int 2001; 87:357

73. Mendels J, Camera A, Sikes C. Sertraline treatment for premature ejaculation. J Clin Psychopharmacol 1995; 15:341

74. Balbay MD, Yildiz M, Salvarci A, Ozsan O, Ozbek E. Treatment of premature ejaculation with sertralin. Int Urol Nephrol 1998; 30:81

75. McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride: a single-blind placebo controlled crossover study. J Urol 1998; 159:1935

76. McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride. Int J Impot Res 1998; 10:181

77. Biri H, Isen K, Sinik Z, Onaran M, Kupeli B, Bozkorli I. Sertraline in the treatment of premature ejaculation: a double-blind placebo controlled study. Int Urol Nephrol 1998; 30:611

78. Kim SW, Paick JS. Short-term analysis of the effects of as needed use of sertraline at 5pm for the treatment of premature ejaculation. Urology 1999; 54:544

79. Seo KK, Kim SC, Lee MY. Comparison of peripheral inhibitory effects of clomipramine with selective serotonin re-uptake inhibitors on contraction of vas deferens: in vitro and in vivo studies. J Urol 2001; 165:2110

80. Basar MM, Atan A, Yildiz M, Baykam M, Aydoganli L. Comparison of sertraline to fluoxetine with regard to their efficacy and side effects in the treatment of premature ejaculation. Arch Esp Urol 1999; 52:1008

81. Giorgi PM, Biagiotti G, Cavallini G. Trattamento dell'eiaculazione precoce primitiva con inibitori selettivi del re-uptake della serotonina (SSRIs). Gior It Androl 1999; 6:193

82. Corvasce A, Ludovico GM, Cardo G, Cirillo Marucco E, Dachille G, Pagliarulo A. Paroxetina v/s citalopram nel trattamento dell'eiaculazione precoce. Giorn It Androl 2000; 7:11

83. Atan A, Basar MM, Aydoganli L. Comparison of the efficacy of fluoxetine alone vs. Fluoxetine plus local lidocaine ointment in the treatment of premature ejaculation. Arch Esp Urol 2000; 53:856

84. Montorsi F, Salonia A, Maga T, Zanoni M, Barbieri L, Deho' F, Scattoni V, Rigatti P. Eiaculazione precoce: studio prospettico di confronto tra paroxetina e paroxetina e sildenafil. Giorn It Androl 2001; 8:73

85. Salonia A, Maga T, Colombo R, Scattoni V, Briganti A, Cestari A, Guazzoni G, Rigatti P, Montorsi F. A prospective study comparing paroxetine alone versus paroxetine plus sildenafil with premature ejaculation. J Urol 2002; 168:2486

86. Chia S. Management of premature ejaculation. A comparison of treatment outcome in patients with and without erectile dysfunction. Int J Androl 2002; 25:301

87. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999; 19:67

88. Montejo-Gonzalez AL, llorca G, Izquierdo JA, Ledesma A, Bousono M, Calcedo A, Carrasco JL, Ciudad J, Daniel E, De La Gandara J, Derecho J, Franco M, Gomez MJ, Macias JA, Martin T, Perez V, Sanchez S, Vicens E. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline and fluvoxamine in a prospective, multicenter and descriptive clinical study of 344 patients. J Sex Marital Ther 1997; 23:176

89. Michelson D, Schmidt M, Lee J, Tepner R. Changes in sexual function during acute and six-month fluoxetine therapy: a prospective assessment. J Sex Marital Ther 2001; 27:289

90. Homonnai ZT, Shilon M, Paz GF. Phenoxybenzamine: an effective male contraceptive pill. Contraception 1984; 29:479

91. Shilon M, Paz GF, Homonnai ZT. The use of phenoxybenzamine treatment in premature ejaculation. Fert Steril 1984; 42:659

92. Beretta G, Chelo E, Fanciullacci F, Zanollo A. Effect of an alphablocking agent (phenoxybenzamine) in the management of premature ejaculation. Acta Eur Fertil 1986; 17:43

93. Beretta G, Chelo E, Catanzaro F, Fanciullacci F, Zanollo A. Treatment of premature ejaculation with an alphablocker (phenoxybenzamine). Min Urol Nefrol 1988; 40:29

94. Caine M. Clinical experience with alpha-adrenoreceptor antagonist in benign prostatic hypertrophy. Fed Proc 1986; 45:2604

95. Rosenberg KP. Sildenafil. J Sex Marit Ther 1999; 25:271

96. Rosen RC. Sexual pharmacology in the 21st century. J Gend Specif Med 2000; 3:45

97. Boyce EG, Umland EM. Sildenafil citrate: a therapeutic update. Clin Ther 2001; 23:2

98. Nurnberg HG, Gelenberg A, Hargreave TB, Harrison WM, Siegel RL, Smith MD. Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Am J Psychiatry 2001; 158:1926

99. Nurnberg HG, Seidman SN, Gelenberg AJ, Fava M, Rosen R, Shabsigh R. Depression, antidepressant therapies, and erectile dysfunction: clinical trials of sildenafil citrate (viagra) in treated and untreated patients with depression. Urology 2002; 6:58

100. Aversa A, Mazzilli F, Rossi T, Delfino M, Isidori AM, Fabbri A. Effetti del sildenafil (Viagra®) sullo spermiogramma e sul periodo refrattario post-eiaculatorio nei maschi sani. Hum Reprod 2000; 15:131

101. Panattoni GL. Anatomia dell'apparato genitale maschile. In: Molinatti GM, Fontana D (Eds), Andrologia Fisiopatologia e clinica, Rome, Verduci, 1997; p 1

102. El-Galley R, Rutland H, Talic R, Keane T, Clark H. Long-term efficacy of sildenafil and tachyphylaxis effect. J Urol 2001; 166:927

103. Pescatori ES. La terapia chirurgica dell'eiaculazione precoce. Gior It Androl 2000; 7:146

104. Laumann EO, Masi CM, Zuckermann EW. Circumcision in the United States. Prevalence, prophylactic effects, and sexual Practice. Jama 1977; 277:1052

105. O'Hara K, O'Hara J. The effect of male circumcision on the sexual enjoyment of the female partner. BJU International 1999; 83:79

106. Tullii RE, Di Iorio JM, Vaccari R, Trefiletti S, Degni M. Neurectomy: new therapeutic technique for premature ejaculation. Int J Imp Res 1992; 4:205

107. Motofei IG. A bihormonal model of normal sexual stimulation; the etiology of premature ejaculation. Med Hypotheses 2001; 57:93

108. Motofei IG. The etiology of premature ejaculation starting from a bihormonal model of normal sexual stimulation. Int J Imp Res 2001; 13:49

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Società Italiana di Ecografia Urologica Nefrologica e Andrologica

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La SIEUN (Società Italiana di Ecografia Urologica Nefrologica e Andrologica) riunisce diversi medici specialisti e non che si occupano di tutte quelle metodiche in cui gli ultrasuoni vengono utilizzati a scopo diagnostico in ambito nefro-uro-andrologico.

La SIEUN organizza un **Congresso nazionale** con periodicità biennale e diverse altre iniziative negli anni in cui non si tiene il Congresso. Il prossimo Congresso della SIEUN si svolgerà a L'Aquila nel 2006. Presidente del Congresso sarà il Prof. Carlo Vicentini.

Dal 2001 la SIEUN **è affiliata** all'ESUI (European Society of Urological Imaging) pertanto tutti i soci si giovano di facilitazioni per l'accesso alle iniziative della Società Europea.

L'Archivio Italiano di Urologia e Andrologia è l'**organo ufficiale** della SIEUN. Questa pagina permette un'informazione puntuale sulle attività della nostra Società e consente al Consiglio Direttivo della SIEUN di comunicare ai soci ogni nuova iniziativa.

Notizie dalla SIEUN

Comitato Direttivo

Il nuovo Comitato Direttivo per il prossimo quadriennio (2004 – 2008) è così composto:

Presidente	Guido Virgili
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Riconoscimento Società Scientifica

Informiamo tutti i soci che la SIEUN ha inoltrato, entro i termini stabiliti, istanza di riconoscimento come società scientifica al Ministero della Salute. Infatti l'entrata in vigore del Decreto Ministeriale del 31 maggio 2004, prevede il riconoscimento delle società scientifiche da parte del Ministero della Salute per poter svolgere attività formativa.
Questo passo richiederà delle modifiche allo statuto in vigore per ottemperare alle indicazioni contenute nel D.M.
I soci saranno convocati per approvare il nuovo statuto.

Biopsie prostatiche ecoguidate: focalizzazione dei punti controversi

La SIEUN è tra i promotori del progetto per l'elaborazione delle Linee Guida sulla Biopsia Prostatica. La prima fase del progetto si concluderà con la Consensus Conference che si terrà a Bologna il 12 febbraio 2005 .
In tale occasione saranno discusse in dettaglio tutte le problematiche legate alla biopsia prostatica e posti in votazione, con l'interattiva, i punti più significativi.
Alla conclusione dei lavori, la giuria stenderà il documento conclusivo.

I Punti SIEUN

(una possibilità d'incontro tra Soci SIEUN e di contatto con altri specialisti)

Presso i Punti SIEUN i nostri soci potranno essere continuamente informati su tutte le attività e le iniziative della Società e rinnovare il pagamento della quota associativa.

La prossima occasione di interazione tra soci e non soci SIEUN:

Bologna 12 febbraio 2005
Biopsie prostatiche ecoguidate: focalizzazione dei punti controversi

La segreteria della Società

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