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Prostate specific antigen through the years.

Chryssanthos Kouriefs, Mukhtar Sahoyl, Philippe Grange, Gordon Muir

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Summary

PSA was first identified in the 1960s. Some controversy exist as to who should be credited with its discovery as different groups, simultaneously, isolated the same protein but gave it a different name. PSA was firstly approved by FDA in 1986 as a test to aid the management of patients diagnosed with prostate cancer. In 1994, it was approved by the FDA as a diagnostic tool and up to date its beneficial role as a screening test is largely unknown. The results of the PLCO and ERSPC trials are awaited. Increasing interest is also emerging on the use of PSA as a tool in the management of BPH. Recently some embryonic data on the use of other novel markers such as EPCA and prostasomes is emerging and the data on PCA3 as a diagnostic tool for prostate cancer is maturing.

Key words: Prostate; PSA; History; PCA3; EPCA.

Submitted 16 February 2009, Accepted 30 June 2009

Introduction

Prostate Specific Antigen (PSA) was first discovered in the 1960s and has since become the most widely used serum tumour marker. It is estimated that over 20,000,000 tests are carried out in North America and another 20 million outside. In 1986, FDA approved PSA, not as a screening test, but as a test to aid in the care of patients already diagnosed with prostate cancer. The breakthrough came in 1994 when FDA approved PSA as the first blood test to help detect prostate caner in men over 50 years old. The test approved was the Tandem PSA assay by Hybritech corp. of San Diego. A “normal” level of 4ng/ml was chosen arbitrarily and supported by a study published in the Journal of Urology in 1994; a study supported by Hybritech and reported a 15% incidence of prostate cancer in men older than 50 years with a PSA higher than the chosen cut-off of 4ng/ml (1). Since then a lot of controversy has risen with regards to the most appropriate cutoff level of serum PSA. This article is aiming to review the history basic science of PSA test as well as the medical and non-medical applications of PSA.

History of PSA

In the late 1960s, Hara and colleagues from Japan identified a semen specific protein which they called gamma-semimprotein (2). Near the same time, Seensabaugh and colleagues also identified a semen specific protein which they called p30 because of its molecular weight of 30KD (3). The following year, Wang et al. (4), from the Roswell Park cancer institute in New York, purified a prostate specific protein from normal, hyperplastic and cancerous human prostate tissue. They called it the prostate antigen. The same group characterised the amino acid sequence of this prostate antigen and reported it to be identical to the p30 and gamma-semimprotein previously identified in the semen (5). They, therefore, called them all collectively as the nowadays known prostate specific antigen (PSA). Wang’s name is the one most commonly linked to the early days of PSA and some consider Wang’s group as the first to have discovered PSA in prostatic tissue. However, it was Richard Ablin who first identified and reported PSA in human tissue (6). The most important discovery came in 1980 from the Roswell Park Cancer Institute when they identified PSA in the serum of men with prostate cancer. In their initial series they used the first generation PSA assay with a low sensitivity (> 500 ng/ml) and identified PSA in the serum of 17 out of 219 men with prostate cancer. Since then more sensitive assays have allowed PSA to gain popularity in screening for prostate cancer, but the increased sensitivity has produced some scepticism due to a reciprocal low specificity.

Basic science of PSA

PSA is a 34KD serine protease of the Kallikrein family. The PSA-gene is located on the long arm of chromosome
13 (13q19). It is almost exclusively produced by the prostate cells and found in the semen at higher concentrations than serum. In the semen, it liquefies freshly ejaculated semen as well as the cervical mucous plug allowing for conception. In the serum, it has a high affinity for serum protease inhibitors (α1-antichymotrypsin and α2-macroglobulin), 75% is complexed to these inhibitors and 25% is free in serum.

In the early days, PSA was believed to be specific for prostate and semen but it was later, with the advent of supersensitive assays, detected in other body tissues and fluids. Other than semen, the greatest concentrations of PSA in biological fluids are detected in breast milk (0.47-1.00 ng/ml) and amniotic fluid (0.60-8.98 ng/ml). Low concentrations of PSA have been identified in the urethral glands, endometrium, normal breast tissue and salivary gland tissue. PSA also is found in the serum of women (0.01-0.53 ng/ml). It has been associated with breast, lung, or uterine cancer, and some patients with renal cancer. Its significantly higher concentration in semen (200 000-5 500 000 ng/ml) and expression in prostate, however, has made it popular in the management of prostatic diseases.

PSA is secreted first as a pre-pro-PSA which is then cleaved to pro-PSA and subsequently to PSA. One could assume that, because serum levels of PSA are higher in men with prostate cancer, prostate cancer cells release more PSA. This is, however, not true and is a bit of a paradox. Osterling reports cells from hyperplastic prostate to produce significantly more PSA (0.3 ng/ml/g) than cells from prostate cancer. This could be explained by the defective basement membrane and loss of polarity of epithelial cells seen in prostate cancer.

The most clinically applicable detail of the PSA chemistry is the serum PSA half-life. Osterling and Stamey have estimated serum half-life of PSA to be 2.3 to 3.2 days (7, 8). This is important in following-up prostate cancer patients who have undergone a curative treatment, especially radical prostatectomy. After radical prostatectomy, one would expect the PSA level to half every 2-3 days and therefore reach a baseline (undetectable) after about 6-7 half-lives. This is the rationale for doing a PSA test 3-6 weeks after radical prostatectomy. Equally, a raised PSA level due to a benign condition, such as a urinary tract infection or prostatitis, will not return to baseline until 3 weeks after the inflammation has resolved.

**APPLICATION OF PSA IN UROLOGY**

**PSA and Prostate cancer**

Since its approval by FDA in 1986, PSA has revolutionised the management of prostate cancer and gained popularity as a screening test for prostate cancer. In 1994, Catalona’s group chose an arbitrary cut-off level of 4 ng/ml above which men over 50 years were advised to undergo prostate biopsies. In this study of 6630 volunteers, 15% of men with a high PSA (> 4 ng/ml) were found to have prostate carcinoma on biopsy. The Prostate Cancer Prevention Trial (PCPT) has reported that there is not such a thing as an absolute PSA cut-off. They report a 17%, 24% and 27% risk of prostate cancer in men with PSA levels of 1-2 ng/l, 2-3 ng/ml and 3-4 ng/ml respectively (9). When lowering the cut-off below 4 ng/ml one would increase the sensitivity of the test but at the same time lower its specificity. In an attempt to avoid over-diagnosing older men and underdiagnosing younger men, Osterling and colleagues, in 1993, proposed the “age-specific PSA range” that has gained a lot of popularity.

In a large cohort of 21,000 men, 45-75 years of age, they report a 21% reduction in the number of biopsies in men older than 60 years and an 8% increase in the number of positive biopsies in younger men. The age specific range refers to an upper limit of normal of 2.5 ng/ml, 3.5 ng/ml, 4.5 ng/ml and 6.5 ng/ml in men < 50, 50-60, 60-70 and > 70 years of age respectively (10).

In further attempts to improve the specificity of PSA as a screening test, Catalona et al. (11), proposed using the free-to-total PSA ratio as an adjunct to total serum PSA. They reported that by using a 25% cut-off level for men with a serum total PSA of 4-10 ng/ml, they would avoid 20% unnecessary biopsies without a loss in the sensitivity and 95% specificity. PSA density and PSA velocity have also been proposed as measures to improve the specificity of total serum PSA for men with PSA between 4-10 ng/ml; a PSA density of > 0.15 ng/ml and a PSA velocity of > 0.75 ng/ml/yr would predict a higher risk of positive biopsies.

One of the essential Wilson-Junger criteria for disease screening is that the available test should be able to detect the disease at an early stage when treatment should be of more benefit than at a later stage. The evidence for that is still lacking. At present there are two large scale randomised trials looking at the effect of PSA screening on cancer treatment outcome; The European Randomised Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer trial (PLCO). The PLCO is a large scale trial trying to determine if screening for Prostate, Colorectal, Ovarian and Lung cancers reduces the overall and cancer related mortality. Between 1993 and 2001, 38,350 men have been enrolled in the screening arm of the study by 10 centres across the USA. Screening stopped in 2006 and an 8 years follow-up will continue to determine the effect of PSA screening on overall and cancer-specific mortality. The result of this study will not be available until 2014. The ERSPC is a European based study. Enrolment started in 1994, with 239,000 men so far been included in the study. The first results of this study on mortality will be expected by 2010.

However, the use of PSA in prostate cancer extends well beyond the screening process. Upon diagnosis of prostate cancer, PSA is one of the determinants of the appropriate staging and treatment. Prostate cancer has a predilection for bone metastasis via the valveless low pressure Barton’s venous plexus. The risk of bone metastasis at diagnosis correlates with the serum total PSA. Most official bodies would agree that a serum PSA > 20 ng/ml warrants staging with bone scan. The yield of bone scan for PSA < 20 ng/ml is very low and therefore not cost-effective unless one is dealing with a clinically high stage or high grade tumour (Gleason score > 7). The management of prostate cancer is partly determined by the serum PSA. Prostate cancer is classified into low, intermediate and
high risk based on serum PSA (<10 ng/ml, 10-20 ng/ml and >20 ng/ml), Gleason score and clinical stage. Active surveillance can be offered to men with low risk prostate cancer. Brachytherapy is on offer for men with low risk or very well selected intermediate risk cases. Most urologists would be reluctant to offer radical prostatectomy to men with PSA >20 ng/ml. These are just general comments but not absolute statements on the management of prostate cancer.

Treatment outcome and follow-up is largely dependent on the serum PSA. Following radical prostatectomy one would expect an undetectable PSA 3-4 weeks after the treatment (note serum PSA half-life of 2-3 days). Treatment failure is defined, by most, as a serum PSA >0.2 ng/ml. A persistent or rising PSA would imply persistent or recurrent disease requiring adjuvant/salvage treatment. The success of such treatment correlates with the serum PSA. Following radiotherapy or brachytherapy one would expect a very low but detectable serum PSA and treatment failure is defined by the ASTRO criteria as 3 successive PSA rises above the PSA nadir. The details of the role of serum PSA and other PSA variables (e.g. PSA doubling-time, PSA velocity) on treatment decision making is a vast topic and is beyond the scope of this article.

PSA and BPH

More recently a lot of interest occurred in relation to serum PSA and BPH. The PLESS study showed that serum PSA correlates with the rate of prostate growth (12). In that study, the prostate was reported to grow by 7.8%, 16% and 22% for serum PSA levels of <1.4 ng/ml, 1.4-3.2 ng/ml and >3.2 ng/ml respectively. Serum PSA was a better predictor of prostate growth when compared to age and baseline prostate volume. The correlation between size of the prostate and severity of LUTS is much debated but serum PSA appears to be a strong predictor of BPH symptom progression, acute urinary retention and need for bladder outlet surgery. The PLESS study concluded that a serum PSA level of >1.4 ng/ml was associated with a 3x increased risk of urinary retention over the 4 years of the study. It also showed conclusively that a serum PSA >1.4 ng/ml was associated with a 2-3x increased risk of needing bladder outlet surgery for LUTS. Similar was the conclusion of the Olmsted county population based study on the natural progression of BPH. They showed that a PSA >1.4 ng/ml was associated with a 3x increased risk of urinary retention (13). There is also evidence to suggest that the higher the PSA the more the benefit from pharmacotherapy with 5α-reductase inhibitors. Serum PSA is therefore a variable used by clinicians to predict disease progression and therefore offer preventative treatment to patients with LUTS. Remember that of the currently available pharmacotherapies, 5α-reductase inhibitors modify disease progression whereas alpha-antagonists do not.

Non-urolological applications of PSA

PSA was first identified by researchers attempting to find a substance in seminal fluid that would aid in the investigation of rape cases. PSA is now used to indicate the presence of semen in forensic serology. The semen of adult male has PSA levels far in excess of those found in other tissues, therefore, a high level of PSA found in a sample is an indicator that semen may be present. Because PSA is a biomarker that is expressed independently of spermatozoa, it remains useful in identifying semen from vasectomized and azoospermic male.

Other prostate cancer tumour markers

PCA3

Prostate Cancer Gene-3 assay (PCA3) is a gene based test. It is prostate cancer specific and can therefore discriminate better than serum PSA between prostate cancer and non-cancerous prostate diseases. It can be used as an adjunct to serum PSA in order to increase serum PSA specificity and avoid unnecessary prostate biopsies. A high PCA3 Score indicates an increased likelihood of a positive biopsy. The positive predictive value of PCA3 is 79% which is double that of serum PSA. During prostate palpation prostate cancer cells which express PCA3 are shed in the urine. The PCA3 assay involves collecting a urine sample (20-30 mls) after prostate “massage” (3 strokes to each lobe) and determining the PCA3 score from that sample. The PCA3 score is calculated from the ratio of PCA3 and PSA mRNA.

PCa score= 1000x (mRNA PCA3)/ (mRNA PSA)

A cut-off of 35 provides the best balance between specificity (74%) and sensitivity (53%) for the PCA3 assay. When the score is more than 35 the test is consider positive and the patient has a 74% of having a positive biopsy. The PCA3 score is not affected by prostate volume. The major drawback of the PCA3 test is that is very expensive compared to serum PSA.

EPCA

Early Prostate Cancer Antigen (EPCA) is a nuclear matrix protein and a novel tumour marker for prostate cancer. EPCA has stained positive in cancer negative core biopsies of men who later were diagnosed with prostate cancer. EPCA can also be identified in the serum using an ELISA based assay. Early evidence suggests a 97% specificity and 90% sensitivity for a cut-off level of 30. A result more than 30 is associated with a higher risk of prostate cancer diagnosis.

Prostasomes

Prostasomes are vesicles secreted by prostate cells and their function is to prevent immunological destruction of the sperm by female antibodies. In vitro studies suggest that malignant epithelial cells express prostasomes and these may protect the cells from immunological insults. The use of prostasomes in the diagnosis of prostate cancer remains experimental.

Pro-PSA

The proenzyme forms of PSA include prepro-PSA and then pro-PSA. The rate limiting step of the conversion of prepro-PSA to pro-PSA and then to PSA is the conversion of pro-PSA to PSA. In prostate cancer there is increased
release of these proenzymes and therefore pro-PSA tends to accumulate. A raised pro-PSA level is therefore associated with an increased risk of prostate cancer.

**CONCLUSION**

PSA is the most widely used tumour marker. Since its FDA approval in 1986 it has revolutionised the management of prostatic disease. As a screening test for diagnosing prostate cancer it has relatively low specificity and it is still unknown if it has a significant impact on the survival from prostate cancer. Large scale randomised trials are underway and their results are awaited. Decision on treatment is largely influenced by serum PSA and its parameters (PSA velocity, doubling time). Prostate cancer treatment follow-up is equally largely dependent on serum PSA. More recently there has been an interest in the association between serum PSA and benign prostatic hyperplasia. The diagnostic popularity of PSA may be under threat as novel tumour markers show promising properties.

**REFERENCES**


Is PSA density still useful in diagnosing prostate cancer?

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Summary

Objective: To evaluate the concordance between the PSAD (PSA density) values calculated using the actual prostate weight and the PSAD values calculated by using the dimensions of the gland given by the pathologist when freshly excised (volume 1) or using TRUS measures (volume 2). Diagnostic accuracy of PSAD in diagnosing PCa (prostate cancer) was evaluated and compared with accuracy obtained using PSA free/total (F/T).

Material and Methods: 102 consecutive patients with PSA included between 2 and 10 ng/mL underwent radical rectal examination. Indications to perform prostate biopsy were: abnormal digital rectal examination, PSA < 2.5 ng/mL, PSA between 2.6 and 4 ng/mL and between 4.1 and 10 ng/mL with PSA F/T (free/total) ≤ 15%, ≤ 20% and ≤ 25%, respectively. We compared the PSAD values obtained using the actual prostate weight (PSAD1) vs those calculated using volume 1 (PSAD2) and volume 2 (PSAD3).

Results: The mean weight of prostate specimen was 55.61 grams, while the estimated mean volumes were 50.02 ml (volume 1) and 48.49 ml (volume 2). A statistically significant difference among actual weight vs volume 1 vs volume 2 (p < 0.0001) was found. In the patients with PSA ranging from 4.1 to 10 ng/mL a cumulative accuracy of 82.6% was found using a cut-off > 0.10 whereas, with a cut-off > 0.15, a diagnostic accuracy of 36.9% (PSAD1), 58.6% (PSAD2) and 60.8% (PSAD3) was reported.

Conclusions: No concordance between the actual prostate weight and the estimated volume was found; moreover PSAD accuracy was of poor value in diagnosing PCa in comparison with PSA F/T.

Key words: Prostate cancer; PSA density; PSA free/total; Prostate volume; TRUS.

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INTRODUCTION

The introduction of PSA test in clinical practice has been associated with a constant increase number of diagnosed PCa (prostate cancer) cases, but when used alone for values included between 2.5 and 10 ng/mL it is not sufficiently specific to consider it an ideal tool for the detection or staging of PCa. To optimize the use of PSA, the concepts of PSA velocity, PSA density (PSAD) and age-related PSA values were developed. In the last years, the molecular forms of PSA, especially the percentage of free/total PSA (PSA F/T) has been preferred because it can yield greater specificity in order to select which patients are eligible for needle biopsy.

PSAD is the ratio of PSA to the volume of prostate gland, which is usually calculated by transrectal ultrasound (TRUS) (1), prostate cancer produces a rise of serum PSA values higher to that produced by adenomatous tissue and various PSAD cut-off equal to 0.10 (2) or 0.15 (12), have been proposed as suspicious for cancer. PSAD has been used also in case of repeat biopsy (3), as predictive of disease recurrence after radical prostatectomy (4,5) and to role out clinically insignificant PCa (6). However, many variables may affect the usefulness of PSAD in clinical practice: the poor feasibility of TRUS in estimating the real prostate volume (7), the impossibility to distinguish the epithelial from the stromal component of the gland, the histological grade of the tumour (8).

In the present study we evaluated the concordance between the PSAD calculated by the actual prostate weight, the TRUS measures and that one obtained using the pathological measures of the gland. Moreover, diagnostic accuracy of PSAD in diagnosing PCa in comparison with PSA F/T was evaluated.
Material and Methods
From June 2006 to December 2008, 102 consecutive patients with PCs and PSA ranging between 2 and 10 ng/mL underwent radical retropubic prostatectomy (RRP) after extended prostate biopsy. Indications to perform extended prostate biopsy were: abnormal digital rectal examination (DRE); PSA ≤ 2.5 ng/mL, PSA between 2.6 and 4 ng/mL, and between 4.1 and 10 ng/mL with PSA F/T ≤ 15%, ≤ 20% and ≤ 25%, respectively (9). PSA was ≤ 4 ng/mL in 10 cases and included between 4.1 and 10 ng/mL in the remaining 92 patients. Prostate needle biopsy was accomplished by transperineal route with a tru-cut 18 Gauge needle using a GE Logiq 500 PRO ecograph supplied with a biplanar transrectal probe (5-6.5 MHz) under local anaesthesia and antibiotic prophylaxis. All specimens were weighed and measured when freshly excised. PSAD was calculated as ratio of total PSA/prostatic volume, according to this definition we used the PSA value showed at time of the diagnosis. We also defined the prostate volume using the ellipsoid formula that considers the prostate gland as an ellipsoid and calculates its volume using the craniocaudal, anteroposterior and transverse diameters in the maximum dimension by a 0.52 coefficient. In the present study volume 1 refers to the prostate volume according to the pathologic diameters and volume 2 to the prostate volume according to the TRUS examination.

The diagnostic accuracy of PSAD in the diagnosis of PCs using a cut off of 0.15 and 0.10 has been evaluated.

Statistical analysis
The statistical analysis was performed using the non-parametric tests, as Friedman test for the comparison of repeated measures and Mann-Whitney U test to compare the spread of PSAD in different groups of patients classified according to the value of PSA at the diagnosis. For describing the distribution of PSADs according to different PSA cut-offs, a boxplot was used. In descriptive statistics, a boxplot (also known as a box-and-wisher diagram or plot) is a convenient way of graphically depicting the five-number summary, which consists of the smallest non-outlier observation, lower quartile (Q1), median, upper quartile (Q3), and largest non-outlier observation.

Results
Mean PSA and PSAD were 6.93 ng/mL (median: 7.1, range 0.5-10 ng/mL) and 0.13 (median: 0.13, range: 0.02-0.39), respectively. The mean weight of RRP specimen was 55.61 grams (median: 42 g, range 23-128); the estimated mean volumes were 50.02 ml (median 42 ml; range 13-121) (volume 1) and 48.49 ml (median 40 ml; range 10-140) (volume 2). A statistically significant difference among actual weight vs volume 1 vs volume 2 (p < 0.0001) was found. The PSAD values calculated using the weight (PSAD1) and volume 1 (PSAD2) and volume 2 (PSAD3) are listed in Table 1. The mean PSAD for PSA ≤ 4ng/mL or included between 4.1-10 ng/mL was equal to 0.036 and 0.150 (PSAD1), to 0.048 and 0.175 (PSAD 2), to 0.06 and 0.18 (PSAD3), respectively (Table 2). The statistical analysis revealed a significant difference between PSAD distribution (p < 0.0001) in the three groups. All the patients with PSA ≤ 4 ng/mL had a PSAD < 0.10; in 92 patients with a PSA ranging from 4.1 to 10 ng/mL no difference was found, using a PSAD cut-off > 0.10, among PSAD1 vs PSAD2 vs PSAD3, whereas, with a cut-off > 0.15, a significant difference was found between PSAD1 (17 patients) vs PSAD2 and PSAD3 (27 and 28 patients, respectively). The statistical analysis showed a significant difference in the distribution of PSAD values in the patients with PSA enclosed between 4.1 and 10 ng/mL vs PSA ≤ 4 ng/mL (p < 0.0001, Mann Whitney U test); PSAD values in the patients whose PSA ranged from 4.1 to 10 ng/mL were higher than those reported in patients with PSA ≤ 4ng/mL. Such difference persists independently from the weight or volumes used to calculate PSAD (Table 2, Figure 1-3). The accuracy of PSAD in diagnosing PCs was fairly poor: in patients with tPSA ≤ 4 ng/mL, PSAD was unable to detect cancer using both cut-off; in patients with PSA ranging from 4.1 to 10

Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD*</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>6.93</td>
<td>2.17</td>
<td>7.1</td>
<td>0.50-10.00</td>
</tr>
<tr>
<td>PSAD1</td>
<td>0.136</td>
<td>0.06909</td>
<td>0.13</td>
<td>0.020-0.39</td>
</tr>
<tr>
<td>PSAD2</td>
<td>0.163</td>
<td>0.09674</td>
<td>0.15</td>
<td>0.030-0.60</td>
</tr>
<tr>
<td>PSAD3</td>
<td>0.172</td>
<td>0.1115</td>
<td>0.15</td>
<td>0.040-0.75</td>
</tr>
</tbody>
</table>

* Standard deviation.

Table 2.

| Correlation between PSAD and PSA (≤ 4ng/mL vs 4.1-10 ng/mL). |
|-------------------|-------------------|-------------------|-------------------|-------------------|
|               | Mean  | SD*   | Median | Range | p-value               |
| PSAD1 (10 pts with PSA ≤ 4ng/mL) | 0.036 | 0.008 | 0.04   | 0.02 - 0.04 | < 0.0001*            |
| PSAD1 (92 pts with PSA ≤ 10ng/mL) | 0.146 | 0.064 | 0.135  | 0.06 - 0.39 |                     |
| PSAD2 (10 pts with PSA ≤ 4ng/mL) | 0.048 | 0.010 | 0.05   | 0.03 - 0.06 | < 0.0001*            |
| PSAD2 (92 pts with PSA ≤ 10ng/mL) | 0.175 | 0.094 | 0.15   | 0.06 - 0.6  |                     |
| PSAD3 (10 pts with PSA ≤ 4ng/mL) | 0.058 | 0.018 | 0.05   | 0.04 - 0.09 | < 0.0001*            |
| PSAD3 (92 pts with PSA ≤ 10ng/mL) | 0.184 | 0.110 | 0.16   | 0.06 - 0.75 |                     |

* Mann-Whitney U Test.
Is PSA density still useful in diagnosing prostate cancer?

ng/mL a cumulative diagnostic accuracy of 82.6% was found, without differences among PSAD1 vs PSAD2 vs PSAD3 using a cut-off > 0.10 whereas, with a cut-off > 0.15, a diagnostic accuracy of 36.9% (PSAD1), 58.6% (PSAD2) and 60.8% (PSAD3) was found.

**DISCUSSION AND CONCLUSIONS**

The diagnostic accuracy of PSAD in diagnosing PCa is a moot point (10, 11) probably because many variables may affect the final value of PSAD in clinical practice, among them the poor reliability of TRUS in estimating the real prostate volume (7). Wolff (12) among 148 patients reported a sensitivity and specificity of 73.3% and 80%, respectively. Manseck (13) reported that the PSAD was greater than 0.15 only in 10 of 22 patients with PSA between 4 and 10 ng/mL and in none of 11 patients with PSA < 4 ng/mL.

It has been widely reported a poor sensitivity of PSAD in the diagnosis of PCa in patients with PSA included between 4 and 10 ng/mL (14-17). However Stephan (18) in 1809 patients demonstrated a greater sensitivity of PSAD in comparison with PSA F/T when PSA values were less than 4 ng/mL, whereas for PSA levels ranging from 4 to 10 ng/mL the PSA F/T showed a greater sensitivity in detecting PCa.

According to Stephan (18) it should be advisable to employ different cut-off of PSAD in relation to the values of tPSA in order to obtain a sensitivity of 95% (PSAD equal to 0.05 for tPSA between 2 and 4 ng/mL; PSAD equal to 0.10 for tPSA between 4 and 10 ng/mL and equal to 0.19 for tPSA between 10 and 20 ng/mL). Lastly, Boulos (19) among 166 patients who underwent prostate biopsy, reported that only 7.9% of the men with PCa had a PSAD > 0.15. Thus, the authors recommended a cut off of 0.10 when PSA is greater than 4 ng/mL.

In our series we were unable to find a concordance between the actual prostate weight and the estimated volume obtained by TRUS evaluation (p < 0.001). We showed that the mean calculated prostate volume underestimates the mean actual weight of the prostatectomy specimen. The estimation of prostate volume by means of triaxial formula is based on the assumption that the prostate is ellipsoidal in shape; as a matter of fact, the prostate shape varies greatly and TRUS underestimates the real prostate weight by 15%-25% according to the size of the gland (7). The possibility to use a PSAD weight related has been used in the recent literature(20), however, in our hands, PSAD weight related was not useful in predicting
PCa even when different cut-off were used. Moreover, no patients with PSA ≤ 4 ng/mL presented a PSAD > 0.10, while in patients with PSA ranging from 4.1 to 10 ng/mL a cumulative diagnostic accuracy of 82.6% was found, without differences among PSAD1 vs PSAD2 vs PSAD3 using a cut-off > 0.10 whereas, with a cut-off > 0.15, a diagnostic accuracy of 36.9% (PSAD1), 58.6% (PSAD2) and 60.8% (PSAD3) was found.

In our series of patients submitted to prostate biopsy because of an abnormal F/T PSA value (9) PCa could be missed in 19 patients (PSAD1, PSAD2, PSAD3) using a PSAD cut-off equal to 0.10 and in 65 (PSAD1), 42 (PSAD2) and 40 (PSAD3) patients using a cut-off equal to 0.15, respectively; these findings make unreliable the use of PSAD in the clinical practice for the detection of PCa in comparison with accuracy obtained using PSA F/T.

In conclusion, PSAD is of poor value in diagnosing PCa even in case the estimated volume is truly indicative of the real prostate weight. The introduction of lower cut-off, proposed by some Authors with the purpose of increasing its sensitivity, leads to an unacceptable loss of specificity, above all if it is compared with PSA F/T.

REFERENCES
6. Allan RW, Sanderson H, Epstein JI. Correlation of minute (0.5 mm or less) focus of prostate adenocarcinoma on needle biopsy with radical prostatectomy specimen: role of PSA density. J Urol 2003; 170:370.
19. Boulos MT, Rifflin MD, Ross J. Should PSA or PSA density be used as the determining factor when deciding which prostate should undergo biopsy during prostate ultrasound. Urology Q 2001; 17:177.

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**ORIGINAL PAPERS**

**PSA repeatedly fluctuating levels are reassuring enough to avoid biopsy?**

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**Summary**

Introduction: Prostate-specific antigen (PSA) levels can show wide fluctuations when repeatedly measured. Here we investigated if: a) biopsy timing influences the prostate cancer (PC) detection rate in patients with fluctuating PSA (flu-PSA) in comparison with patients with steadily increasing PSA (si-PSA); b) PSA slope estimated in patients with flu-PSA predicts a different risk of cancer detection; c) flu-PSA and si-PSA patients develop PC in topographically different sites; d) the behaviour of pre-operative PSA is an expression of a disease with different characteristics to the following radical prostatectomy.

Methods: The study involved 211 patients who underwent at least a second biopsy after a first negative prostate biopsy. PSA Slope, PSA velocity (PSAV) and PSA doubling time (PSADT) were estimated. Flu-PSA level was defined as a PSA series with at least one PSA value lower than the one immediately preceding it.

Results: 82 patients had flu-PSA levels and 129 si-PSA levels. There were no significant differences between the two groups in terms of cancer detection, clinical or pathological stage, but the si-PSA group with cancer had a higher Gleason score. No difference was found for PSA Slope between flu-PSA patients with cancer and those without.

Conclusions: Our study demonstrates no difference in PC detection rate at repeat biopsy between patients with flu or si-PSA levels. PSA Slope, PSAV, and PSADT were not found helpful tools in cancer detection.

**KEY WORDS:** Fluctuating PSA levels; Prostate cancer; PSA slope; PSA doubling time; PSA velocity.

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**INTRODUCTION**

Over the last years several methods have been proposed to evaluate the increase of PSA (1-4). A number of authors have also discussed the role of PSAV (PSA velocity) and its predictive and prognostic value (5, 6). PSAV has also been proposed as an useful tool in predicting treatment outcome (7-10). The selection of patients to be subjected to prostate biopsy and/or re-biopsy, in relation to the PSA levels, however, depends on several factors including the individual variability (11), even after a biopsy (12), and the heterogeneity of available laboratory tests which influence the outcome by 20% (13, 14). Other factors include the period of patients observation, the method employed for measuring the PSAV and the timing of biopsies.

In this regard the findings of Carter et al. (5) have not been confirmed by Porter et al. (15) and Smith et al. (16) who used a period of observation brief than that proposed by Carter et al. who made at least three PSA measurements with a minimum interval of six months (17). Carter et al. (5) estimated the PSAV using the formula:

\[ 0.5^* \left[ (\text{PSA}_2 - \text{PSA}_1) / (\text{time in years}) \right] + [\text{PSA}_3 - \text{PSA}_2] / (\text{time in years}) \].

A further method was proposed by Connolly et al. (18) who considered only two PSA values and calculated the PSAV as the increase of PSA (PSA last – PSA first/time in years). However, this method does not take into account all the intermediate PSA values which have an inherent meaning from a mathematical point of view, as well as in clinical practice. It is recognized that PSA values can float in time and these fluctuations often determine changes in the clinical approach (18, 19). A more accurate index, called PSA Slope can be
obtained using linear regression of absolute PSA values against time, and represents PSA change over time as linear change (20). This method has been shown to be helpful for analysing three or more values, as it considers all intermediate values (18, 20).

To give a prognostic value to PSA kinetics, the PSA doubling time (PSADT) has been introduced for patients with PC after treatment. However, this assessment, which is simple to obtain for two PSA values, is difficult for three or more PSA levels (21). The above considerations demonstrate the difficulty of interpreting the behaviour of PSA over time and its relationship to the risk of developing PC for each single patient. Here we analysed PSA Slope, PSAV, and PSADT in 211 consecutive patients, in order to verify whether there were any differences in terms of cancer detection rate at re-biopsy between patients with flu-PSA (fluctuating PSA) and those with si-PSA (steadily increasing PSA). Here we investigated if: a) biopsy timing influences the prostate cancer (PC) detection rate in patients with fluctuating PSA (flu-PSA) in comparison with patients with steadily increasing PSA (si-PSA); b) PSA slope estimated in patients with flu-PSA predicts a different risk of cancer detection; c) flu-PSA and si-PSA patients develops PC in topographically different sites; d) the behaviour of preoperative PSA is an expression of a disease with different characteristics to the following radical prostatectomy (RP).

**METHODS**

We analyzed PSA levels, PSA density (PSAD), and the free to total PSA ratio (f/t ratio) in 211 consecutive patients (median age: 68 years; range 44-86 years) who underwent at least a second biopsy after a first negative prostate biopsy. Indications for prostate biopsy were represented by a biochemical rise in PSA levels, and/or suspect findings at digital rectal examination (22, 23). All PSA measurements were performed in our Institution with the same method (Abbott CMLA - Thera 16200 Abbott) in order to avoid technical variability (13). Exclusion criteria were treatment with finasteride or dutasteride, hormonal therapy, and previous or simultaneous findings of High-Grade Prostatic Intraepithelial Neoplasia (HGPIN) or Atypical Small Acinar Proliferation (ASAP) (24). None of the patients had previously undergone prostatectomy. Additionally, all the patients treated with Ciprofloxacina for three weeks that reached a normalised PSA value before the first biopsy (25, 26, 27) as well as those with an interval between the biopsies and measurement of PSA less than 6 months (17) were excluded from the study.

All of the prostatic biopsies were performed trans-rectal, taking a median of 13 cores (range: 11-19 cores) per patient (22, 28, 29). The PSA Slope (ng/ml/year) was obtained using the linear regression (20), and according to the method of Connelly et al. (18).

To investigate whether the length of the period of PSA observation influences the sensibility of PSA Slopes, we have arbitrarily grouped the patients in four categories: 180 days, from 181 to 360 days, from 361 to 720 days and beyond. The PSADT was calculated using the formula PSADT = [tLN (2)]/[LN (PSA2) - LN (PSA1)], where PSA2 is the level of PSA at the last measurement, PSA1 is the level of PSA at the first measurement and t is the time between the two measurements (21). Whether the topographical cancer localisation was different between patients with flu or si-PSA levels was investigated observing all of the biopsy cores. The qualitative data are expressed as numbers and percentages, and the quantitative data as median values and ranges. All of the data were analysed by means of Pearson’s χ2 or Fisher’s test, and the t test or Wilcoxon’s test for unpaired data, when appropriate. Logistic regression analysis was used to assess the association between the change in PSA levels and PC. The statistical analysis was made using Statas9 software, and a p value of < 0.05 was considered statistically significant for all of the tests.

**RESULTS**

The median PSA level in the 211 study patients was 6.6 ng/ml (range: 1.5-40 ng/ml) at the time of the first biopsy and 8.1 ng/ml (range: 0.25-50 ng/ml) at the time of the second biopsy. The 50 patients who underwent a third biopsy had a median PSA level of 8.9 ng/ml (range: 3.1-43 ng/ml), and the ten who underwent a fourth, had a median PSA level of 10.6 ng/ml (range: 3.9-43 ng/ml). PSA levels were found < 10 ng/ml in 167 (79.1%) patients at the time of the first biopsy, and in 129 (61.1%) at the time of the second biopsy. The median f/t ratio at the time of the first biopsy in the 142 (67.3%) patients for whom the data were available was 15% (range: 3-60%).

The median interval between the first and second biopsy for 151 (71.6%) patients was 360 days (range 180-2000 days). The median interval in 50 (23.7%) patients between the second and third biopsy was 300 days (range 210-1500 days). The median interval in 10 (4.7%) patients between the third and fourth biopsy was 200 days (180-400 days). Median prostate volume measured in 211 patients at the time of the first biopsy was 50 ml (range: 11-180 ml), and median PSAD was 0.12 (range: 0.03-1.13). 130 (61.6%) patients presented PSAV exceeding 0.75 ng/ml/year.

**COMPARISON BETWEEN PATIENTS**

**WITH OR WITHOUT CANCER**

74 of the 211 patients were positive for cancer (Table 1). The median PSA level in this group was 5.65 ng/ml, the median f/t ratio was 13%, and the median PSAD was 0.11; 60/74 patients had cancer at the second prostate biopsy, 8/74 at the third, and 6/74 at the fourth. The remaining 137 patients were cancer-free (Table 1) and had a median PSA level of 7 ng/ml, median f/t ratio of 16%, and a median PSAD of 0.13.

PSAV exceeding 0.75 ng/ml/year was found in 49/74 (66.2%) in the group with cancer and 81/137 (59.1%) in the group without cancer (p = 0.312) (Table 1). There was no significant difference in the age (p = 0.861) and PSAD (p = 0.133) of the patients with and without biopsy revealed cancer, but, PSA levels were significantly higher in the group without cancer (p = 0.009). The f/t ratio was significantly lower in the patients with biopsy-documented cancer (p = 0.004).
PSADT was 2.22 years (0.26-38.4) and 3.23 years (0.24-5.46) in the cancer and cancer-free groups, respectively (p = 0.011) (Table 1). PSADT to 1 year was found in 20 patients of whom 11 with cancer and 9 without. PSA Slope calculated by means of the regression line did not show statistically significant differences between cancer group and cancer-free group (p = 0.263) (Table 1). PSA Slope calculated with the method of Connelly et al. did not show statistically significant differences between cancer group and free cancer group (p = 0.121) (Table 1). No statistically significant difference was found, at 180 days, between the PSA Slope estimated with the regression line in cancer group versus cancer-free group (p = 0.311) and the PSA Slope obtained according to Connelly et al. in cancer group versus free-cancer group (p = 0.301).

Neither were any statistically significant differences found between the cancer and free-cancer groups even at 181-360 days (PSA Slope, p = 1, PSA Slope according to Connelly et al. (16), p = 0.6468), 361-720 days (PSA Slope p = 0.2068; PSA Slope according to Connelly et al. (16), p = 0.2443) and for a period of observation > 720 days (PSA Slope, p = 0.38; PSA Slope according to Connelly et al. (16), p = 0.2478).

**Comparison flu- versus si-PSA levels**

The patients were classified into two groups on the basis of the evolution of PSA in time (Table 2). 82 (38.8%) had flu-PSA levels and 129 (61.2%) si-PSA levels. The median age of the patients in the two groups was respectively 69 years and 68 years (p = 0.276). The

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**Table 1.**

*Baseline characteristics of patients with cancer and cancer-free.*

<table>
<thead>
<tr>
<th></th>
<th>Patients with cancer</th>
<th>Patients cancer-free</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 (41-83)</td>
<td>68 (54-86)</td>
<td>0.861</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>5.05 (2.7-34)</td>
<td>7 (1.5-40)</td>
<td>0.000</td>
</tr>
<tr>
<td>f/t ratio (%)</td>
<td>13 (3.30)</td>
<td>16 (6.60)</td>
<td>0.004</td>
</tr>
<tr>
<td>PSAD</td>
<td>0.11 (0.03 1.13)</td>
<td>0.13 (0.04 0.93)</td>
<td>0.133</td>
</tr>
<tr>
<td>PSAV (&gt;0.75 ng/ml/year)</td>
<td>49 (66.7%)</td>
<td>81 (59.1%)</td>
<td>0.317</td>
</tr>
<tr>
<td>PSADT</td>
<td>2.22 (0.25-38.4)</td>
<td>3.23 (0.24-5.48)</td>
<td>0.011</td>
</tr>
<tr>
<td>PSA Slope</td>
<td>1.48 (-12.33-34.61)</td>
<td>1.11 (-5.07-13.15)</td>
<td>0.283</td>
</tr>
<tr>
<td>PSA Slope</td>
<td>1.86 (-16.04-15.66)</td>
<td>1.08 (-8.06-18.29)</td>
<td>0.121</td>
</tr>
</tbody>
</table>

*Data are expressed as mean values (range). a Data obtained with the regression line method. b Data obtained according to Connelly et al. (16).*

---

**Table 2.**

*Baseline characteristics of patients with flu PSA and si PSA.*

<table>
<thead>
<tr>
<th></th>
<th>Patients with flu PSA</th>
<th>Patients with si PSA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>82 (36.8)</td>
<td>129 (61.2)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (44-83)</td>
<td>68 (52-86)</td>
<td>0.276</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>7.4 (2.7-40)</td>
<td>6 (1.5-26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>f/t ratio (%)</td>
<td>14.5 (3-30)</td>
<td>15 (6-60)</td>
<td>0.875</td>
</tr>
<tr>
<td>PSAD</td>
<td>0.15 (0.05-1.13)</td>
<td>0.11 (0.03-0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer detected (%)</td>
<td>26 (31.7)</td>
<td>46 (37.2)</td>
<td>0.2875</td>
</tr>
</tbody>
</table>

*Data are expressed as mean values (range). a Value at the time of first biopsy.*
median PSA level at the time of the first biopsy was significantly higher in the flu-PSA group (p < 0.001). There was no significant between-group difference in the f/t ratio (p = 0.875). PSAD was significantly higher in the flu-PSA group (p < 0.001) (Table 2). We found that there was no difference in the number of a positive result at repeat biopsy between the flu-PSA group (26/82, 31.7%) and the si-PSA group (48/129, 37.2%), p = 0.414, (Odds ratio = 0.78, p = 0.414).

There was no statistically significant differences in si-PSA group between cancer and cancer free groups either with the PSA Slope obtained with the regression line (si-PSA cancer free group 1,846 (0-13.5) versus si-PSA cancer group 2,196 (0-34.61) (p = 0.1787)) and the PSA Slope obtained according to Connely et al. (16) (p = 0.1963). Additionally, there was no statistically significant differences in flu-PSA group between cancer and cancer free patients, either with the PSA Slope obtained with the regression line (flu-PSA cancer free group -0.0472 (-5.307-3.99) versus flu-PSA cancer group -0.1635 (-12.33-9.56) (p = 0.4855)) and the PSA Slope obtained according to Connely et al. (16), (p = 0.98).

Analysing the PSADT in flu-PSA group, no statistically significant differences were observed between patients with cancer [6.2 years (1.23-38.4)] and those without cancer [6.08 years (0.94-55.1)] (p = 0.96). However, the PSADT in si-PSA group showed statistically significant differences between patients with cancer [1.7 years (0.25-17.9)] and those without cancer [2.96 years (0.24-546)] (p = 0.005). In the si-PSA group using a logistic regression an increasing PSADT corresponds to a decreasing risk associated with cancer (Odds ratio = 0.96) but it is not statistically significant (p = 0.533). We then evaluated the cancer detection rate between flu-PSA and si-PSA groups considering the timing of PSA observation (Table 3). 51/211 (24%) patients were subjected to re-biopsy after 180 days. Cancer was detected in 18/32 (56.2%) patients with si-PSA and in 10/19 (56.6%) with flu-PSA. (p = 0.802). 59/211 (28%) patients were subjected to re-biopsy between 181 to 360 days. Cancer was detected in 13/38 (34.2%) patients with si-PSA and 7/21 (33.3%) with flu-PSA. (p = 0.946). 61/211 (29%) patients were subjected to re-biopsy between 361 to 720 days. Cancer was detected 12/37 (32.4%) patients with si-PSA and 4/24 (16.6%) with flu-PSA. (p = 0.237). 40/211 (19%) patients were subjected to re-biopsy with timing > 720 days. Cancer was detected in 5/22 (22.7%) patients with si-PSA and 5/18 (27.7%) with flu-PSA (p = 0.714).

**Patients with cancer underwent RP**

We considered the 74 patients (35.07%) with biopsy-documented PC, 70 of whom underwent RP and four received radiotherapy. 24 patients had flu-PSA levels and 46 had si-PSA levels (p = 0.337). There was no significant difference between the flu and si-PSA groups in terms of age (p = 0.3) and f/t ratio (p = 0.77). PSAD was significantly higher in flu-PSA group (p < 0.001) (Table 4). Among the 70 patients who underwent RP, the clinical stage of the cancer was T1c in 91.3% of those with flu-PSA levels and in 97.7% of those with si-PSA levels (p = 0.199) (Table 4). In the si-PSARP patients group there was a significant

**Table 3.**

Lenght of PSA observation and cancer detection in patients with flu PSA and si PSA.

<table>
<thead>
<tr>
<th>Timing (days)</th>
<th>Patients with flu PSA</th>
<th>Patients with si PSA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>10/19</td>
<td>18/32</td>
<td>0.802</td>
</tr>
<tr>
<td>181-360</td>
<td>7/21</td>
<td>13/38</td>
<td>0.496</td>
</tr>
<tr>
<td>361-720</td>
<td>4/24</td>
<td>12/37</td>
<td>0.237</td>
</tr>
<tr>
<td>&gt; 720</td>
<td>5/18</td>
<td>5/22</td>
<td>0.714</td>
</tr>
</tbody>
</table>

**Table 4.**

Baseline characteristics of patients with flu PSA and si PSA underwent radical prostatectomy.

<table>
<thead>
<tr>
<th>Patients with fluPSA</th>
<th>Patients with siPSA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>74 (78.9)</td>
<td>46 (35.6)</td>
</tr>
<tr>
<td>Gleason score ≥ 7 (%)</td>
<td>6 (26)</td>
<td>30 (65.2)</td>
</tr>
<tr>
<td>Clinical stage T1c (%)</td>
<td>91.3</td>
<td>97.7</td>
</tr>
<tr>
<td>f/t ratio (%)</td>
<td>14.5 (3.30)</td>
<td>15 (6.60)</td>
</tr>
<tr>
<td>PSA (%)</td>
<td>0.15 (0.06-1.13)</td>
<td>0.11 (0.03-0.93)</td>
</tr>
</tbody>
</table>
higher rate of patients with a Gleason score of ≥ 7 (p = 0.002). There was no statistically significant between-group difference in pathological stage (p = 0.199).

CANCER TOPOGRAPHICAL BIOPSY LOCALISATION
No differences were found in the cancer biopsy topographical localisation between patients with flu or si-PSA levels.

DISCUSSION
The last few years have seen the development of a growing evidence that PSAV and PSA Slope are more important than PSA levels, and this has changed the attitudes of urologists. However, several authors recommend that other methods should be explored to incorporate information about PSA kinetics that could ultimately improve — and even transform — how we detect and treat PC (30). We therefore have retrospective studied a consecutive series of patients who had undergone at least a second biopsy after a first negative biopsy because there are still no guidelines regarding when or how to re-biopsy patients (14). This is precisely one of the most difficult dilemmas that urologists have to face in their everyday clinical practice. We selected a homogeneous group of patients to eliminate all known variables influencing the PSA levels. The present study shows that there are no statistically significant differences in the cancer detection rate at the re-biopsy between patients with flu-PSA and si-PSA. Our findings are also confirmed by using two different mathematical methods for calculating PSA Slope and classifying the patients on the basis of the time interval between two or more PSA evaluations. Analysing PSADT when considering all patients enrolled in the study, we found a statistically significant difference between those with and without cancer, but when we analysed PSADT at one year of observation (21) we found only 20 patients with positive PSADT, of whom 11 with cancer and 9 without cancer. Even though the number of patients is limited, it would appear that the PSADT has proved useful only over a long period of observation. The PSADT in flu-PSA group yielded not statistically significant differences between patients with cancer, it is however noteworthy that this parameter necessarily excluded patients who have a negative PSADT. Considering the PSADT in the si-PSA group of patients, statistically significant differences were found between patients with cancer and those without cancer. This finding proved that PSADT is predictive only over a long period of observation and only in the presence of a si-PSA over time. However, it should be underline once again that no differences in cancer detection rate between si-PSA group and flu-PSA group were observed. These findings all suggest that the analysis of PSAV, PSA Slope and PSADT might be of interest only in the group of patients with si-PSA levels, although the present study demonstrates that they are not helpful in the decision process to re-biopsy the patient. The main finding of the present study is that in the presence of flu-PSA levels above the cut-off of 2.5 ng/ml, the risk of cancer is absolutely consistent in respect to a si-PSA levels with or without positive PSAV and PSA Slopes. It is noteworthy that despite the limited number of patients, the Gleason score of ≥ 7 was predominantly found in si-PSA group. The I/f ratio was significantly lower in men with cancer, but there was no difference between the flu and si-PSA groups. Moreover in the flu-PSA group there was no significant difference in the PSA Slope between the patients with and without cancer. Finally, no differences were found on the biopsy topographical localisation between cancer patients with flu or si-PSA levels. In conclusion, the present study shows no difference in the PC detection rate at repeat biopsy between patients with flu or si-PSA levels. PSAV, PSA Slope, PSADT and timing observation affect the cancer detection rate only in patients with si-PSA.

REFERENCES


23. Saito S. Prostate-specific antigen cut off point off 2.5 ng/ml and increasing the number of prostate biopsies results in detection of curable prostate cancer even in Japanese population. Int J Urol 2007; 14:709-712.


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Periprosthetic nerve block before ultrasound-guided prostate biopsy: A comparison of two local anesthetics.

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Summary

The objective of the present study was to evaluate the efficacy of the periprosthetic nerve block (PNB) of the prostate-vesicular junction with low volume and high concentration of anesthetics in relieving pain during prostate biopsy. Two hundred and twenty patients were enrolled and randomized to receive PNB with 5ml 2% lidocaine (group 1,110 pts) and PNB with 5ml 2% mepivacaine (group 2, 110 pts). The anesthetic was administered through a single puncture on each side at the prostate-vesicular junction using a 22-gauge needle. All patients filled in a ten visual analogue pain score scale (VAS) from 0 = no discomfort to 10 = severe pain, for the assessment of pain experienced during biopsy. The two groups were homogeneous concerning the anthropometrical data. The mean pain score with lidocaine was 1.4 ± 1.02 (CI 95% = 1.53 to 3.57) and with mepivacaine was 1.3 ± 1.06 (CI 95% = 2.66 ± 4.84) with no statistical significant difference between groups (p = 0.43). No general or local adverse effects were observed between the anaesthetics. The use of a low volume (2.5 ml on each side) and high concentration (2%) of local anesthetics (lidocaine/mepivacaine) almost completely suppresses pain and discomfort associated with prostate biopsy. The anatomy of neurovascular bundle regions appears favourable to the administration of small amounts of anesthetic.

Key words: Local anesthesia; Lidocaine; Mepivacaine; Prostate-vesicular junction injections; Prostate biopsy.

INTRODUCTION

The transrectal ultrasound (TRUS)-guided biopsy of the prostate in men with high prostate-specific antigen (PSA) levels or abnormalities at digital rectal examination (DRE) is the mainstay for the diagnosis of prostate cancer (CaP). In order to improve diagnosis and obtain a better diagnosis and more prognostic information, we use extensive biopsy protocols with higher number of samples but at the same time we increased discomfort and pain for the patient. In the attempt to decrease the pain and discomfort during prostate biopsy (PB) we use local anesthetics in accord with the current literature. Anaesthesia during TRUS-guided PB is currently considered mandatory, and a PB executed without local anaesthesia is considered “malpractice” (1, 2). Periprosthetic nerve block (PNB) is, nowadays, the most effective method to reduce pain and discomfort during prostate biopsy (2). The optimal dose of anesthetic and the best site of injection for PNB is still controversial (2). The aim of the study is to assess the effectiveness of periprosthetic nerve block of the prostate-vesicular junction with low volume and high concentration of local anesthetics in relieving pain during prostate biopsy.

PATIENTS AND METHODS

From January 2007 to February 2009, 220 consecutive men with abnormal PSA levels and/or suspicious DRE underwent TRUS-guided prostate needle biopsy. Patients were randomized to receive PNB with 5ml 2% lidocaine (group 1,110 pts) and PNB with 5ml 2% mepivacaine (group 2,110 pts). Mepivacaine is similar to lidocaine, although less toxic and with higher anesthetic index,
and the time it takes to produce its effect is similar to that of lidocaine (they are used at same doses and concentrations). After the patients being positioned in left lateral decubitus, transrectal ultrasound was performed using an ultrasound scanner (LOGIQ 5 GE Medical Systems) with a 7.5 MHz endorectal multiplanar ‘end-fire’ probe. Using a 22-gauge needle through the biopsy guide, in a longitudinal section, 2.5 ml of anesthetic were injected with a single puncture on each side close to the prostate base. The anesthetic was infiltrated into the hyperechogenic space between the bladder and rectum, at the level of the prostate-vesicular junction. There was no use of analgesia or concomitant sedation. The biopsies were performed 3 minutes following the injection of the anesthesia. Biopsies were taken using an 18-gauge tru-cut needle powered by a biopsy gun. In all cases 10-12 core biopsy samples were taken: six standard sextant biopsies, with at least four additional cores taken more laterally (anterior horn) to the base and medially to the apex, as well as biopsies directed to lesions focused by ultrasound imaging. At the end of the procedure the patients filled in the visual analogue scale (VAS) from 0 (no discomfort) to 10 (severe pain).

**Results**

The groups were comparable for patient age, prostate volume, PSA value, number of biopsy core, pathological results (Table 1). Injection of local anesthetics was completed in less than 30 sec in all patients. The mean number of biopsy cores for each patient was 10.8 in the lidocaine group, and 10.3 in the mepivacaine group. Mean pain score during biopsy in the lidocaine group was 1.4 ± 1.02 (range 0-4) and in the mepivacaine group was 1.3 ± 1.06 (range 0-4) with no statistically significant difference between the two groups (p = 0.43). No general or local adverse effects were associated with the anaesthesiological procedure. The most frequent complications observed were mild hematuria, mild rectal bleeding and haemospermia, with no differences between the two groups (Table 2).

Vaso-vagal symptoms (lipotimia with bradycardia) were found in 10 patients of the lidocaine group and in 7 patients of the mepivacaine group. Severe rectal bleeding was recorded in two patients of group 1, who were hospitalized and treated by rectal package.

**Discussion**

Periprostatic nerve block is now considered the standard procedure recommended before prostate biop-

### Table 1.

<table>
<thead>
<tr>
<th>Patients’ characteristic.</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>66.1 ± 11.4</td>
<td>65.6 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean prostate volume ±/SD (ml)</td>
<td>50.1 ± 20.1</td>
<td>56.23 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PSA value ±/SD (ng/ml)</td>
<td>13.5 ± 18.7</td>
<td>11.9±18.2</td>
<td>NS</td>
</tr>
<tr>
<td>No. of core biopsy</td>
<td>10.8</td>
<td>10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal DRE (%)</td>
<td>20%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal TRUS finding (%)</td>
<td>25%</td>
<td>23%</td>
<td>NS</td>
</tr>
<tr>
<td>Prostate cancer (%)</td>
<td>39%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td>VAS score ±/SD</td>
<td>1.4 ± 1.02</td>
<td>1.3 ± 1.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2.

**Minor complications.**

<table>
<thead>
<tr>
<th>Minor complications</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute urinary retention</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Persistent hematuria</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Mild rectal bleeding</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Hematospermia</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>Fever up to 38.5°C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lipotimia with bradycardia</td>
<td>11%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>
correct site for the injection is easily identified by the hypechoic (due to periprostatic fat) pyramidal space between prostatic base and seminal vesicle (Figure 1). When this site is injected, the anesthetic is seen to separate the rectal fascia from the prostate and seminal vesicles. Therefore, periprostatic nerve block of prostate-vesicular junction is a very effective and useful technique and the use of low volume (2.5 ml on each side) and high concentration (2%) of local anesthetics (lidocaine/mepivacaine) almost completely abolishes pain and discomfort associated to the prostate biopsy.

**Figure 1.** Site for the injection.

### References


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CASE REPORT

Disseminated intravascular coagulation secondary to metastatic prostate cancer: case report and review of the literature.

Francesco Pinto, Antonio Brescia, Emilio Sacco, Andrea Volpe, Mario Gardi, Gaetano Gulino, PierFrancesco Bassi

Department of Urology, Catholic University School of Medicine, Rome, Italy

Summary

Disseminated intravascular coagulation (DIC) is the most frequent coagulation disorder associated with metastatic prostate cancer. We report a case of a 60-year-old white man who was admitted in our department with ecchymoses and haematuria secondary to a DIC associated with metastatic prostate cancer. A review of this clinical scenario is also reported.

Key words: Hemorrhage; Paraneoplastic syndrome; Prostate cancer

Submitted 19 October 2009; Accepted 30 October 2009

Introduction

Disseminated intravascular coagulation (DIC) is an acquired coagulation disorder that may occur in different clinical conditions, including infectious diseases, severe trauma, obstetric disorders, vascular diseases, solid tumors and haematological cancers.

DIC is the most frequent coagulation disorder in patients with prostate cancer (PC) and its clinical features may vary from bleeding to thrombosis, or involve both. We report a case of a 60-year-old man who was admitted in our clinic with haematuria and spontaneous ecchymoses secondary to metastatic PC associated with DIC and review the entire literature.

Case report

A 60-year-old white male was referred to our Department with a 10-day history of spontaneous ecchymoses localized in both legs and inguinal areas and right leg pain. His past medical history included hypertension and type 2 diabetes mellitus both under control with medications. He had never smoked and had an occasional alcohol consumption. Prostate specific antigen (PSA) rate was 338 ng/ml and a trans-rectal ultrasonography (US) revealed a 3 cm hypoechoogenic solid lesion localized in the peripheral zone of the prostate right lobe. Digital rectal examination revealed a nodule increased in consistency in the posterior-right lobe of the prostate with no other abnormalities.

At the admittance patient presented with heamocoagulative parameters abnormalities described in Table 1 and the total alkaline phosphatase level was 919 UI/l (normal: 98 to 279 UI/l). Shortly after admission, the patient presented macroscopic haematuria with subsequent acute anemia (Hb = 6,9 g/dl) treated with packed red blood cells transfusion.

The patient was started on an antiandrogen (bicalutamide – 50 mg/die), and luteinizing hormone releasing hormone (LHRH) agonist (leuprolide). An ultrasound guided transperineal prostate biopsy performed on hospital day 12, after partial haematuria resolution, showed a Gleason Score 5+5 adenocarcinoma in all the specimens.

Abdominal and pelvic computed tomography (CT) was normal without lymphadenomegalies and a bone scan identified the presence of extensive bone lesions involving the spine, the ribs and upper and lower extremities. After 10 days of hormonal manipulation, the coagulation parameters returned to normal, except for slightly elevated D-dimers, and both ecchimoses and haematuria disappeared.

Table 1.

Patient’s laboratory haemocoagulative altered parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>12.6 (normal: 13 to 17)</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>135 x 10^9/l</td>
<td>(normal: 140 to 450 x 10^9/l)</td>
</tr>
<tr>
<td>PT (%)</td>
<td>64 (normal: 70 to 125)</td>
<td></td>
</tr>
<tr>
<td>APT (sec.)</td>
<td>61.8 (normal: 20 to 39)</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>155 (normal: 200 to 400)</td>
<td></td>
</tr>
<tr>
<td>D-Dimers (ng/ml)</td>
<td>15858 (normal: &lt; 300)</td>
<td></td>
</tr>
</tbody>
</table>
The patient was discharged and completed palliative radiation to the right femur was performed. On subsequent follow-up visits, there was a progressive decrease in serum PSA level (0.7 ng/ml at 3 months after hormonal manipulation start) and patient presented no more bleedings.

**Comment**

DIC is the most frequent coagulation complication in PC (1-2). The first reports published in 1950 were presented as cases of apparent primary fibrinolysis (3). A revision by Rapaport et al. in 1959 and Straub et al. in 1967 recognised them as DIC with secondary fibrinolysis (4-5). DIC incidence in PC was found to be close to 25% (6). Rafion et al. reported this rate to be 13 to 30%, but clinical signs of DIC are evident only in 0.4 to 1.65% of patients with PC (7).

PC is the second solid malignancy, after gastric or pancreatic cancer, responsible for inducing DIC (8). The pathogenesis of DIC proceeds from the simultaneous occurrence of systemic fibrin production with impaired mechanisms to prevent coagulation and inadequate fibrinolysis. Increased formation and abnormal removal of fibrin, through thrombin generation, will lead to widespread intravascular deposition of this protein, resulting in thrombotic occlusion of medium and small vessels. Simultaneous use and subsequent depletion of platelets and clotting factors, resulting from the ongoing coagulation, may induce severe bleeding (9, 10).

The actual mechanism of this coagulopathy occurring in cancer patients is not clear. Some studies indicate that different procoagulant substances such as tissue factors expressed on the surface of tumour cells and a cancer procoagulant may be involved (11, 12). Elsewhere, some authors have demonstrated that prostate tumour cells are rich in thromboplastin (13). Several proinflammatory cytokines, such as interleukin-6 and tumour necrosis factor, are supposed to be involved in DIC (14, 15).

The clinical presentation of DIC depends on the underlying condition that triggers this medical disorder. Some patients may have a mild or protracted clinical course, with consumption of coagulation factors and minor or no symptoms (chronic or low-grade DIC). This clinical scenario is mostly observed in patients with malignant tumours or vasculitis and it often presents with spontaneous ecchymoses, epistaxis, gingival haemorrhage and haematuria. In other patients activation of the fibrinolytic system may dominate over the excessive coagulation, resulting in massive generation of thromboplastic material and consumption of haemostatic elements (acute bleeding DIC) and it has been associated mostly with sepsis, obstetrical complications, gross tissue injury, or promyelocytic leukaemia (16, 17).

The diagnosis of DIC combines any disease known to be associated with DIC, clinical manifestations, and a combination of laboratory tests. The most frequent laboratory abnormalities observed are thrombocytopenia, elevated fibrin/fibrinogen degradation products, prolonged PT, prolonged thrombin time, prolonged PTT, and low fibrinogen (18). Other coagulopathies less frequently associated with PC include thrombotic thrombocytopenia purpura (TTP), thrombosis, primary fibrinolysis and acquired factor VIII inhibitor development. The differential diagnosis between these entities is based on platelet count, coagulation parameters and antithrombin III levels (Table 2).

The management of DIC associated with PC requires treatment of the tumour in combination with supportive measures to control the abnormal coagulation. Hormonal treatment with an LHRH agonist in conjunction with a previous short course of an antiandrogen to avoid a “flare reaction” is the treatment of choice in patients who are likely to be hormone sensitive (19).

Patients with severe uncontrolled bleeding can be treated with high-dose ketoconazole (200 to 400 mg) that has been described as an effective way to bring about a rapid decrease in serum testosterone level through inhibition of adrenal production of testosterone (20).

Chemotherapy is reserved for patients who do not respond to hormone therapy and has provided some results, particularly mitoxantrone (21) but also docetaxel and cisplatin (22).

Radio- and chemotherapy treatment is controversial: two publications have reported two patient deaths related to streptomycin-89 therapy (23, 24). However Rafion et al. described the case of a 61-year-old man with symptomatic DIC due to metastatic prostate carcinoma treated successfully with samarium 153 (7). The severity of bleeding, the platelet count, and the levels of coagulation factors will determine the need to replace blood components. The use of heparin is still debated in the management of DIC: two not randomized studies showed clinical benefit and no increase in bleeding in patients with DIC (25, 26). In case of important and life-threatening bleeding, fresh frozen plasma can be used (27).

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>Laboratory findings in different coagulopathies.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LABORATORY FINDINGS</strong></td>
<td><strong>DIC</strong></td>
</tr>
<tr>
<td></td>
<td>↑ APT</td>
</tr>
<tr>
<td></td>
<td>↓ PT</td>
</tr>
<tr>
<td></td>
<td>↓ Fibrinogen</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Positive D-dimer test</td>
</tr>
<tr>
<td><strong>TTP</strong></td>
<td>↑ LDH</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Normal D-dimer test</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>Increased platelet count</td>
</tr>
<tr>
<td></td>
<td>Positive D-dimer test</td>
</tr>
<tr>
<td><strong>Anti-FVIII</strong></td>
<td>↑ APT</td>
</tr>
<tr>
<td></td>
<td>PT normal</td>
</tr>
<tr>
<td></td>
<td>↓ FVIII</td>
</tr>
<tr>
<td></td>
<td>PT normal</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen normal</td>
</tr>
<tr>
<td></td>
<td>Normal platelet count</td>
</tr>
</tbody>
</table>

DIC: disseminated intravascular coagulation; PT: prothrombin time; APT: activated partial thromboplastin time; TTP: thrombotic thrombocytopenia purpura; LDH: lactate dehydrogenase.
CONCLUSIONS
The presence of spontaneous bleedings in an adult man lead to the suspicion of a coagulation disorder caused by metastatic PC. DIC is the most frequent coagulation complication associated with metastatic PC. Its diagnosis is based on clinical signs and laboratory tests and the differential diagnosis include TTP thrombosis, primary fibrinolysis and acquired factor VIII inhibitor development. LHRH agonist with a short course of antiandrogen is the treatment of choice in hormone sensitive patients while chemotherapy is reserved for hormone refractory patients.

REFERENCES

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Dosimetry doesn’t seem to predict the control of organ-confined prostate cancer after I-125 brachytherapy. Evaluation in 150 patients.

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Department of Surgery, Division of Urology, San Paolo Hospital, Savona, Italy; Division of Radiotherapy, San Paolo Hospital, Savona, Italy; Division of Physical Health, San Paolo Hospital, Savona, Italy

Objective: To evaluate the dose-response relationship (D90 > 144 Gy: probable absence of biochemical failure) in patients with prostate cancer treated by iodine-125 (I-125) brachytherapy.

Material and methods: From May 1999 to December 2006, 150 patients were treated by I-125 brachytherapy. The median follow-up was 60 months. All patients had clinical stage T1-T2, PSA ≤ 10 ng/ml, Gleason Scores ≤ 3+3=6, IPSS > 14 ml/sec. and prostate weight < 50 gr. Implantation was ultrasound-guided, using a real-time technique and loose seeds of I-125 (dose 160 Gy). After 30 days, a post-implantation assessment was performed by pelvic CT scan for a definitive evaluation of the D90. All patients were subjected to clinical evaluation, PSA dosage and compilation of IPSS and Efficacy questionnaires. In the event of biochemical failure (ASTRO), a prostate biopsy was performed. A D90 > 144 Gy was considered the cut-off in order to predict the absence of biochemical failure.

Results: Biochemical failure was observed in 9 patients: 5 with positive and 4 with negative prostate biopsies. The D90 > 144 Gy cut-off was not achieved in 18 patients at the post-implantation assessment, however only 2 of them (one of whom had a positive biopsy) had biochemical failure (11.1%). On the other hand, only 2 of the 9 patients with biochemical failure had a D90 < 144 Gy while 6 patients had D90 > 150 Gy, 5 with positive prostate biopsies.

Conclusions: In our experience, the D90 > 144 Gy cut-off does not seem to predict, in a reliable way, the control of prostate cancer following brachytherapy. Limitations of the analysis were the number of the patients, the learning curve, dosimetry processing and the relatively short follow-up.

Key words: Prostate cancer, Brachytherapy, Dosimetry.

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Introduction

Prostate brachytherapy is a procedure by now consolidated for the treatment of organ-confined prostate cancer with recent data which shows results equal to those obtained by radical prostatectomy and external radiotherapy (1). The majority of literature has focused attention on the dose received from 90% of the prostate (D90) or on the percentage of volume that receives 100% of the dose (V100) (2). Numerous Authors have observed a dose-response correlation in patients treated by brachytherapy observing that patients with higher dosimetry rarely encountered biochemical relapse in comparison to those with low values (3, 4).

The aim of our study was to evaluate whether a dose-response relationship exists (D90 > 144 Gy correlated with a high probability of the absence of biochemical failure) in patients with organ-confined prostate cancer treated by I-125 brachytherapy (5).

Materials and methods

From May 1999 to December 2006, 150 patients of median age 65 years (range 55-73) underwent I-125 brachytherapy. The median follow-up was 60 months (range 24-97 months). All patients were selected accord-
ing to the following parameters: life expectancy greater than 10 years, biological age inferior or equal to 70 years, no previous prostate surgery, total PSA inferior or equal to 10 ng/mL, clinical stage T1-T2, Gleason score inferior or equal to 3+3=6, a negative seminal vesicle biopsy, prostate volume ≤ 50 gr with absence of the medium lobe, Qmax > 15 mL/sec and an IPSS score ≤ 10. The mean prostate volume was 35 gr (in 10% of the cases a preoperative hormonal therapy was necessary for 60 days in order to reduce the prostate volume). The median total PSA was 7.0 ng/mL (range 0.4–11.3, 2 patients reported PSA values of 11.0 and 11.3 ng/mL), the Qmax was 18.0 mL/sec and the IPSS score was 4.0 (range 0–12).

Ultrasound-guided implantation was performed by a urologist, a radiotherapist and a Health Physicist using a real-time technique and loose seeds of 1-125 at the prescribed dose of 160 Gy. The procedure was performed under general or spinal anaesthesia with the patient placed in the lithotomic position. Using the transrectal ultrasound-guide the needles were positioned perineally, first the outer and then the central ones. Each localization of the needles was recorded in real-time by the health physicist using software that charted the treatment (Variseed 7.1). Cross-sectional scanned images were acquired, from the base to the apex of the prostate at 5mm intervals and the prostate, urethra and rectum were outlined. The software elaborated the dosimetric map and I-125 seeds (62-123 per patient) were inserted in the needles using the Mick applicator. The needle selected for seed insertion was visualized using a longitudinal ultrasound scan and the seeds were positioned according to the dosimetric map. The implantation envisaged a D90 > 160 Gy to the prostate. After 30 days a post-implantation assessment was performed by pelvic TAC using 5mm sections which were computer elaborated by means of the Variseed 7.1 software for a definitive evaluation of the D90. All patients were subjected to clinical evaluation, PSA assays, uroflowmetry and IPSS questionnaire compilation every three months in the first year, every six months the second year and then annually. Biochemical failure was defined as 3 consecutive PSA increases as described by ASTRO. In case of failure a transrectal prostate biopsy was performed by ultrasound-guide under local anaesthetic with 12 samples taken (6 per lobe). A D90 > 144 Gy was considered the cut-off value in order to predict the absence of biochemical failure.

RESULTS

The PSA levels evaluated 2 years after implantation varied from 0.1 to 3.9 ng/mL (being ≤ 0.5 ng/mL in 66.6% of the cases). Biochemical failure was observed in 9 (6%) patients, 5 with positive and 4 with negative prostate biopsies. At the post-implantation assessment, 18 patients (12%) had a D90 < 144, however only 2 of them (one of whom had a positive biopsy) had biochemical failure (11.1%). On the other hand, only 2 (22.2%) of the 9 patients with biochemical failure had a D90 < 144 Gy (one with a positive biopsy) while 5 had a D90 > 150 Gy with positive prostate biopsies. From these case histories a learning curve is clearly visible since 90% of the D90 values < 144 Gy were observed in the first 50 patients. The 5 patients in whom biochemical failure occurred, 2 with positive prostate biopsies, were subjected to complementary radiotherapy while in the remaining 3 cases a radical prostatectomy was performed (final Gleason score 4+3=7 and 4+5=9 respectively in 2 and in 1 patients). The remaining 4 patients with biochemical failure opted for complementary radiotherapy or hormonal therapy.

DISCUSSION AND CONCLUSIONS

For some authors the D90 value was associated with biochemical relapse-free survival (6). However in disagreement with previously published data, other authors, even though biochemical relapse-free survival had been demonstrated in 85% of cases 5 years after treatment, showed that patients with D90 > 144 Gy had a percentage of biochemical relapse similar to patients with D90 < 144 Gy (7). In our experience the D90 > 144 Gy cut-off value does not seem to predict, in reliable way, the control of prostate cancer after brachytherapy. It is necessary to consider, as possible limitations of the analysis, the number of patients and the median follow-up (in this study the number of biochemical relapses is low even if linked to the patient selection criteria), the learning curve, the operator-dependent elaboration of the dosimetry (possible errors in the computer reconstruction of the CT contours). It could moreover be that the resulting dosimetric quantification is an insufficient marker of the dose that the neoplasm receives. In fact the assumption with dosimetric quantifiers such as D90 and V100, is that the distribution of the neoplasm is uniform within the prostate gland, whereas the neoplasm is more frequently found in the peripheral zone. Therefore the dose in the peripheral zone is more important than that of the entire gland and is the crucial component for success of the brachytherapy (7). Therefore the Gleason score and the PSA course still appear to be the only markers which can predict biochemical failure after brachytherapy.

REFERENCES


Dosimetry doesn’t seem to predict the control of organ-confined prostate cancer after I-125 brachytherapy


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Second surgery for renal relapse after nephron sparing surgery: Review of seven cases.

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**Summary**

Objective: Anatomo-pathologic review of the cases which underwent a second surgery operation for a renal neoplasm relapsed after conservative surgery, in order to find possible relations with the surgical technique.

Patients and methods: At our institution nephron sparing surgery (NSS) is currently indicated for neoplasms smaller than 4 centimetres in diameter. The technique involves the removal of the neoplasm with a margin of healthy parenchyma and with the perilesional fat. Patients are firstly monitored by a CT check after 4 months and then with ultrasound/CT checks every 6 months in the first 2 years and then once a year. In this study we analyze in the 1994-2005 period the records of cases undergoing a second operation for a renal tumour relapsed in the operated kidney after NSS. All specimens were reviewed by an individual experienced uro-pathologist who determined the size of surgical margins and relations between the site of the recidivism and the site of the preceding NSS procedure.

Results: Seven cases with renal relapse have been found out of 267 undergoing conservative surgery in the same period (incidence 2.6%). The diagnosis has always been made in the lack of other localizations of disease at a complete re-staging and the average latency of the relapse was 19.4 months (8-46 months). In 5 cases the second tumour has been found in the site of the previous NSS: for these cases the minimum margin of the enucleo-resection was lower than 3 millimetres (median minimum margin 1.6 mm). Differently, in the remaining 2 cases, both with a wider surgical margin (median minimum margin 12.0 mm), the site of the first and that of the second neoplasm were distant. In particular, in one case a multifocal recidivism with a spread microvascular embolisation has been found, while in the other the primary neoplasms and the relapse presented a different histotype.

Conclusions: In the 5 cases with a narrow resection margin and relapsing tumour in the site of the enucleo-resection one can hypothesise the persistence of a peritumoral microscopic neoplastic disease. In the other 2 cases with a wider surgical margin the relapse can be attributed to the widespread microscopic multifocality in one case and to the development of a second de novo neoplasm in the other one. The extension of the surgical margin seems then to have played a role in determining a relapse in the site of enucleo-resection.

**Key words:** Nephron sparing surgery; Renal neoplasm; Surgical margins; Relapse.

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**Introduction**

The indication to nephron sparing surgery (NSS) for neoplasms smaller than 4 centimetres is widely agreed (1-5) as well as suggested by international guidelines. It is commonly accepted that the removal of the neoplasm should include a margin of healthy parenchyma in order to prevent the risk of local relapse, event that concerns a rate ranging between 0% and 10% of the main series of the literature (3, 6). This study reassesses the anatomo-pathologic data of the cases submitted to second surgery for a renal relapse after NSS occurred in our experience.

**Patients and methods**

At our institution it is indicated elective NSS for smaller than 4 centimetres and preferably exophytic lesions. The procedure is performed with an open or retroperitoneal
Table 1.
Anatomo-pathological features of the neoplasm treated by NSS (first neoplasm) and of the relapse (second neoplasm).

<table>
<thead>
<tr>
<th>FIRST NEOPLASM</th>
<th>SECOND NEOPLASM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diameter (mm)</td>
</tr>
<tr>
<td></td>
<td>(cm)</td>
</tr>
<tr>
<td>1</td>
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</tr>
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<td>4</td>
<td>middle</td>
</tr>
<tr>
<td>5</td>
<td>up</td>
</tr>
</tbody>
</table>

A laparoscopic approach and consists of removing the neoplasm with a margin of healthy parenchyma and the perilesional fat. The negativity of the surgical margin and of the resection bed is verified by an intraoperatory frozen sections and re-resection or nephrectomy (when re-resection is judged unfeasible for oncological or technical reasons) is performed if a positive margin is found. The possible presence of multifocality undetected preoperatively is assessed macroscopically once the perirenal fatty tissue has been removed and, in specific cases, through an intraoperative ultrasound evaluation; the haemostasis is obtained with stitches passed through the renal capsule and eventually with biological haemostatic agents.

The patients are followed with a first CT check after 4 months and then with ultrasound/CT checks every 6 months in the first 2 years and then every year.

In this study, out of an institutional database dedicated to patients with renal cancer, we searched in the 1994-2005 period for patients who underwent a second surgery due to the diagnosis of a renal relapse in the kidney previously treated by NSS. We excluded the cases of bilateral neoplasm. During the period considered, all the anatomopathologic preparations have been assessed by two experienced uropathologists only. The tumour histotype has always been determined according to the Heidelberg classification, the cytonuclear grading according to Fuhman score, the anatomopathological staging to the TNM 2002 system. For this study all the hematoxylin-eosin stained tumor specimens of the selected cases have been newly examined by one uro-pathologist (R.T.) who has reassessed the sizes of the surgical margins of the enucleo-resection and has ascertained the relation between the site of the enucleo-resection and the site of the recidivism in macroscopically and microscopically terms.

Results

Out of 267 patients who underwent NSS in the period of the study, followed for an average period of 53 months, a second surgical procedure to treat a recidivism in the operated kidney has been performed in 7 cases (6 males, 1 female, average age of 67 years, 53-74 years range), with an incidence equal to 2.6%. The first neoplasm had been incidentally diagnosed in 6 cases. There was an elective indication in 4 cases (incidence of renal relapse in the cases with elective indication 4/221, 1.8%), an imperative indication in 3 (incidence of relapse 3/46, 6.5%); in all the patients at the clinical and intraoperative staging there were no evident lymph node or distant metastasis. The relapse was diagnosed in an asymptomatic way in 5 cases, for pain in 1 case (n. 5) and for macroscopic haematuria in one (n. 4), always in lack of other metastasis localizations at a complete thoraco-abdominal and bone re-staging. The average latency of the recidivism has been of 19.4 months. At the second surgical operation 6 patients underwent a nephrectomy, while one (n. 3) underwent a partial nephrectomy in the site of the preceding intervention. Table 1 summarises anatomopathologic data.

Figure 1.
Gross specimen of nephrectomy in patient n. 1, showing the correspondence between the site of the previous NSS (arrows) and the relapse.
In 5 patients (cases no. 1-5) a new tumour in the site of the previous resection has been noted, macroscopically demonstrated by the correspondence of the two neoplasms' sites (Figure 1) and microscopically confirmed by the detection of a mixture between the neoplasm cells and the foreign body granulomatous reaction due to the stitches (Figure 2). In these cases the minimum resection margin was equal to or less than 3 millimetres (1.6 mm average). In 3 of these cases the second neoplasm was upstaged and/or upgraded when compared with the first one.

Differently, in the remaining two cases (no. 6 and 7) the site of the enucleo-resection and that of the relapsing tumour were distant and the surgical margins were wider with an average minimum margin of 12.0 mm. In particular, in case no. 6 the relapsing tumour presented as a locally advanced disease invading the caval wall and with a widespread diffusion in the renal parenchyma in the form of microvascular emboli. In case no. 7, instead, the two neoplasms were not just distant, but they also presented a different tumoral histotype (Figures 3 and 4).

Currently, 4 patients are alive with no evidence of disease (cases no. 1, 2, 3, 7) at an average of 9 months from the second operation (range 3-17 months), one (no. 5) died because of other causes without evidence of disease after 32 months, one (no. 4) is alive with a local relapse in the renal fossa after 3 months, the last one (no. 6) died after 20 months due to progression of the disease at local and distant sites.

**DISCUSSION**

Several clinical studies supported by consistent statistics allowed to prove the oncological equivalence between conservative surgery and radical nephrectomy in the treatment of organ-confined small renal neoplasms (1-5).

The relapse into the operated kidney is an infrequent event, whose incidence is comprised between 0.5 and 5% for intracapsular neoplasms smaller than 4 centimetres, and up to 10% in the event one considers more extended neoplasms (3-6).

The lack of surgical radicality, the non recognised multifocality and the development of a de novo neoplasm represent the three possible reasons for the recidivism in the kidney submitted to NSS. Though some authors support the oncological equivalence of the simple enucleation techniques, where the resection is done following the tumoral pseudo capsule (7-12), the technique of enucleo-resection and partial nephrectomy have obtained a wider consensus since they offer greater guarantees to obtain a radical removal of the neoplasm, particularly if one takes into account the chance of a microscopic peritumoral disease outside the pseudocapsula, as shown in some anatomo-pathological studies (13-
18. Yet, it is still discussed what should be the optimum minimum size of the resection margin: after the initial indication to the removal of 1-2 centimetres of healthy tissue (19), several authors, not finding links between margin size and progression risk, simply suggest to attain to margins smaller than 1 centimetre (20-23). The multifocality of the renal neoplasm has been reported up to 25% of cases and it has been initially placed in relation with the diameter of the neoplasm. Nevertheless several studies on consistent series of nephrectomized patients have demonstrated that the papillary histotype and the presence of extracapsular or vascular extension are the factors that can better predict the risk of multifocality (24-30). Starting from such considerations, the proposals to enlarge the indication to elective NSS also to intracapsular tumours up to 7 centimetres have been recently supported (31-32).

The relapse rate we observed (2.6%) is in line with what reported by other authors. In particular, the adoption of restrictive criteria in the choice of elective NSS (tumor diameter lower than 4 centimetres) can explain the particularly low rate in this subgroup of patients (1.8%) and, indirectly, the higher values in the cases with imperative indication (6.5%). Nevertheless, in 6 out of 7 cases we studied the features of the first neoplasm could have allowed a conservative indication also in elective conditions, and only in one case there was a more extended neoplasm (5 cm, pT3a). Considering the whole amount of cases undergoing conservative surgery at our institution and comparing the renal relapse rate among the case with lower or greater diameter than 4 centimetres (6/206 vs. 1/60, 2.9% vs. 1.6%, respectively) it is possible to confirm that the risk is not linked to the tumour diameter. For the five cases relapsed after an enucleo-resection with a small surgical margin, the evidence of a relapse in the site of enucleo-resection allows to hypothesise the persistence of a peritumoral microscopic disease. Differently, in the remaining two cases with a wider surgical margin, where there was no coincidence between the sites of the neoplasm and that of the relapse, the latter is more reasonably attributable to a widespread multifocality in one case and to the development of a second neoplasm in the other.

On the whole, the development of a renal relapse in the site of the preceding NSS has been the most frequent event, and the evidence of a small surgical margin takes to attributing the relapse of the disease to an incomplete surgical radicality. About this aspect, we have to report that in our experience there are 4 patients who underwent immediate nephrectomy after NSS with a positive margin without histological evidence of persistence of the disease, and 22 patients with positive or doubtful margin not presenting evidence of relapse after an average of 31 months follow up. As recently established (33, 34) then, surgical margin is probably not the only cause of the relapse, which is also due to the aggressive nature of the neoplasm, not always easily predictable. The general trend is to using and upgrading in the relapsed neoplasms, though being diagnosed at a short span in patients who undergo a strict follow up, can suggest the aggressive nature of these cases.

In conclusion, we confirm that, by adopting a selected indication for conservative surgery, the risk of local relapse is low. The relapsing disease generally originates in the sites where was the previous neoplasm and is correlated with small surgical margin. In such cases an aimed and close follow up is indispensable. The unknown multifocality and the development of a completely independent second neoplasm are possible but less frequent.

References


ORIGINAL PAPER

Efficacy and safety of the haemostasis achieved by Vivostat System during laparoscopic partial nephrectomy.

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Summary

Introduction: Haemostasis remains the greatest challenge during laparoscopic partial nephrectomy. We describe the use of the Vivostat™ system helping effective haemostasis during laparoscopic partial nephrectomy (LPN).

Patients and method: Twenty-eight patients underwent LPN. Autologous fibrin sealant was prepared with the Vivostat™ system and applied to the resection bed. This system is an automated medical device for the preparation of an autologous fibrin sealant from the patient’s blood. Pre and postoperative clinical parameters and laboratory values were evaluated, for acute and delayed bleeding.

Results: Median patient’s age was 58 years (range, 25-75). All patients underwent LPN for renal tumors (mean size 2.5 cm; range 0.9-4.5 cm). Six resection were performed without vessels clamping, and 22 were realized with selective arterial Bulldog clamping. Haemostasis was achieved by a cellulose bolster (80%), by stitches (67%) and by sealant application after declamping (100%) (mean amount applied: 5.1ml). The mean warm ischemia time was 26 minutes (range, 16-45) for 22 interventions. Mean blood loss was 128cc (range, 20-500). Pre-operative and post-operative creatinine values (mean, 0.91 vs 1ng/ml) did not differ significantly; whereas mean Hb levels slightly decreases after surgery (mean, 14.7 vs 12.5 g/dl). Mean operative time was 131 minutes (range, 60-190). All but one had negative surgical margins. One intraoperative bleeding occurred needing blood transfusion (1 unit). Postoperatively, we observed only 1 perirenal hematoma treated conservatively requiring blood transfusion.

Conclusions: In this study, an effective haemostasis was achieved and maintained after kidney reperfusion. These data support the previous finding with the same system and encourage its use in LPN.

KEY WORDS: Renal cancer; Laparoscopy; Partial nephrectomy; Autologous fibrin glue; Haemostatic agent; Sealants.

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INTRODUCTION

The widespread diffusion of imaging techniques detect an increasing number of incidentally diagnosed renal masses. These lesions are often small (less than 4 cm in diameter), peripherally located, and with benign histology in nearly 20-25% of the cases (1). Even if the radical nephrectomy still remain the gold standard, in several cases should be considered an excessive treatment, and laparoscopic nephron-sparing surgery has gained a wider acceptance in the urologic community for the treatment of these masses, with oncologic results similar to those obtained with a more radical procedure (2-5).

A nephron-sparing laparoscopic approach to the renal masses is also experiencing a widespread diffusion; nevertheless, the laparoscopic partial nephrectomy (LPN) still considered as one of the most difficult procedures in laparoscopy urology due to the control of bleeding of the resection bed (2, 3, 6).

Several agents and different strategies were adopted, alone or in combination, to achieve an adequate haemostasis of the renal surface. Among all the haemostatic tools available, “glues” or tissue sealants, are the only alternatives for bleeding control, and their use as unique...
haemostatic agent is adequate in cases of small peripheral lesions. However, in cases of greater masses and wider excisions, a consistent number of authors recommended and practised the use of sealants in association with “sutured bolster” (7).

We previously proposed (8) and adopted an innovative and effective sealant to be used during laparoscopic partial nephrectomy. The Vivostat system has the innovation of being an autologous fibrin glue, so that it can be prepared directly from the blood patient. Thus, after this first exciting report in LPN renal surgery we decided to extend its use in a greater surgical series, and here we report on the efficacy and safety of this haemostatic agent after 28 procedures.

Patients and Methods

Between August 2005 and January 2007, 28 consecutive patients underwent LPN for small-size renal mass. The selection criteria for the laparoscopic approach included a single, organ-confined renal mass up to 5 cm, without evidence of venous or lymph nodes involvement. Computed tomography (CT) scanning was performed before surgery, and informed consent was obtained from all patients. All patients received 40mg low molecular heparin until discharge. The operation was performed by a single surgeon (L.S.); the choice of the laparoscopic approach was dictated primarily by the location and technical complexity of the renal mass. The transperitoneal approach was used for anterior or lateral lesions, and the retroperitoneoscopic approach was used for posterior, posteromedial or posterolateral lesions.

In general our decision to perform selective arterial clamping was not strictly defined, and depended on lesion location and size. Only in six cases, for a very small superficial exophytic lesion, the renal artery was not clamped. In 22 cases we performed a selective arterial Bulldog clamping. All patients received a 250-ml mannitol-sodium chloride solution before the vascular clamp.

After tumour excision, when clear marginal vessel bleeding occurred, the bipolar electrocautery was used. Two or three separate U-shaped stitches (with a 2-0 Monocryl suture) were placed on the parenchymal defect over a Surgicel bolster (Johnson & Johnson, New Brunswick, NJ, USA) in 22 cases. The arterial clamp was then removed, and subsequently the autologous fibrin sealant was sprayed by the specific endoscopic Vivostat™ system applicator (Figure 1), as previously described (8-9).

Finally, the kidney was carefully inspected for bleeding. In the six cases treated without stitches or bolster application, the haemostasis was quickly achieved by direct fibrin glue spray (Figure 2).

A Jackson Pratt drain was placed in all patients. Pre-operative and post-operative serum haemoglobin and creatinine, time until complete haemostasis, estimated blood loss, warm ischemia time, length of surgery and postoperative bleeding or urine extravasation was recorded, as well as histopathological features. A haemorrhagic complication was defined as intra-operative or post-operative bleeding requiring transfusion.

Wilcoxon two sample test was used to identify significant relationships between pre-operative and post-operative continue laboratory values.

Results

Clinical and pathological characteristics of patients are reported in Table 1. The median age was 58 years (range, 25 to 75 years), with an higher prevalence of male gender. The masses were equally distributed on both sides. In all cases a laparoscopic partial nephrectomy was carried out; in one case a contextual renal cyst resection was added.

In the wide majority of cases (more than 70%) a malignant histology was revealed at histological examination, with a mean diameter of 2.5cm (range, 0.9-4.5 cm). All tumors were localized (T1a-T1b stage), but only one have positive surgical margins.

The warm ischemia time was 26.1 minutes (range, 15-45 minutes) in patient that underwent Bulldog arterial clamping. In all cases, the entire amount of the prepared sealant was applied (mean 5.1 ml; range, 4.5-6.1 ml). A good haemostasis was achieved in all cases after application of the sealant to the resection site.

Mean operative time was 131 minutes (range, 60-190°). Estimated blood loss ranged from 20 to 500ml (mean
At 6-month follow-up, no additional complications were observed. A further analysis restricted to the seven patients with an ischemia time ≥ 30 min did not show statistically significant differences in serum creatinine values (p = 0.2).

As far as the serum haemoglobin level is concerned, the intraoperative estimated blood loss plus the mean drain output causes a postoperative decrease of Hb level [preoperative mean: 14.7 g/dl (range: 13.7–17.8 g/dl); postoperative mean: 12.4 g/dl (range: 8.1–16.1 g/dl)]. There was no evidence of immediate or delayed urine extravasations in any of the patients and no ureteral stenting was required. At 6-month follow-up, no additional complications were shown in any patient, the one with positive surgical margins is still under follow-up with periodic CT scan, and he has no evidence of progression or recurrence at two years follow-up.

**Table 1.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>(N=28)</th>
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<tbody>
<tr>
<td>Date of surgery</td>
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</tr>
<tr>
<td>Age, years</td>
<td>Median (range) 58 (25-75)</td>
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<tr>
<td>Gender</td>
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</tr>
<tr>
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<td>Histology</td>
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<td>stage T (only for tumours)</td>
<td>1a 90</td>
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<tr>
<td>Tumor Size (cm)</td>
<td>≤ 2.0 39.2</td>
</tr>
<tr>
<td>Fuhrman’s Grade (only for tumours)</td>
<td>1 57.9</td>
</tr>
</tbody>
</table>

*Table entries are percentages of sample but for date of surgery and age.*

**Discussion**

Laparoscopic partial nephrectomy is a feasible, minimally invasive and increasingly performed technique for small renal masses. Many retrospective large multicenter studies on LPN have come from centers of excellence with experienced surgeons performing the procedure. These studies show that using haemostatic agents and/or glue the overall rate of haemorrhage requiring transfusion and urine leakage were 2.6% and 1.9%, respectively (7). However, the same results was not confirmed by others (10) that report a 3.7-fold higher rate of haemorrhage requiring transfusion (9.5%) and a 2.4-fold higher rate of urine leakage (4.5%).

The technological advance can aid in flattening the long learning curve of the LPN improving haemostasis and final clinical outcome. We firstly describe a simple, effective and durable method to help haemostasis during LPN using an autologous fibrin sealant (the Vivostat™ system) (8). In this present series we report two interesting complications. First, the intraoperative blood loss (about 500 ml) concerned a patient with a right-sided 4.5 cm pT1bG3 clear cell carcinoma, located in the upper pole in which we need a 40° warm ischemia time to complete resection and haemostasis. This complication was intraoperatively managed with transfusion and the haemostatic strategy was based on both bipolar cautery, stitches, bolster and sealant. The second complication was a postoperative perirenal haematoma conservatively treated. A left renal mass (2.5 cm) deeply located in the middle third was resected with a 30° warm ischemia time and an intraoperative 150 ml estimated blood loss. A conservative approach instead of surgical reinterention lead us to properly manage this complication. It is very important to underline as both in the previous (10 cases) and in present LPN series (28 cases) we did not perform any reintervention or conversion to dominate severe bleeding. Of course, the variation in postoperative serum Hb level is an important point in critical evaluation of the surgical procedure; we found a 2.3 g/dl mean reduction of Hb level, that is generally well tolerated by the patients and justified in every ablative surgical operation. Moreover, no urinary leakage was detected and no ureteral stent was placed. These evidences support the concept of a very good synergistic interaction between a skilled and meticulous surgical technique and an effective fibrin glue, as demonstrated in the six cases in which the bleeding control was achieved by the exclusive use of the sprayed glue over the reseciton bad alone.

Even if this work was not intended to perform a cost/benefit analysis, the costs savings may be potentially come from the Vivostat™ autologous sealant in surgery with heavy haemorrhage and requiring at least 7 ml of fibrin sealant.

It is important to consider that Vivostat™ System offers a multitude of benefits to both the patient and the surgeons. As the fibrin sealant is autologous, it shows excellent biocompatibility and eliminates the risks of viral infection from products based on single donor blood, pooled blood or bovine components. As the system is composed of three elements, a processor unit for the preparation of fibrin sealant, an applicator unit to control the delivery of fibrin sealant and a disposable kit as pre-
viously described (8) of course the initial supply cost is high. Nevertheless, considering that Vivostat™ fibrin sealant can be used in a wide range of surgical procedures and environments, the costs should be critically shared and evaluated in a multidisciplinary perspective. We recognize the limitations of this study as a monocentric study that may add by itself some bias to our findings. In spite of these limitations, however, this research confirm that there is a widespread interest for haemostatic agents and fibrin glues in urological community (7, 11). Randomized studies aimed to investigate the efficacy of haemostatic agents and/or glues are required; this may be difficult to perform due to the widespread their use and the several products with different adhesive and haemostatic properties (12-13).

In our opinion, the system offers to the surgeon a pressure controlled, accurate and efficient method of fibrin sealant application with advantages over conventional application systems. Furthermore, medical devices available on the market differ in one or several features (addition of bovine derivatives, lesser degree of automation, open systems, preparation techniques, volume sampled and final volume). Vivostat™ sealant is not toxic (bovine-derived and exogenous thrombin free), and no adverse reactions have been reported in the present and in previous preclinical studies (14). These our recent results, even if in a small selected group, confirmed that Vivostat™ system for autologous fibrin glue may be an effective and safe solution to minimize blood loss during laparoscopic partial nephrectomy (8). This study largely confirm the previous findings about the use of Vivostat™ sealant in obtaining immediate haemostasis of the surgical bed after laparoscopic partial nephrectomy, providing a durable and safe haemostasis. Further studies, including comparative trials with other fibrin sealants in a larger number of patients, are needed to extend our results.

References


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Appendix 1: The Use of Tissue Glues and/or Sealants in Laparoscopic Nephron Sparing Surgery: An International Survey

Name .............................................. Last name ..............................................
Institution .............................................. Country ..............................................
Address ..............................................................................................................................
Phone .............................................. Fax .............................................. e-mail ..............................................

How many laparoscopic partial nephrectomy have you performed at your Institute? [ ]

Mean tumor size:
Exophitic lesions (# )
Central lesions (# )

Laparoscopic technique
• Transperitoneal
• Extraperitoneal
• Both

Do you use renal function protection? YES [ ] NO [ ]
If yes:
• Mannitol
• Lasix
• Other:

Use of intraoperative ultrasound YES [ ] NO [ ]
Clamp of the hilum YES [ ] NO [ ]
If yes:
• Only the artery
• Artery and vein together

Methods used:
• Bulldog
• Umbilical tape
• Satinsky
• Other:

Mean ischemic time:
| ≤ 30 min |
| Between 30 and 60 min |

Tumor resection:
• Cold scissors
• Monopolar hook
• Scissors+bipolar
• Harmonic scalpel
• Ligasure
• Laser
• Other (please state)

Pre-op. ureteral catheterization YES [ ] NO [ ]
Intra-op. dye test YES [ ] NO [ ]
In case of collecting system violation, do you stent the ureter? YES [ ] NO [ ]

Parenchymal hemostasis
Do you use tissue glues or sealants? YES [ ] NO [ ] If yes, please write the composition and/or the trade name:
Which is your indication for sealants use?
| Always |
| Only when the urinary cavities are opened |
| Only when the urinary cavities are not opened |
| Only for cortical small tumors |
| Only for deep intra-cortical tumors |
| Other:

How much do you rely on sealants? *
[ ] Always sealants only
[ ] Central hemostatic suture + sealants
[ ] Sealants + bolstering suture
* You can check more than one

With respect to frozen section:
| Never |
| Sometime |
| Always |

Technique of frozen section:
[ ] Random biopsies of the bed of resection
[ ] Inspection of excise tumor and select biopsies from the specimen

Specimen retrieval
[ ] with endobag
[ ] without endobag

Intraoperative conversion to laparoscopic radical nephrectomy:
A) For bleeding #:
- with sealants #
- without sealants #
B) For oncologic reasons #:

Conversions from laparoscopic to open partial nephrectomy
A) For bleeding #
- with sealants #
- without sealants #
B) For technical difficulties
- with sealants #
- without sealants #
C) For other reasons #

Post-op. complications specifically related to sealants
| Bleeding |
| Urine leak |
| Infections |
| UPJ obstruction* |
* If yes please specify if correlated with lower pole partial nephrectomy YES [ ] NO [ ]

Management of post-op complications
[ ] Re-operation with sealants use
• Laparoscopically
• Open
[ ] Nephrectomy
• Laparoscopically
• Open
[ ] Stent placement
[ ] UPJ repair
• Laparoscopically
• Open

Tumor seeding on trocar access or peritoneal spread (please specify if tissue sealants were used or not) YES [ ] NO [ ]

% of positive margins:

In case of positive margins, what do you do?
[ ] Re-operation with resection of tumor bed and frozen section
[ ] Nephrectomy
[ ] FU with CT/MRI
• Every 3 months for the first year, than every 6 months for 2 years and than yearly
• Every 6 months for 2 years and than yearly
• Every year for at list 5 years

Disease free survival
3 years [ ] 5 years [ ]
CASE REPORT

The role of directional power Doppler in early detection of the onset of neoangiogenesis in a case of small hyperechoic renal lesion.

Pasqualina Di Siervi, Federico Pagano, Vincenzo Bellizzi, Anna Rega, Vincenzo Terracciano, Domenico Ricciardi, Raffaele Fiorillo, Biagio Rossi

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2 Unit of Nephrology and Dialysis, Hospital “L. Curto”, Polla (SA), Italy;
3 Unit of Nephrology and Dialysis, Hospital “Lamberti”, Solofra (AV), Italy

Summary

Case report: A small hyperechoic renal mass was detected in a 57 year old female. This renal mass was further characterized by the absence of peripheral or intratumoral vascularity using directional power Doppler (dpD); however, there were intralesion spots colored after Levovist (pattern 1, according to Jinzaki). By computer tomography (CT) scan, the renal mass was considered a benign lesion. Three months later, no changes were detected using ultrasonography (US), while there was evidence of a focal intra-lesion neovascular zone using dpD (pattern 1 of Jinzaki). Magnetic resonance imaging (MRI) did not display evidence for malignancy. After six months, the MRI considered the mass an angiomylipoma (AML). However, a vascular pattern around and inside the mass (pattern 4 of Jinzaki) was evident by using US-dpD and a percutaneous renal biopsy revealed a renal cell carcinoma.

Conclusion: This case suggests that directional power Doppler is useful for the detection of small hyperechoic renal masses considered benign by both CT scan and MRI, since dpD allows for early detection of the onset and development of neo-vascular structures. Therefore, directional power Doppler sonography would be useful in the follow up of renal masses which mimic benign lesions.

KEY WORDS: Renal mass; Directional power Doppler; Ultrasonography; Neoangiogenesis.

Submitted 29 January 2009; Accepted 30 June 2009

INTRODUCTION

Renal neoplasiae, because of their slow increase rate and the very frequent lack of specific symptoms, are often casually detected by echography, radiography scans for other reasons (1). The latent and non specific character of symptoms in renal neoplasiae are such as to cause mis-match and diagnostic delay.

Neoangiogenesis is strictly linked to the growth of neoplasiae, even if such causal relationship with the malignancy of the tumors themselves has not been definitely assessed by imaging techniques.

Renal imaging has improved since the introduction of Ultrasound (US), Computer Tomography (CT) and Magnetic Resonance imaging, RM (2). The B-Mode US is characterized by a low specificity in the definition of renal lesions compared with TC and RM. In fact, with CT and MR equipment, the diagnosis of most renal masses is usually straightforward and accurate (10) but even TC and RM cannot carry out a differential diagnosis above all as regards small hyperechoic renal lesions. Power Doppler (pD) with and without contrast medium improved detection of vascularity for the characterization of small hyperechoic renal masses. The availability of pD improves the assessment of angiogenesis, basis for tumour growth in human tissues; pD is characterized by high sensibility in the evaluation of small dimension blood vessels and low blood flow rate, thus allowing evaluation of the vascular structure of small renal masses (5). In literature an increase in the diagnostic accuracy of echography has been showed, as regards the characterization of small renal masses, just thanks to pD (4). The vascular distribution by pD in a renal lesion was classified, according to Jinzaki, as follows: pattern 0, no vascular signal; pattern 1, intratumoral focal pattern which indicated persistent focal color flow signal (spotty or linear) which could be detected...
within the lesion not extending to the margins; pattern 2, penetrating pattern, which indicated that blood vessels arose outside the lesion and coursed towards the center; pattern 3, peripheral pattern which indicated blood vessels arose outside the lesion and surrounded the lesion; and pattern 4, mixed penetrating and peripheral pattern (4). However, pd may not show evidence of the neo-vascular structure of renal masses, and therefore does not allow for certain classifications of small renal lesions. Although, when pd is associated with administration of us contrast media, it is very efficient in evaluating the vascular structure of small renal masses (5).

The use of percutaneous biopsy in the evaluation of indeterminate renal masses is controversial and its role in management remains largely unclear, but it not only differentiates benign from malignant tissue but can also help in deciding the management option for patients undergoing minimally invasive treatments (20). Some of the suggested indications in recent literature include small solid renal masses that do not fit the radiological features of typical RCC and can form up to 50% of suspicious renal masses (21).

In the present case-report we describe the advantage of directional power Doppler (dpD), compared with both CT scan and MR, in the early detection of both onset and development of the neo-vascular structure of small hyperechoic renal masses considered benign by conventional CT scan or MR.

CASE REPORT
A 57 year-old, obese female with normal renal function and urinalysis, without symptoms attributable to renal diseases, was subjected to abdomen sonography. The B-mode ultrasound (US) study (Toshiba SSA70A with directional power Doppler), displayed evidence of a small hyperechoic renal mass, diameter ≤4 cm. The lesion was homogeneous in structure with defined borders, without cystic areas, central scar or attenuation of the posterior US faces and contained the middle third of the left kidney. DpD analysis revealed no evidence of any peripheral or intratumoral vascularization (pattern 0 of Jinzaki, Figure 1A). Since both US and dpD did not better define the small mass, 300 mg of Levovist was administered i.v., which allows pattern 1 according to Jinzaki: intratumoral focal pattern which indicated focal color flow signal that did not extend to the margins (Figure 1B). The woman underwent a conventional (nonhelical) CT scan. The CT scan shows, “in the left mesorenal area, a clearly hypodense mass of about 3 cm, which after contrast media shows a poor contrast media impregnation even in later scans, this picture is compatible with a renal cysts diagnosis”. The biopsy was refused by the patient. Three months later, no changes were detected at US B-mode.
with regard to echogenicity, borders and dimensions of renal lesion. However, there was evidence of a focal intra-lesion neovascularization using dpD without contrast media, pattern 1, according to Jinzaki (Figure 2). Thus, the patient underwent an MR: “evidence on the left, on the superior polar area, of an oval area, of about 3 cm, deforming the antero-lateral profile of the organ; the above mentioned build-up appears to be lightly dishomogenous, substantially isointense at the cortical level in all sequences after the e.v. injection of contrast media; it shows an impregnation similar to the remaining parenchyma (lobar dysmorphism?)”. A renal biopsy was proposed due to the presence of an intra-lesion neovascular zone observed by dpD, but the biopsy was refused by the patient. Follow up after six months, no changes were detected with regard to dimension, outline and echogenicity of the lesion using US-B mode, but dpD showed that blood vessels arose outside the lesion and surrounded the lesion, pattern 4 of Jinzaki (Figure 3A). This was confirmed by the intra-lesion blood-flow: systolic peak velocity measured 100-135 cm/sec and RI = 0.59, at Doppler (Figure 3B). The next MR, “compared with the foregoing scan, shows a substantially equal finding, in particular no substantial volume changes of the above described area involving the left kidney, are found. Such a lesion in the spin sequences appears to be clearly hypointense compared with the surrounding renal parenchyma and to have clear margins. The RM finding, after a new evaluation of the foregoing scans, is revealing of an angiomylipoma”.

The clear modification of vascularization of the renal mass, was not observed in the first echo-graphic scan and dpD appeared to be marked in pattern 4, mixed peripheral and penetrating blood vessels and high frequency of systolic peak velocity at Doppler during follow up, were suggestive of malignancy. A percutaneous renal biopsy was performed with a subtle needle which gave evidence of fair cell carcinoma (dark cell variant). The patient underwent standard surgery, and the kidney biopsy confirmed the previous histological pattern: renal cell carcinoma, dark cell high histological degree (histological degree 3), evidence of invasion of the capsule and the perirenal fat in many places, the renal pelvis and the ilium vessel are unaffected, there are no metastases in the renal vein, necrosis areas are less than 10% of the neoplasia total volume (high-degree, dark cells type, histological level 3) consequently the left kidney was removed. After 7 years the patient is still living and is free from metastatic lesions.

**Discussion**

Even if hyperchogenic renal masses strongly suggest the presence of an angiomylipoma, the same aspect can be also found in small renal carcinomas (4). Recently, it has been suggested that the hyperchogenicity of small renal masses does not definitively demonstrate the effective parenchymal structure and, therefore, additional examinations are required (3, 16). In clinical practice, sonography and CT are often combined to reveal and characterize renal lesion. MR of renal lesions is useful when sonographic or CT finding are inconclusive or when the administration of IV iodinated contrast material is contraindicated.

The small renal hyperchogenic lesions are a prerogative both of benign diseases such as angiomylipoma and of renal carcinomas, which together represent the largest number of solid nodular lesions in the kidney (3, 4, 16), they cause the problem of differential diagnosis in contrast with the more common imaging techniques.

The most characteristic and frequent aspect of angiomylipopmas in ultrasonography consists of a hyperchogenic mass compared with the surrounding renal parenchyma having clear margins, without hypoechoic halo and/or cystic area and/or central scar with attenuation of the ultrasonographic beam.

Since echography scanning is not specific enough for the

---

**Figure 3.**

*B-mode US with directional power Doppler (6 month observation, without Levovist administration): hyperchoic renal mass at the middle third of left kidney. A): presence of peri- and intra-lesion vascularization, pattern 4 according to Jinzaki; B): intra-lesion blood flow at 116 cm/sec of systolic peak velocity measured at the Doppler.*
characterization of renal masses, directional power Doppler
was used with and without contrast media, for identifying
the vascularization of the small hypervascular renal lesion.
The hypervascular lesion, during the follow up, appears to
be unchanged as regards its size, echostructure and mar-
gins in the US B-mode study, but it drastically changes as
regards the kind of vascularization. Such lesion, after some
months shows, by directional power Doppler scanning, an
increasing neoangiogenesis which later causes first a lack of
vascularity or intraluminal color spots, after Levovist i.v. (pat-
temolo and 1 according to Jinzaki), then the appearance of
peri and intraluminal vascularity (pattern 4). Pattern 0 (lack
of color sign), pattern 1 (local intratumoral color sign) and
pattern 2 (vessels which penetrate into the lesion having an
only vascular pole) seem to be only typical of angiomy-
olipomomas. While pattern 3 (peripheral vascularity) and pat-
tem 4 (mixed penetrating and peripheral pattern) seem to be
only present in renal malignant tumors. Furthermore,
high frequency signals in Doppler scanning are specific of
RCCs, however, the slow systolic peak velocity is associ-
ated with either benign or malignant lesions (19).
In our case the conventional CT scan (non helicoidal),
without contrast media, showed a renal mass clearly
hypodense compared with the surrounding parenchyma
with a very poor impregnation after endovenous admin-
istration of contrast media. The lesion must be 3 cm in
diameter, must not enhance upon intravenous adminis-
tration of contrast media and its configuration must
remain unchanged, these lesions can be assumed to be
benign cyst. As a matter of fact most cysts are small, they
appear either isodense or hypodense compared with the
renal parenchyma, after intravenous administration of
contrast medium (17, 18).
MR evaluation of a renal mass was required because of a
lesion revealed by sonography, studies using TC scans
require further evaluation. MR evaluation of suspected
renal masses is required because venous involvement
cannot be excluded or delineated by contrast-enhanced CT.
The differentiation of an angiomyolipoma from a renal
cell carcinoma is important because, in most cases,
angiomyolipomas do not need to be surgically removed.
The diagnosis of an angiomyolipoma is made by demon-
strating fat within a solid mass. A small number
of angiomyolipomas (hamartomas) do not contain macro-
scopic fat (angiomyomas), and the imaging differentiation
to a renal neoplasm is impossible. These lesions often
have a higher attenuation than that of renal tissue (on the
unenhanced CT scan) or may demonstrate homogeneous
and prolonged enhancement (11), but these finding are
not specific enough to make a sure diagnosis of a non-fat-
containing hamartoma. There have been a few case
reports of fat occurring in renal cell carcinoma that also
contain calcification (12, 13). Angiomyolipomas rarely
contain calcification and, therefore, a diagnosis of
angiomyolipoma should not be made if a lesion contains
fat and calcium. Rarely, a renal cell carcinoma may con-
tain a small amount of fat, and differentiating this from an
angiomyolipoma is impossible (14).
Most solid renal lesions appear isointense compared with
the surrounding normal renal parenchyma on T1-
weighted images and variable in signal intensity on T2-
weighted images (6), these images are often difficult to
be evaluated and small lesions may be inconspicuous on
these pulse sequences (7). After administration of i.v.
contrast medium, renal cell carcinoma show enhance-
ment in either a homogeneous or heterogeneous pattern
(8). Although enhancement is enough for diagnosing
malignancy, non enhancement is not enough to exclude
malignancy. In general, any enhancing solid mass in the
kidney should be considered a renal neoplasm. However,
it should also be kept in mind that all enhancing solid
renal masses do not represent a renal neoplasm (9).
However, angiomyolipoma, lymphoma, metastatic dis-
ese, renal anomalies, and other pseudotumors can all
mimic renal cell carcinoma. The imaging characteristic
of renal cell carcinoma are extremely varied (10).
In this case, because there is a diagnostic clash between
the different imaging techniques and since the patient
does not accept to undergo a surgical exploration of his
renal lesion, a percutaneous echo-guided biopsy of the
lesion itself was carried in order to identify it from a his-
torical point of view.
Renal biopsy for the diagnosis of renal cancer has a limit-
ed but definite role. A group of indeterminate renal mass-
es remains and poses a vexing problem in terms of deter-
mining the underlying abnormality. For them, a clinical
decision must be made concerning establishing the diag-
nosis, either by means of frequent follow up examinations
or by intervention to provide a histopathologic diagnosis.
Among these interventions, a choice between surgical
exploration versus guided biopsy by imaging studies must
be made. Renal biopsy guided by imaging has an impact
on the management of renal mass lesions and is safe and
minimally invasive. Surgical exploration can be reserved
for those lesions that defined characterization by biopsy or
imaging. Biopsy guided by imaging of indeterminate renal
mass lesions is a safe, reliable, and accurate modality that
could substantially reduce the current existing manage-
ment problems in this group of patients (15).

Conclusions
Therefore, to characterize small hyperechoic tumors it is
essential to possess accurate methods of detection.
A hyperechoic mass at US B-mode strongly suggests the
presence of angiomyolipomas (AMLs) and since small
RCCs may have the same features (5), scans such as the CT
scan and MR are recommended to confirm diagnoses. In
this case report, both CT scan and MR failed to diagnose
a small renal mass. Therefore, this case suggests that a small
hyperechoic renal mass with no vascular pattern at the
time of onset may develop a neovascular pattern before the
cancer mass becomes more evident. The directional power
Doppler may be more sensitive in comparison to CT scan
or MR in evaluating changes of angiogenesis of this lesion.
Thus, dpD is a useful tool to survey and monitor the clin-
ic outcome of small renal masses considered benign by
the other imaging techniques. To our knowledge, the
change in progress of vascular structure of small hypere-
choic renal masses has never been previously described.
This study suggests that small hyperechoic renal masses
should be evaluated with directional power Doppler, in
order to detect neo-angiogenesis, which is characteristic of
cancer.
REFERENCES


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The role and extension of lymphadenectomy in bladder cancer: a review of the current literature.

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Summary

Radical cystectomy (RC) with pelvic lymph node dissection (LND) is the gold standard for high grade and muscle invasive bladder cancer. Although consensus exists on the need for node dissection, its extent and role are still matter of debate. However, an ever-growing body of data supports an extended dissection since it may provide a survival advantage in both node positive and node negative patients without significantly increasing morbidity and mortality. Besides dissection extent, the modality of specimen submission and node retrieval have a key role in the quality of node assessment. Moreover, the stage of primary bladder tumor, the total number of lymph nodes removed, the lymph node tumor burden, the extracapsular extension and the lymph node density have been demonstrated to be important prognostic variables in patients undergoing cystectomy with node metastases and could be useful to accurately stratify patient risk in order to identify those who may benefit from adjuvant therapies. Even if evidence from the literature is only based on retrospective studies, an extended dissection at the time of cystectomy appears to provide a more accurate staging and enhance survival; future prospective studies taking into account the new prognostic factors are needed.

Key words: Bladder cancer; Radical cystectomy; Lymphadenectomy; Lymph node metastases.

Submitted 28 July 2009; Accepted 30 October 2009

Introduction

Despite an aggressive approach toward high-grade and muscle invasive bladder cancer, nearly 25% of patients demonstrate lymph node metastases at the time of RC (1-3); bilateral pelvic LND has been included as part of RC since it may improve pelvic disease control and possibly enhance survival (4). However, the exact anatomic limits of lymphadenectomy have not yet been identified, as well as its role in staging and prognosis is still under debate (1, 5) even if, due to growing evidence from the literature, it is becoming increasingly accepted as a fundamental factor for staging and outcome (1-7). In this paper we review the historical and contemporary characteristics of lymphadenectomy in patients undergoing RC for transitional cell carcinoma of the bladder.

Anatomy of the lymphatic drainage of the bladder

The understanding of the lymphatic system of the bladder is of fundamental importance when considering the specific sites of metastases, as well as trying to define the appropriate extension of the pelvic lymphadenectomy. Laedbetter and Cooper in 1950 (8) studied the lymphatic drainage system of the bladder identifying 6 distinct areas: 1) the visceral lymphatic plexus inside the bladder wall (which extends from the submucosa to the muscular layer of the organ), 2) the intercalated nodes (i.e. juxtavesical nodes located inside the perivesical fat divided into anterior, lateral and posterior groups), 3) pelvic collecting nodes and vessel located between the perivesical fat and the pelvic wall (medially to the iliac and hypogastric nodes); 4) regional pelvic lymph-nodes (external iliac, hypogastric and sacral lymph nodes); 5) trunks linking the regional lymph nodes and 6) common iliac nodes (Figure 1).

Regional distribution of metastases

RC series reported that the two most common sites of metastases are the obturator and external iliac lymph nodes. The study by Smith and Whitmore (7) reported the involvement of obturator and external lymph nodes in 74 and 65%, respectively; moreover this series showed metastases in 19% of the cases in the common iliac lymph node site. This was one of the first studies...
supporting the importance of an extended LND which included nodes located along the common iliac vessels. Commenting on more extended dissection Leadbetter and Cooper (8) concluded that aortocaval lymph nodes removal could not be completed and should not be considered part of node dissection during cystectomy. Conversely, more recently it has been demonstrated (1, 2) that an extended lymphadenectomy involving lymphatics distal to the inferior mesenteric artery can be safely performed. In fact, the presence of node metastases in the region between the aortic bifurcation and the inferior mesenteric artery may be relatively common and they can be removed surgically (2). The distribution of node metastases has been carefully evaluated in a multicenter study by Leissner et al. (2). In nearly 300 patients undergoing RC with LND cranially extended up to the inferior mesenteric artery, when considering the regional distribution of 599 lymph node metastases, approximately 56.3% of metastases were located below the common iliac bifurcation and 83.5% below the aortic bifurcation. It is worth noting that 8.2% of metastases were located in the presacral region. More interestingly, when considering the anatomic distribution of metastases in 29 patients with only one positive node (i.e. probably a more accurate model reflecting initial lymphatic diffusion of bladder cancer), 89% were located at sites below the common iliac bifurcation and 100% below the aortic bifurcation; no patients were found with one positive node above the aortic bifurcation. Moreover in 7% of patients, nodal metastases were located only at common iliac sites, whereas no patients with positive nodes located only at sites above the aortic bifurcation were reported. With regard to bilateral way of spreading, in patients with strictly unilateral bladder cancer, nodal diffusion to the opposite side was found in nearly 24% of cases, underlining the need for a bilateral dissection. Hence the article by Leissner underlines some important aspects of lymphadenectomy: 1. bilateral dissection is mandatory (contralateral metastases rates up to 24% of patients with unilateral tumor); 2. extended dissection (up to the aortic bifurcation including presacral region) is advisable since 27% of metastases occur at sites between aortic and common iliac bifurcation. 3. the absence of positive nodes below the aortic bifurcation rules out metastases above it (conversely the presence of positive nodes at common iliac artery sites without positive nodes below it, termed skipped lesion, has been reported) (3). The need for an extended lymphadenectomy was further sustained by Bochner and coworkers (9) who reported 33% of patients with nodal involvement to have metastases to the common iliac nodes. Another recent study by Vázina et al. (3) reported on regional distribution of metastases in 176 patients undergoing RC with extended lymphadenectomy which started above the aortic bifurcation. In 24% of node positive patients, as expected, the most frequent sites of metastases were located in the pelvic region including obturator, external iliac, hypogastric and perivesical nodes; 5% of metastases involved presacral nodes and 4% were located above the aortic bifurcation. The Authors found that the rate of lymph node metastases and cranial extension of node involvement was proportional with stage progression of the primary tumour. Only 2% of pT1 patients showed node metastases and 23%, 46 and 28% of pT2, pT3 and pT4 patients respectively. One patient with a single positive node at common iliac/aortic bifurcation showed no metastases at more distal sites, demonstrating the possibility of skipped lesion at that level. Moreover the Authors noted that 9% of node positive disease without common iliac node involvement had positive presacral nodes, supporting previous anatomical studies which clearly identified lymphatic drainage from the bladder directly into the presacral nodes. Hence the findings reported by Vázina et al. support the subsequent issues: 1. the more the pathologic stage of the primary tumor progresses, the more node metastases number increases and extends cranially. 2. skipped lesions at common iliac/aortic bifurcation sites are rare but cannot be ruled out; extended dissection up to aortic bifurcation is advisable even if negative pelvic nodes are encountered. 3. presacral nodes dissection should be routinely performed since it constitutes a primary station of lymphatic drainage from the bladder. The occurrence of contralateral node involvement in patients presenting unilateral bladder cancer is supported by Leissner et al. (2) and by other studies (10, 11). More recently Mills (12) reported the presence of contralateral node metastases in 41% of patients with unilateral bladder tumor. Abol-Enein et al. (13) also reported on 200 patients undergoing RC and lymphadenectomy extended from the origin.
of the inferior mesenteric artery; 40% of node positive patients had bilateral involvement. Collectively these studies emphasize the importance of an extended lymphadenectomy in order to remove all tumor bearing tissue; LND should be bilateral and extended cranially up to the aortic bifurcation due to the elevated metastases rates at this sites and the possible occurrence of skipped lesions. Conversely, because of the absence of skipped lesions reported cranially to the aortic bifurcation, we postulate that probably the possibility for a more cephalad dissection should be tailored on a case by case basis, according to an accurate intraoperative tumor staging.

**INCIDENCE OF LYMPH-NODES METASTASES**

The incidence of lymph node metastases in patients undergoing RC ranges from 24 to 28% (Table 1). In the largest series reported from the University of Southern California a total of 246 out of 1054 cystectomy cases (24%) were found to have nodal metastases (1).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total number patients</th>
<th>N+ patients</th>
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<tr>
<td>Stein JP (1)</td>
<td>1971-1997</td>
<td>1054</td>
<td>24%</td>
</tr>
<tr>
<td>Leissner J (2)</td>
<td>1999-2002</td>
<td>290</td>
<td>28%</td>
</tr>
<tr>
<td>Vazina A (3)</td>
<td>1992-2002</td>
<td>176</td>
<td>24%</td>
</tr>
<tr>
<td>Abdel Latif M (4)</td>
<td>1997-1999</td>
<td>418</td>
<td>26%</td>
</tr>
<tr>
<td>Poulsen AL (15)</td>
<td>1990-1997</td>
<td>194</td>
<td>26%</td>
</tr>
</tbody>
</table>

**LYMPHADENECTOMY: SURGICAL BOUNDARIES**

Three different types of LND have been described: extended, standard and limited lymphadenectomy.

**Extended lymphadenectomy**

It must include all the lymph nodes in the boundaries of the aortic bifurcation and common iliac vessel (cranially), the genitofemoral nerve laterally, the circumflex vein and Cloquet lymph node (caudally), the hypogastric vessel posteriorly including the obturator fossa, presciatic nodes. An extended dissection may comprise the lymph nodes located up to the level of the inferior mesenteric artery. (Figure 2 A-B)

**Standard lymphadenectomy**

The standard lymphadenectomy is more limited with the upper limit beginning at the level of the common iliac bifurcation; the lateral, distal and posterior limits are the same as those described in the extended dissection (Figure 3).

**Limited lymphadenectomy**

It is generally described as the removal of lymphatic tissue within the obturator fossa, namely the space limited by the external iliac vein laterally, the hypogastric vessels cranially, the obturator nerve medially and the circum-
lymphadenectomy. Outmost nodes are identified visually and by palpation with frequent evaluation of specimen. All these factors contribute to determining the extent of lymph node involvement. Accurate pathologic evaluation plays a fundamental role in the identification of the total number of node removed and in the subsequent evaluation of the number of metastases. Generally, most nodes are identified visually and by palpation without the need of clearing techniques or solvents; by using this procedure it was possible to retrieve a median number of 30 lymph nodes in patients undergoing RC and lymphadenectomy cranially extended up to the aortic bifurcation (17).

Moreover in a cohort of 32 patients, Bochner et al. compared the number of lymph nodes retrieved by submitting lymph nodes en bloc or as distinct packets; the Authors concluded that submitting lymph nodes as separate specimens significantly improves the pathologist’s ability to retrieve lymph nodes to be examined (18). The simple conversion of specimen submission, from en-bloc to distinct packets, demonstrated to increase the number of nodes retrieved for histologic evaluation by more than threelfold (19). Data from the University of Southern California (20) support this concept further on, by submitting the lymphatic tissue as 12 distinct packets, the median number of node retrieved increased from 30 to 56. A more recent work by Ather et al. reported on the comparison between separate and en-bloc submission of lymph nodes in 77 patients undergoing RC, the median number of nodes removed per patient was significantly different; 15 and 7 nodes retrieved in those with separate and en-bloc lymphadenectomy respectively (21). Moreover, it is worth noting that the anatomic limits of LND represent one of the most important factors influencing the number of nodes removed; in three large cystectomy series, in which an extended LND was performed, including two series with the cranial extension beginning at the level of the inferior mesenteric artery and the series by Stein with the dissection beginning 2 cm above the aortic bifurcation, the number of lymph node removed ranged from 30 (median) to 51 (mean). (Table 2). Moreover, the direct comparison between extended and limited approach in terms of lymph node amount has supported what above said. In the laparoscopic series by Finelli (22), 3 and 21 nodes have been retrieved by using the limited and extended dissection respectively. Moreover Poulsen and coworkers extending the dissection from the level of the common iliac vessels up to the aortic bifurcation obtained a significant increase of the median number of nodes from 14 to 25 (15).

Other factors have been proposed to influence the number of lymph nodes retrieved; the surgeon and pathologist accuracy, obviously, have a certain role in obtaining an adequate number of lymphnodes. Interestingly, Bochner et al. prospectively evaluated a variety of surgical, pathological and patient characteristics (9), in order to identify better the relative importance of the various factors in relation to lymph nodes yield. They found only

**Figure 4.**

Limited lymphadenectomy.

**How to increase the number of nodes retrieved and evaluated**

The amount of lymph nodes evaluated from the pathologist depends upon several factors including: the extension of lymphadenectomy, the pathologist accuracy in searching and preparing the lymph nodes for the histological evaluation and the modality of submission of the specimen. All these factors contribute to determining the number of nodes retrieved, the exact incidence and the extent of lymph node involvement. Accurate pathologic evaluation plays a fundamental role in the identification of the total number of node removed and in the subsequent evaluation of the number of metastases. Generally, most nodes are identified visually and by palpation without the need of clearing techniques or solvents; by using this procedure it was possible to retrieve a median number of 30 lymph nodes in patients undergoing RC and lymphadenectomy cranially extended up to the aortic bifurcation (17).

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**Table 2.**

Number of node retrieved according to different extension of lymphadenectomy. (Lap = laparoscopic)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Lymphadenectomy</th>
<th>Nodes retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leissner (2)</td>
<td>1999-2002</td>
<td>Extended (up to inferior mesenteric artery)</td>
<td>43 (mean)</td>
</tr>
<tr>
<td>Aboul-Enein H (13)</td>
<td>1999-2002</td>
<td>Extended (up to inferior mesenteric artery)</td>
<td>51 (mean)</td>
</tr>
<tr>
<td>Stein JP (1)</td>
<td>1971-1997</td>
<td>Extended (2 cm above aortic bifurcation)</td>
<td>30 (median)</td>
</tr>
<tr>
<td>Finelli A (22)</td>
<td>1999-2003</td>
<td>(Lap) Extended vs (Lap) Limited</td>
<td>21 (mean) vs 3 (mean)</td>
</tr>
<tr>
<td>Poulsen AL (15)</td>
<td>1990-1997</td>
<td>Extended vs Standard</td>
<td>25 (median) vs 14 (median)</td>
</tr>
<tr>
<td>Bhatta Dhar N (23)</td>
<td>1987-2000</td>
<td>Extended dissection vs Standard dissection</td>
<td>22 (median) vs 12 (median)</td>
</tr>
</tbody>
</table>
the extent of dissection to significantly influence the amount of nodes retrieved whereas curiously neither surgeon nor pathologist performances showed a significant association; however in this study no fat clearing solutions were used by the pathologist.

Some methods to improve the ability in finding out lymph nodes in the specimen have been proposed. Koren et al. tested the lymphnodes revealing solution (24) which assists the pathologist in discriminating nodes, particularly those with a smaller diameter, allowing for an increased yield and improved staging ability. Indeed, comparing the conventional procedure of palpation and sectioning with the revealing solutions they reported an increase by twofold of the number of node retrieved as well as a size reduction of the glands with the mean diameter shifting from 8 to 4 mm.

In summary, we can state that extending the surgical boundaries of lymphadenectomy and submitting the lymphnodes as distinct packets allows for an increasing number of nodes retrieved and evaluated. The use of fat dissolving solutions has demonstrated to significantly improve pathologist ability for assessing smaller size nodes allowing for a more accurate staging procedure; this improvement could reveal a subset of patients with node positive disease, otherwise misdiagnosed as organ confined, who could benefit of adjuvant therapy. Moreover, due to the emerging role of total node positive count and node density as important prognostic factors, it can be easily argued how it is of key importance retrieving and evaluating the greatest number of nodes as possible.

**LYMPH NODE ASSESSMENT AND MICROMETASTASES DETECTION**

Once lymphnodes have been removed, processing and histologic evaluation should be performed. According to the recommendations for Processing and reporting of Lymph node specimen from the Association of Directors of Anatomic and Surgical Pathology (ADASP) (25), each lymph node should be submitted for microscopic examination and any fat clearing solution is considered necessary, even though it may represent an institutional or individual preference. In the absence of gross tumor involvement the entire node should be submitted for microscopic examination after cutting it into 3 to 4 mm slices in the longitudinal or transverse plan; moreover the ADASP recommends the examination of several levels of each slice, stained with H&E only. The report from the pathologist should accurately mention the number and size of metastatic lymph nodes, the total amount of node examined and the presence of extracapsular extension. As showed in two different papers by Liedberg (26) and Yang (27), immunohistochemical analysis does not seem to improve the accuracy of conventional histopathology in detecting micrometastasis and it should not be routinely used.

Molecular staging techniques have been recently proposed in order to improve pathologic staging by detecting micrometastases. The expression of cytokeratin 19 and uroplakin II was evaluated in 40 patients submitted to RC and pelvic LND; the Authors found that patients with micrometastases detected by these biomarkers showed a statistically lower disease-specific survival rate if compared with patients without positive biomarkers, independently from the presence of pathologically positive nodes (28). The role of mucin-7, detected by RT-PCR technique, in identifying micrometastasis has been further investigated in 25 bladder cancer patients; the presence of mucin-7 was detected in 29% of lymph nodes which had been previously defined as negative by conventional histopathology (29). More recently Marin-Aguilera et al. tested the role of specific genes in identifying nodes harbouring micrometastases, using the quantitative RT-PCR technique, the specific combination of two genes (FXYD3 and KRT20) yielded a 100% sensitivity and specificity differentiating positive nodes from controls allowing the identification of tumor cells in about 20% of previous histologically negative nodes (30). In conclusion molecular staging techniques allow to improve the ability of detecting micrometastasis in about 20-30% of histopathologically negative lymph nodes. Although the real prognostic value of these micrometastases has not yet been clearly understood, it can be postulated that removal of “negative” nodes may provide some benefit.

**LYMPHADENECTOMY ASSOCIATED MORBIDITY AND MORTALITY**

In order to accurately evaluate lymphadenectomy in bladder cancer patients, particular attention should be paid to the risks related to the procedure as well as the additional time required to complete an extended dissection. Moreover, this aspect is particularly important in bladder cancer patients who tend to be elderly with comorbidities in which time extension could increase the risk for intraoperative complications. The impact of extended LND on operative time extension, morbidity and mortality within and after has been recently evaluated in the paper by Brossner et al. (31). A total of 46 patients submitted to RC with limited pelvic lymphadenectomy was compared to 46 patients who had undergone node dissection extended up to the inferior mesenteric artery. The two groups were comparable with regard to ASA (American Society of Anesthesiologists) grade and comorbidities. With respect to limited dissection, the extended lymphadenectomy showed to significantly increase the median operative time by 53 minutes (277 vs 330, p < 0.01); conversely there was no significant difference in terms of perioperative mortality, early complications or the need for blood transfusions. The aforementioned results are further confirmed in the study by Poulsen (15) and Leissner (2) who reported no significant difference in term of mortality, lymphocele formation and lymphedema comparing limited with extended node dissection.

In conclusion, the morbidity of extended and a more limited node dissection result similar, even if the additional time and related complications necessary for an extended dissection should be taken into account according to the characteristics of each single patient.

**THE PROGNOSTIC SIGNIFICANCE OF NODE INVOLVEMENT**

Patients with nodal metastases after RC have a higher risk of tumour recurrence and progression compared with other pathological groups (organ-confined, extrav-
escal) without node involvement (1, 15, 16) even if nearly one out of three patients will have prolonged survival after RC (1, 17). However, various prognostic factors have been identified in node positive patients; these factors should provide risk stratification in order to better identify patients who may benefit from any adjuvant treatment. These factors include the primary tumour stage, the number of positive nodes, the total amount of nodes removed and lymph node density.

**Primary tumour stage**
The extent of the primary tumour represents one of the strongest prognostic factors in patients with node positive disease submitted to RC (1, 14, 17, 19, 32). Estimated five years survival was 46-58% and 22-30% in organ confined and extravesical primary tumour respectively (17, 19). Moreover, a multivariate analysis pointed out primary tumour stage as a significant and independent prognostic factor in patients with node positive disease (19).

**The number of positive nodes**
The total amount of tumour harboring nodes, also called tumour burden, is a well recognized prognostic factor in node positive bladder cancer patients (1, 7, 14, 17, 22). In the largest series reported of more than 1000 bladder cancer patients submitted to RC with LND extending just above the aortic bifurcation, 224 were found with node metastases (17).

The median number of nodes removed was 30 while the median number of nodes with tumor involvement was 2 (range 1-63). The total number of nodes removed did not significantly influence the recurrence-free and overall survival, whereas the total amount of positive nodes resulted a significant prognostic variable. Patients with 8 or less positive nodes at definitive histology showed significantly better survival rates compared with those with more than 8 nodes.

Five and 10-year recurrence free survival in patients with 8 or less positive nodes were 41% and 40%, respectively, compared with only 10% recurrence-free survival at 10 years when more 8 lymph nodes were involved with tumour. Similarly, 5 and 10 years overall survival rates were significantly better in patients harboring 8 or less positive nodes with 37% and 28% respectively versus 4% and 2% in patients with a greater amount of metastatic nodes.

Moreover, on multivariate analysis, the total number of lymph nodes involved resulted a significant risk factor for recurrence-free and overall survival. Lerner et al. reported similar results (33); in 132 node positive patients following RC, the presence of 6 or more metastatic nodes was associated with increased risk of progression (significantly) and death (strongly predictive). Likewise, Herr et al. (34) analyzed 322 bladder cancer patients who underwent RC with node dissection extended up to the aortic bifurcation, the Authors found that in the node positive subgroup, survival was significantly better for patients with 4 or less positive nodes compared to patients with more than 4 nodes. Moreover, in the group of patients with nodal metastases, an improved survival resulted if more than a total of 11 nodes had been removed; curiously that was true also in the group with negative nodes. Finally, the data reported show that a greater number of positive nodes retrieved is significantly related to worse outcomes even if the exact cut-off value of nodes has not been identified yet.

**The total amount of nodes removed**
Although the exact extension of lymphadenectomy have not been clearly identified yet, several studies indicate that the total number of nodes removed has a prognostic significance in lymph-node positive as well as lymph-node negative patients (2, 35). Leissner and coworkers (36) found, considering patients with tumours stage T1-2 without node involvement, disease-free interval was significantly better when more than 16 node were removed; in stage T3 patients, an increased disease-free interval was obtained if more than 16 nodes were removed regardless node involvement. In pT4 the number of nodes removed had no effect on the disease free interval and survival.

In node positive patients, the positive effect of removing more than 16 nodes was noted only if 5 or fewer positive nodes were found, suggesting that probably the disease has already escaped from possible surgical control. In addition, in this subgroup with 5 or less positive nodes, 35% of patients with 16 or more nodes removed were free from recurrence at 5 years of follow-up, in comparison with 23% of patients with less than 16 nodes removed.

The effect of an extended node dissection seems to influence also the outcomes of patients after adjuvant chemotherapy since significant benefit in node positive, T3 or T4 tumors was noted if lymphadenectomy yielded at least 16 nodes. Moreover the Authors pointed out that if at least 20 nodes were removed, approximately 80% of node positive patients would be identified, suggesting that this would be a reasonable limit of nodes to be removed in order to assure a sufficient staging accuracy. In the retrospective study by Poulsen et al. (15), the Authors assessed the influence of extending the limits of pelvic node dissection on outcomes after RC, comparing two different series of patients from the same institution. Five-year recurrence-free survival was slightly better in the group of extended compared to limited dissection even if not significant; however, when considering patients with primary tumour confined to the bladder (stage pT3a or less), extended dissection was significantly associated with greater 5-year recurrence free survival and showed to reduce the 5-year risk of pelvic recurrence and distant metastases.

Data from the Surveillance, Epidemiology, and End Results (SEER) registry including nearly 2000 bladder cancer patient submitted to RC (32) showed that the risk of death was significantly higher in patients with less than 4 nodes removed at surgery, regardless of T-stage and nodal status.

Moreover, controlling for age, tumour stage, histology, chemotherapy and radiation therapy, the most important survival factor in patient undergoing cystectomy was the removal of 10-14 nodes at the time of surgery. A more recent paper using data from the same SEER registry (35)
analysed more than 1200 bladder cancer patients with at least 1 positive node after RC, in multivariate analysis the number of positive nodes and the total number of nodes removed were independent predictors of survival and the removal of more than 10 nodes was associated with increased overall survival.

**Lymph node density**
Lymph node density is defined as the ratio of the number of positive nodes to the total number of examined nodes; it simultaneously incorporates the two concepts of tumour burden and extent of dissection that have been recently emerged as important prognostic factors in bladder cancer patients following RC. Data from the University of Southern California from Stein et al. (17) support the prognostic value of node density showing that patients with density greater than 20% had a significantly worse 10-year recurrence free survival (17%) compared to those with density of 20% or less (43%). Herr et al. (34), who defined node-density as ratio-based lymph node staging, noted that node density of less than 20% was associated with a significant improvement in 5-year survival in comparison with patients with density more than 20%; similar results were further reported by Cheng et al. (37) in a series of 133 radical cystectomies. Recently Kassouf et al. (38) compared the utility of lymph-node density with TNM nodal status in predicting disease-specific survival after RC; analysing data of 248 patients with node positive disease. On univariate analysis both TNM nodal status and lymph node density resulted significant predictors of disease-specific survival; conversely, in a multivariate model, only node density greater than 20% was significantly associated with decrease disease-specific survival. The Authors proposed the superiority of node density to TNM nodal status in predicting disease-specific survival after RC and pelvic lymphnode dissection.

On the other hand it should be mentioned that lymph node density is a multifactorial entity being influenced by several factors. Due to the interindividual variability of lymphatic tissue in the pelvic region well described by Weingartner (39), node density may reduce its prognostic power in patients with scarce lymphatic tissue; moreover lymph-node density is strictly related to pathologist accuracy in processing and evaluating the material received.

However, in most cases, lymph node density simultaneously reflects the quality and the extent of node dissection showing a high prognostic value in node positive bladder cancer patients following RC.

**Extranodal extension**
Metastatic tumour extending beyond the capsule of the lymphnode has been recently recognized to worsen patient prognosis (40). In the group of patients with extranodal extension a significantly decreased recurrence-free survival and overall survival were demonstrated compared with patients with intranodal disease. Moreover in a multivariate model including tumour stage, number of lymph nodes involved and lymph node density, extracapsular extension was the strongest negative predictive factor for recurrence free survival.

**Benefits deriving from an extended lymphadenectomy**
Patients with pelvic recurrence after RC have a poor prognosis even if further therapy is administered, stressing the need for accurate radical dissection in order to obtain optimal disease control at the time of initial treatment. Dhar et al. (41) evaluated 130 patients with pelvic recurrence who had been previously submitted to RC for clinically organ-confined disease. Of the 130 patients, 128 (98.5%) died with a median survival from the time of recurrence of 5 months; pelvic recurrence occurred in 76% of pT3bN0 and 67% of pN+ patients. As aforementioned Leissner (36) and Poulsen (15) demonstrated that an extended dissection was significantly associated with an improved survival and a reduced rate of local and systemic recurrence in node positive as well as node negative patients.

These results seem very encouraging, but it must be taken into account that the Will Rogers phenomenon, that consists in stage migration and new diagnostic technique as a source of misleading statistics for survival in cancer, (42) may overestimate the positive effects of extended lymphadenectomy when evaluating these series. A recent study (23) compared recurrence rates and survival in two series of patients from Cleveland Clinic and University of Bern, who either had standard or extended node dissection. The 5-year recurrence-free survival of node-positive patients was 7% for standard and 35% for extended node dissection. The 5-year recurrence free survival for pT2N0 patients was 67% for standard and 77% for extended dissection, for pT3N0 were significantly different namely 23% and 57% (p < 0.001) for standard and extended dissection respectively. The 5-year recurrence-free survival for pT2N0-2 patients was 63% for standard and 71% for extended dissection and for pT3N0-2, 19% and 49% respectively (p < 0.001). These retrospective studies suggest that standard and limited LND are associated with suboptimal staging and poorer outcome for patients with node positive and node negative disease; extended dissection allows for removal of micrometastases improving survival of patients with or without nodal metastases detected with conventional histology.

**What is the role of TNM classification in node positive patients?**
The current TNM system uses dimension and number of positive nodes as criteria to categorize patients as N1, N2 or N3. It should be noted that, this classification system probably underestimates the prognostic value of the number of positive nodes, since all patients harbouying more than 1 positive node could be theoretically be classified as a unique category including patients with a highly variable number of positive nodes. Moreover, in recent studies, node diameter has not been identified as an independent prognostic factor in node positive patients even if a possible link between node diameter and extranodal tumour extension could be postulated. Vieweg et al. (19) showed a strong association between nodal status, as reported by the TNM classification, and prognosis. Five-year disease specific survival was signifi-

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cantly different in N0, N1, N2 and N3 patients (67%, 44%, 27% and 0 respectively), even though, when considering patients with organ-confined primary tumours, no significant difference was noted between pN0 and pN1 groups.

Moreover Fleischmann et al. (40), on a univariate analysis, found no significant difference in recurrence-free survival and overall survival between pN1 and pN2 patients; Herr et al. (34), in a multivariate analysis of prognostic features for survival and local recurrence, failed to demonstrate that nodal status was an independent prognostic variable.

In conclusion, the present classification system seems to need some adjustments since it lacks to incorporate different important prognostic factors including the number of positive nodes, the total number of nodes removed, the node density and the extranodal extension.

**Prognosis of Node Positive Patients After Radical Cystectomy**

Several studies have demonstrated that there is a chance of long term survival in patients with lymph-node positive disease. Data from large studies (1, 33, 40, 43–45) show a mean 5-year recurrence free survival of 30% ranging from 20.9 to 35% in this group of patients. Moreover even if gross node positive involvement is found during cystectomy, surgical removal alone may provide long term survival as reported by Herr et al. (46).

**Conclusions**

Although the extent of lymphadenectomy remains a matter of debate, increasing data from the literature support a more extended dissection at the time of cystectomy, appearing that an extended dissection may provide a more accurate staging and enhance survival in both node negative and node positive patients without a significant increase in the morbidity and mortality related to surgery. The primary tumour stage, the number of nodes removed, the number of positive nodes and the node density are important prognostic factors that should be taken into account when adjuvant therapies or clinical trials are planned and may also be useful in future staging system.

**References**


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From methylene blue (methylthionine chloride) to Al-Ghorab procedure: The therapy of priapism (our experience).

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Summary

Objective: The better knowledge concerning the anatomo-physiology of erection has brought important changes to the management of priapism. We experimented with a staged therapeutic protocol for this condition.

Materials and Methods: 17 patients, aged from 27 to 71 (mean age 43) were treated for ischemic priapism; the pathogenesis was idiopathic in 9 cases, in 4 cases secondary to intracavernous injection (iC) of PGE1, in 2 cases to papaverine iC, in 1 case to haemolympho-pathy and in another patient to treatment with heparin. Cavernous PO2, PCO2 and pH were checked. All patients underwent removal of 100cc of blood, irrigation with NaHCO3 solution of the cavernous corpora and Methylene blue (MB) iC 10mg every 5 minutes 10 times, repeated twice.

Results: From 3 to 6 hours from the beginning of therapy, detumescence was achieved in 10 cases. In 5 cases the priapism persisted and we administered adrenaline 20mg every 5-10 minutes: 2 cases had detumescence respectively in 5 and 7 hours whereas in the patient with leukaemia the erection persisted and we desisted from further therapy; in 2 other cases the erection persisted and we did a distal cavernosum-glans shunt and the detumescence a was achieved in 30 and 38 hours respectively. In the last 2 cases, before adrenaline we administered an iC of ethylephrine 5 mg every 5 minutes for 4-5 times but finally we had to perform a shunt. In all cases, during the treatment, and during the following 6-8 hours, we administered 200 mg of MB intravenous.

Conclusions: The introduction of oral drugs has changed the epidemiology of priapism. A better knowledge of the molecular mechanisms that govern the cavernous contraction and myo-relaxation has allowed us to use adrenergic drugs and also the MB. This staged therapeutic protocol goes from a less invasive therapy (irrigation with NaHCO3, MB, ethylephrine, adrenaline) to a surgical procedure which must not be delayed and this progression could allow a reduction in the collateral effects.

Key words: Priapism, Methylene blue, Guanylate cyclase.

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Introduction

Priapism is a medical condition known since ancient times and usually defined as an erection persisting for more than 4 to 6 hours, not associated with any sexual excitement (1) and without any pleasure (2). During the last ten years of the last century, priapism changed its epidemiology. By the end of the 70s, owing to the use of injectable drugs in erectile dysfunction (ED) treatment (papaverine first and then PGE1), the number of cases of low flow priapism increased greatly. Papaverine causes priapism with an incidence of about 6% (3), while PGE1 causes priapism or prolonged erections in around 0.6% of cases (4). Since the introduction of oral 5-phosphodiesterase inhibitors (5PDE) the incidence of pharmacological priapism greatly changed. A better knowledge of the anatomy and physiology of the cavernous corpora and the molecular mechanisms of erection allowed the formulation of the new protocols in treating priapism. In particular high flow priapism is treated with endo-vascular surgery (5) and the therapy of the low-flow priapism relies on medicines which modulate the molecular mechanisms of erection. We experimented with a staged therapeutic protocol...
which started with a less invasive pharmacological therapy and in some cases ended with a surgical procedure.

**Materials and methods**

17 cases, from 27 to 71 aged (mean age 43.3) were treated for ischemic priapism.

The pathogenesis was idiopathic in 9 cases, whereas in 4 cases the priapism was observed after intracavernous injection (IC) of 20 µg of alprostadil, in 2 cases after IC of 40 mg of papaverine, in 1 case in a patient suffering from chronic lymphatic leukaemia and in 1 case in a patient treated with heparin.

Cavernous blood PO2 ranged from 44 to 84 mmHg (m 54,6), PCO2 from 47 to 61 mmHg (m 52,2) and pH from 6,2 to 7,3 (m 6,76).

The therapy started by introducing in the cavernous corpora two 19G needles, from a minimum of 6 to a maximum of 36 hours after the beginning of the erection (m: 12,5 hours).

All patients underwent a removal of 100cc of blood from the cavernous corpora (CC) and an irrigation with NaHCO3 solution to raise the pH of the blood within the CC; then we did an IC of 1ml (10 mg) of methylene blue (MB) every 5 minutes for 10 times; this protocol was repeated twice. (as approved by Ethical committee).

**Results**

From 3 to 6 hours (m 4,4) from the beginning of the therapy, detumescence was achieved in 10 cases.

In 5 cases the priapism persisted and we administered an IC of adrenaline of 20 µg every 5-10 minutes for an hour: 2 cases had detumescence after 5 and 7 hours respectively but in the patient with leukaemia the erection persisted and we desisted from further therapy; in 2 other cases the erection persisted and we did a distal cavernosum-glands shunt, according to Al-Ghorab procedure (6-7), and the detumescence was achieved in 30 and 58 hours respectively.

In the last 2 cases, before adrenaline we administered an IC of ethyllephrine (derived from phenylephrine) 5 mg every 5 minutes for 4-5 times. In these cases we also performed an Al-Ghorab procedure for a total of 4 Al Gorab procedures.

We performed this procedures with 2 cuts on the glans, then we reached the albuginea of the CC from which we removed a little lozenge of tissue and after we anastomosed the CC to the glans and closed again the glans incisions. In all cases, during the treatment, and during the following 6-8 hours, we administered 200 mg of MB intravenously.

**Discussion**

Low-flow priapism is the most frequent modality of this condition and it is characterised by an erection persisting for more than 4-6 hours with inactivation of the contraction of the smooth muscular cells to impede the erection. Veno-occlusive mechanisms remain active leading to intracorporal blood stasis, hypoxia, acidosis and causing trophic damage of the cavernous tissue (1).

The epidemiology of the ischemic priapism has changed in the last years, in fact it has become more frequent in consequence of the use of intracavernous injectable drugs (papaverine especially and PGED) (8), but, after the introduction of ED oral drugs its incidence has lowered drastically.

The occurrence of the other forms of priapism haven’t changed (2, 9).

During the 80’s of the last century the molecular and biochemical mechanisms of the erectile physiology were explained; this knowledge permitted the development of different drugs, which could contract and relax the smooth muscular cells (9, 10).

Among the molecules which contract the smooth muscular cells, the most effective is adrenaline; it is used in little doses (20 µg every 5 minutes) (10) but has some collateral effects: hypertension crisis, cephalalgia, reflected brady-cardia, tachycardia, palpitation and arrhythmia (11).

Metaraminol is similar to adrenaline and it has been used in the past, but it has severe collateral effects (8, 11).

In order to counteract the acidosis connected with the hypoxia, irrigations with sodium bicarbonate solution (1,4%) are suggested.

The use of methylene blue dates back to the end of the 80’s when, experimenting on animal erection, it was noted that MB inhibits guanylate cyclase preventing the conversion of GTP to 3-5 GMPc (12). In fact this drug has been used to counteract experimentally induced erections by different substances (12) and subsequently it has been recommended also to treat the priapism (13, 14) and the intraoperative anaesthesia-linked erection (15).

Our work experimented on a staged protocol to treat the low-flow priapism.

After the application of two 19G needles in the cavernous tissue, we removed some cavernous blood to decompress the CC and then we irrigated them with 5 ml of sodium bicarbonate solution every 5 minutes. The treatment proceeded with intracavernous injections every 5 minutes of 10 mg of methylene blue diluted in 4-5 ml of physiological solution. The MB didn’t cause any collateral effects except a transitory blue coloration of the glans (13).

After these steps, in 10 cases we resolved priapism in 3-6 hours. In the remaining cases we used the IC of adrenaline alone or of adrenaline and ethyllephrine (we couldn’t use the phenylephrine which has been suggested with good results (16), because it is not available at our institution).

We recoursed to the Al-Ghorab procedure (6, 7), when the pharmacological therapy failed to resolve the priapism in an acceptable amount of time; in fact we didn’t delay surgery to minimise damage of the cavernous tissue. The cases treated with the shunts were 3 idiopathic forms and 1 case after therapy with heparin, where it was necessary to carry out the surgical procedure before any damage of tissue could occur.

**Conclusion**

Today the therapy of priapism is a multidisciplinary treatment, our protocol is a staged treatment of the ischemic priapism; it starts with a less invasive and less toxic procedure and finishes with a surgical treatment. It is impor-
tant to check the PO₂, PCO₂, pH of the cavernous blood to understand when tissue damage occurs and to develop a therapeutic protocol step by step until obtaining the detumescence. This progression could allow a reduction in the collateral effects and in fact we use the more invasive and more toxic procedures only when the less invasive ones have failed. We think, therefore, that this experience could offer a small contribution in codifying practice in the therapy of the low-flow priapism.

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REFERENCES

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Spermatogenic and ultrasound characterization of young diabetic patients.

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**Summary**

Aim: Different authors showed clear correlations between diabetic disease and male reproductive damage (es. rate of nuclear DNA fragmentation, mitochondrial DNA mutations, increased of enzymatic glication products, etc…). The aim of this observational study carried out on a selected group of diabetic patients (average age 36) with primary infertility was to determine reactive oxygen species (ROS) production in sperm in connection with duration of disease, glicemic control and seminal vesicular emptying in the post ejaculatory.

Methods: All diabetic patients enrolled (20) were submitted to two consecutive spermograms, ROS sperm analysis and transrectal ultrasound evaluation before and after ejaculation, performed according to standard conventional methods.

Results: Diabetic patients with better glicometric compensation (HBA1C < 7%) and duration of disease < 3 years showed spermatic rate of ROS production significantly lower regarding the group with worse glicemic control and greater duration of disease. Diabetic patients with altered vesicular emptying in the post ejaculatory showed spermatic rate of ROS production significantly higher regarding patients with normal vesicular emptying.

Conclusion: The degree of oxidative stress in sperm of diabetic patients follows the course of the other chronic complications, getting worse in connection with duration of disease and glicemic control. Altered vesicular emptying in the post ejaculatory could be an important mechanism for initiation of this higher response.

**Key Words:** Diabetes; Reactive oxygen species; Spermogram; Male infertility.

Submitted 12 January 2009; Revised 5 March 2009; Accepted 5 June 2009

**Introduction**

The pathogenetic role of the oxidative stress supported by a leucocitary and/or iuxta-sperm overproduction of oxygen free radicals (reactive oxygen species, ROS) in the determining of possible spermatic alterations is known by a long time. The sectors that have better explored such role have moved with time from the idiopathic model to the infertility from excretory causes as post-infective/inflammation of the sexual accessory glands (Male Accessory Gland Infections, MAGI), witnessed also by the scientific contribution of our group (1-6). Recently, a new clinical model of radicalic pathology is represented by the diabetic illness evolved in not conventional chronical complicances, like male infertility. In such care, different authors show important physiopathological correlations between diabetes and male reproductive damage (es. rate of nuclear DNA fragmentation, mitochondrial DNA mutations, increased of enzymatic glication products, etc.) (7-9).

**Aim and Design of the Study**

An observational study was carried out on a selected group of diabetic patients (average age 36) with primary infertility to determine reactive oxygen species (ROS) production in sperm in connection with duration of disease, glicemic control and seminal vesicular emptying in the post ejaculatory.

**Materials and methods**

20 selected diabetic patients of age comprised between 28 and 44 years old (average age 36), 17/20 (85%) with...
diabetes mellitus diagnosis (DM) type 2, 2/20 with DM type 1 (10%), 1/20 (5%) with L.A.D.A. (Autoimmune Diabetes of Adults) (10, 11). All diabetic patients were submitted to two consecutive spermograms (after 15 days), ROS sperm analysis was performed according to standard conventional methods and techniques (12), and transesophageal ultrasound evaluation before and after ejaculation. The concentration of leukocytes was determined through the morphological identification using the conventional immunohistochemical coloring. A part of the same sample was examined in order to determine the production of ROS-leucocytes correlated (ROS-L). Briefly, the spermatic preparation was set in double, through separation on discontinuous gradient (45/90%) of Percoll and the misuration of the production of basal ROS and (f-MLP)-stimulated, ([formil-leucil-fenil-alanina/ Sigma Chemicals Co., ST. Louis, MO, USA) was done on aliquot of 400 l cells in suspension, derived both from the sediment (fraction 90%) and from the interface 45/90% of Percoll as previously reported. The misuration of ROS was determined, adjusting the final concentration to 2.5 x 106 spermatozoa/ml in order to reduce the number of leucocytes in the percentage (fraction 90%; fraction 45%) otherwise responsible of an “overflow” reading signal in the chemiluminescence. To reduce to the minimum the methodological errors, all the spermogram were performed by the same operator in a random way.

In this study we have compared the results coming from a parametric test with those of a not parametric test, analyzing the discrepancies. Parametric Test: Student’s test for multiple comparison without correction of Bonferroni - Non parametric Test: Mann-Whitney rank-sum Test.

Last ejaculation 4 days before for all patients. Ultrasonographic evaluation was conducted with transrectal probe (7.5 MHz) (BK Medical Mini Focus) before and immediately after ejaculation always by the same researcher.

RESULTS

Diabetic patients with better glicemic control (HbA1C < 7%) showed a spermatic rate of ROS production significatively lower than patients with lack of balance of moderate degree (HbA1C 7-10%) and severe (HbA1C > 10%) both in the fraction of Percoll at 45 % and at 90%, and in basal conditions and after adding of f-MLP. The only statistic discrepancy emerges from the comparison between the patients with values of HbA1C comprised between 7 and 10% and the patients with values of HbA1C > 10%; in terms of lack of statistic coherence between the parametric test (significative difference) and the not parametric test (not significative difference) in the fraction of Percoll at 90% after adding of f-MLP (Table 1).

Diabetic patients with duration of illness < 5 years showed a spermatic rate of ROS production significatively lower than patients with duration of illness comprised between 5 and 10 years (test of Student; Mann - Whitney Test).

| Table 1. |
| Seminal ROS (cpm x 1000): differences for levels of glicomo-metabolic compensation.|

<table>
<thead>
<tr>
<th></th>
<th>HbA1C &lt; 7% (n. 7)</th>
<th>HbA1C 7-10% (n. 6)</th>
<th>HbA1C &gt; 10% (n. 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percoll 45% basal</td>
<td>130,71±25,10*</td>
<td>289,00±10,68</td>
<td>368,83±14,06</td>
</tr>
<tr>
<td>Percoll 45% f-MLP</td>
<td>218,43±28,00*</td>
<td>413,50±18,34</td>
<td>526,83±20,90</td>
</tr>
<tr>
<td>Percoll 90% basal</td>
<td>8,57 ± 1,17*</td>
<td>20,00±2,00</td>
<td>37,00±3,00</td>
</tr>
<tr>
<td>Percoll 90% f-MLP</td>
<td>27,00 ± 2,73*</td>
<td>42,00±1,47</td>
<td>51,00±1,37</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. subgroup with HbA1C > 10% (test of Student; Mann - Whitney Test).

| Table 2. |
| Seminal ROS (cpm x 1000): differences for duration of diabetic disease. |

<table>
<thead>
<tr>
<th></th>
<th>Years of disease &lt; 5 (n. 6)</th>
<th>Years of disease 5-10 (n. 7)</th>
<th>Years of disease &gt; 10 (n. 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percoll 45% basal</td>
<td>117,17±25,00*</td>
<td>286,86±15,63</td>
<td>389,75±7,12</td>
</tr>
<tr>
<td>Percoll 45% f-MLP</td>
<td>204,83±28,96*</td>
<td>419,00±26,44</td>
<td>545,50±25,53</td>
</tr>
<tr>
<td>Percoll 90% basal</td>
<td>7,83 ± 1,08*</td>
<td>21,71±2,49</td>
<td>40,75±2,84</td>
</tr>
<tr>
<td>Percoll 90% f-MLP</td>
<td>24,80±3,37*</td>
<td>42,29±2,00</td>
<td>52,75±1,25</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. subgroup with diabetes from more than 10 years (test of Student; Mann - Whitney Test)
Table 3.
Seminal ROS (cpm x 1000): differences for post ejaculatory vesicular emptying.

<table>
<thead>
<tr>
<th></th>
<th>Thickness unchanged (n. 6)</th>
<th>Sub-optimal variation thickness (&lt; 3 mm) (n. 7)</th>
<th>Normal variation thickness (&gt; 3 mm) (n. 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percoll 45%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal</td>
<td>377.13 ± 11.06*</td>
<td>219.00 ± 4.68</td>
<td>136.71 ± 20.10</td>
</tr>
<tr>
<td>Percoll 45%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f-MLP</td>
<td>530.12 ± 19.90*</td>
<td>400.50 ± 13.22</td>
<td>221.33 ± 26.00</td>
</tr>
<tr>
<td>Percoll 90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal</td>
<td>39.00 ± 2.00*</td>
<td>21.30 ± 1.00</td>
<td>9.14 ± 1.11</td>
</tr>
<tr>
<td>Percoll 90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f-MLP</td>
<td>54.00 ± 2.37*</td>
<td>41.18 ± 3.17</td>
<td>22.00 ± 2.43</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. sub-group with normal variation of thickness (test of Student; Mann - Whitney Test).

CONCLUSIONS
The degree of oxidative stress in sperm of diabetic patients follows the course of the other chronic complications, getting worse in connection with duration of illness and glycemic control. In future it will be important to analyze determined clinic problematic:
1) the prevailing source of spermatogonial production (leukocytes or spermatocyte);
2) role of diabetic illness when associated to male accessory gland infections, considered main clinical model for sperm oxidative stress;
3) seminological characterization of greater number of young diabetic (infertile) patients;
4) ultrasonographic characterization of male gland accessory in diabetic patients with high degree of sperm oxidative stress.
Altered vesicular emptying in the post ejaculatory could be an important mechanism for initiation of this higher response (13, 14).

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Preoperative and postoperative seminal nitric oxide levels in patients with infertile varicocele.

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Summary

In vitro studies have shown that nitric oxide (NO), inhibits sperm motility at high concentrations. In this study we aimed to determine the NO levels in the seminal fluid of patients with infertile varicocele both pre and postoperatively and in the control group, and compare the results. 20 men with varicocele presented to our clinic for primary infertility and 15 normal fertile men as controls were involved to study. NO levels in the seminal fluid were determined as the total nitrite by Griess reaction and results were compared with Mann-Whitney U test. Preoperative and postoperative mean seminal fluid NO levels in patients with varicocele were 114.82 ± 33.02 µmol/L and 93.17 ± 27.24 µmol/L, respectively. In the control group it was 89.4 ± 20.82 µmol/L. There was a statistically significant different between mean preoperative and postoperative seminal NO levels (p < 0.05), whereas there was no significant difference between mean postoperative seminal NO levels and that of control group (p > 0.05). According to the results of present study, an increase in the level of seminal NO levels may play a role in the sperm dysfunction in infertile patients with varicocele.

Key words: Varicocele; Seminal fluid; Nitric oxide; Infertility.

Submitted 4 June 2008, Accepted 30 June 2008

Introduction

It has been known that varicocele is one of the underlying problems in male infertility, that there is distorted spermiogram parameters in varicocele, and that pregnancy rates increases as sperm quality improves after the surgical treatment of varicocele (1-3). Many studies have been done in order to explain the pathophysiology of testicular dysfunction in varicocele. Despite the exact mechanism of infertility due to varicocele has not been understood completely, the most favorably theory is Leydig and germinal cell dysfunctions secondary to hypoxia due to obstruction of small vessels and venous stasis (4). Back flow of adrenal and renal metabolic products through left internal spermatic vein, an increase in scrotal temperature, endocrinological changes are other theories proposed in order to explain infertility in varicocele (5-8).

Studies have shown that nitric oxide (NO) is toxic on spermatozooids and inhibits sperm motility (9). In this study we looked at NO levels in seminal fluids of infertile patients with varicocele both pre and postoperatively and compared these with that of control group.

Patients and Methods

Twenty men with unilateral varicocele (left sided, grades 2/3) presented to our clinics for the treatment of infertility for at least one year of unprotected sexual intercourse (patient group) as well as 15 fertile men (control group) were included into the study. Exclusion criteria were atrrophic testicles, previous surgery or treatment for infertility, presence of azoospermia, pyospermia (WBC > 10/µl), presence of urinary infection, criptoochidism and any endocrinological disorders.

Surgery for varicocele was done with the high inguinal incision. Spermograms were done on ejaculates obtained after at least 48 hours of sexual abstinence preoperatively and 6 months after surgery according to WHO guidelines (10) (Table 1). After semen analysis, samples were fractioned on Percoll gradients (40-60-95%) according to WHO guidelines (10). Semen was layered on the top of the gradient and centrifuged at 2000 x gravity for 5 minutes at room temperature. Seminal plasma collected on the top of the Percoll gradient was discharged and stored at -20°C until used and biochemical determinations were done at 4°C.
Nitrite analysis: Nitric oxide was quantified by measurements of the NO metabolite, nitrite, using the Greiss reagent as described before (11). In short, seminal fluid (250 μl) was incubated at room temperature with 250 μl of substrate buffer (imidazole 0.1 mol/l, NADPH 210 μmol/l, flavine adenine dinucleotide 3.8 μmol/l; pH 7.6) in the presence of nitrate-reductase (Aspergillus niger, Sigma) for 45 min. to convert nitrate to nitrite. Excess reduced nicotinamide adenine dinucleotide phosphate, which interferes with the chemical detection of nitrite, was oxidized by continuation of the incubation of 5 μg (1μl) of LDH (Sigma), 0.2 mmol/L (120 μl) pyruvate (Sigma) and 70 μl of water. Total nitrite was then analysed by reacting the samples with Greiss reagent (1% sulfanilamide, 0.1% naphthalene-ethylene diamine dihydrochloride in 5% H3PO4 spectroquant (Merck, Darmstadt, Germany). Reacted samples were treated with 500 μl of trichloroacetic acid (20%), centrifuged for 15 min at 8000 g and the absorbance at 548 nm was compared with that of NaN02 standard (0-100 μmol/L).

Statistics: Comparison between the samples was made using Mann-Whitney- U test. P < 0.05 was considered significant.

RESULTS
Preoperatively, mean seminal NO levels in infertile male with varicocele was significantly higher compared with that of control group (p < 0.05). Whereas, there was no significant difference between mean seminal NO levels postoperatively and that of control group (p > 0.05) (Table 2).

DISCUSSION
NO is synthesized from L-arginine via NO-synthetase (NOS). It is a free radical half life of which is considerably short and plays many physiological roles in various biological systems (12, 13). Since it is a labile and a diffusible molecule, NO can be detected as its stable metabolites such as nitrates and nitrites (11). It is cytotoxic at high concentrations and in longer exposure times (14).

Recent studies showed that NO is elaborated from human spermatozoa and in the male reproductive system and suggested that this may impact upon sperm physiology and male reproductive organ functions (15, 16). It was also reported that spermatozoa capacitation is enhanced with NO donors and inhibited with its inhibitors, in vitro (17). Some other studies revealed that, NO inhibits sperm motility and increases toxicity whereas all these can be prevented with the administration of L-NAME (18). In another study it was reported that, seminal fluid NO levels are increased and suggested that this is an inhibiting factor on sperm motility (19).

The reason of increase in NO levels in seminal fluids of patients with varicocele is not known precisely, but proposed mechanisms are excessive NO synthesis by spermatozoa, venous stasis and hypoxia induced excessive NO synthesis (20) and as a result of changes in reproductive tract secondary to varicocele.

The exact mechanism of negative regulation on sperm functions has not been known, but the following mechanisms may be involved in this process: Sperm lipid peroxidation is stimulated by peroxynitrates which subsequently may result in sperm dysfunction (21), inhibition of mitochondrial respiration and DNA synthesis (22), an increase in the levels of cGMP which has already been shown inhibitory to sperm motility in humans and may in turn cause sperm dysfunction (23).

The hypothesis of increased seminal NO levels being the underlying reason of decreased motility is an attractive idea. In the presented study a reverse correlation was found between seminal NO levels and sperm motility (sperm motility is decreased when seminal NO levels are higher as encountered preoperatively, and vice versa or even getting closer to the levels in the control group, postoperatively) which supports the above hypothesis.

In conclusion, we suggest that sperm dysfunction and secondary infertility as a result can in fact be due to increased seminal NO levels in patients with varicocele. Further studies are needed to explore the reason(s) of the increase in seminal NO levels and subsequent sperm dysfunction.

REFERENCES


Asymptomatic chronic urachal abscess mimicking a bladder tumor.

Emanuele Baldassarre, Beatrice Lillaz, Ivano Vittoria, Paolo Pierini

Division of Urology, "Umberto Parini" Hospital, Aosta, Italy

Summary

A 72-year-old man was admitted with a lower abdominal mass, occasionally detected during a previous laparoscopy. The cystoscopy revealed a bulging mass 5 cm in diameter at the vesical dome. The computed tomography (CT) scan showed an extravesical extension in close relationship with the posterior abdominal wall. Two consecutive endoscopic biopsies and a CT-guided percutaneous biopsy were not helpful. At surgery, a mass about 10 cm in diameter was found at the vesical dome and removed “en-block”. The microscopic examination showed a chronic urachal abscess. To our knowledge, this is the second case of asymptomatic urachal abscess mimicking a bladder neoplasm. The reasons of a surgical approach are discussed.

Key words: Chronic urachal abscess; Bladder tumor; Urachal anomalies; Vesical dome; Bulging mass.

Submitted 1 December 2008; Accepted 5 January 2009

Introduction

An urachal abscess is uncommon and represents a diagnostic challenge for clinicians and urologists. The complaint usually consists in abdominal pain, fever, umbilical inflammation or discharge and dysuria, however rarely these symptoms are contemporary present. In particular a chronic urachal abscess may simulate a bladder neoplasm and a correct diagnosis may be delayed. In literature, we found only two cases of symptomatic chronic urachal abscess mimicking a vesical tumour (1, 2), while only one case of an asymptomatic urachal abscess misdiagnosed with a bladder tumour has been described (3).

Case report

A 72-year-old man was referred to our Division with a lower abdominal mass, occasionally detected during a laparoscopic cholecystectomy. The mass appeared as a bladder tumour, emerging from the dome. His past medical history was positive for a right colectomy for cancer nine years before and a right Lichtenstein hemioplasty, two years earlier. The cystoscopy demonstrated the presence of a bulging mass 5 cm in diameter at the vesical dome. The computed tomography (CT) scan revealed an extravesical extension in close relationship with the posterior abdominal wall (Figure 1). Two consecutive endoscopic biopsies and a CT-guided percutaneous biopsy were not helpful.

Figure 1.
CT scan shows the mass in contiguity with the bladder and the posterior abdominal wall (arrow key).
Suspecting an urachal carcinoma or a migration of the inguinal mesh the patient was sent to surgery. A mass about 10 cm in diameter was found at the vesical dome and removed "en-bloc". The intraoperative frozen section and the definitive microscopically examinations revealed a chronic urachal abscess. The post-operative course was uneventful. The catheter was removed on 14th postoperative day, after the cystography.

**Discussion**

The urachus is anatomically located between the transversalis fascia and the peritoneum, within the anterior abdominal wall. It extends from the vesical dome to the umbilicus. It may persist in toto or partially. In literature we found 4 types of anomalies: patent urachus, urachal sinus, urachal cyst and vesicourachal diverticulum (4). An urachal remnant (sinus or cyst) is usually silent up to adulthood. However only a small number of cases of infected urachal remnant have been described, with a pick of incidence in infancy or in early adulthood (5, 6). The singularity of our case is the complete absence of signs and symptoms of urachal abscess, in a 72-year-old man. The bladder mass was detected only occasionally after an explorative laparoscopy and only after the imaging and three negative biopsies we decided for surgery to exclude an urachal carcinoma, a wall sarcoma, a peritoneal metastasis from previous cancer or an inflammatory mass involving a migrated mesh (7-9). The CT scan is usually helpful in similar cases, as described (10), however the chronic inflammation and the organisation of the abscess did not permitted to ascertain the neoplastic nature of the mass in our patient.

We retain that an asymptomatic urachal abscess may be only suspected, however, also if the biopsies are negative, a surgical exploration is recommendable to exclude a neoplasm. In 1997 Minevich et al. reported a large series of 17 infected urachal cysts, proposing an interesting algorithm of surgical management (11).

In conclusion we retain important to consider routinely the presence of an inflamed urachal remnant approaching a mass at the level of the vesical dome. Regarding the treatment of an urachal cyst, if asymptomatic the biopsies and the surgical approach are necessary while, if symptomatic, we suggest to proceed according with the algorithm proposed by Minevich et al.

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c) first, middle and last name of each Author without abbreviations;

d) University or Hospital, and Department of each Author;

e) last names, addresses and e-mails of all the Authors

f) corresponding author

g) phone and/or fax number to facilitate communication;

h) acknowledgement of financial support;

i) list of abbreviations.

SUMMARY

The Authors must submit a long English summary (300 words, 2000 characters).

Subheadings are needed as follows:

Objective(s), Material and method(s), Result(s), Conclusion(s).

After the summary, three to ten key words must appear, taken from the standard Index Medicus terminology.

TEXT

For original articles concerning experimental or clinical studies and case reviews, the following standard scheme must be followed:

Summary – Key Words – Introduction – Material and Methods - Results – Discussion - Conclusions - References - Tables - Legends - Figures.

SIZE OF MANUSCRIPTS

Literature reviews, Editorial and Original articles concerning experimental or clinical studies should not exceed 20 typewritten pages including figures, tables, and reference list. Case reports and notes on surgical technique should not exceed 10 type written pages (references are to be limited to 12). Letters to the editors should be not longer than 1000 words.

REFERENCES

The Author is responsible for the accuracy of the references. References must be sorted in order of quotation and numbered with Arabic digits between parentheses. Only the references quoted in the text can be listed. Journal titles must be abbreviated as in the Index Medicus. Only studies published on easily retrieved sources can be quoted. Unpublished studies cannot be quoted, however articles “in press” can be listed with the proper indication of the journal title, year and possibly volume. References

must be listed as follows:

JOURNAL ARTICLES

All Authors if there are six or fewer, otherwise the first three, followed by “et al.” Complete names for Work Groups are Committees. Complete title in the original language.

Title of the journal following Index Medicus rules. Year of publication, Volume number: First page.


BOOKS

Authors - Complete title in the original language. Edition number (if later than the first). City of publication: Publisher, Year of publication.


BOOK CHAPTERS

Authors of the chapters - Complete chapter title. In: Book Editor, complete Book Title, Edition number. City of publication: Publisher, Publication year. First page of chapter in the book.


TABLES

Tables must be aimed to make comprehension of the written text easier. They must be numbered in Arabic digits and referred to in the text by progressive numbers. Every table must be accompanied by a brief title. The meaning of any abbreviations must be explained at the bottom of the table itself. (If sent by surface mail tables must be clearly printed with every table typed on a separate sheet).

FIGURES

(graphics, algorithms, photographs, drawings)

Figures must be numbered and quoted in the text by number. The meaning of all symbols, abbreviations or letters must be indicated. Histology photograph legends must include the enlargement ratio and the staining method. Legends must be collected in one or more separate pages. (If sent by surface mail figures must be submitted in duplicate. On the back side of each figure the following data must appear: figure number, title of the paper, name of the first Author, an arrow pointing to the top of the figure).

Please follow these instructions when preparing files:

• Do not include any illustrations as part of your text file.

• Do not prepare any figures in Word as they are not workable.

• Line illustrations must be submitted at 600 DPI.

• Halftones and color photos should be submitted at a minimum of 300 DPI.

• Power Point files cannot be uploaded.

• Save as art either TIFF or EPS files.

• If all possible please avoid transmitting electronic files in JPEG format. If this is unavoidable please be sure to save the JPEG at the highest quality available and at the correct resolution for the type of artwork it is.

• Color art must be saved as CMYK, not RGB.

• PDF files for individual figures may be uploaded.

MANUSCRIPT REVIEW

Only manuscript written according to the above mentioned rules will be considered. All submitted manuscripts are evaluated by the Editorial Board and/or by two referees designated by the Editors. The Authors are informed in a time as short as possible on whether the paper has been accepted, rejected or if a revision is deemed necessary.

The Editors reserve the right to make editorial and literary corrections with the goal of making the article clearer or more concise, without altering its contents. Submission of a manuscript implies acceptance of all above rules.

PROOFS

Authors are responsible for ensuring that all manuscripts are accurately typed before final submission. Galley proofs will be sent to the first Author. Proofs should be returned within seven days from receipt.

REPRINTS

A copy of the issue in which the article appears will be provided free of charge. Reprints are not provided. The cost to obtain the PDF file of the article is Euro 50.
Il ruolo della SIEUN

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 ed interventistico in ambito uro-nefro-andrologico.

La SIEUN organizza un Congresso Nazionale con cadenza biennale e diverse altre iniziative in genere con cadenza annuale (corsi monotematici, sessioni scientifiche in occasione dei congressi nazionali delle più importanti società scientifiche in ambito Uro-Neuro-Andrologico).

Dal 2001 la SIEUN è affiliata all’ESUI (European Society of Urological Imaging); pertanto tutti i soci possono partecipare alle iniziative della Società Europea.

L’Archivio Italiano di Urologia e Andrologia è l’organo ufficiale della SIEUN. Questa pagina permette una informazione puntuale sulla attività della nostra Società e consente al Consiglio Direttivo della SIEUN di comunicare non solo ai soci, ma ad una platea più ampio, ogni nuova iniziativa.

Notizie dalla SIEUN

17º CONGRESSO NAZIONALE SIEUN
Bari, 4-6 Novembre 2010

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<td><strong>Programma preliminare</strong></td>
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<td>del paziente trattato con terapia</td>
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I PUNTI SIEUN

(una possibilità di 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.

I PROSSIMI APPUNTAMENTI SIEUN

34º Congresso Nazionale SIUD (Verona, 17-19 giugno 2010)

nell’ambito del quale si terrà la Tavola Rotonda SIEUN

“Ecografia del pavimento pelvico”

RINNOVO PAGAMENTO QUOTA 2010

I soci sono invitati a pagare la quota associativa 2010 entro il 30 marzo 2010.

Chi intende iscriversi alla Società o rinnovare la sua iscrizione sappia che la quota associativa è di EUR 50,00; dal 2009 è prevista anche una quota ridotta di EUR 30,00 per i medici specializzandi.

È possibile pagare:
- effettuando un bonifico sul conto corrente intestato a “the office - SIEUN” - ANTONVENETA - Sede di Trieste Cod. IBAN: IT63H0504002230000003049000 avendo cura di specificare l’ordinante e di inviare copia via fax
- inviando un assegno non trasferibile intestato a “the office - SIEUN”

La segreteria della Società

the office
Via San Niccolò 14 - 34121 Trieste
E-mail: sieun@theoffice.it
Tel. 040.368343 int. 17 - Fax 040.368808
è a disposizione per ulteriori informazioni.