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Urological and Andrological Sciences

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65° Congress "Associazione Urologi Lombardi" January 29th, 2005 - Milan, Italy

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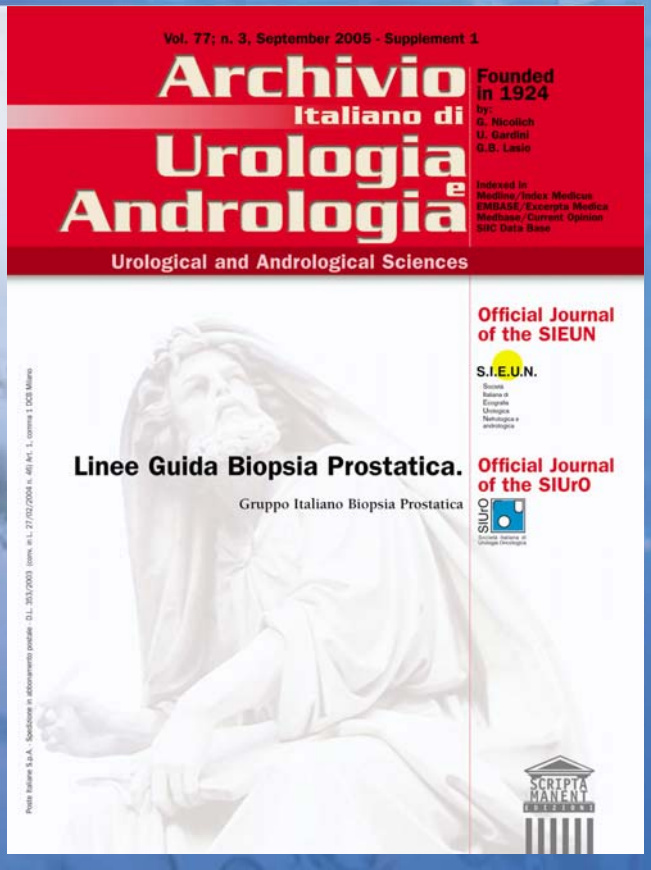
SCRIPTA MANENT EDIZIONI

Società Italiana di Urologia Oncologica

Linee Guida Biopsia Prostatica

Questo volume è stato redatto da un gruppo multidisciplinare di cultori della materia e di rappresentanti di società scientifiche.
Il documento di sintesi finale è stato corretto ed approvato da una giuria esterna al termine di una Consensus Conference Nazionale.
La proposta di preparare una linea guida nazionale è stata spontanea ed è nata dall'osservazione che le biopsie prostatiche, in Italia, frequentemente vengono eseguite senza che vi sia uniformità delle procedure.
Una profonda incertezza esiste non solo su quando eseguire la biopsia e con quale metodica, sul consenso informato, sulla refertazione, ma specialmente su quanti prelievi effettuare, su come interagire con i patologi, quali siano le indicazioni alla rebiopsia e come eseguire tale ricampionamento.
Le Linee Guida sulla Biopsia Prostatica saranno aggiornate periodicamente: a tale proposito è stato fondato un "CLUB ITALIANO BIOPSIE PROSTATICHE" "P.B.I.C."



Il Club è aperto a nuove iscrizioni, chiunque abbia voglia di lavorare può partecipare a questo affascinante progetto e proporre eventuali altre iniziative scientifiche che possano migliorare le nostre conoscenze sui numerosi punti controversi della biopsia prostatica.

SIUrO
Società Italiana di Urologia Oncologica

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

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Contents

Original Paper

Role of risk factors for erectile dysfunction in patients undergoing transurethral resection of the prostate: early impact on sexual function. Pag. 143

Gioacchino De Giorgi, Lorenzo G. Luciani, Claudio Valotto, Miriam Isola, Filiberto Zattoni

Our experience in endoscopic treatment of vesico-ureteral reflux in children. Pag. 146

Igor Osipov, Dnitriia Lebedev, Evjenij Sosnin, Anton Osipov, Alexander Levandovsky, Mana Lifanova, Vladimir Yu Startsev

Detection rate of ultrasound vs CT scan in clinical staging accuracy of renal tumors pT1NxMx. Pag. 149

Giuseppe Dachille, Michele Erinnio, Giuseppe Cardo, Francesco Paolo Maselli, Gianni Vestita, Giuseppe Mario Ludovico

Case Report

A case report of a "smouldering" uretero-vascular fistula. Pag. 151

Stefania Ferretti, Umberto Maestroni, Nicola Azzolini, Pietro Cortellini

A rare case of penile fracture with complete urethral rupture during sexual intercourse. Pag. 153

Marco Tanello, Edoardo Bettini, Simone Griggi, Attilio Ivan Moretti, Silvia Elena Panizza, Giuseppe Pezzotti, Ezio Frego

Sepsis due to asymptomatic Candida prostatitis. Pag. 155

Alois Mahlknecht, Valentina Pecorari, Astrid Richter

Review

Cyproterone acetate in the therapy of prostate carcinoma. Pag. 157

Valter Torri, Irene Floriani

PROSTATE CANCER: TO BE DIAGNOSED AT ALL COSTS?
65° CONGRESS "ASSOCIAZIONE UROLOGI LOMBARDI" JANUARY 29TH, 2005 - MILAN, ITALY

FIUGGI

Trends in prostate cancer epidemiology in the year 2000. Pag. 164

Alberto Trinchieri, Roberto Moretti

The natural history: how has prostate cancer trend modified? Pag. 167

Eugenio Schiaffino

Early diagnosis of prostatic cancer: disease-related survival improvement or extension of observation time? Pag. 169

Michele Ruoppolo

Detection and diagnosis of prostate cancer: what's new. Pag. 173

Vincenzo Scattoni, Mattia Sangalli, Marco Roscigno, Marco Raber, Andrea Gallina, Fabio Fabbri, Antonio Saccà, Andrea Salonia, Francesco Montorsi, Patrizio Rigatti

ORIGINAL PAPER

Role of risk factors for erectile dysfunction in patients undergoing transurethral resection of the prostate: early impact on sexual function.

Gioacchino De Giorgi[1], Lorenzo G. Luciani[1], Claudio Valotto[1], Miriam Isola[2], Filiberto Zattoni[1]

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Summary

Introduction. Transurethral resection of the prostate (TURP) has been long debated as a possible cause of erectile dysfunction (ED). We investigated the role of common risk factors for ED in patients aged 60 to 70 undergoing TURP. Factors related to the treatment were also considered. Materials and methods. Ninety patients underwent TURP for benign prostate hyperplasia (BPH) from June 2002 to February 2003. Fourty-two of them, sexually active aged 60 to 70, were administered preoperatively and 3-month postoperatively the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF-5) questionnaires. A complete assessment of risk factors for ED was performed in the preoperative setting (treated hypertension, diabetes, cigarette smoking, hypercolesterolemy, cardiovascular disease). IIEF score was related to age, comorbidities, operative time, resected tissue weight, retrograde ejaculation, IPSS score. Results. Nine (21.4%) patients reported worsened IIEF-5 score after TURP, and 33 (78.6%) unchanged/improved score. Cardiovascular disease was present in 56% of patients with worsened IIEF-5 score and in 12% of patients with improved/unchanged IIEF-5 score; it was the only factor that correlated significantly in the regression model. Conclusion. In general, most patients report a stable sexual function after TURP. Patients with known cardiovascular disease undergoing TURP had an increased risk of sexual impairment after this procedure.

KEY WORDS: *Erectile dysfunction; TURP; Comorbidities; IPSS score; IIEF-5 score; Cardiovascular disease.*

INTRODUCTION

Transurethral resection of the prostate (TURP) is commonly considered the gold standard for surgical treatment of benign prostatic hyperplasia (BPH). Recently, an increasing attention has been reserved to quality of life and sexuality as important outcomes of this procedure (1). The incidence rate of erectile dysfunction (ED) after TURP is classically reported in 5 to 40% of patients (2). However, earlier (retrospective) studies suggested higher rates of impotence, whereas more recent (prospective) studies tend to report lower rates (3). BPH and ED are widespread diseases with a reported prevalence of 43% in patients 60 to 69 and a prevalence of 67% in 70-years old men, respectively (4, 5). Importantly, prevalence of lower urinary tract symptoms (LUTS) in men suffering from ED was significantly higher than in men with normal erections (6).

Several conditions (age, operative time, amount of resected tissue) have been advocated as potential risk factors for ED after TURP without conclusive evidence. In general, conditions such as hypertension, cigarette smoking, diabetes, cardiovascular disease, dislipidemia have been extensively studied as common risk factors of ED. However, their role in patients undergoing TURP has not been clearly elucidated.

We investigated the early impact of TURP in sexually active patients aged 60 to 70, in an attempt to identify risk factors for sexual impairment following this procedure.

MATERIAL AND METHODS

From January 2002 to February 2003, a total of 90 patients underwent TURP for BPH at our department. Forty-two sexually active patients aged 60 to 70 were administered the International Prostate Symptom Score (I-PSS) (7, 8) and the short form of the International Index of Erectile Function (IIEF-5) (9) questionnaires preoperatively and 3-month postoperatively. Questions on observation of retro-

Table 1.

Patients' characteristics at first visit and comorbidities (n=42).

Characteristics	
Mean age	68 y/o (range 60-70)
Hypertension	21 patients
Cigarette smoking	16 patients
Cardiovascular disease	9 patients
Hypercholesterolemy	6 patients
Diabetes	2 patients

grade ejaculation and time to first sexual intercourse were added to the IIEF-5 questionnaire. Table 1 shows patients' characteristics and comorbidities at preoperative visit (Table 1). Data about operating time and resected tissue weight were obtained from medical records. Patients' postoperative scores were categorized as improved or worsened when they switched from an IPSS category to another (mild symptoms: 0-7, moderate 8-19, severe 20-35) and an IIEF-5 category to another (severe ED 5-7, moderate 8-11, mild to moderate 12-16, mild 17-21, none 22-25). Statistical analysis was performed using Wilcoxon, Mann-Whitney U, Fisher test, and logistic regression model.

Results

Forty patients (95%) of 42 reported significant improvement of I-PSS score. Table 2 shows mean preoperative and postoperative I-PSS and IIEF-5 scores. Results were considered subdividing patients with worsened scores and unchanged/improved scores at the IIEF-5 questionnaire. Nine (21.4%) patients reported worsened IIEF-5 score after TURP, and 33 (78.6%) unchanged/improved score.

Age, operative time, amount of resected tissue and retrograde ejaculation did not differ significantly between the worsened and unchanged/improved IIEF-5 groups. Retrograde ejaculation was reported by 31 (74%) of 42 patients (Table 3). Mean time to the first sexual intercourse was 29 days (range 7 to 60 days). Cardiovascular disease was present in 56% of patients with worsened IIEF-5 score and in 12% of patients with improved/unchanged IIEF-5 score; it was the only factor that correlated significantly in the regression model (Table 4).

Discussion

It has been long debated as to whether TURP could impact sexual function. The incidence of ED after TURP varies greatly according to the different published series. In our series, the rate of worsening of erectile function was as high as 21%, as previously reported (2).

Several hypotheses have been formulated to explain the pathogenesis of this condition. Age and stress of surgery have been ruled out as possible causes in age-matched groups receiving TURP or general surgery procedures. Temperature variations, capsular perforation localization, adenoma size, lesions of nerve bundles have also been advocated in different studies (10, 11). None of them appeared to show conclusive evidence. In our series, age, operative time, amount of resected prostatic tissue and retrograde ejaculation were not statistically different in patients with worsened or unchanged/improved sexual function after TURP, confirming previous results (12).

The impact of LUTS on sexual function and its potential improvement after TURP have also been frequently debated (6, 13). The IIEF postoperative variations were independent from the relief from BPH symptoms, since nearly all patients undergoing TURP reported a concomitant significant improvement of IPSS score. Nonetheless, such relief might have played a role in a portion of patients who reported an improved IIEF-5 score after TURP.

Several studies investigated the role of risk factors for ED in general population (14). Particularly, cardiovascular disease is considered as a strong risk factor for ED (15). In our study, the presence of cardiovascular disease was associated with worsened sexual function after TURP. This condition might have prevented, or at least delayed, a complete restoration of sexual function even in patients who referred a normal sexual life or mild ED before the inter-

Table 2.

IPSS and IIEF score pre and postoperatively (42 patients).

	Mean preoperative score	Mean postoperative score	P*
IPSS	31.5 (range 18-35)	4 (range 1-28)	< 0.001
IIEF	15 (range 8-24)	16.5 (range 1-24)	n.s.

*Wilcoxon test; n.s. = non significant

Table 3.

Age, operative-related factors, among IIEF-5 subgroups.

	Worsened score (n=9)	Improved/unchanged score (n=33)	P*
Age	66 y/o	68 y/o	n.s.
Mean operative time (min)	45	68	n.s.
Mean resected tissue weight (g)	25	25	n.s.
Retrograde ejaculation	9	22	n.s.

*Mann-Whitney U test; n.s. = not significant

Table 4.

Comorbidities among IIEF-5 subgroups.

	Worsened IIEF-5 (n=9)	Improved/unchanged IIEF-5 (n=33)	P*
Hypertension	7 (78%)	14 (42%)	n.s.
Cigarette smoking	4 (44%)	12 (36%)	n.s.
Cardiovascular disease	5 (56%)	4 (12%)	0.013
Dislipidemia	2 (22%)	4 (12%)	n.s.
Diabetes	0	2 (6%)	n.s.

*Logistic regression model; n.s. = non significant

vention. In other words, TURP might have made evident a latent problem, breaking a delicate balance in men who are already at risk for ED.

However, the limitations of our study should be remarked. This is a preliminary report that analyses the outcome of a small series of patients with a relatively short follow-up. Our conclusions should be confirmed by larger studies incorporating a much larger number of patients. Anyways, the 3-month period was chosen because data from a longer follow-up time could overlap with the natural incidence and progression of ED in this age group.

Furthermore, some authors underline that subjective questionnaires should not replace completely instrumental testing, such as NPT (nocturnal penile tumescence) or penile color-Doppler, in the evaluation of ED (16).

Conclusions

In general, most patients report a stable erectile function after TURP. Candidates to TURP with known cardiovascular disease should be particularly aware about the possibility of erectile dysfunction after this procedure. These patients should receive a detailed informed consent on possible impact of TURP on their sexual life.

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ORIGINAL PAPER

Our experience in endoscopic treatment of vesico-ureteral reflux in children.

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Summary

Aim of the study: *To define the guidelines of endoscopic treatment of vesico-ureteral reflux (VUR) in children in relation to grade of VUR, of the location of the ureteral orifice, of the stage of reflux nephropathy and of the association with other urinary tract malformations.* ***Materials and Methods:*** *498 children with vesico-ureteral reflux (VUR) were observed in 702 ureters. All the patients were submitted to a complete urological evaluation and to endoscopic treatment (ET) of the VUR with the implant of a stable polyacrylamid gel (DAM+).* ***Results:*** *The reflux was degree I in 53 ureters, II in 174, III in 301, IV in 165 and V in 9 ureters. VUR was primary in 149 children, secondary to a neurogenic dysfunction of the bladder in 271 patients, complex in the remaining cases. An overall 90.5% success rate of endoscopic treatment with "DAM+" implantation was observed. Success of VUR endoscopic treatment was obtained in 80% of cases with orifice lateralisation, in 60% of cases with high and low intravesical orifice ectopy, and in 10% of cases with extravesical orifice. In 151 ureters (21.5%) endoscopical treatment of VUR had to be repeated, while a third procedure was necessary in 42 ureters (5.9% of cases). In total 895 endoscopic procedures were performed. Open surgical ureteral reimplantation was performed in the cases with persisting VUR after the third attempt of endoscopic procedure.* ***Conclusion:*** *These results of the endoscopic treatment of VUR in children confirm the high efficacy and safety of this method. In any case, before choosing the method of VUR correction, it is necessary to inform the parents of the child about the potential rate of success of the endoscopic treatment in function of the peculiarity of the individual patient.*

KEY WORDS: *Vescico ureteral reflux; Endoscopic treatment; Ureteral orifice.*

INTRODUCTION

Vesico-ureteral reflux (VUR) is one of the most frequent urodynamic alterations in children that can result in the development of secondary pyelonephritis, reflux nephropathy, scarring and renal atrophy. Endoscopic manipulation of the vesico-ureteral orifice allows to avoid pathological urine regurgitation in the ureter restoring normal physiology. The experience of endoscopic treatment in children with VUR has a 20- year period of existence. However, the guidelines of endoscopic treatment in relation to various grades (G) of VUR, of different positions of the ureteral orifice, of various stages of reflux nephropathy and of the association with other urinary tract malformations have not been well defined yet.

METHODS

Since 1995 to 2003 we carried out endoscopic treatment of VUR in 702 ureters of 498 children in the Urologic Clinic of Saint Petersburg's State Pediatric Medical Academy. In our experience we included 391 girls and 107 boys with median age of 9.3 years and disease duration ranging from 2 months to 15 years. All the patients were studied by voiding cystography and voiding US-pyeloscopy. In order to look at the intermittent VUR, bladder filling and ureter voiding were investigated under electron-optical transformer control and radioisotope investigation with Tn 99 DMCA. In 92% of children with VUR G 4-5 split renal function was investigated by radioisotopic, functional and ultrasound methods. The worse alterations were diagnosed in cases with high activity of reflux nephropathy (renal scarring and atrophy with renal hypertension).

Associated urinary tract malformations were found in 85 children (renal duplication in 70 patients, horseshoe kidneys in 5, renal dystrophy in 4, renal hypoplasia in 6). Alterations of split renal function developed more often in this group of patients.

Renal sclerosis and hypertension were diagnosed in 10% of children with VUR G 1-3 and disease duration more than 7 years, but in half of these cases a "sterile reflux", without urine infection and pyelonephritis symptoms, was found.
High vesical pressures were revealed in 69.8% of children by means of cystometry.
Abnormal ureter orifice position was found in 250 cases by means of cystoscopy (orifice lateralisation in 81%, low and high intravesical ectopy in 18%, cervical and diverticular localisation in 1% of children).
Initial monolateral VUR degree I-II in 17 children with a short disease history and a low activity of pyelonephritis were followed for a 6-12 month period while on antibotic prophylactic treatment obtaining a spontaneous remission in 5 cases (29.4 %).
In 75 children with secondary VUR degree I - II endoscopic treatment was deferred after conservative therapy of neurogenic bladder dysfunction within 36 months: out of them 15 children (20%) recovered.
In cases of initial vesico-ureteral reflux degree I -II with a disease history > 4 years, bilateral VUR, and VUR degree III - V immediate endoscopic treatment was offered in order to prevent kidney damage.
A stable biopolymer-polyacrilamid water-structuring gel (DAM+) was implanted under the ureteral orifice. Average gel amount for each implant was 1 ml (0.4-2.9 ml).

Results

The diagnostic work up showed VUR G 1 in 53, VUR G 2 in 174, VUR G 3 in 301, VUR G 4 in 165, VUR G 5 in 9 ureters.
Two hundred and four patients suffered bilateral VUR.
In 151 ureters (21.5%) endoscopical treatment of VUR had to be repeated, while a third procedure was necessary in 42 ureters (5.9% of cases). In total 895 endoscopic procedures were performed.
Cystoscopy and ultrasound investigation were used for the implant settlement revision, the results being successful in 99.6%. Granulate inflammation was revealed in the zone of implantation in 2 cases.
Intravesical implant displacement (caudal, lateral or cervical) was found in 35% of children with orifice lateralisation and extravesicalisation. Fifty per cent of children with VUR G 5 and 25% of children with VUR G 4 had extravesical implant displacement. In case of extravesical displacement the effect of endoscopical treatment was low and the correction had to be repeated 2 and 3 times, with 6-month intervals. Repeated injections were requested in particular for children with ureter extravesicalisation and high pressure in neurogenic bladder.
Complete overall correction of VUR after endoscopical "DAM+" implantation was achieved in 91.5% of cases.
The efficacy of VUR's endoscopical treatment was optimal in cases with VUR G1-3 (97%), while the efficacy in cases with VUR G 4 was 75% and in G 5 38%.
The results also depended on the ureter's orifice position. VUR was cured in 99% of patients with typical orifice localization. Orifice lateralisation led to a reduction of treatment success to 80%, high and low intravesical ectopy to 60%, cervical and diverticular ectopy to 10%.
After the endoscopical treatment of VUR a yearly follow-up was carried out looking for remote results of treatment, renal functional and reflux nephropathy progression.
Patients were followed for 5 years. The activity of reflux nephropathy considerably decreased, pyelonephritis attacks and leucocyturia decreased or disappeared in 78% of cases, proteinuria and bacteriuria levels decreased in 62% of cases.
Children with persisting VUR after 3 endoscopic procedures, high activity of reflux nephropathy and absence of renal hypertension underwent antireflux operations: Gregoir procedure in 18, Politano-Leadbetter procedure in 2, Cohen procedure in 2, ureterocystoneostomy in 6. Four nephroureterectomy and ten heminephrureterectomy were performed in cases of renal hypertension and scarring with persisting VUR G 4-5..
During the surgical procedures, the implants were removed without technical difficulties. Histology investigations did not show inflammatory alterations in the ureters. The implants were surrounded by a thin capsule of connective tissue. Neither giant cells nor granulomatous tissue were found.

Discussion

Our investigation showed that the efficacy of "DAM+" implantation in endoscopic treatment of VUR was about 90%. According to Puri (6) , VUR was cured in 86% of cases after the 1st implantation of dextranomer/hyaluronic acid copolymer and in 100% of cases after the 3rd implantation. According to.Kirsch (4) the efficiency of dextranomer/hyaluronic acid copolymer implantation was only 72%, owing to frequent caudal displacement of the implant.
The efficiency of "DAM+" application was higher than that obtained by dermal collagen use with 65-87.5% immediate success according to Ortenberg (5) and only 9% long-term success according to Haferkamp (3).
A 80% success of VUR endoscopic treatment was obtained in cases with orifice lateralisation, a 60% success in cases with high and low intravesical orifice ectopy, a 10% success in cases with extravesical orifice, in agreement with the experience of Trsinar (7). In his work, Trsinar noted a reliable correlation between bladder pressure values, orifice location and efficiency of endoscopic treatment of VUR.
In any case, before choosing the method of VUR correction, it is necessary to inform the parents of the child about the potential rate of success of the endoscopic treatment in function of the peculiarity of the individual patient.
These results of the endoscopic treatment of VUR in children confirm the high efficiency and safety of this method.

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ORIGINAL PAPER

Detection rate of ultrasound *vs* CT scan in clinical staging accuracy of renal tumors pT1NxMx.

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Summary

Objective: Renal ultrasound is very important in the diagnosis of renal tumors. Material and Methods: From Jannuary 2000 to Jannuary 2005 we retrospectively examined the records of 116 patients, 37 women and 79 men (mean age 54 years, range 22-77), who underwent radical nephrectomy for kidney cancer in clinical stage CT1N0M0. 2.5 cm was the tumor dimension limit between the nephron sparing surgical technique and radical nephrectomy. We subdivided the sample into 2 groups, the first of 45 patients with tumor lesions smaller than 2.5 cm and the second with tumor lesions between 2.5 cm and 7 cm in diameter all patients underwent preoperative staging including ultrasound scan (ETG) and computer tomography scan (CT). Results: Ultrasound has showed 35% sensitivity and 49% specificity for lesions under 2.5 cm in diameter, and 65% sensitivity and 75% specificity and 80% specificity for lesions under 2.5 and 80% sensitivity and 95% specificity for lesions between 2.5 and 7 cm. Conclusions: Ultrasound is the first step in the staging of renal cancer before surgery; to assess. 2.5 and 7 in diameter CT scan is the gold standard for solid and cystic lesions.

KEY WORDS: *Ultrasound scan (ETG); Computer tomography scan (CT).*

INTRODUCTION

Renal ultrasound is very important in the diagnosis of renal tumors, as it can provide a lot of information about the kidney anatomy, function, organization and position. It can demonstrate both benign and malignant situations (stones, cysts, calicopyelectasy, benign and malignant lesions, abscesses) (1). We have examined our experience comparing the accuracy of renal ultrasound with CT (computer tomography) scan in the clinical staging of parenchiymal renal tumors pT1NXMX in patients undergoing radical nephrectomy in our urological department.

MATERIAL AND METHODS

From Jannuary 2000 to Jannuary 2005 we retrospectively examined the records of 116 patients, 37 women and 79 men (mean age 54 years, range 22-77), who underwent radical nephrectomy, in the urological department at Monopoli Sant Giacomo Hospital, for kidney cancer in clinical stage CT1N0M0. In this group of patients 2.5 cm was the tumor dimension limit between the nephron sparing surgical technique and radical nephrectomy, being the 2.5 cm lowest limit of the TNM scale (tumor node metastasis) since the new 1997 TNM scale was introduced. We subdivided the sample into 2 groups, the first of 45 patients patients with tumor lesions smaller than 2.5 cm and the second, 71 patients, with tumor lesions between 2.5 cm and 7 cm in diameter. Since 1997, 7 cm is the greatest limit in the T1N0MO scale (2); all patients underwent preoperative staging including ultrasound scan (ETG) and computer tomography (CT) scan. The clinical measurements were compared with the histological findings. We did not perform other techniques.

RESULTS

Ultrasound has showed 35% sensitivity and 49% specificity for lesions under 2.5 cm in diameter, and 65% sensitivity and 75% specificity and 80% specificity for lesions under 2.5 and 80% sensitivity and 95% specificity for lesions between 2.5 and 7 cm.

Ultrasound was performed by only two operators. After radical nephrectomy the comparison was made between the imaging techniques and pathological findings. We observed no errors and satisfactory correlation between clinical and pathological staging using ultrasound and CT scan. Nephron sparing surgery was performed in 20

patients and radical nephrectomy in all the others cases. All patients had regular oncological follow-up oncological and all are alive and well.

Discussion

Ultrasound is the first step in the screening of solid kidney lesions and this technique is very important in the differential diagnosis between solid and cystic lesions. In this study we have found that ultrasound imaging is sufficiciently accurate in the clinical staging of solid, especially those between 2.5 and 7 cm in diameter, which are currently at the limit between nephron sparing and radical surgery (3). The sensitivity and specificity of the ultrasound technique is comparable to that of TC scan for lesions between 2.5 and 7 cm in diameter. We do not adopt other techniques in the diagnosis of renal lesions (RMI, Helical CT, 3D-CT, vascular MRI) because they are useless in clinical practice.CT scan is today the gold standard in the diagnosis of the suspicious renal lesions, while in metastatic lesions CT scan together with hematological assessment is very important during the oncological follow-up. The use of new techniques (helical CT, 3D-CT) can improve the sensitivity and specicfity of CT scan. The limit of the ultrasound technique is the experience.

Conclusions

Ultrasound technique is very easy to use, cheap and not invasive. The limit of this technique is the operator's experience. Ultrasound is the first step in the staging of renal cancer before surger; to assess. 2.5 and 7 in diameter CT scan is the gold standard for solid and cystic lesions (4). This technique is also very important in oncological follow-up of the patients who have undergone to radical nephrectomy or nephron-sparing surgery.

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CASE REPORT

A case report of a "smouldering" uretero-vascular fistula.

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Summary

Uretero-vascular fistulae are rare. As compared to aortic, uretero-iliac fistulae are by far more frequent according to a 1:8 ratio. We present one case of uretero-prosthetic fistula in a man operated upon the resection of an aortobisiliac aneurysm and Dacron prosthetic graft; six years later, a blunt trauma to the body was followed by a threatening shock, resistant to medical measures. Two subsequent emergency operations allowed to a difficult diagnosis and a life-saving repair of the fistula. Some hypotheses on the pathogenesis of the condition are discussed as well as its clinical problems.

KEY WORDS: Uretero-vascular fistula; Ureteral likage; Hematuria.

INTRODUCTION

Uretero-vascular fistulae are rare: Batter et al. (1) reported a record of 37 cases; further 12 cases were described between 1997 and 2000. Puppo et al. (2) have critically reviewed only 20 "well documented" cases.

As compared to aortic, uretero-iliac fistulae are by far more frequent according to a 1:8 ratio (3). One case of the former, rare type of fistula was described by Goff et al. (4).

Here we report the unusual course of events due to an uretero-iliac artery fistula that followed a closed renal trauma in a patient who underwent vascular surgery for an aortoiliac aneurysm 6 years before.

CASE REPORT

DB. 70 years old, male. Six years before he underwent elective surgery for an aortobisiliac aneurysm. An inverted Y Dacron graft was implanted and the postoperative course was uneventful. On March 2001, due to a bike accident he reported left femoral bone and L1 fractures and a right flank non penetrating trauma (Figure 1).

After the orthopedic surgery (hip prosthesis) the patient became hemodynamically unstable. At the esplorative lombotomy the kidney appeared hydronephrotic, the parenchyma was almost completely destroyed, the dilated pelvis and lumbar ureter were filled with clots. A right nephrectomy was carried out and the patient was discharged on 7th day.

A month later a new admission became necessary for the onset of gross hematuria, urinary retention and severe anaemia. Cystoscopy showed that the source of bleeding was the right ureter. A retrograde pyeloureterogram visualized a residual ureter full of clots but no contrast medium leakage (Figure 2).

The diagnostic hypothesis of an ureteral carcinoma prompted us to carry out an explorative laparatomy: the right ureteral stump resulted strictly stuck to the omolateral iliac prosthesis. Proximally to the crossing point the ureter was dilated and filled with clots while the distal portion resulted patent. The ureterotomy revealed a little herniation of the Dacron prosthesis in the ureteral lumen and a small gap through which a pulsating, hard to control bleeding was evident. The prosthetic wall was sutured and the residual ureter was exsected. The patient was discharged 5 days later.

Figure 1.

CT-scan: blunt trauma of the right kidney.

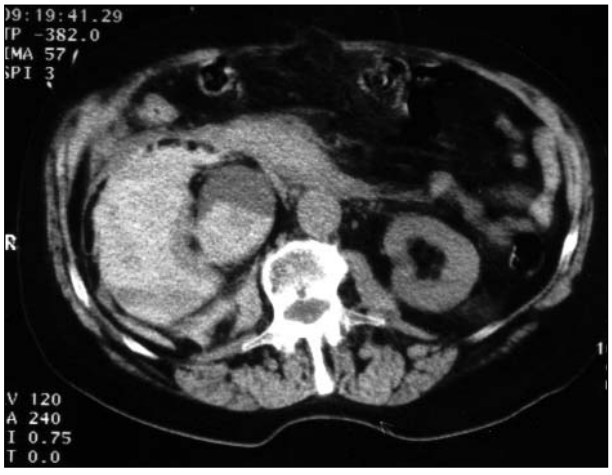


Figure 2.

Right Retrograde pyeloureterogram during cystoscopy.

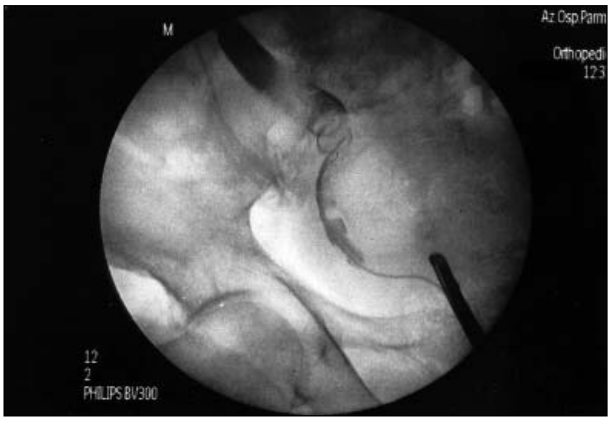
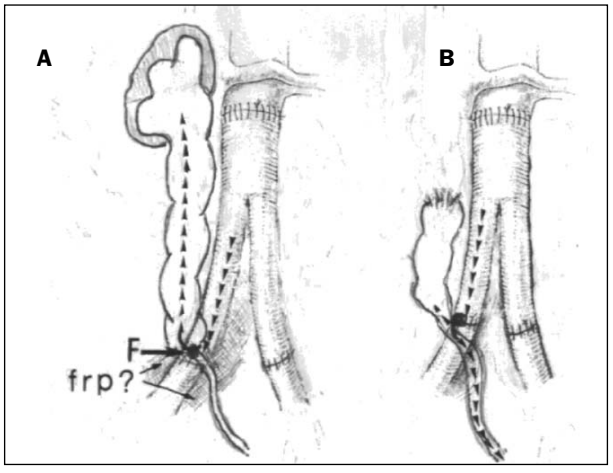


Figure 3.

Schematic explanation – A. After vascular surgery, a periureteral fibrosis (frp) created a stenosis and then a fistula (F); a slow haemorragic dilation of urinary system upon the stenosis induced a destruction of the kidney – B. After nephrectomy, the blood pressure of the fistula won the stenosis with secondary gross haematuria.



Discussion

In this case the coincidence of a flank trauma with signs and symptoms of internal bleeding requires a pathogenetic interpretation since the peculiar anatomy of the excretory route at the time of the onset of the fistula determined a sequence of atypical clinical settings with the relevant therapeutic options.

The first issue to be elucidated is the genesis of the prominent but completely asymptomatic hydroureteronephrosis proximally to the uretero-vascular crossing point. Following the trauma, this huge dilation collected a sudden wave of high pressure blood and it must be emphasized that at the first admission hematuria was absent. The severe haemorrhage following nephrectomy gives evidence that although in the absence of an anatomic stenosis something have hampered the urinary flow creating a slowly obstructing uphill stasis. At the second operation we found that the pelvic portion of the ureter was adherent to the prosthetic branch for a tract but patent. What happened in the six years following the implant of the vascular by-pass? A slow onset stenosis at the crossing site explains the onset of an asymptomatic, although devastating for the right kidney, hydronephrosis. An inflammatory reaction followed by a post-surgical fibrosis is a putative explanation for the focal stenosis. On the occasion of the flank trauma a longitudinally vectored force was applied at the stuck uretero-prosthetic crossing leading to the patency of a fistula that emptied proximally in the dilated excretory route (Figure 3).

After the nephrectomy and the relevant tight ligature of the proximal ureteral stump the blood found its way through the pelvic ureter giving rise to a gross hematuria. Such a sequence of events recalls the multiple parenchymal lesions that can follow a flank or a lumbar trauma in condition of distended renal pelvis. In the case reported by Holmes (3), autopsy revealed that the prosthesis was pulled away at the uro-prosthetic crossing.

In this case we found that, at the site of the pulsating bleeding, a small prosthetic fragment was torn from the prosthesis and adhered to the ureteral wall.

Also in two out of the eight cases reported by Holmes et al., patients underwent a useless nephrectomy followed by a second operation for ureterolysis and prosthesis repair. The mortality of uro-vascular fistulas is still high despite a clear-cut trend toward better outcomes: it declined from 69 to 31% and from 63 to 23% according to two different records (1, 5) in the last 20 years.

The better awareness of the clinical problem, progresses in diagnostic tools, and a multidisciplinary approach have possibly contributed to such an improvement.

Conclusion

In conclusion, haematuria is not an unfailing sign of uretero-prosthetic fistula and an accurate anamnesis for vascular abdominal surgery could be life-saving in the case of an abdominal surgical emergency.

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A rare case of penile fracture with complete urethral rupture during sexual intercourse.

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Summary

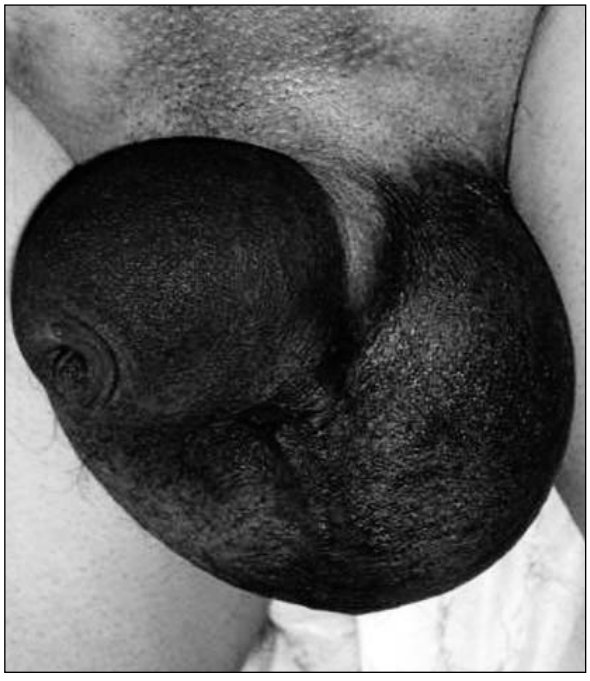
Fracture of the penis during intercourse is a relatively uncommon condition. We report a rare case with laceration of bilateral corpora cavernosa and associated complete urethral rupture. The patient underwent immediate surgical repair of the penile fracture with primary urethroplasty. After 1 year follow-up he presents excellent results with normal sexual function and normal postoperative urethrogram with no voiding problems.

KEY WORDS: *Corpus cavernosum; Fracture; Penis; Urethra; Urethral trauma.*

CASE REPORT

A 45-years old man presented at emergency room with penile swelling, following a blunt trauma against his partner's mons pubis during sexual intercourse, and complete urinary retention. On physical examination he presented blood at the urethral meatus and a subcutaneous hematoma in the penis, scrotum and perineum (Figure 1); the bladder was distended. Retrograde urethrography showed complete urethral rupture (Figure 2). After a percutaneous supra-pubic drainage, the patient underwent surgical exploration with a penile-scrotal incision in the ventral midline. The hematoma was evacuated; there were bilateral transverse tears in the tunica albuginea and a complete disruption of the urethra (Figure 3). The tunica albuginea was repaired bilaterally using an absorbable monofilament; a 18 Ch Foley catheter was passed and the urethra was anastomosed end-to-end with 4/0 vicryl in a tension-free manner, with excellent tissue approximation. A sterile pressure dressing was applied and removed on the first postoperative day, as the supra-pubic drainage. An urethrogram was obtained 3 weeks later after removing the Foley catheter; it demonstrated an excellent healing without stricture or fistula. The patient was able to obtain painful erection with full sexual fuction 6 weeks postoperatively. After 1 year follow-up urethrogram shows a good urethral silhouette (Figure 4), with no stricture and no residual urine; uroflowmetry is normal with average and maximal flow rates of 20 and 26 mL/sec.

Figure 1.
Penis and scrotum enlarged with hematoma.



DISCUSSION

Fracture of the penis is defined as a tear to the tunica albuginea; during erection it thins from 2 mm to between 0.5 and 0.25 mm. The mecha-

Figure 2.
Retrograde urethrogram demonstrating the site of urethral injury.

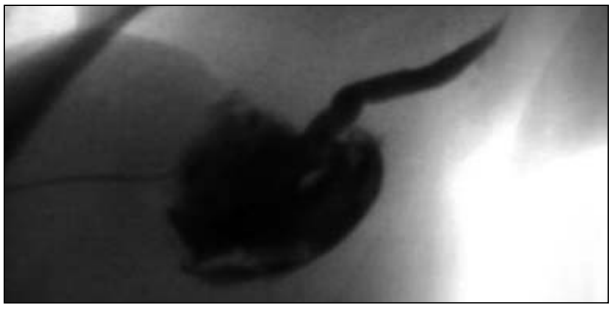
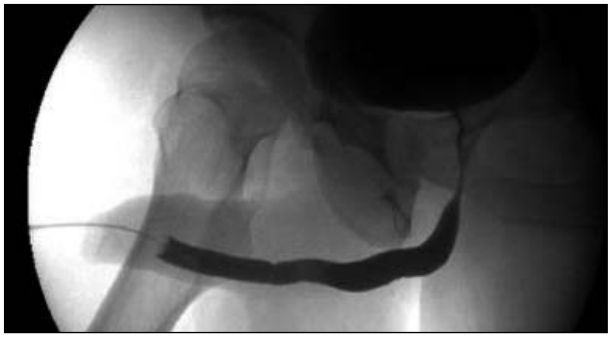


Figure 3.
Complete disruption of the urethra.

Figure 4.
Retrograde urethrogram 1 year postoperatively.



nism of injury is usually a direct blunt trauma to pubis or perineum during intercourse, with a sudden bending of the penis; less common causes are masturbation or manipulation to achieve detumescence (1, 2). The injury presents usually as a sudden cracking sound with detumescence and pain, followed by penoscrotal swelling and ecchymosis. More uncommonly the injury is associated with concomitant urethral disruption (10 to 38%) and rarely with a complete rupture; it presents classically with blood at the meatus and inability to void (3, 4). Early surgical exploration and repair of corpora cavernosa is the gold standard; with associated urethral injury primary urethroplasty can be performed over a urethral catheter. Immediate surgery for repair penile fracture offers the best chance for uncomplicated healing and preservation of erectile function (1-6). Our patient presented with common findings for a fracture of the penis and associated urethral rupture. Urethrogram localised the site of injury; cavernosography was not performed. The patient underwent surgical repair of the bilateral tears of the tunica albuginea and primary urethroplasty (end to end anastomosis); at 1 year he presents a normal sexual function and a normal micturition. In fracture of the penis with complete urethral rupture, we think that primary urethroplasty decreases the complication rates (strictures and voiding difficulties).

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CASE REPORT

Sepsis due to asymptomatic Candida prostatitis.

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Summary

A case of a asymptomatic prostatitis due to Candida Albicans that caused a sepsis is presented. Up today in Literature only 3 cases of Candida infections of the prostate gland without general illness were described. In this case the transurethral electro-resection of prostate was the adequate treatment.

KEY WORDS: *Corpus cavernosum; Fracture; Penis; Urethra; Urethral trauma.*

INTRODUCTION

Fungal prostatitis is an uncommon entity and only in exceptional cases does it occur isolated. It is generally secondary to systemic disease in immunosuppressed patients, in septic patients, in those who have had major surgical procedures, especially transplantation, or that have had antibiotics, steroids, immunosuppressive therapies.
Already in 3 cases (Induhara 1992, Elert 2000 and Collado 2001) have been described isolated Candida infections of the prostate gland without general illness. Emphysematous prostatitis secondary to Candida albicans infection has reported in diabetic patients.
We present the case of a asymptomatic prostatitis due to Candida albicans that caused a sepsis with many diagnostic trouble.

CASE REPORT

L.H., a 49-year-old patient presented with septic fever recovered in Medicine and treated with doxiciclin and co-trimoxazole for suspected acute prostatitis with multi resistant Staphilococcus epidermidis in the secretus. 4 days after his discharge, the patient came back to hospital for high-grade fever without other symptoms. On hospital admission PCR was 14.60 mg/dl (n: <0.5), WBC 10,600/mmc, PSA 3.60 ng/ml (ratio 3.3%).
Next days we noted a progression of infection parameters (PCR 17.90 dann 18.60).
Urine examination was negative for sugar and proteins; microscopy revealed some pus cells and was sterile on culture. Blood culture war negative for bacteria.
Rectal examination revealed a little painful prostate, without any fluctuations or nodularity.
The urethral swab test was negative for Chlamydia and Gonococcus. The result on fungus was still pending.
Cultures for tubercle bacilli IgG and IgM, for Chlamydia trachomatis and pneumonie were negative. On transrectal ultrasound the prostate was measured 31x31x35 mm, the right seminal vesicle was enlarged and there were some micro-abscesses in the left lobes. PSA was 1.28 ng/ml.
After a new prostatic massage, there was a positivity for Candida albicans, without positivity for bacteria.
Therapy with high doses of fluconazol was initiated. Remaining the fever high, a computer tomography was performed that revealed numerous abscesses up to 10 mm in diameter in the spleen. Rx thorax was negative.
Thereafter we changed the therapy to amphotericin B with fever remission and improvement of infection parameters. But after some days serum creatinin has a progression up to 2.27 mg/dl.
The patient was given oral itraconazol (400mg x2) with normalization of laboratory findings.
Transurethral electro-resection of the prostate was carried out. Histopatological examination revealed massive chronic prostatitis with dense mixed inflammatory exudates.
After a six months' follow-up, the patient is doing well, he voids satisfactorily and the urine cultures are negative.

DISCUSSION

Candida albicans is a commensal yeast which has two forms in the human body - budding (yeast) and penetrating (pseudohyphae form) and exists as a saprophyte in the vagina, oral cavity and colon.
It is uncertain whether a yeast overgrowth in the gut lowers general body resistance by attacking the immune system, or whether the effects on the immune system result in non-bacterial inflammation to the prostate tissue, or indeed whether the organism actually infects the prostate tissue directly. Identification of Candida in the

urine, in absence of underlying chronic medical disease (diabetes mellitus, renal failure, vascular disease) may represent colonization or low-grade infection that often resolves but the persistence of candiduria may result not only in regional or ascending infection but in blood-borne dissemination.
Standard microbiologic cultures may not detect fungemia, and prostatic mycosis may be clinically diagnosed as non-bacterial prostatitis.
This case can be another reason to think, in a "era" of increased numbers of immuno-compromised patients and increased use of multiple antibacterial antibiotics, that fungal infection have assumed a greater role, also in case of prostatitis.

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REVIEW

Cyproterone acetate in the therapy of prostate carcinoma.

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Summary

Prostatic carcinoma is one of the most commonly neoplasm in men, with the strongest incidence around the age of 70 years. In consideration of the high hormonodependence of prostatic neoplasm the reduction of testosterone levels represents the choice of treatment for the patients with metastatic disease, and has an application also in the treatment of patients with a more limited disease, but not elegible to local treatment with a curative aim. The circulating testosterone can be maintained to the lowest levels by the use of drugs that can obtain, with different mechanism of action, a "medical castration". Cyproterone acetate (CPA) is a steroideal antiandrogen which has affinity with progesteron and with glucocorticoidal receptors. It centrally inhibits the release of lutehinizing hormon blocking in this way the secretion of testosterone of testicular origin. Besides, it inhibits the action of the androgens of surrenalic and testicular origin to the cellular level through a competitive direct interaction with the cellular receptors. This review illustrates the main evidences of efficacy and safety of CPA in the treatment of prostatic carcinoma.

KEY WORDS: *Prostatic carcinoma; Cyproterone acetate.*

INTRODUCTION

General aspects of prostatic carcinoma

Prostatic carcinoma is one of the most commonly neoplasm in men, with the strongest incidence around the age of 70 years. At present, in many western countries, it is the second most common tumor in the male. In the Countries of the European Union the rate of incidence of prostate carcinoma is of 55 cases per100.000, while mortality is extimated in 22.6 deaths per 100.000

The cumulative incidence of prostate carcinoma, considered until the age of 74 years, is 3.9%, and the risk of death for this disease is of 1.2%. In the last decade, in the USA, in Canada and in many other western industrialized Countries, the incidence increased up to 10 times, and then decreased on values of 1.5-2 times compared to what it could be expected in consideration of the trend of the last 30 years. The mortality has not increased in the same measure and the discrepancy between the incidence increase and the substantial stability of the mortality still lasts after a decade from peak of incidence. This could suggest that the most part of the prostatic carcinomas have been over-diagnosed and, in absence of screening, they are destined to not clinically emerge ("latent" carcinoma). As a matter of fact, the existence of a predominance in post mortem examination of more than 30% of "latent" carcinomas in men with more than 50 years is largely documented (1).

Even if prostate carcinoma is considered a slow-growing tumor (50% of patients die for causes not correlated), some researchers recommend the use of non aggressive treatment for patients with a life expectation of more than 10 years, while other researchers suggest this approach only at an initial stage of the disease (2). The prostate carcinoma includes a heterogeneous population of cells, but in 70-80% of cases it is androgen-dependent, with cancerous prostatic cells requiring the presence of androgens (3, 4). The reduction of the androgen-dependent cells due to the treatment can give place to cellular proliferation of clones immune to the androgens and, then, to a clinical disease progression.

Since testosterone, which is produced at 85% by testicles, is the main circulating androgen (5), orchiectomy can be considered effective in reducing the androgenic production. Alternatively, estrogens and LHRH agonists may prevent the production of androgens. Nevertheless, these therapies do not block the surrenal glands androgens production. The proliferation of the prostatic tissue requires the presence of testosterone, together with an enzyme able to synthesize diidrotestosteron from testosterone, and with a receptor able to recognize diidrotestosteron and to facilitate its transportation into the target cells (6). Therefore, the effects of the androgens either of testicular or surrenal origin can also be eliminated by blocking the androgenic action in the target tissues.

Treatment of the prostatic carcinoma: state of the art

The prognosis in patients affected by prostate carcinoma depends not only on the histological grading and on the clinic state of the disease, but also on other factors, such as the age of the patient, the performance status and the levels of acid alkaline phosphatasis. The most commonly used classifications are those of the American Urologic System (Tumor staging from A1 to D2) and those of the lnternational Union against Cancer (7). The patients with localized disease (stage A or BI) are generally candidates to surgical treatment with eradication of the tumoral mass by radical prostatectomy. Patients with prostate carcinoma at an early stage show a 10 year survival rate around 87%; for this reason the radical prostatectomy should be limited to patients under the age of 70 years. Considering that the disease at an early stage can be surgically treated, pharmacological therapy or surgical castration is recommended for the patients with a more advanced stage, B2, C or D. The survival ratio depends on the initial stage of the tumor: for patients surgically or pharmacologically treated, the rate of survival at 5 year is 67.3% for the carcinoma at stage III (corresponding to stage B2) and 56.7% for the carcinoma at stage IV (corresponding to stage C). Only a few patients who suffer from metastatic carcinoma usually survive more than 3 years.

Treatment of prostate carcinoma has different aims, in consideration of local extension, the aggressiveness of the disease, but also of expected prognosis and presence of comorbidity. Comorbitity itself can be a higher risk factor of death than prostatic neoplasm. As a matter of fact a relevant proportion of patients (nearly 40%), even in advanced status of disease, with a diagnosis of prostatic neoplasm will die "with" and not "in consequence of" prostatic neoplasm. In patients with a disease which is apparently confined to the prostate, the aim of the treatment should be cure, even if there is a risk of overtreatment, since it is not clear yet in which cases the tumor is destined to remain localized: not all the patients with localized desease require a treatment that, on the other hand, might be ineffective for a part of these patiens. This could justify a choice of "watchful waiting" policy in patients with a lower probability of dying "in consequence" of their prostatic tumor, such as patients with intracapsular (T1a-b-c T2a) and well differentiated (Gleason ≤ 6) tumor and low levels of PSA (≤ 10 ng/ml), with less than 10 year life expectative. As regards all the other patients with apparently intraprostatic disease elegible to locoregional therapies, the therapeutic choice cannot be based on results of prospective studies. For this reason radical prostatectomy, external radiotherapy and brachitherapy should be mainly based on the patient choice (also in consideration of the collateral effects related to these different therapeutical options) and on the availability of technical devices.

In patients suffering from extracapsular disease the prognosis is generally poor, but an adequate local control of the disease is usually obtained by external radiotherapy and multimodal treatments; in particular neoadjuvant and adjuvant hormonotherapy can reduce the relapse rate and improve survival for a part of these patients. In patients with metastatic disease palliation is the most concretely pursuable goal, in particular in the symptomatic ones. At present different hormonal therapy options exist for these patients and, in hormono-refractory, the use of chemotherapy, together with analgesic, radiometabolic, and diphosphonate therapy, can have a significant impact on the quality of life. Moreover there are various conditions (biochemical relapse after locoregional treatments with radical intent, biochemical progression after failure of the hormonal therapy) where the absence of symptoms can suggest a watchful waiting conduct delaying the treatment to the appearance of disturbing symptoms. Even in these cases the choice will be based on the patients preferences and expectations and on the compatibility of the available therapeutic options with the patient health condition and age (8).

As regards of the endocrine therapy, the main aim of this review, in consideration of the high hormonodependence of prostatic neoplasm the reduction of testosterone levels represents the choice of treatment for the patients with metastatic disease, and has an application also in the treatment of patients with a more limited disease, but not elegible to local treatment with a curative aim. Bilateral orchiectomy, that permanently reduces the levels of circulating testosterone to less than 50 ng/dl, still represents the faster and less expensive method to achieve such target. The circulating testosterone can be maintained to the lowest levels also by the use of drugs that can obtain, with different mechanism of action, a "medical castration". In this review the main relevant evidences referred to the therapeutic options will be illustrated. It is important to note that, according to the reports on usage of drugs for prostate carcinoma, in Italy the most used hormonal therapies are GHRH analogs and antiandrogen: within this class of drugs, cyproterone acetate (CPA) is widely used: therefore it may be important describe the evidence related to efficacy and safety of this old and relative inexpensive drug in the context of the suggestion provided by international guidelines.

Pharmacinetics and farmacodinamic of cyproterone acetate

CPA is a steroideal antiandrogen which has affinity with progesteron and with glucocorticoidal receptors. It centrally inhibits the release of lutehinizing hormon blocking in this way the secretion of testosterone of testicular origin. Besides, it inhibits the action of the androgens of surrenalic and testicular origin to the cellular level through a competitive direct interaction with the cellular receptors and it can inhibit the growth of cellular malingnant prostatic lines in vitro and in vivo the proliferation of prostatic tumoral masses (9). In patients undergoing androgen deprivation treatment, reduced testosterone levels may increase hypothalamic release of catecholamines and stimulate the thermoregulatory centre, resulting in hot flushes. CPA acts centrally and inhibits the release of mediators, reducing the incidence of hot flushes.

CPA, orally administered, results to be well absorbed in the young volunteers as in the elderly ones, reaching the maximum serum concentration within 4 hours from the administration in the volunteers. CPA is metabolized in

a pharmacologically active metabolite, with pharmacokinetic profile similar to the original compound (10).

Therapeutic effects

Monotherapy

Antiandrogens have been employed in several studies as the only therapy in patients with advanced prostatic cancer. The employment of such treatment protects gonadic function and guarantees a better quality of life, even if it's linked to the development of ginecomastia in around 50% of cases and to the appeareance of breast pain in 10-40% of cases. As regards the specific data on oral CPA, monotherapy to variable doses from 100 to 300 mg/per day (11-18), the available evidences are mainly derived from not comparative and of small size studies.

Nevertheless, an improvement of bone pain and urinary obstruction, together with a reduction of volume and hardness of the prostatic gland, were verified in percentages up to 80% of the patients treated with CPA. Reduction of the prostatic volume and prostatic hardness, normalization of the levels of acid phosphatase and/or decrease of the symptoms were observed in more than 50% of the patients. In comparative studies conducted on larger samples of patients, CPA yielded objective and subjective results similar to those obtained with LHRH agonists. A meta-analysis of 24 randomized studies conducted on 6600 patients with advanced prostatic carcinoma has been recently published. It evaluated survival after a therapy with diethylstilbestrol, LHRH agonists (leuprorelin, goserelin, buserelin), orchiectomy, non steroidal antiandrogen (flutamide, bicalutamide) and steroideal antiandrogen (CPA). Results suggest that there are not substantial differences between treatments in terms of effectiveness, but there is evidence of a lower period of survival in patients treated with the non steroideal antiandrogens. Nevertheless in some recent randomized studies, bicalutamide, at the dose of 150 mg/per day, showed results comparable to those of the castration or LHRH in combination with antiandrogens in terms of overall and disease-free survival in patients with non metastatic locally advanced disease; tolerability was increased. Such results have been confirmed in patients with locally advanced and metastatic disease, with the exception of patients with poor differentiated tumours.

Considering these data, it can be concluded that the employment of antiandrogens as monotherapy should be suggested to patients with limited and non-aggressive disease, or to patients not elegible to definitive locoregional treatment in consideration of age or presence of comorbidity or, finally, to patients who want to avoid the effects of androgenic deprivation. However, the choice of the kind of hormonotherapy is still not based on definite evidences, because of the lack of direct randomized comparisons.

Adjuvant and neoadjuvant endocrinotherapy

Hormonal treatment, when used before radiotherapy, seems to produce a positive effect on the local control of the disease. The following evidences are from randomised studies (19-25): an EORTC study indicated that in patients with locally advanced disease treated with definitive radiotherapy the concomitant employment of goserelin, for 3 years, can improve both the local control and the overall survival. Similarly, from the study of the Radiation Therapy Oncology a significant advantage emerged in terms of local control and of survival free from progression in patients with locally advanced illness treated with goserelin (indefinitely or until progression of illness) since the last week of radiant therapy.

Studies on patients who underwent limphoadenectomy. randomized to receive definitive radiotherapy or combined treatment with radiotherapy and surgical castration, showed a significant advantage for the combination treatment in patients with nodal metastases, either in terms of overall and disease-free survival. Finally, the randomized study lead by the Early Prostates Cancer Trialist Group showed that the use of bicalutamide in addition to standard treatment (surgery, radiotherapy) either in alternative to watchful waiting in patients with locatelized disease or locally advanced disease significantly reduced the risk of disease progression. As regards of CPA, the evidences are based on non comparative studies. CPA allowed a local control in 80% of 15 patients that were given the drug as cytoreductive therapy before radiotherapy. A similar pilot study obtained responses in 16 of the 18 patients treated with CPA before radiotherapy; these results conducted to the accomplishment of a prospective study on the use of CPA as cytoreductive agent before radiotherapy in patients with carcinoma in stage B2 or C. In another not controlled study 38 patients who were treated with CPA and surgical castration have been evaluated showing a reduction of symptomatology in 70% of the patients, with partial responses obtained in 32% of the cases. However, these evidences are based on non comparative studies.

Considering the results of these studies, the adjuvant hormonal therapy seems widely justified in patients with positive nodes after to surgical treatment, as well as in patients with locally advanced disease or scarcely differentiated histotypes after definitive radiotherapy. There are still some doiubts concerning type and optimal duration of adjuvant treatment, even if, taking into consideration the side effects related to endocrine therapy and the results of the above mentioned studies it seems reasonable not to prolong the treatment for more than 2–3 years. The randomized studies concerning the neoadjuvant hormonal treatment before radical prostatectomy so far conducted could show a reduction of positive margins incidence, but no advantage in terms of overall survival. Concerning patients candidates to prostatectomy, an EORTC randomised trial on 213 patients evaluated the effect of CPA administered to the amount of 300 mg/per day for 12 weeks, with the aim of determining if such therapeutic approach could reduce the probability of a biochemical progression of PSA. After a 3-year follow-up, results are not definite, though a slower progression has been observed in a subgroup of patients with a relatively low PSA (25-50 ng/ml).

For hormonal neoadjuvant therapy before radiotherapy, some studies showed an improvement in free-disease survival and a reduction of the rate of relapses, but there

was not evidence an prolongation of overall survival. Nevertheless, in patients with a large prostatic volume, who were candidates to radiotherapy, neoadjuvant treatment reduced the toxicity of the radiant therapy, by reducing the prostatic volume to radiate.

Total androgenic block

It is well known that antiandrogens antagonize, at a tissue level, the androgens action not only of testicular origin but also of adrenal origin, whose levels are not abolished during the surgical of medical castration. This constituted the rationale for the combined administration of antiandrogens with medical or surgical castration, to get a total androgenic blockage (TAB) and to obtain, in this way, effects virtually superior to the ones obtained by castration alone.

In the last 15 years several studies analysed the problem of the potential superiority of the TAB compared to the antiandrogenic monotherapy. The recent meta-analysis of the Prostates Cancer Trialists' Collaborative Group, that reviewed the results of 27 randomized studies comparing TAB and medical or surgical castration, evidenced that TAB determined an enhancement of the 5 year overall survival from 2 to 3% (due to the inclusion or exclusion of the studies with CPA from the analysis). No evidence of effect have been shown instead in patients treated with castration and CPA, due to the increase of mortality not correlated to cancer (26). This finding is however of difficult interpretation, due to different modalities of data collection and different case-mix of patients in the considered studies.

Combination with LHRH agonists

The use of the TAB can, however, in some cases, can be preferable to monotherapy, for example in the treatment of highly symptomatic patients or when negative effects due to flare up can be expected. The LHRH agonists determine reduction of testicular testosterone due to their ability to interfere with hypothalamus-hypophysis-gonad axis, that determines the reduction of testosterone released from testicles (27). Nevertheless, at the initial phase of treatment with LHRH agonists, before the hypophysis desensibilization caused by drugs, there is an increase of testicular testosterone and the prostatic disease can show an acute flare at least in about 33% of patients (28). For this reason during the initial period of treatment with LHRH agonists, it is advisable to give the patients also an antiandrogen to avoid the flare up (29). The results of a study on 525 patients with Stage D prostate carcinoma who had been given goserelin depot 3,6 mg for 28 days or CPA 100 mg/tid per os, or a combination of two drugs with CPA given a week before goserelin, indicate similar effect in terms of time to the progression of the disease among the three treatments evaluated. The study concluded that the total androgenic suppression by means of CPA and goserelin did not offer advantages in terms of clinical response and control of progression, but could reduce some of the side effects, such as acute flare up, caused by the treatment with LHRH agonist. On the contrary, CPA was not as effective as goserelin in term time of progression (median time of progression for goserelin: 346 days; for CPA: 225 day p=0.016) (30). Other studies demonstrated that the use of CPA, given for short periods of time, hindered acute flares in patients who were given buserelin. The results of these studies suggest that the addition of CPA 200 mg/per day to the treatment with intramuscular goserelin 3.6mg every 28 days obtains a more rapid improvement in the performance status in comparison with patients treated only with goserelin (8 vs 12 weeks to get a subjective reply) (31-34).

Intermittent androgenic blockage

Intermittent androgenic blockage consists in the administration of hormonal therapy until PSA decreases to normal levels (PSA <4 mg/L)), with restarting of the treatment when there is a further increase of PSA (> 20 mg/L). The aim of this approach is the delay the selection of androgen-independent clones, the reduction of the side effects and the reduction of costs (35). In fact the use of an intermittent hormonal treatment could produce reduction of side effects related to the androgenic deprivation, as well as a reduction of the costs.

The trials with intermittent therapy demonstrated the recovery of libido and improvement of the sense of wellness in the periods of suspension of the treatment, as well as an effective hormonal suppression at the renewal of the therapy. A recent international study (36) compared the effectiveness of androgenic intermittent versus continuous blockage in 766 patients (age <85 years) with locally advanced or metastatic prostate cancer. After an initial induction treatment of three months, with CPA 200 mg alone for 2 weeks, monthly depot injections of triptorelin in association with CPA 200 mg/day were administered in 626 patients. Patients who showed a PSA decrease below 4 or below 80% of the initial value, were randomised to intermittent or continuous therapy with triptorelin + CPA 200 mg/day. The period off therapy was a median of 70 weeks, and the period on therapy was a median of 14 weeks. Estimate survival at 5 years was 53.8% in the intermittent group and 51% in the continuous group. The main differences were related to QoL, particularly to sexual function. Sexual activity was significantly greater ($p < 0.01$) in the intermittent group. The most common side effects were hot flushes (8%). The Authors conclude that intermittent therapy is an option to use in clinical practice.

Deferred treatment

In relation to the potential side effects of hormonal treatment and to the impact on the quality of life, it seems reasonable to delay the treatment after the appearance of symptoms. The studies of the Veterans Cooperative Administration Urological Research Group (VACURG) showed that the hormonal treatment could be delayed, not having shown significant differences in terms of survival among patients with metastatic disease treated with DES (5 mg/per day), DES + orchiectomy, orchiectomy or simple observation; in particular for the patients treated with DES was observed a reduced cancer-specific mortality but a higher mortality not cancer-specific, because of the cardiovascular effects of the treatment. On the contrary a later study, in which the treatment with DES to three different dosages (0.2, 1 and 3 mg/per day) was compared with the

simple observation, has shown an advantage, in terms of survival, of the immediate treatment.
More recently the Medical Research Council (MRC) Prostates Cancer Working Party Investigators Group, in a randomized study on patients with locally advanced disease with metastatic disease without symptoms, demonstrated the advantage of the immediate treatment, associated with a significant reduction of the cancer specific mortality and with a significant extension of the survival. The Authors pointed out that, in at least 10% of the patients, the treatment does not become necessary for the entire life, and that in elderly patients with not metastatic disease the deferred treatment can be considered a valid option (37).

Effects on hot flashes

One of the most common collateral effects associated to the androgenic suppressive therapy are the hot flushes. Symptoms are generally controlled with the administration of 100 to 300 mg of CPA. In a crossover, placebo controlled study, CPA at 300 mg /per day reduced the incidence of hot flashes after orchiectomy (mean number of heat flushes per day 2.26 vs 9.44) (38) In a larger study conducted on 273 patients previously submitted to orchiectomy, the number of patients who suffered hot flushes was reduced after treatment with CPA (150 mg/perday) in comparison to placebo (39): 33 and 24% of the patients treated with CPA had hot flashes with respect to 61 and 47% of the patients treated with placebo. In another study, after administration of CPA at 200 mg/per day in association with goserelin (3,6 mg subcutaneously) for 28 days, a reduction of the rate of patients that had hot flashes was observed (36.9 vs. 47.6%). Similarly a lower number of patients treated with buserelin at 1,2 mg/per day associated to 150 mg/day of CPA in comparison with patients treated with buserelin alone (40 vs 53%) suffered from hot flushes.

Tolerability

As regards the toxicity profile (16) a good tolerability emerges for CPA and LHRH agonists (leuprorelin, goserlin, buserelin) in comparison with DES and flutamide and nilutamide, in relation to the percentages of suspension of the therapy (1-4 and 0-4% vs 14-19 and 4-10%, respectively). CPA is associated to a mild asthenia in 10% of the patients; nevertheless, this effect is relevant only for patients who are given the higher doses. CPA 300 mg/per day seems to be associated to a lower incidence of cardiovascular events with respect to DES (3.6 vs 18% of the patients), similarly to goserelin. Accordingly, an EORTC study showed that CPA is associated to a lower risk of cardiovascular events in comparison to DES or medroxyprogesterone (10 vs 34 and 18%, respectively) (40).
While it was demonstrated that the therapy with estrogens increases the risk of thromboembolia in patients with carcinoma of the prostate (41), in patients treated with 200 mg/day of CPA was observed a significant increase of the fibrinolitic activity only after 8 weeks of treatment (42-45). It is assumed that the patients submitted to treatment with CPA are exposed to a minor risk of thromboembolic disease than those treated with estrogens.

Weakness and loss of libido, consequent to the reduction of testosterone levels, are the more common side events in patients submitted to pharmacological or surgical castration (46). A recent study by the EORTC (study 30892) evaluated the effects of treatment with CPA or flutamide, on the sexual function of patients with prostate carcinoma (CPA: n = 156; flutamide: n = 154; middle age of the patients: 71 years) (47). A progressive and slow loss of the sexual function with a similar incidence in the two groups of treatment was observed; after 2 years the loss of the spontaneous erectyle ability and of sexual activity was observed respectively in 78% and in the 88% of the patients treated with CPA and in the 80 and in 92% of those treated with flutamide. The patients treated with CPA developed ginecomastia in a significantly lower rate with respect to those treated with flutamide (7.1 vs 42.2%). After at least 6 months of CPA 100 mg/day it was observed a statistically significant reduction of plasma levels of cortisol compared to patients not submitted treatment or treated with estrogens; the circadian variation of the serum levels of cortisol was maintained, and the levels of cortisol were abolished by the test of stimulation. Therefore, even if the potential effect of CPA on the hypothalamus-hypophysis-surrenal axis should not be underestimated, it seems unlikely that, in patients treated with CPA, a therapy of substitution with corticosteroids also in phases of acute stress will be necessary (48).
Long term therapy with CPA was associated with side effects on liver function the Medicines Control Agency (MCA)/Committee on Safety of Medicines (CSM) has indicated a risk of liver toxicity, correlated to the dosage, after prolonged treatment with CPA (49). However, epidemiologic surveys seem to rule out association between prolonged CPA exposure and increase of hepatic enzymes.

Conclusions

The role of hormonal therapy in the treatment of the prostatic carcinoma is quite extablished: evidenced of the usefulness hormonal therapy are documented in the treatment of the patients with locally advanced disease, where the TAB is associated to an increase of the survival. In metastatic patients, early use of hormonotherapy improves the control of the progression. In the hormonal therapy, data show that the effect of the CPA, in terms of impact on the survival, is equal to DES, but with less relevant cardiovascular effects. A possible use of CPA, like other treatments with non steroidal antiandrogens, is the association in the first month of therapy with LHRH for the reduction of the flare effect. The choice of hormonal treatment is not always simple. Controlled trials are scarce in this field, particularly for 'old' drugs, but the large experience of use of cyproterone in the clinical practice, the perceived good tolerability and the favourable cost (both in monotherapy and in association) may explain why cyproterone is still a drug of interest for physicians in the treatment of prostatic carcinoma. However further controlled studies or outcome research are needed in order to have more data for the evaluation of both the risk-benefit and cost profile of these drugs.

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65° CONGRESS "ASSOCIAZIONE UROLOGI LOMBARDI" JANUARY 29TH, 2005 - MILAN, ITALY
PROSTATE CANCER: TO BE DIAGNOSED AT ALL COSTS?

Trends in prostate cancer epidemiology in the year 2000.

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Summary

In North America and Europe during the last 20 years prostate cancer incidence rates progressively increased, peaked in early 1990s and then declined. Newly diagnosed prostate cancers are being detected at an early stage in men presenting with no symptoms with abnormal prostate specific antigen (PSA) level. The proportion of patients treated by radical prostatectomy has increased and the proportion of those treated with hormonal therapy has decreased. The widespread of PSA testing seems to be the cause of the changes in the prostate cancer incidence rates and of the stage migration towards localized disease, but the effective benefit of prostate cancer screening in terms of reduction of cancer related mortality is still to be demonstrated. Definitive evidence on the effectiveness of prostate cancer screening with PSA should come from the results of large-scale screening trials that are still ongoing. In Italy the total number of newly diagnosed cases has been steadily increasing from the early 1980s to the mid 1990s both in Lombardia and Umbria regions. Survival rates dramatically improved from 37-48% to 74-76%, but no trend for mortality was observed.

KEY WORDS: Prostate cancer; Prostate specific antigen; Incidence; Mortality rate.

INTRODUCTION

In the late 1980s a marked increase in prostate cancer incidence rates has been registered in North America and Europe following the introduction of prostate-specific antigen (PSA) testing in the mid 1980s.

In the United States data from the Surveillance, Epidemiology and end Results (SEER) showed that prostate cancer incidence rates peaked in 1992 and then declined (1). Similar trends of prostate cancer incidence were observed in Canada and in Europe.

Newly diagnosed prostate cancer are being detected at an early stage in men presenting with no symptoms with abnormal PSA level (2). In fact the proportion of patients with distant metastases at diagnosis fell from 20.6% to 11.6% and the mean age at diagnosis declined. Consequently the proportion of patients treated by radical prostatectomy increased from 9.9% to 29.2% and the proportion of those treated with hormonal therapy decreased from 14.7% to 11%.

The widespread of PSA testing seem to be the most relevant cause of the large changes in the prostate cancer incidence rates and of the stage migration towards localized disease.

The American Cancer Society recommends annual PSA screening starting at the age of 50 years (3) and in 2001 a study in the United States demonstrated that 75% of the interviewed men aged 50 years or older reported having had a PSA test (4). Similar recommendations are suggested by national urological societies in Italy.

However the effective benefit of prostate cancer screening in terms of reduction of cancer related mortality is still to be demonstrated. After a continuous increase in the previous years, since 1991 in the United States prostate cancer mortality rates have been decreasing with a cumulative fall of 9.7% in mortality between 1991 and 1997 (1). Also in Canada mortality rates decreased by 9.6% from 1991 to 1996 (5).

Similar trends have been reported for some European countries, including Austria, France and Italy (6-8).

In Italy data from the Varese Tumor Registry show a constant increase of the total number of prostate cancer cases registered per year. The number of high-risk cancers at presentation decreased dramatically from 1989-90 to 2001-02, with a parallel decrease in the overall risk of death, mostly because local tumours are detected earlier (9).

As a consequence, an improvement of the 5-year survival rates from 48% in 1978-82 to 76% in 1991-92 was observed, in association with a reduction in the detection of metastatic cancers at diagnosis (10).
In the Umbria region (11) the number of newly diagnosed cases in 1997-99 period was almost four times higher than in the 1978-82 period. The incidence rate registered a three times increase and the age-adjusted incidence increased by about 125%. An improvement of relative survival rate from 37% in 1978-82 to 74% in 1994-98 was observed, although no trend for mortality was apparent.
Data from the ASL Lecco showed a mortalty rate ranging from 96 to 140 (16) (Table 1).
The decline in prostate cancer mortality could be attributed to other factors including increased awareness of the problem, more aggressive and effective treatment and changes of the risk factors.
Controversial data have recently been reported to confirm or not the beneficial role of PSA screening on prostate cancer mortality.
It has been observed that a comparable fall of mortality rate has been observed in countries with considerable differences in the policy of PSA testing, such as USA and Great Britain (12).
Coldman et al. (13) reported that, in areas of British Columbia (Canada) with low, medium and high intensity of PSA screening, the incidence rates were related to screening intensity, but the reduction of mortality rate was surprisingly lower in the area with the higher screening intensity.
On the other hand Chu et al. (14) using the incidence-based mortality rates by stage at diagnosis observed that the decrease in the mortality rate among patients with metastatic disease at diagnosis, consequent to the decline in the incidence of metastatic disease, accounted for the overall decrease of mortality for prostate cancer.
The effectiveness of PSA prostate screening could be evaluated only by prospective randomised controlled studies comparing the mortality rate for carcinoma of the prostate of the screened population with a control population.
Two large-scale prostate cancer screening trials are ongoing having already recruited 215.000 men: the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the Prostate Lung Colorectal Ovarian (PLCO) trial (15).
The ERSPC involves subjects from 7 European centres in Europe (Spain, Finland, Sweden, Italy, Portugal, Belgium, Netherlands) following a common protocol targeting populations with age range between 55-69 years. The patients are screened yearly by PSA testing for 4 years, while additional DRE and TRUS are used in some centres. The rate of patients demonstrating a PSA level > 4 ng/ml ranged between 7-15% across the different centres, 38-94% of them being submitted to biopsy of the prostate with a rate of positve biopsies of 11-28%. The overall cancer detection rate was 1.1-4.2% out of the subjects screened, the majority of the diagnosed cancer being organ confined and moderately differentiated (Gleason 5-7).
The PLCA trial involves ten centres across the USA planning to recruit 74.000 men in the range age 55-74 years. Screening includes PSA and DRE with four subsequent annual screening visits.
The results of these two studies will be combined and the mortality results are still expected.

Table 1.

Standard mortality ratios in the Lecco area (Italy)(modified from Gulisano P, Gattinoni A, Moretti R: Atlante di mortalità della Provincia di Lecco 1990-2000, Grafiche Cola, Lecco 2003).

		Males			
District	**Zone**	**Center**	**SMR**	**Observed**	**Expected**
Bellano	Riviera	Bellano	116	27	23.274
		Mandello	63.6	13	20.435
	Valsassina	Introbio	71.9	14	19.47
Lecco	Calciziocorte	Calciziocorte	126	28	22.22
		Galbiate	95	12	12.629
		Olginate	116.2	14	12.044
		Lecco	93.2	62	66.539
	Oggionese	Bosisio Parini	94.3	8	8.484
		Costamasnago	124.6	13	10.436
		Oggiono	140.7	30	21.327
		Valmadrera	107.4	22	20.486
Merate	Casatenovo	Casatenovo	89.2	35	39.224
	Merate	Olgiate Molgopra	93.5	20	21.385
		Cernusco Lombardone	99.9	43	43.046
ASL di Lecco vs Regione Lombardia*			96	167	173.90
*90-94					
Atlas of mortality			51		ASL di Lecco 1990-2000

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65° CONGRESS "ASSOCIAZIONE UROLOGI LOMBARDI" JANUARY 29TH, 2005 - MILAN, ITALY
PROSTATE CANCER: TO BE DIAGNOSED AT ALL COSTS?

The natural history: how has prostate cancer trend modified?

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Summary

The patients' number submitted to prostate fine-needle biopsy has constantly increased in the last years, posing technical and diagnostic problems to the pathologist. The use of immunohistochemical tests can help to solve some questions. In other cases, when only a few atypical glands are presents, a very cautious behaviour is the rule. The acronym "ASAP" (atypical small acinar proliferation) has been suggested in such cases.

KEY WORDS: *Prostate; Adenocarcinoma; ASAP; PIN.*

INTRODUCTION

In the space of ten years, time trend for prostate cancer has been greatly affected by a various combination of three different diagnostic approaches:

- screening for raised levels of serum PSA;
- recognition of PIN (Prostatic Intraepithelial Neoplasia) as a precancerous lesion;
- systematic use of transrectal ultrasound-guided core biopsies (sextant protocol).

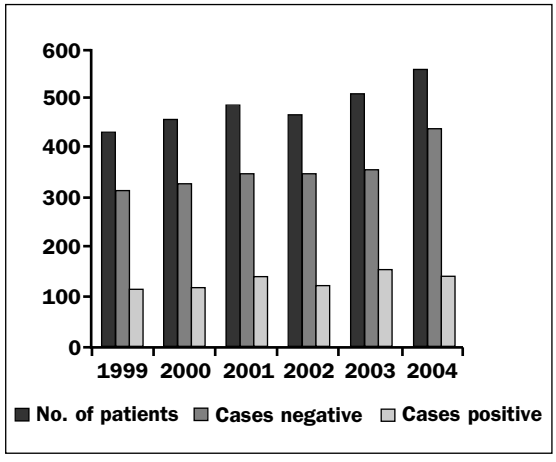
Consequently, the number of patients submitted to needle biopsy has constantly increased. From 1999 (the last year in which the bioptic sampling of both right lobe and left lobe was done) to 2004, the Urology Department of San Carlo Borromeo Hospital produced a 28.9% increase in patients submitted to biopsy with a 128.0% increase in biopsy specimens. In 1999 the Urology Department carried out 1538 biopsy samples (433 patients); the same Unit in 2004 carried out 3358 biopsy samples (558 patiens)!

Figure 1 depicts a constant increase of biopsied patients from 1999 to 2004 (only a slight decrease occured in 2002). Despite this increase, the number of positive biopsies was always in a steady state. This trend can be variously interpreted: first at all, this trend parallels the trend observed in Unites States of America, where, after an increase in positive biopsies, the trend stabilized and now tends to fall. Second, it may be that the cut-off value of PSA must be reconsidered.

A third (and personal) consideration regarding biopsies modalities: we do not appreciate substantial differences in results obtained with the "old" lobe procedure respect to the sextant protocol.

However, such increase in specimen numbers poses some problems to the pathologist and challenges his work much more than before.

Figure 1.



We are facing with technical, diagnostic and differential diagnostic problems, plus the so-called "vanishing cancer phenomenon".

From a technical point of view we come back again to the use of formalin as a fixative instead of bouin fluid (this was used because it stains tissues yellow, rendering them much easier to handle). Bouin fluid does not permit immunohistochemical tests, whereas formalin allow these procedures.

An increase in the number of biopsy specimens requires also an increase in technical skill,

especially for the preparation of wax blocks. The correct alignment of biopsies in the squared wax blocks, permits the best exposition of the specimen surface to the cutting microtome.
Before a diagnostic discussion, some comments about prostate cancer are useful.
In prostatic adenocarcinoma, a low power view of architectural features of tissue can offer some clues about structural derangement, but is not sufficient for making a diagnosis. It is worth noting that grading of acinar cells prostate cancer (Gleason score) definies five histological patterns (or grades) with decreasing differentiation.
Histological grading of prostatic adenocarcinoma has a strong prognostic predictive value and correlates with PSA and PAP levels, possible metastasis and response to therapy. Moreover, for the diagnosis of prostate cancer, cytological features are also important (nuclear enlargement with prominent nucleoli, amphophilic cytoplasm).
Perineural invasion of malignant glands is considered a diagnostic element if the glands are circumferentially involving the perineural space, as in some benign forms the glands are present at only ine edge of the nerve. Mitotic figures are relevant, but rare to find.
Glomerulations (glands with a cribriform proliferation) are of great diagnostic value, whilst crystalloids structures in glands lumina are of little diagnostic value because they are present also in normal glands.
Last but not least we consider high grade PIN, an histological alteration variously associated with prostate cancer. Cribriform variant o PIN can cause problems of differential diagnosis with Gleason 3 cribriform pattern. The use of monoclonal antibodies against high molecular weight cytokeratins (34βE12, P63) can help to solve the question (1-3).
Some pathological forms can simulate prostate cancer and pose important diagnostic problems:

- in chronic prostatitis architectural derangement can simulate cancer but a careful high power field microscopic evaluation usually solve the problem;
- in atypical adenomatous hyperplasia (adenosis), the form that more closely resembles well differentiatied adenocarcinoma. The use of monoclonal antibodies against HMW cytokeratin (34βE12, P63) can be very useful, because the antisera stain the basal cell layer of glands. This layer is retained in benign proliferations but is completely absent in malignant forms;
- in basal cell hyperplasia recognition of benignity is easier, whilst in acinar atrophy (a well know mimicker of cancer) absence of cytological atypia helps to make the diagnosis.

Very difficult diagnostic problems arise when tissue alterations are limited to few glands. In this case the experience of large casistic studies is unquestionable. We agreed with Bostwick that when we evaluate specimens containing few glands, even neoplastic in aspect, we have to be very cautious in judgment.
For these forms, the term “ASAP” (Atypical Small Acinar Proliferation suspiciuos for, but not diagnostic of malignancy) has beeen suggested.
Improvement in technical field and in diagnostic imaging submit to pathologist’s attention new cases in which the simple logic of “positive sample/negative sample” can no longer be accepted and in which the sole morphologic evaluation cannot predict the biological behaviour.
From these considerations is evident that a strict collaboration between clinicians and pathologists can improve diagnosis and a better chosing of the correct therapy.
Another challenging problem for the pathologist is the so-called “vanishing cancer phenomenon”, i.e. the inability to demonstrate in surgical material the prostatic cancer previously diagnosed in fine needle biopsies. This distressing situation will probably increase in the future, as better techniques can be able to find more localized, little and low grade forms of prostate cancer.
Finally, coming back again to the provocative meaning of the title, and as a pathologist, I think that not always a diagnosis is needed at any rate (considering diagnostic pitfalls on bioptic material), but that a closer collaboration between clinician and pathologist can greatly improve diagnostic work-up, not only for prostate cancer.

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65° CONGRESS "ASSOCIAZIONE UROLOGI LOMBARDI" JANUARY 29TH, 2005 - MILAN, ITALY
PROSTATE CANCER: TO BE DIAGNOSED AT ALL COSTS?

Early diagnosis of prostatic cancer: disease-related survival improvement or extension of observation time?

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Summary

It is well recognized that prostate cancer represents the most common cancer in men in western countries and it is the second leading cause of cancer death. Although prostate cancer detection has improved, we still have to establish to what extent our diagnostic tools are correlated with the clinical prognosis. This task of distinguishing more aggressive disease from relatively benign cases remains a major goal. The findings of ongoing randomised screening studies should aid us in this task, so that we can avoid the treatment of those who do not need it and tailor our treatment strategy more closely to the individual prognosis.

KEY WORDS: *Prostate cancer; Early diagnosis; Screening.*

INTRODUCTION

It is well recognized that prostate cancer represents the most common cancer in men in western countries and it is the second leading cause of cancer death. It has been estimated that 679.000 men worldwide were diagnosed with prostate cancer and 221.000 men died of the disease in the year 2002 alone. In the same year 189.000 new cases of prostate cancer were estimated in USA with 30.200 deaths. In 2003, 220.000 new cases and 28.900 deaths (1). This dramatic rising trend of neoplasm during the last decades, induced in the population a considerable social alarm. Many authors have described the recent increase of incidence in prostate cancer like an epidemic worldwide disease (2). In some countries, i.e. Austria and Scandinavia, people, to day, demand a better information on prostate cancer and ask for something will be done (3). Nevertheless few people, in USA and Europe, are aware of many issues concerning prostate cancer: awareness of simple tests for detecting prostate cancer is low, the risk factors for prostate cancer are poorly understood and the full range of treatment options for early disease is unknown (4). In contrast to breast cancer in women, prostate cancer in men has had a much lower profile and it seems unlikely that the population at risk is sufficiently aware of the disease and the possibilities for early treatment and cure (5).

The debate around the effectiveness of prostate cancer screening is wide open. On the basis of scientific evidence there are currently no indications for mass screening using PSA, while there is a wide consent on the utility of opportunistic and addressed screening (6). It is important to distinguish between primary and secondary prevention. The effort of primary prevention is to reduce the cancer incidence by aging on the risk factors of the disease. Secondary prevention also called early diagnosis delays the cancer progression. Early diagnosis seems to increase the overall survival rate but it is unclear if to increase disease-related survival, since the 50% of patients with metastatic disease deaths for other reasons rather than cancer-related reasons. Nevertheless cancer is going on and mortality raises after 12 to 15 years of follow-up (7). Three well-known studies from Sweden (7-9) have reported the long-term survival rates in men with prostate cancer managed conservatively. In these studies the disease-specific survival rate at 10 years was 90% but, surprisingly, decreased to 63% after 15 years of follow-up. The authors concluded that while deferred treatment was an appropriate option for patients with life expectation of 10 years or less, early efficacious treatment might be beneficial for patients with a longer life expectation.

Although prostate cancer screening is highly debated, and its beneficial effect has not yet been estabilished in randomised trials, the American Cancer society recommends annual PSA screening starting at the age of 50 years (10).

Early diagnosis required a large population-based screening trials. It is important to clarify that oncological screening since designed for non symptomatic people,

should address some important issue: 1) High incidence, prevalence and mortality of the cancer; 2) Biological trend of disease and its natural history well-known; 3) Long period of non symptomatic disease; 4) High life-expectation; 5) Sensitive, highly specific and non-invasive screening test available; 6) Definitive curative treatment availability; 7) Acceptable morbidity of the screening and of the treatment; 8) Reasonable costs.

It is widely assumed that latent prostate cancer occurs with the same frequency around the world. However, geographical variations in the incidence of clinical prostate cancer are much considerable, with a 120-fold greater incidence in the black population of the United States than in China (11). Dietary and environmental factors are thought to play a role in the progression of a tumour from its latent stage into its clinical phase. If certainly dietary factors and supplements delay tumour progression in the latent phase, it is not unlikely that they may also be effective in delaying tumour progression. Several epidemiological studies have correlated serum vitamin E levels with prostate cancer mortality (12).

Supplementation with vitamin E reduced all stages of prostate cancer incidence with 32% and mortality from prostate cancer by 41%. The overall prevalence of small latent cancers has been reported to be about 12% and this was unrelated to age or area. In contrast, the frequency of medium and large latent cancers increased steadily with age in 5% of the men dying between the ages of 45 and 54 and in 29% of the men dying at ages > 75 years. Breslow (13) concluded that the demographic behavior of latent cancer of the prostate is similar to that of clinical cancer in its geographical and age distribution. The question of how to avoid detecting so-called "minimal" cancers remain an important issue.

Insignificant prostate cancer is considered a disease that are not clinical relevant. The latter is of growing importance as the widespread application of PSA testing may lead to overdetection and probable overtreatment of some prostate cancers without the propensity of causing patient morbidity or mortality (14). Whereas collateral effects of active treatments (surgery, endocrine) may be reasons for un increase of mortality (15). Etzioni (16) assesed the relative benefits of several serial PSA screening strategies as well as drawbacks in terms of number of tests, number of false positive-tests and rates of over diagnosis.

Prostate specific antigen (PSA) is the foremost cause of the large changes in the prostate cancer statistics. PSA has contributed to the rapid increase in the incidence of prostate cancer and the stage migration towards the detection of localized disease (17). But an important question demands attention because of the enormous costs associated with population screening and the high prevalence of clinically insignificant detectable prostate cancer in the population: how often should healthy men have a PSA test. Etzioni (14) used a computer Markov models to predict the clinical benefits and liabilities of screening PSA-based strategies. In this model the benefit of 18-years anticipation of diagnosis by early screening is effectively 2 years of life saved. Nevertheless in this model, patients with pathologically localized disease (stages A1, A2, B1) on screening are considered cured and death occurred by other causes. The hypothetical patient represented in table, with annual screening, is diagnosed at approximately age 56 with pathological stage A1 disease and dies at age 80 years. Without screening diagnosis happens at approximately age 74 years with clinical stage C disease and death occurs at age 78 by cancer. Etzioni concluded that biannual screening PSA-based is suitable as annual screening. The correlation between PSA and age is significant only in younger patients. In patients older than 65 years the development and progression of BPH lead to insignificant correlation (18).

The possibility of treating with radical and definitive intent, prostate cancer is related to forward identification of disease when minimal occult spread outside the gland did not occur. Other site diffusion is a precocious event in natural development of cancer. It seems happen even in minimal but non insignificant tumour (19). Since the doubling time of malignant prostatic cells is longer than others cancer, time of observation must also be greatly extended. An early diagnosis might lead to a wrong deduction: a long observation time may be explained by a better prognosis of disease.

According to many authors, radical prostatectomy reduces the risk of death due to prostate cancer. Holmberg (20), in Sweden, found a statistically significant difference in the risk of death due to prostate cancer after radical prostatectomy as compared with watchful waiting, yet there was no significant difference between the two groups in the overall survival rate. This difference could be due to unknown adverse effect of the prostatectomy. At eight years after radical prostatectomy, the absolute reduction in both overall and disease-specific mortality rates was approximately 6 percent. Surgical removal of the primary tumour will prevent spread and provide cure only in men with localized disease at time of diagnosis; the effect of prevention will be tangible beyond five years after surgery. The authors found only a small difference between the two groups within the first years after radical prostatectomy. The most likely explanation is that proportion of patients with undetectable, disseminated disease at the time of diagnosis and randomisation was similar in the two groups and that these patients account for the majority of deaths from prostate cancer during early follow-up. The absolute benefit of reduction in development distant metastasis associated with radical prostatectomy has to be weighted against the well-documented side effects of surgery, such as impotence, incontinence and local recurrence and the lack of a demonstrated difference in overall survival. In men with cancer detected by screening, the baseline risk of death from prostate cancer may be even lower, and thus the absolute benefit of radical treatment may be even less pronounced than in some studies. Furthermore, the lead time in screening, which may be many years, would add to the time before the benefit emerges.

Some authors (3, 7, 8, 12, 21, 22) deem that the decrease in mortality rate for prostate cancer is due to a overdiagnosis of insignificant tumours. For many

years insignificant cancer was considered according to MacNeal (23), cancer with volume 0.5 cc or less. Recently, Hugusson (18) showed that only cancer with volume 0.2 or less must be considered entirely harmless. Stamey (24) reported an incidence of 6.4% of insignificant cancer in 896 radical prostatectomy and remarked that PSA screening should be expanded and not restricted.

The Tyrol screening trial (25), launched in 1993, firstly demonstrated in Europe a decrease in PCA-related mortality (PCA deaths declined to 32% in 1997 and 42% in 1998 among men 40 to 79 years of age) that was significantly greater in Tyrol than in the other nine federal states of Austria, where PCA screening was less widespread. In England, in 2003, Evans (26) reported a change in the occurrence of prostate cancer entirely due to changes in the incidence of localised cases. Incidence of non-localised cases and mortality remain almost costant. Sandblom (18) in a prostate-cancer screening, in Norrkoping, started before PSA availability, did not found a significant difference in total and prostate cancer-specific survival between the groups.

Currently, to obtain a final answer whether prostate cancer screening can reduce disease-specific mortality, two large-scale randomised screening trials are ongoing in the world and have already recruited over 215.000 men: ERSSP: the European Randomized Study of Screening for Prostate Cancer; and PLCO (Prostate Lung Colorectal and Ovarian trial) in the United States. The first study started in 1994 involving seven European countries. The initial PSA cut-off has been reduced in this trial from 4.0 to 3.0 ng/ml. As stated by Schroeder and Kranse (27) a furher reduction of the PSA cut-off to a value below 3.0 or 2.5 ng/ml would further increase overdiagnosis. The cancer detection rate at PSA levels less than 2.0 is 4%. In 2003, reports of specific (intermediate) indicators came from the ERSPC trial (28-30). The Finnish ERSPC section provided encouraging results on tumours characteristics after a comparison of the screening and the control arm (28). The proportion of localized-stage and potentially curable cancer was clearly lower in the control group. Comparable outcomes were reported for the Dutch ERSPC section in which the proportion of localized cancers at initial screening was 79%, increasing to 945 in the second screening round, against 69% in the control arm (29). The ERSPC trial is able to demonstrate a significant reduction of 25% in prostate cancer mortality by 2008, or at least 20% if contamination remains limited (30). Contamination means the rate of opportunistic PSA screening in the control arm. The second study started in the same period, it provides annual screening and 4.0 ng/ml as the PSA cut-off (31). In summary, although prostate cancer detection has improved, we still need to establish to what extent our diagnostic tools are correlated with the clinical prognosis. This task of distinguishing more aggressive disease from relatively benign cases remains a major goal. The findings of ongoing randomised screening studies should help us in this task, so that we can avoid the treatment of those who do not need it and tailor our treatment strategy more closely to the individual prognosis.

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65° CONGRESS "ASSOCIAZIONE UROLOGI LOMBARDI" JANUARY 29TH, 2005 - MILAN, ITALY
PROSTATE CANCER: TO BE DIAGNOSED AT ALL COSTS?

Detection and diagnosis of prostate cancer: what's new.

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Summary

Objective: Prior the widespread use of PSA screening in asymptomatic men, prostate cancer was historically detected by a simple digital rectal examination. Although the gold standard for prostate cancer still remains prostate biopsy, current researches in the area of detection and diagnosis of prostate carcinoma are focusing on identification of better sampling protocols, biologic markers and imaging strategies in order to detect disease at an earlier stage. We reviewed all the recent literature on the detection of clinically meaningful prostate cancer.
Methods: A systematic review of the literature using Medline up to 2005 was performed. Electronic searches were limited to the English language using the keywords prostate cancer, diagnosis, transrectal ultrasound, prostate biopsy. Unpublished information known by the authors and that were considered of interest to the readers were also included.
Results: The prostate biopsy technique has extremely changed from the original Hodge's sextant biopsy protocol. Several authors have already reported high rates of false negative biopsy using sextant protocols. The optimal protocol should, nowadays, include six standard sextant biopsies with additional biopsies weighted more laterally (anterior horn) and medially to the apex. Repeat biopsies should also be based on an extended scheme and should include the transition zone especially in patient with at initial negative biopsy. To increase accuracy of prostatic biopsy and reduce unnecessary prostate biopsy, TRUS, power Doppler imaging (PDI), colour Doppler TRUS (CDUS), and 3-dimensional Doppler (3DD) can be successfully adopted, but their routine use is still controversial. Several types of local anaesthesia are now available and can be safely performed to reduce the pain of multi-sites biopsy protocol.
Conclusion: Extended biopsy schemes should be performed not only at first biopsy but especially at repeated biopsy for premalignancy lesions. The widespread use of local anesthesia makes the procedure more comfortable.

KEY WORDS: *Prostate cancer; Diagnosis; Transrectal ultrasound; Prostate biopsy..*

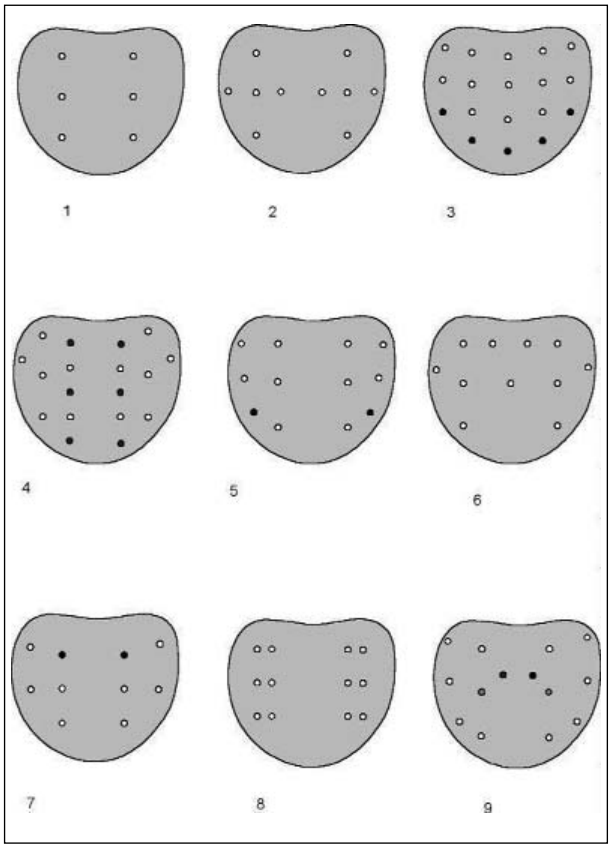
INTRODUCTION

Prior to the widespread use of PSA screening in asymptomatic men, prostate cancer was detected via digital rectal exam (DRE), and only 25% of newly diagnosed prostate cancers were clinically organ-confined (1-3). Since the advent of PSA testing, the percentage of newly diagnosed organ-confined and locally advanced disease has increased to upwards of 80% (1). The current concept regarding diagnosis of prostate cancer is that systematic sextant biopsies do not provide adequate sampling of the prostate. Several extended protocol and different imaging strategies have recently been introduced that improve the prostate cancer detection rate. In this review we report the most recent data in order to increase detection of clinically meaningful prostate cancer.

SYSTEMATIC SEXTANT PROSTATIC BIOPSY AND OPTIMISING BIOPSY METHODS

Multiple new techniques for biopsying tissue have an eye toward increasing the amount of tissue sampled to obtain a more complete picture of the disease burden.

Figure 1.
The figure shows the most important prostatic biopsy schemes. (1 - Hodge's scheme, 2 - Norberg's scheme, 3 - Eskew's scheme, 4 - Nava's scheme, 5 -Ravery's scheme, 6 - Babaian's scheme, 7 - Presti's scheme, 8 – Naughton's scheme, 9 – Gore's scheme).



Further, the diagnosis can be quite difficult for the pathologist, given the small sample and the fact that there are many benign histologic lesions that can mimic cancer (4-6).

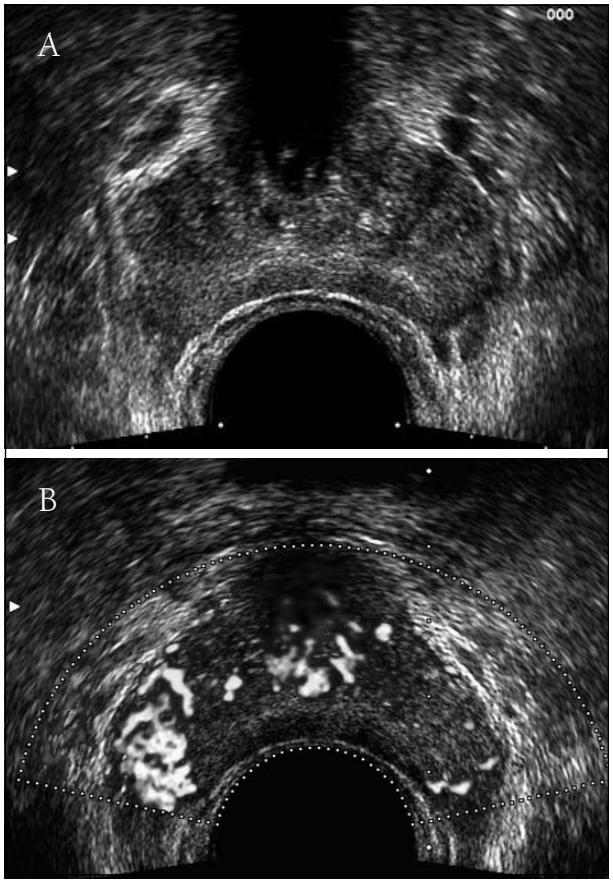
In the original sextant technique, six sites were biopsied: the apex, middle, and base of the prostate in the mid-parasagittal plane of each lobe of the prostate. With sextant biopsy the cancer detection rate was superior to lesion-directed biopsies in 136 men with palpable abnormalities (7). This technique was accepted at the time as the standard of care and helped to emphasize that TRUS was more useful for biopsy than for imaging. Based on cancer mapping of radical prostatectomy specimens, Stamey (8) suggested that biopsies near the middle or the base should be directed laterally into the anterior lateral crescent of the peripheral zone. As much as 75% of all prostate cancer originates from the peripheral zone: most of these cancers are located in the posterolateral peripheral zone (especially in the so-called "anterior horn" at the prostatic base) and near the midline at the apex. However, the standard sextant technique samples a limited portion of the peripheral zone and does not take advantage of the common extension of peripheral-zone cancers into the anterior lateral aspect of the peripheral zone (8). Recent reports have shown that a single set of sextant biopsies may miss clinically detectable prostate cancer in 15-34% of men (9-15). Newer prostate biopsy procedures include the use of 2 consecutive sets of sextant biopsies, strategies that are more laterally directed than the sextant biopsy procedures and that take 8-32 core biopsy samples. The reliability of systematic biopsy for cancer detection relates to the number of cores as well as to their placement (14) (Figure 1). Comparing different protocols in different patients in order to discover which is the most accurate is almost impossible since, in order to obtain a precise comparison, these biopsies schemes should be used in the same patients. In 1997, Eskew et al. introduced the systematic extended biopsy technique, which involves a systematic five-region biopsy, including the conventional sextant biopsies two cores from the far lateral lobe from each side and three cores from middle of the gland (15). When the prostate volume is over 50 cc, one additional core is obtained per region. These Authors have demonstrated that a systematic 5 region biopsy protocol with 13-18 biopsies is capable of detecting cancer in 40% of patients and that 35% of cancers detected would have been missed through use of standard sextant biopsy alone. Presti et al. investigated a 10-core systematic biopsy technique comprising four lateral biopsies of the peripheral zone and conventional sextant biopsies in 483 patients (16). Patients with prostate volumes greater than 50 cc also underwent TZ biopsy. The conventional systematic sextant biopsy missed 20% of the cancers. TZ biopsies increased the detection rate by 5.5%. The difference in cancer detection rates between glands less than 50 cc and greater than 50 cc was lower using the 10-core biopsy strategy compared to the rate using the sextant approach (9.5 versus 19.6%, respectively). An eight-core biopsy scheme, eliminating the sextant base biopsy from the 10-core biopsy technique, minimally decreased the cancer detection rate to 95% from 96% (16). Chen et al sought to determine the optimum biopsy strategy based on a stochastic computer simulation model of ultrasound-guided biopsies using mathematically reconstructed radical prostatectomy specimens. Sextant biopsies reliably detected cancer in only 107 (73%) of 147 patients in whom the total cancer volume was greater than 0.5 cc. The authors demonstrated that a 10-core biopsy regimen that included the parasagittal base and apex, the inferior anterior horn (far lateral peripheral zone), the midline peripheral zone, and the anterior transition zone reliably detected 96% of cancers. They suggested that sampling of these additional areas be incorporated into an initial or repeat biopsy regimen (17). Gore et al. have reported that a 10 core protocol that includes laterally directed biopsies obtained from the base, mid gland and apex of the prostate with cores obtained from the mid lobar base and apex achieved an optimal detection rate in all patient subgroups regardless of prostate volume or PSA levels (18). Recently Presti et al. investigated a 12-core biopsy strategy, including sextant biopsies and laterally directed sextant biopsies, in a multi-practice community study involving 2299 men. The laterally directed sextant biopsies detected 83% of the cancers and was superior to the sextant biopsies, which detected 78%. The 10-core biopsy scheme that included apex, base, and late-

rally directed sextant biopsies detected 97% of the cancers and was superior to the 10 core biopsy that included the sextant, lateral mid and lateral base (93%) (19). All data presented demonstrates that the direction and number of biopsies performed determines procedure sensitivity; furthermore, the above also demonstrated that prostate sampling gives the best results in the diagnosis of prostate cancer using a 10 or 12 biopsy scheme. Nowadays, the optimal protocol should include six standard sextant biopsies with additional biopsies weighted more laterally at the base (anterior horn) and medially to the apex (possibly more distal to the anterior part of the transitional zone where transition zone cancers are more likely to be located).

Colour Doppler TRUS and Doppler Imaging

To increase its accuracy and utility, researchers have investigated a number of alternatives to standard TRUS, including power Doppler imaging (PDI), colour Doppler TRUS (CDUS), and 3-dimensional Doppler (3DD). TRUS technology has limits in specificity and sensitivity, which has led investigators to explore the potential use of colour Doppler imaging with and without intravenous contrast administration. Doppler sonography is based on the principle that the frequency of a sound beam changes when that beam is reflected by a moving target. In the case of Doppler sonography of the prostate, the transducer generates the sound beam, and the moving target is blood. This technique allows real-time visualization of blood flow. The utility of colour Doppler ultrasound rests on the theory that tumours in general, and prostate tumours in particular, have different blood flow characteristics from the surrounding normal tissue

Figure 2.
Transrectal ultrasound view of the prostate showing an isoechoic lesion (a) of the right lobe which appears as a hypervascular lesion at colour Doppler TRUS (b).



At present, few data are available on the ability of either CDUS or 3DD to accurately stage localized cancer, and reports on their use compared with TRUS as detection tools have shown mixed results (20-22). Doppler imaging is a tool that may be used to improve biopsy performance. Increased microvascularity accompanies cancer growth (Figure 2A e 2B). Neovascularity may be detectable by colour Doppler imaging due to abnormal blood flow patterns in larger feeding vessel. In one retrospective study, CDUS-guided biopsies showed a sensitivity of 89% and a specificity of 100% in detecting perineural invasion as an indicator of extracapsular spread. In recent times several Authors have demonstrated that targeted biopsy with transrectal sonography during infusion of a microbubble contrast agent has been shown to be advantageous in comparison to a modified sextant approach, although the contrast enhancement at the apex may be less efficacious (23). However, the conspicuity of hypervascular prostate cancer for Doppler sonography may be improved with short-term oral therapy with a 5α-reductase inhibitor (24). The same group of investigators reported the use of sonography with manual compression of the prostate gland with the transrectal probe in order to generate elastograms (25). The basis for improved detection of cancer is that the elasticity of the neoplastic tissue is less in comparison with normal prostate.

From studies evaluating prostate cancer detection on repeat biopsy, it is known that a significant number of prostate cancer were missed on initial biopsy, especially between prostate specific antigen (PSA) levels of 2.5 to 10 ng/ml, where the probability of finding curable localized prostate cancer is highest. Remzi et al. recently have evaluated the role of Power Doppler enhanced transrectal ultrasound (PD-TRUS), its guided prostate biopsies in men with PSA levels between 2.5 and 10 ng/ml and its impact on prostate cancer detection in men undergoing first and repeat biopsies. They concluded PD-TRUS signals have an adequate sensitivity and specificity, especially on the first biopsy, and provide additional information during "conventional" gray-scale prostate biopsy. A normal PD-TRUS signal might help to exclude prostate cancer patients. It was able to reduce unnecessary prostate biopsy in 51.5% (52/101) and 48.6% on first and repeat biopsy, respectively.

Repeated biopsies

The management of patients in whom a first set of prostate biopsies was negative for cancer is a daily problem for urologists. As prostate cancer is often multifocal and the volume of prostate sampled by the standard sextant biopsy technique relatively small, there is a real possibi-

lity that these individuals may harbour cancer (26). Cancer detection rate on repeat biopsy ranges between 10% and 20% (27-28). Djavan and coll. (29) evaluated biochemical parameters and pathological features, as well as biopsy related morbidity of prostate cancer detected on biopsies 2, 3 and 4 in men with total serum PSA between 4 and 10 ng/ml. Cancer detection rates on biopsies 1, 2, 3 and 4 were 22%, 10%, 5% and 4%, respectively. Despite statistically significant differences in regard to multifocality and cancer location, including cancer on biopsy 2 showing a lower rate of multifocality and a more apico-dorsal location, there were no differences in regard to stage, Gleason score, percent Gleason grade 4/5, serum PSA and patient age between biopsies 1 and 2. They concluded that biopsies 3 and 4 should only be obtained in select patients with a high suspicion of cancer and/or poor prognostic factors on biopsy 1 or 2. Catalona and coll. (30) examined the usefulness of measurements of free PSA and PSA density for predicting prostate cancer in men who had had a prior negative biopsy, a serum PSA level of 4.1 to 10.0 ng/ml. and benign findings on prostate examination. Of 99 men who had repeat biopsies 20 (20%) had prostate cancer detected and the use of percent free PSA cutoffs of 28 and 30% would have detected 90 and 95% of cancers, respectively. Furthermore PSA density cutoffs of 0.10 and 0.08 would have detected 90 and 95% of cancers, respectively, and avoided 31 and 12% of biopsies, respectively. The Authors concluded that these parameters may be used to avoid unnecessary biopsies with an acceptable decrease in sensitivity.

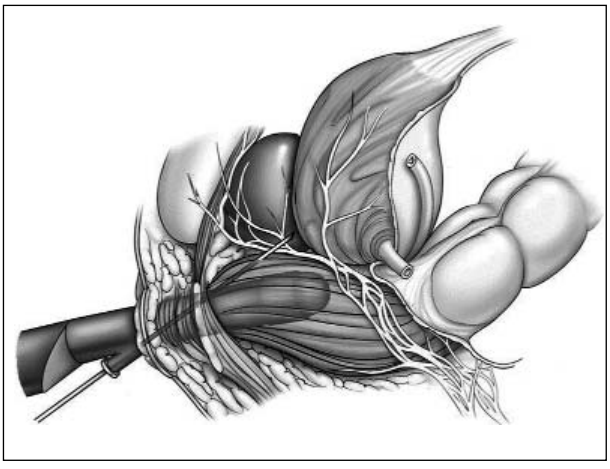
The association between high-grade prostatic intraepithelial neoplasia (HGPIN) and prostatic cancer was investigated; Some studies have suggested targeting biopsies to known HGPIN areas and to the ipsilateral sextants (31); others have shown a statistically significant prostate cancer detection rate in the contralateral lobe only, and thus have advocated repeat biopsy bilaterally in all sextant sites.(31-34). Roscigno and coll. evaluated factors predicting cancer detection by extended repeat prostate biopsies in patients with an initial, isolated, monofocal or plurifocal, HGPIN diagnosis (35). Forty-seven patients with an initial HGPIN diagnosis underwent repeat biopsy using the same technique (mean repeat biopsy cores 11.5) after a median follow-up of 11.4 months (range 3 to 24). Cancer was detected at the second biopsy in 21 patients (44.6%). Cancer detection was significantly greater in patients with plurifocal HGPIN than in those with monofocal HGPIN (70% vs. 10%, respectively; P=0.005) and in patients who underwent repeat biopsy more than 6 months after the first biopsy set (65%) compared with patients who underwent repeat biopsy within 6 months. They concluded that, after a 10 to 12-core biopsy, plurifocality of HGPIN is an important predictive factor for cancer detection.

Use of anesthesia

Several papers reported that local anesthesia relieved pain associated with prostate biopsy. Up to today, two local anesthesia techniques are currently available during transrectal ultrasound (TRUS)-guided biopsy: local anesthesia with 2% lidocaine gel and periprostatic nerve block (figure 3).

Nash and coll. (36) randomized 64 patients to receive a unilateral injection of a sterile solution of 5 ml. 1 percent lidocaine or 5 ml. saline (0.9 percent sodium chloride). Injections were done via a 7-inch 22 gauge spinal needle under ultrasound guidance into the region of the prostatic vascular pedicle at the base of the prostate just lateral to the junction between the prostate and seminal vesicle. In this prospective randomized placebo-controlled study of this technique the Authors found that patients receiving a unilateral prostatic nerve blockade with lidocaine had pain scores that were significantly lower on the injected than noninjected side, and also significantly lower than in patients receiving saline solution. On the noninjected sides pain scores were lower in patients injected with lidocaine on the contralateral side although this difference was not statistically significant. Seymour and coll. (37) evaluated the efficacy and safety of periprostatic local anaesthesia during prostatic biopsy guided by transrectal ultrasonograph. All patients were prospectively recruited and sequentially randomized to receive either periprostatic local anaesthesia or no anaesthesia. Sextant biopsies were taken in all men but some had more than six biopsies. Patients given periprostatic local anaesthesia had significantly lower pain scores at the time of biopsy than those given no anaesthesia and there was no apparent difference in pain between those patients having multiple and sextant biopsy. Vaidya and Soloway (38) had evaluated the advantage of injecting of lidocaine into the area of neurovascular bundles during performing transrectal ultrasound-guided biopsy. Two hundred patients underwent transrectal ultrasound-guided biopsy; all of them received periprostatic nerve block with 10 cm3 of 1% plain lidocaine and the number of biopsies ranged from 6 to 14. The pain during the procedure was very low, and was not correlated with the number of patient's age. Patients who had undergone previous biopsies indicated that there was a dramatic difference when receiving a peri-

Figure 3.
The figure shows the technique to perform a peri-prostatic injection of lidocaine in order to reduce pain during prostate biopsy.



prostatic nerve block. Von Knobloch et al. (39) investigated in a prospective randomised trial the efficacy of fine-needle administered local anaesthesia for bilateral prostatic nerve block prior to transrectal ultrasound guided prostate biopsy (from 10 to 12 cores biopsy were taken). One hundred and eight men suspected of having cancer of the prostate were randomised to receive TRUS-guided bilateral prostate nerve block prior to biopsy or not, when having no history of previous prostate biopsies (groups I and II). In group III all patients with history of previous procedure performed without periprostatic nerve block, exclusively received local anaesthesia injection. In the group I without local anesthesia nerve block, the main pain was statistically higher than randomised group II with nerve block. In group III the difference in pain stated for the present biopsy with local anaesthesia nerve block in comparison to the pain experienced with the previous biopsy was even higher. Pain relief was independent of the number of biopsy cores sampled. Alavi et al. (40) performed a randomized prospective study to compare periprostatic infiltration with 1% lidocaine with intrarectal instillation of 2% lidocaine gel before prostate biopsy. Patients were randomized into 2 groups and 6 to 14 biopsies per groups were performed. There was a statistical difference in the mean pain after periprostatic infiltration and intrarectal instillation with patients receiving periprostatic infiltration reporting significantly less pain. Stirling et al. (41) compared the effectiveness of periprostatic nerve blockade versus intrarectal lidocaine during transrectal ultrasound-guided biopsies. They randomised patients in three groups: group I received no anesthetic, group II received 10 mL of 2% lidocaine gel intrarectally, and group III received a periprostatic injection of 5 mL of 1% lidocaine solution before undergoing prostate biopsy. The Authors demonstrated that both techniques of local anesthesia are effective in reducing patient discomfort, but whereas the use of topical lidocaine may reducing the discomfort associated with probe insertion, the periprostatic nerve blockade using injectable lidocaine appears to be more specific in reducing pain during the biopsy portion of the procedure. In a recent randomized study involving 50 patients who underwent 12-core biopsy, Matlaga et al. (42) compared the effectiveness of local anesthesia with a 20 cc injection of 1% lidocaine to that of a 10 cc rectal application of 2% lidocaine jelly. The difference was statistically significant in favour of the injection. Rodriguez et al. (43) reported a similar result using this approach. More recently Kravchick et al. (44) compare the use of standard local anaesthesia techniques (local anesthesia with 2% lidocaine gel and periprostatic nerve block), with two additional techniques (10-mL perianal injection of 1% lidocaine and 10 mL intrarectal 40% dimethylsulfoxide (DMSO) with lidocaine gel). They concluded that intrarectal 2% lidocaine gel offers little anesthetic benefit to patients, periprostatic nerve block decreased pain only during needle biopsy but was not effective during probe insertion. However, 40% DMSO with lidocaine instilled into the rectal vault for 10 minutes was a safe, rapidly acting, and effective method of anaesthesia for procedure-related discomfort or pain during probe insertion and prostate biopsy. Perianal local anaesthesia possessed the strongest potential for decreasing discomfort and pain and should be used in those patients with anorectal problems.
Therefore local anesthesia using a transrectal ultrasound guided lidocaine injection is recommended to reduce pain associated with prostate biopsy even if, nowadays, there is no consensus as to the optimal dosage of lidocaine or the location of the injection.

Imaging strategies

Imaging is used to aid in the detection of prostate cancer, to help in clinical staging, primarily in patients at high risk for advanced disease. For determining the extent of disease, computed tomography (CT) and magnetic resonance imaging (MRI) of the pelvis and abdomen are the most widely used techniques; bone scintigraphy and positron emission tomography (PET) have more limited roles. MRI has shown sensitivity rates of around 80% and above, and specificity rates of around 50% in patients with extracapsular extension; lower rates were consistently seen in patients with seminal vesicle invasion (45-46). In a study that examined 876 patients from three different hospitals, the accuracy of endorectal MRI in predicting extracapsular extension in intermediate-risk patients after radiation therapy was 78% (47). Combining MRI with magnetic resonance spectroscopy (MRS), which provides information on tumor metabolism, may increase the accuracy of MRI in assessing the location and stage of prostate cancer. MRS produces an image based on the presence of small quantities of certain biomolecules (ie, citrate, choline, and creatine), the ratios of which change in prostate cancer compared with benign prostate tissue, resulting in a "chemical fingerprint" that can aid in discriminating cancerous from noncancerous tissue (48). Preliminary data indicate that MRI/MRS has a sensitivity of 46% to 54% and a specificity of 93% to 96% in predicting extracapsular penetration (49).
Menard et al. (50) reported on the integration of diagnostic and interventional MRI for biopsy of prostate gland. The technique provided precise MRI-guided needle biopsy of the prostate during a diagnostic MRI procedure. The use of the newer imaging methods using highly lymphotropic superparamagnetic nanoparticles in conjunction with high-resolution MRI for detection of small and otherwise undetectable lymphnode metastases were also discussed (51, 52). Despite the very encouraging initial results, however, the exact clinical utility of such diagnostic imaging approach in well-defined cohorts of patients will need to be determined prospectively.

Conclusions

Prostate cancer detection and diagnosis is an area currently fraught with many unanswered questions and much controversy. As far as the biopsy protocol are concerned, the sextant biopsy scheme, as originally described by Hodge et al. is over. Extended biopsy approaches are now commonly used to decrease the false negative

rate. The current recommendation is to use an extended biopsy scheme (8 to 12 biopsy cores without transition zone cores) as the initial biopsy strategy. The location of the cores should include laterally directed biopsies from the anterior horn. Repeat biopsies should also be based on an extended scheme and should include the transition zone. In patient with HGPIN at initial biopsy, HGPIN plurifocality seem to be the main predictive factor for a positive repeated biopsy. Local anaesthesia using a transrectal ultrasound-guided lidocaine injection is now recommended to reduce the pain associated with prostate biopsy.

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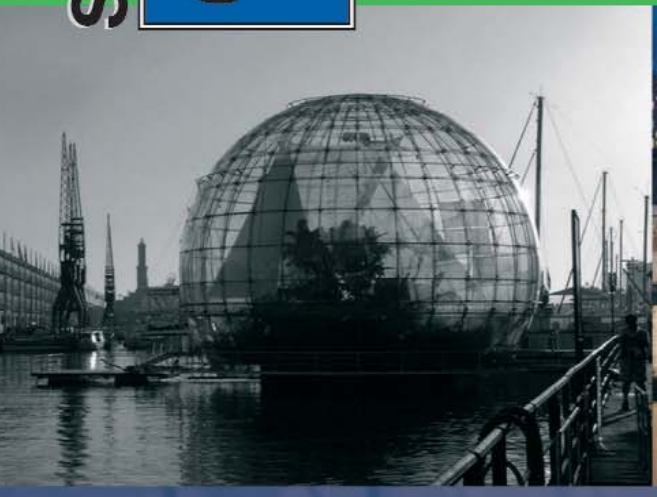

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Società Italiana di Ecografia Urologica Nefrologica e Andrologica

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

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

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

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

Notizie dalla SIEUN

Sessione SIEUN dedicata all'Ecografia Andrologica - Perugia, 3 luglio 2005

Domenica 3 luglio in occasione della Riunione della Sezione Tosco-Umbro-Ligure della Società Italiana di Andrologia - SIA si è tenuta una Sessione congiunta SIEUN-SIA dedicata all'Ecografia Andrologica nel corso della quale sono stati affrontati e discussi gli aspetti ecografici relativi alle più importanti patologie andrologiche come il varicocele, la disfunzione erettile, le prostato-vesciculiti e il priapismo.

16° Congresso Nazionale SIEUN

Il prossimo Congresso Nazionale della SIEUN si terrà a L'Aquila nel 2006. Le date e il luogo sono in definizione e a breve verranno comunicate ai Soci.
Durante il 16° Congresso SIEUN verrà consegnato il Premio in memoria della dott.ssa Monica Moretti al dott. Vincenzo Scattoni, risultato vincitore al 15° Congresso SIEUN, tenutosi a Torino dal 25 al 27 giugno 2004, per il miglior contributo scientifico di "ecografia urologica" con il lavoro dal titolo "*Proliferazione microacinare atipica (ASAP) alla prima biopsia: fattori predittivi alla seconda e terza biopsia con 12 prelievi*". Il lavoro è stato pubblicato sul numero 1, marzo 2005 dell'Archivio Italiano di Urologia Andrologia contenente gli Atti del 15° Congresso SIEUN.

Unificazione quota associativa

Il Comitato Direttivo ha ritenuto di non variare la quota di iscrizione alla Società per il 2005 che ammonta a Euro 50,00. È stata abolita la quota junior, per i soci al di sotto dei 35 anni.
Pertanto, ci sarà un'unica quota di Euro 50,00.
Si ricorda a tutti i soci di voler rinnovare la quota associativa per il 2005, in modo da poter usufruire delle facilitazioni riservate ai soci:

- **riduzione della quota di iscrizione** al prossimo Congresso Nazionale (L'Aquila 2006).
- **abbonamento alla Rivista ufficiale** della Società *Archivio Italiano di Urologia Andrologia*
- **possibilità di acquistare** il volume *Ecografia Andrologica* di Lelio Mario Sarteschi e Giuseppe Fabrizio Menchini-Fabris, 1.000 immagini, 300 pagine a prezzo ridotto contattando direttamente l'editore athena@athenamedica.it

I Punti SIEUN

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

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

I prossimi appuntamenti SIEUN (da non mancare!)

Roma, 12-16 novembre 2005 – Cavalieri Hilton
XVII Congresso Nazionale SIUMB, durante il quale si terrà il Corso SIUMB-SIEUN di **"Ecografia Uro-Andrologica"** (sabato 12 novembre)

La segreteria della Società
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