Dear readers, in this last Editorial of 2004, it is my great pleasure to inform that the *International Braz J Urol* was reviewed in October 2004 by the Literature Selection Technical Review Committee of the National Library of Medicine and received a score between 3.5 and 3.9, the equivalent of “very good”, and was therefore included in the Index Medicus PubMed/MEDLINE.


Of course, this positive result was thanks to the effort and support of our Editorial Board, Reviewers and Collaborators. The Editor personally acknowledge in deep to the more than 400 experts, from many countries, who dedicated a considerable fraction of their time to our Journal, contributing to the “peer-review” process during the last five years. I would like to express my sincere recognition for it.

Also, during the last years, the *International Braz J Urol* is continuing growing in acceptance and circulation. Now, in addition to the 6,000 copies of the printed version, the electronic version has been receiving around 15,000 to 16,000 visits on-line every month, from 90 to 98 different countries, and these figures include the *International Braz J Urol* among the most read urological journals.

The November - December 2004 issue of the *International Braz J Urol* incorporates interesting contributions and the Editor’s Comment will highlight some important papers.

Doctor Sciarra and colleagues, from University La Sapienza, Rome, Italy, presented on page 455 a thorough discussion on which patients with prostate cancer are actually candidates for hormone therapy. The article addressed important topics, as which factors are responsible for the introduction of new candidates for hormone therapy in prostate cancer, who are actually candidates for hormone therapy, classifying them on the basis of the stage of the disease, and which treatment modalities can be proposed for each candidate. The authors pointed out that the use of hormone treatment for younger patients, longer periods and early prostate cancer, absolutely requires a whole re-evaluation of which therapy is indicated and it may produce new problems such as higher risk of over-treatment, need of a better evaluation of quality of life in younger patients and the research for
better-tolerated therapies. As conclusion, we are still waiting for therapies that resist for longer periods without the production of a hormone-refractory disease.

Doctor Tamanini and co-workers, from four tertiary referral centers in São Paulo, Brazil, evaluated on page 479, the concurrent validity, internal consistency and responsiveness of the Portuguese version of the King’s Health Questionnaire (KHQ) in patients who underwent sling procedures for the treatment of stress urinary incontinence. Sixty-eight female patients were enrolled with urodynamically diagnosed urinary stress incontinence. The results showed moderate concurrent validity, strong internal consistency and high responsiveness for the Portuguese version of KHQ, indicating that it is suitable for measuring outcomes in clinical trials among female patients with stress urinary incontinence.

Doctor Dall’Oglio and co-workers, from Federal University of São Paulo, Brazil, studied on page 472, the probability of involvement of the seminal vesicles in patients undergoing radical prostatectomy though the analysis of preoperative serum PSA level, Gleason score on biopsy and percentage of fragments affected by tumor on biopsy. After selecting 899 patients for the study, the authors found on multivariate analysis, that PSA, Gleason score and the percentage of involved fragments were independent prognostic factors for invasion of seminal vesicles. The preoperative variables used in the present study allowed the identification of men with minimal risk (lower than 5%) if involvement of seminal vesicles.

Doctor Cheng and colleagues from the Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China, compared on page 466 the accuracy of estimating prostatic volume with digital rectal examination by urological staffs with different experiences. Measurement of prostatic volume with transrectal ultrasonography serves as the reference standard. The authors found that the trained urologist is more accurate in estimating prostatic volume with digital rectal examination than a urology junior trainee and than a urology higher trainee. This implies that the technique of DRE can be improved with practice.
WHICH PATIENTS WITH PROSTATE CANCER ARE ACTUALLY CANDIDATES FOR HORMONE THERAPY?

ALESSANDRO SCIARRA, ANTONIO CARDI, GIANFILIPPO SALVATORI, GIUSEPPE D’ERAMO, GIANNA MARIOTTI, FRANCO DI SILVERIO

Department of Urology U Bracci, University La Sapienza, Rome, Italy

ABSTRACT

In this article, we will try to address the following aspects: which factors are responsible of the introduction of new candidates for hormone therapy in prostate cancer, who are actually candidates for hormone therapy, classifying them on the basis of the stage of the disease, and which treatment modalities can be proposed for each candidate.

Since the introduction of hormone therapy for the treatment of prostate cancer, there has been a debate about the optimal timing of hormone therapy. A modification in the timing of hormone therapy produced new candidates for hormone manipulation.

In particular, the use of hormone treatment for younger patients, longer periods and early prostate cancer, absolutely requires a whole re-evaluation of which therapy is indicated and it may produce new problems such as higher risk of over-treatment, need of a better evaluation of quality of life in younger patients and the research for better tolerated therapies. Therapies that resist for longer periods without the production of a hormone-refractory disease are also required.

Key words: prostatic neoplasms; hormone therapy; carcinoma

INTRODUCTION

Hormone treatment of prostate cancer is based on the demonstration that malignant prostate cells are target tissues of androgen action. Today, more than 50 years later the first evidence, endocrine manipulation remains one of the principal corner stone in the management of prostate cancer.

Unfortunately, the use of androgen deprivation in patients with prostate cancer has limitations. Most importantly, endocrine treatment can be considered palliative in nature, and relapse of the malignancy occurs if the patient survives competing with causes of death.

Different issues are still open for discussion, in particular actually new candidates for androgen manipulation are considered.
HORMONE THERAPY IN PROSTATE CANCER

malignancy in men, and seems poised to overtake lung cancer as the major cause of cancer death (1). These aspects, added to the well known demographic shifts toward an increasingly aged society, have led epidemiologists to predict a dramatic increase in both the incidence of and death rate from prostate cancer by the year 2020, unless effective improvements in prevention, early diagnosis and treatment are forthcoming (2).

Unlike most other forms of cancer, however, not every prostate tumor constitutes a serious threat to life of the individual affected, and consequently does not automatically warrant treatment (3).

The PSA Era

In the era of increasingly widespread prostate specific antigen (PSA) testing, the result is an early detection and early treatment of prostate cancer disease. Since the introduction of hormone therapy, there has been a debate about the optimal timing of hormone therapy. A modification in the timing of hormone therapy produced new candidates for hormone manipulation.

In particular, at the time of the Veteran’s Administration Cooperative Urological Research Group (VACURG) studies, the clinicians’ choice was fairly limited: they could either carry out surgical castration or give estrogens, which were associated with a high risk of complications (4). For many years, the VACURG studies formed the scientific basis for withholding endocrine therapy until symptoms appeared. An elderly man may die from an unrelated cause before he develops symptoms requiring treatment.

Other studies, in particular the Medical Research Council (MRC) (5) and the European Organization for Research and Treatment of Cancer (EORTC) 30846 (6), changed this point of view. Prostate cancer is treated at diagnosis in the hope of delaying the onset of symptoms and it may also prolong survival.

A following reason to change timing for hormone therapy has been also the introduction of the concept of biochemical progression. Several studies underlined that a PSA progression is indicative of a subsequent clinical disease progression; it can precede clinical progression by up to 4 years (7). Moreover, approximately 22% of patients within 3 years of the primary local treatment will experience biochemical progression (7). The management of a rising PSA level after primary therapies with curative intent is an increasingly common problem facing clinicians. The use of hormone therapy in this setting is now common.

Very recently, moreover, the high incidence and mortality rates associated with prostate cancer have stimulated much interest in developing ways to prevent prostate cancer. Prevention medicine is a relatively new concept in urology. It may be distinguished as primary or also as secondary prevention, but both means an earlier phase to start hormone therapy and new candidates for treatment.

All these aspects may actually produce new candidates for new hormone therapy modalities, in particular younger candidates with early prostate cancer rather than advanced prostate cancer candidates and longer periods of treatment.

POSSIBLE CONSEQUENCES OF HORMONE THERAPY IN EARLY PROSTATE CANCER: WHICH THERAPY FOR WHICH CANDIDATE?

The use of hormone treatment for younger patients, longer periods and early prostate cancer, absolutely requires a whole re-evaluation of which therapy is indicated and it may produce new problems, that is, higher risk of over-treatment, need of a better evaluation of quality of life in younger patients and the research for better tolerated therapies, and therapies that resist for longer periods without the production of a hormone-refractory disease.

Risk of Over-Treatment

While no upper limit has been established over which PSA testing is not recommended, there is general agreement that men with less than a 10-year life-expectancy are unlikely to gain years of life for early detection and treatment is associated with an increased chance of quality of life reduction. Some elderly men in fact, die with rather than of prostate cancer, leading historically to some urologists adopting a stance of therapeutical nihilism for this malignancy (8,9).
Risk of Hormone-Refractory Disease

Our androgen deprivation therapy can select androgen independent cells or stimulate re-differentiation of transient promoter cells: the result is the development of a hormone-insensitive disease (D3). Different mechanisms can be used by prostate cancer to develop hormone-resistance, and we particularly focused on the activation of neuroendocrine prostate system.

Some experiences underlined that the long-term administration of a continuous complete androgen deprivation (CAD) therapy produces a progressive increase in chromogranin A (CgA) (10). It should be possible that continuous CAD may determine a hyperactivation of neuroendocrine (NE) system in the prostate gland. This may be one of the mechanisms used by the prostate adenocarcinoma to progress during hormone therapy in an androgen-insensitive disease.

We published data demonstrating a significant increase in tissue mRNA and serum expression of CgA after 3 or more months of CAD therapy for prostate cancer (11). If longer periods of hormone therapy will be used, new treatment modalities that resist without the production of a hormone-insensitive disease are needed. Also, from this point of view, the introduction and comparison of an intermittent versus continuous administration of the therapy or the use of antiandrogen monotherapy versus castration, all either as primary, adjuvant or neoadjuvant treatments, can be better analyzed.

We published results from a prospective randomized trial, showing that the intermittent administration when compared with the continuous administration of CAD and non-steroidal antiandrogen monotherapy compared to castration therapy, may prevent or reduce the risk of CgA increase and NE hyperactivation during treatments (12,13) (Figure-1).

Quality of Life Considerations

As the result of the use of hormone therapy in the management of patients with early prostate cancer, there is a strong likelihood of patients receiving this therapy for a longer duration (14). Therefore,
A major consideration in the choice of hormone therapy is the physiological and psychological impact it has on patients. For this reason in the last International Consultation on Prostate Cancer, our Committee underlined some questions (15):

1) Under the consideration of the new candidates for hormone therapy, is it not better to initiate endocrine treatment in a less aggressive fashion and step it up later or when progression occurs?

2) If quality of life can really be improved for a prolonged period of time and the therapies were less effective in terms of disease specific and overall survival, would patients be ready to exchange quality of life for lifetime?

On the basis of all these considerations, we will try to analyze the actual indication for hormone therapy for each stage of the disease.

**CANDIDATES FOR HORMONE THERAPY: LOCALIZED PROSTATE CANCER**

In the localized stage of prostate cancer the first question is: Is there a role for a deferred hormone treatment, that means no initial treatment with close surveillance followed by active treatment when and if the tumor progresses with symptoms?

In this stage, the rational for deferring treatment is the often-protracted course of localized prostate cancer and the fact that many patients with such tumors die with the disease and not of it (16). The result of the Surveillance Epidemiology and End Results Program from USA (17), analyzing 19,898 patients managed conservatively, was that the overall disease-specific survival rate 10-year after diagnosis was 90% for those with well or moderately differentiated tumors, but at 10-years the metastasis free survival was lower for cases with moderately differentiated compared to those with well differentiated tumors (17). The conclusion of the International Consultation on Prostate Cancer (16) is that deferred treatment may be an option for patient with clinically localized low-grade prostate cancer with a life expectancy of 10 to 15 years or less.

However, indications for hormone therapy in localized prostate cancer are restricted as described in (Table-1). A possible indication for hormone therapy in this stage of the disease is as neoadjuvant treatment prior to radiation or surgical therapy. The rationale for neoadjuvant hormonal therapy is the induction of early regression of the primary tumor bulk and a coincided treatment of micrometastatic disease.

However, the use of neoadjuvant hormone therapy prior to radical prostatectomy is highly controversial. As concluded by the International Consultation on Prostate Cancer (16), the only positive result suggested for a hormone therapy neoadjuvant to radical prostatectomy, seems to be a reduction of positive surgical margins in clinical T2 tumors.

More positive results are described for the use of neoadjuvant therapy prior to radiotherapy, but longer follow-up and more data in terms of survival are needed (18).

**Table 1 – Role of hormone therapy in localized prostate cancer. Recommendation of the International Consultation on Prostate Cancer (ref. 7).**

<table>
<thead>
<tr>
<th>Role of Hormonal Therapy in Localized Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage T1a or T1b</td>
</tr>
<tr>
<td>• No reported date available</td>
</tr>
<tr>
<td>Stage T1c – T2</td>
</tr>
<tr>
<td>• Patient’s refusal of active treatment</td>
</tr>
<tr>
<td>• Older patient’s with less than 5 years life-expectancy who refuse watchful waiting</td>
</tr>
<tr>
<td>• Older men who are unable to undergo radical therapy</td>
</tr>
<tr>
<td>• Comorbid conditions which preclude definitive therapy</td>
</tr>
<tr>
<td>• Failure of previous definitive local therapy</td>
</tr>
</tbody>
</table>
The recommendations of the International Consultation on prostate cancer regarding as the neoadjuvant hormone therapy have been:

- it seems to yield improved results in terms of local control in cases considered for radiotherapy
- no demonstrated benefits prior to radical prostatectomy have been demonstrated; longer period of neoadjuvant hormone therapy may be analyzed (19).

**CANDIDATES FOR HORMONE THERAPY: LOCALLY ADVANCED PROSTATE CANCER**

In this last years the use of different formulations of hormone therapy in locally advanced prostate cancer has been strongly analyzed.

The recommendations of the international consultation (7) are referred to locally advanced disease as T3-T4 N0-M0 or T1-T4 N1-M0. In unscreened populations, over 30% of all patients present with locally advanced disease (7). The current treatment recommended for this stage lists radical prostatectomy, external beam radiotherapy and hormone therapy (Figures-2 and 3). However, the information of several phase II studies suggests that in patients treated with radical prostatectomy or radiotherapy, adjuvant hormone therapy improves disease-free and overall survival (7,20,21).

Fewer data are in favor of hormone therapy alone and, in this case, a deferred treatment has been considered only for Gleason score < 7, older age, and asymptomatic cases (7,22,23).

Approximately 30-50% of patients with clinical T3-T4 tumors are found to have pathologically involved pelvic lymph nodes (24,25). Several phase II trials suggested an improved outcomes in patients treated with radiotherapy and hormone therapy or radical prostatectomy and hormone therapy, but no

![Figure 2 – Treatment options for T3-T4 N0 M0 prostate cancer candidates. Recommendation of the International Consultation on Prostate Cancer (ref. 7). HT = hormone therapy; R = radiotherapy.](image-url)
good evidence from phase III randomized trials is available to support a routine use of combined modalities in patients with lymph nodes involvement (7,26,27). Messing et al. (28) reported results of a randomized phase III trial of immediate versus deferred hormone therapy in N+ cases treated with radical prostatectomy. At 7.2 years of follow-up, the overall risk of death was 13% in the group who received immediate hormone therapy versus 34% in those in the deferred group. However, in the absence of perfect evidence, clinicians who make treatment recommendations to patients with locally advanced prostate cancer, should be aware of the range of treatment options available (7).

From the point of view of quality of life results, in recent years, discussion on alternative hormone therapy modalities for locally advanced disease has been developed.

Antiandrogens may represent a treatment modality which given as monotherapy, is associated with few adverse effects. In particular the comparative analysis of the 480 non-metastatic patients with locally advanced T3-T4 M0 disease in the 2 randomized studies of bicalutamide 150 mg as monotherapy and castration, has been performed after a median follow-up of 6.3 years and a 56% deaths (30,31). Bicalutamide monotherapy was statistically equivalent to castration in terms of overall survival and it was possible to estimate median survival, which was 63.5 months in bicalutamide and 69.9 months in the castration group. No significant difference in terms of time to progression between the 2 groups was found. On the other hand, most of the parameters related to quality of life showed a positive treatment effect in favor of bicalutamide, with sexual interest and physical capacity showing statistically significant advantages compared to castration (31).

**Adjuvant Hormone Therapy in Locally Advanced Disease**

Most of locally advanced candidates for hormone therapy will receive the therapy as an adjuvant treatment. There is now considerable interest in the use of adjuvant hormone therapy after primary treatment. Adjuvant therapy may have a role although not all patients can be expected to benefit.

The bicalutamide early prostate cancer program (EPC) is being undertaken to investigate the efficacy of bicalutamide as an adjuvant therapy of primary curative intent or as immediate hormone therapy in men with non-metastatic prostate cancer. A total of 8,113 men have been considered. Patients were assigned in a 1:1 ratio to receive either bicalutamide 150 mg or placebo. See et al. reported results on 3,603 cases as part of the EPC program (32), the median follow-up was 2.6 years. A significant reduction of 43% was found in the risk of objective progression for bicalutamide compared with placebo. This benefit was consistent regardless of whether bicalutamide was given as adjuvant therapy or after watchful waiting. The survival
data were immature. It is important to analyze the role of adjuvant hormone therapy in T3 tumors for each primary therapy used.

Bolla et al. (21) reported improved overall survival with adjuvant hormone therapy added to radiotherapy versus radiotherapy alone, on T1-T4 diseases (goserelin for 3 years) (HR = 0.50; 95% CI = 0.33 - 0.76; p = 0.001). However other studies, for example Radiation Therapy Oncology Group (RTOG) 92-03 on T3 tumors showed that adjuvant therapy (goserelin during the last week of radiotherapy until progression) significantly improved clinical local control (85% versus 71% in radiotherapy alone) and disease free survival (60% versus 44%), but not overall survival.

If we stratify the results of EPC program in patients who underwent radiotherapy as primary therapy, the highest advantage of adjuvant therapy in terms of reduction of progression, was obtained in locally advanced, N+ and moderately to poorly differentiated tumors (32).

Similarly, stratifying cases of the EPC program who underwent radical prostatectomy as primary treatment, the advantage of adjuvant therapy on placebo was significant in locally advanced, N+, and Gleason score > 7 tumors (32).

Therefore, the conclusion of our Committee in the International Consultation on Prostate Cancer (15) was that, as nonsteroidal antiandrogen are associated with potential quality of life benefits when compared to castration, in early prostate cancer candidates to hormone therapy, it may be preferable to use antiandrogen as first line therapy and then step up therapy with the use of more invasive forms of hormone deprivation. However, at now, the answer to the question “must we treat all cases submitted to radiotherapy or radical prostatectomy with adjuvant hormone therapy”, is negative.

**CANDIDATES FOR HORMONE THERAPY: ADVANCED PROSTATE CANCER**

Patients with advanced prostate cancer represent the traditional candidates for hormone therapy. Despite recent advances in the early detection of prostate cancer, 10% to 50% of clinically localized prostate cancer will progress (34). Our concept of incurable or advanced prostate cancer has changed considerably in recent years. It was proposed that the definition of advanced prostate cancer must include not only soft tissue or bone metastases (M+), but also stage D1 as a rising PSA after failed local therapy. Men presumed to have localized prostate cancer, now undergo neoadjuvant and adjuvant hormone therapies. Their response to subsequent hormone therapy may not be the same as a male newly diagnosed with metastatic disease who has not received prior hormone therapy (7). Thus, more men who have had prior hormone manipulations are drifting to advanced disease. Prior studies have confirmed that an initial response may be obtained in 60% to 80% of untreated metastatic prostate cancer. However, in men who have previously received treatment, this may not be the case (7).

Also in patients with advanced metastatic disease the quality of life issue is important in the decision of treatment. Hormone therapy is the principal treatment strategy for metastatic prostate cancer, however, discussion on timing and on the type of androgen deprivation is actual.

In men with symptoms or with complications, immediate treatment is mandatory. Even without evidence of improved survival, Medical Research Council Prostate Cancer Working Party Investigator Group (MRC) study in M1 (5), additional arguments favor immediate treatment in most patients with asymptomatic metastases. Delay before an indication for treatment occurs, will be brief; 50% of M1 patients were treated within 9 months of entry in MRC study (5). The excess of complications such as spinal cord compression and pathological fractures in deferred treatment patients was mainly seen in those with M1 disease at presentation. This increased risk may not be reduced when the deferred treatment is commenced. Deferring treatment also increases the early risk of local progression sufficient to require transurethral resection of the prostate (36).

Therefore the recommendation of the International Consultation on Prostate Cancer (30) are that patients with metastases should be advised to commence hormone therapy immediately at diagnosis. If
treatment is deferred, this should be in well motivated
patients with low risk disease, such as small number
of low density metastatic hot spots on scintigraphy
and low PSA (30).

The discussion is also pointed on which
therapy for these candidates. Two different modalities
of hormone therapy has been analyzed so to im-
prove quality of life and reduce toxicity from therapy
in metastatic prostate cancer: non-steroidal
antiandrogen monotherapy and intermittent androgen
deprivation (IAD).

In protocol 306 and 307 comparing
bicalutamide monotherapy with castration, data on
metastatic cases were considered mature as 43% of
M1 cases had died (31). Bicalutamide 150 mg
monotherapy resulted inferior to castration with re-
spect to time to death. However, the difference in
median survival between the 2 treatment groups was
only 6 weeks. Again, most of the parameters on qual-
ity of life, including sexual function, showed a posi-
tive treatment effect in favor of bicalutamide (31).

IAD therapy has been proposed as primary
therapy in M1 cases (37), but also as adjuvant to radi-
cal prostatectomy (38) or radiotherapy (39) in locally
advanced cases. Few randomized trials compared
IAD to continuous CAD in metastatic disease. The
recommendation of the International Consultation on
Prostate Cancer (30) is that IAD must be yet consid-
ered an investigational regimen.

NEW CANDIDATES FOR HORMONE
THERAPY

Patients with androgen deprivation therapy
refractory prostate cancer (D3 stage) are men with
poor prognosis, limited survival and limited chances
of response to conventional therapies. In these cases
also salvage chemotherapy cannot extent survival of
more than 10 months (40).

It has been hypothesize that some factors
may act as “survival factors”. Survival factors may
interfere in the apoptotic processes, conferring a sort
of immortalization to the neoplastic cell. In particu-
lar insuline-like growth factor (IGF) may act as sur-
vival factor for prostate adenocarcinoma cells. NE
differentiation and activity may be another factor

**Rationale of our combination therapy**

- **Somatostatin analogue**
  - Inhibition of the protective effect of NE system on prostate adenocarcinoma cells (antiapoptotic)
  - Anti-survival factor therapy

- **Estrogens**
  - New mechanism to induce castration
  - Direct cytotoxic effect on prostate cells

**Apoptosis of prostate cancer cells**

*Figure 4 – Antisurvival combination therapy for advanced prostate cancer.*
used by prostate adenocarcinoma to progress during hormone therapy in an androgen insensitive disease. NE cells can produce and release several peptides that can protect the prostate adenocarcinoma cell from apoptosis. We and other authors (40,41) proposed the use of “antisurvival factor therapies” for the treatment of D3 prostate cancer. Koutsilieris et al. (40) proposed the combination therapy with somatostatin analogue and dexametasone so to prevent the effect of IGF on D3 prostate cancer and to restore a sensibility to androgen deprivation therapy. We proposed the combination therapy of somatostatin analogue (lanreotide acetate) and ethinylestradiol in D3 tumors (41) (Figure-4). The rationale of our combination therapy is: somatostatin analogue may act reducing NE activity and NE peptides release from NE prostate cells. In this way somatostatin analogue may reduce the activity of the survival factors produced by the NE component and therefore may restore a normal apoptotic process. We used estrogen as second line therapy after progression from CAD therapy, and so to add a direct cytotoxic effect from estrogens on prostate tumor cell (41). It is important to underline that antisurvival therapies cannot be used as monotherapy but only in combination therapy with agents that can produce a direct cytotoxic effect on prostate cancer cells. Somatostatin analogue, reducing IGF activity or NE activity on the prostate gland, may produce a new response to androgen deprivation therapy.

Therefore, it is possible that new candidates for hormone therapy will be those that today are considered androgen refractory D3 tumors but that instead represent cases with only a reduced androgen sensitivity.

REFERENCES


Correspondence address:
Dr. Alessandro Sciarra
V. Nomentana 233
00161 Rome, Italy
Fax: + 39 06 446-1959
E-mail: sciarrjr@hotmail.com
INTEROBSERVER VARIATION OF PROSTATIC VOLUME ESTIMATION WITH DIGITAL RECTAL EXAMINATION BY UROLOGICAL STAFFS WITH DIFFERENT EXPERIENCES

WAI C. CHENG, FAI C. NG, KWOK C. CHAN, YUEN H. CHEUNG, WAI L. CHAN, SANG W. WONG

Division of Urology, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

ABSTRACT

Purpose: To compare the accuracy of estimating prostatic volume with digital rectal examination (DRE) by urological staffs with different experiences. Measurement of prostatic volume with transrectal ultrasonography (TRUS) serves as the reference standard.

Materials and Methods: Thirty-nine consecutive male patients admitted with acute urinary retention had their prostatic volume estimated with DRE by a urology junior trainee, a urology higher trainee and a trained urologist. All patients had TRUS to measure their prostatic volumes. Pearson correlation coefficients (r) were used to assess the relationships between the prostatic volume measured with TRUS and that estimated with DRE by the 3 urological staffs. Wilcoxon signed ranks tests were used to compare the discrepancies between the prostatic volume measured with TRUS and that estimated with DRE for the 3 Urological staffs, and to assess the inter-observer differences of these discrepancies.

Results: The correlation coefficients for the 3 urological staffs were r = 0.573 for the urology junior trainee, r = 0.541 for the urology higher trainee, and r = 0.640 for the trained urologist. The median discrepancies between the prostatic volume measured with TRUS and that estimated with DRE were -9.1 mL for the urology junior trainee, -1.3 mL for the urology higher trainee and 0.9 mL for the trained urologist. These discrepancies were statistically significant only in the case of urology junior trainee (p = 0.015, Wilcoxon signed ranks test). The difference in these discrepancies was statistically significant only between the urology junior trainee and the trained urologist (p = 0.003, Wilcoxon signed ranks test).

Conclusions: The trained urologist was more accurate in estimating prostatic volume with DRE than the urology junior trainee.

Key words: prostate; physical examination; inter observer variation; ultrasonography

INTRODUCTION

Estimation of prostatic volume may be useful in a variety of clinical settings. Although minimal correlation had been reported between prostatic volume and lower urinary tract symptoms (1,2), it may help in predicting treatment response and selecting therapeutic options. For example, large prostates may respond better with 5 alpha reductase inhibitors (3). Open prostatectomy rather than transurethral resection of prostate (TURP) should be employed for prostate larger than 80 to 100 mL, though TURP was recently reported to be safe with prostate of 70 to 150 mL (4). DRE remains the cornerstone of diagnosis of prostate...
DIGITAL RECTAL EXAMINATION BY UROLOGICAL STAFFS

cancer. Moreover, the decrease in prostatic volume after hormonal or radiation therapy may be used as an indication of therapeutic efficacy (5,6). Also prostatic volume can help in the interpretation of serum prostate specific antigen levels (7).

Urologists perform numerous DRE everyday. The general belief is that the accuracy of prostatic volume estimation with DRE will improve with experience. The aim of the study is to compare the accuracy of estimating prostatic volume with DRE by urological staffs with different experiences. Measurement of prostatic volume with TRUS serves as the reference standard.

MATERIALS AND METHODS

Thirty-nine consecutive male patients with acute urinary retention admitted to The Prince of Wales Hospital from July 1998 to September 1998 were included, after signing informed consents.

All patients had their prostatic volume estimated with DRE by a urology junior trainee, a urology higher trainee and a trained urologist, in turn. Each observer had no knowledge of the physical findings of the others. The urology junior trainee had 2 months working experience in urology, whereas the urology higher trainee had 20 months and the trained urologist had over 5 years experience.

All patients had TRUS to measure their prostatic volume. The Bruel & Kjaer Medical Cheetah Ultrasound Scanner type 2003 was used for all ultrasound examinations, together with the Bruel & Kjaer Endosonic Multiplane Transducer type 8551 of 7.0 MHz, which offered both transverse and sagittal views of the prostate gland. At the area of greatest transverse diameter in the transverse view, the antero-posterior and transverse dimensions of the prostate were measured. Sagittal scanning was then performed and the distance from the base to the apex in the median plane measured the longitudinal dimension. All measurements were made by a single urological staff that had more than 3 years experience in urology, had no knowledge of any of the findings on DRE by his colleagues, and did not perform any DRE on any of the patients prior to their TRUS.

The formula antero-posterior dimension x transverse dimension x longitudinal dimension x \(\pi / 6\) was used for the calculation of prostatic volume on TRUS, assuming the prostate gland was elliptical. With this formula, a correlation coefficient of 0.9 had been reported, when compared to actual prostatic weights obtained from prostatectomy or cystoprostatectomy specimens (8).

The Pearson correlation coefficients (r) were employed to assess the relationships between the prostatic volume measured with TRUS and that estimated with DRE for each of the 3 urological staffs. The discrepancy between the prostatic volume estimated with DRE and that measured with TRUS was calculated for each staff, by subtracting the latter from the former, for each patient. The Wilcoxon signed ranks tests were used to compare these discrepancies for the 3 urological staffs, and to assess the inter-observer differences of these discrepancies for the 3 pairs of urological staffs. It was a non-parametric test of equality of medians for paired groups.

RESULTS

The studied patients had a mean age of 73.8 years (standard deviation 9.3, range 50 - 89). The mean postvoid residual urine volume was 715 mL (standard deviation 260, range 400 - 1500).

Scatter plots of measured prostatic volume on TRUS and estimated prostatic volume on DRE for the 3 urological staffs were shown in Figures-1 to 3. The correlation coefficients for the 3 urological staffs were r = 0.573 for the urology junior trainee, r = 0.541 for the urology higher trainee, and r = 0.64 for the trained urologist. Hence the finger of the trained urologist exhibited the strongest relationship with TRUS.

The median discrepancies between the prostatic volume estimated with DRE and that measured with TRUS were -9.1 mL (range -96 to 42.6) for the urology junior trainee, -1.3 mL (range -96 to 27.3) for the urology higher trainee, and 0.9 mL (range -86 to 29.3) for the trained urologist. The urology junior trainee had the largest discrepancy. The urology junior trainee and the urology higher trainee
DIGITAL RECTAL EXAMINATION BY UROLOGICAL STAFFS

underestimated the prostatic volume in 64% and 51% of patients respectively, while the trained urologist overestimated in 54% of cases. The frequency distributions of discrepancies for the 3 urological staffs were shown in Figures-4 to 6.

The discrepancy was statistically significant for the urology junior trainee (p = 0.015, Wilcoxon signed ranks test). The discrepancies for the other 2 urological staffs were not statistically significant (p = 0.209 for the urology higher trainee, and p = 0.610 for the trained urologist).

There was significant interobserver difference between the discrepancy of the urology junior trainee and that of the trained urologist (p = 0.003, Wilcoxon signed ranks test). The differences in discrepancies for the 2 other pairs of urological staffs (i.e. for the urology junior trainee and the urology higher trainee, and for the urology higher trainee and the trained urologist) were not statistically significant (p = 0.267 and 0.096 respectively).

**COMMENTS**

DRE of the prostate gland is an important diagnostic tool for the Urologist, in the context of both benign and malignant diseases. Moreover,
prostatic volume is a useful parameter in a variety of clinical settings. However, like many other clinical findings, prostatic volume estimated with DRE is subjected to interobserver variation.

Many authors had commented on DRE or prostatic volume. Varenhorst et al. (9) discussed on the interobserver variation in assessment of the prostate with DRE and concluded that DRE had a higher positive predictive value concerning prostate cancer when performed by the urologist rather than the general practitioner. Roehrborn et al. (10) showed significant correlation between prostatic volumes estimated with DRE and that measured with TRUS, and suggested posterior surface area of the prostate correlated with overall volume. Bissada et al. (11) reported that the preoperative estimate of gland weight did not correlate with the actual resected weight during TURP (11). Terris & Stamey (8) reported on the correlation between prostatic volume measured with TRUS and prostatic specimen weight, using 15 separate methods of volume estimation, and showed that the most accurate method varied according to different volume ranges.

The present study aims at defining the interobserver variation of urological staffs with different experiences in estimating prostatic volume.
with DRE, with measurement with TRUS serving as the reference standard. We choose a group of patients presenting with acute urinary retention, which should not be a selected group, as far as prostatic volume is concerned.

Our patients do have prostates with a wide range of volume on TRUS (9 - 145 mL). Preferably, different formulae should have been used for different volume ranges, according to Terris & Stamey (8). We employed the widely used elliptical formula (antero-posterior dimension x transverse dimension x longitudinal dimension x π/6) for the calculation of prostatic volume on TRUS for all patients, as it provides a good correlation with actual prostatic weights (8).

The results of the present study show that both the urology junior trainee and the urology higher trainee have a tendency towards underestimation of prostatic volume, while the trained urologist has a tendency towards overestimation.

The urology junior trainee has the largest discrepancy, which is statistically significant. However even the trained urologist can have a high degree of discrepancy between the prostatic volume estimated with DRE and that measured with TRUS (from -86 to 29.3 mL). This observation can be explained by the fact that DRE is assessing only the posterior surface area of a 3 dimensional structure. The intravesical extension of a median lobe and the antero-posterior diameter of the prostate are not taken into account. The antero-posterior diameter can only be estimated by the convexity of the posterior surface of the prostate gland. The consideration of convexity should therefore be included in estimating prostatic volume on DRE.

The high degree of discrepancy between the prostatic volume estimated with DRE and that measured with TRUS of all 3 urological staffs means that DRE only provides a rough estimate of prostatic volume, which is perhaps sufficient to guide therapeutic options, but is inadequate for use in clinical studies involving prostatic volume.

**CONCLUSION**

The trained urologist is more accurate in estimating prostatic volume with DRE than a urology junior trainee, as the difference between their discrepancies is statistically significant. The difference between the discrepancies becomes insignificant if the trained urologist and the urology higher trainee are compared. This implies that the technique of DRE can be improved with practice.

**REFERENCES**

10. Roehrborn CG, Girmian CJ, Rhodes T, Hanson KA, Collins GN, Sech SM, et al.: Correlation between

Correspondence address:
Dr. Cheng Chi Wai
Division of Urology, Department of Surgery
The Chinese University of Hong Kong
Prince of Wales Hospital, Hong Kong, China
Fax: + 852 2635-9307
E-mail: drmchung@hotmail.com
ANALYSIS OF RISK FACTORS OF INVOLVEMENT OF SEMINAL VESICLES IN PATIENTS WITH PROSTATE CANCER UNDERGOING RADICAL PROSTATECTOMY

MARCOS F. DALL’OGLIO, ALEXANDRE C. SANT’ANNA, ALBERTO A. ANTUNES, LUCIANO J. NESRALLAH, KATIA R. LEITE, MIGUEL SROUGI

Division of Urology, Paulista School of Medicine, Federal University of São Paulo, UNIFESP, and Section of Pathology, Syrian Lebanese Hospital, São Paulo, SP, Brazil

ABSTRACT

Objective: To determine through preoperative serum PSA level, Gleason score on biopsy and percentage of fragments affected by tumor on biopsy, the probability of involvement of the seminal vesicles.

Materials and Methods: During the period between March 1991 to December 2002, we selected 899 patients undergoing radical prostatectomy for treatment of localized prostate adenocarcinoma. The analyzed preoperative variables were PSA, percentage of positive fragments and Gleason score on the biopsy. Pre-operative PSA was divided in scales from 0 to 4.0 ng/mL, 4.1 to 10 ng/mL, 10.1 to 20 ng/mL and > 20 ng/mL, Gleason score was categorized in scales from 2 to 6, 7 and 8 to 10, and the percentage of affected fragments was divided in 0 to 25%, 25.1% to 50%, 50.1% to 75%, and 75.1% to 100%. All these variables were correlated with the involvement of seminal vesicles in the surgical specimen.

Results: Of the 899 patients under study, approximately 11% (95% CI, [9% - 13%]) had involvement of seminal vesicles. On the multivariate analysis, when PSA was ≤ 4, the Gleason score was 2 to 6, and less than 25% of fragments were involved on the biopsy, only 3.6%, 7.6% and 6.2% of patients respectively, had involvement of seminal vesicles. On the multivariate analysis, we observed that PSA, Gleason score and the percentage of involved fragments were independent prognostic factors for invasion of seminal vesicles.

Conclusion: The preoperative variables used in the present study allow the identification of men with minimal risk (lower than 5%) if involvement of seminal vesicles.

Key words: prostatic neoplasms; neoplasm staging; prostate-specific antigen; biopsy; seminal vesicle

INTRODUCTION

Radical prostatectomy (RP) is the most effective approach for treating localized prostate cancer (PCa) (1). However, almost 30% of patients will present biochemical recurrence of the disease on the long term (2). The involvement of seminal vesicles constitutes one of the main prognostic factors following RP (2-4), since these patients present higher incidence of lymph nodal metastases and rates of biochemical recurrence in up to 60% of cases within 5 years (3,4). Moreover, (6 to 26%) of patients undergoing RP have involvement of the seminal vesicles (4,5), and for all these reasons, since its original de-
scription in 1905 by Young (6), the classic technique of retropubic RP involves the en-bloc removal of all prostate and seminal vesicles.

With the advent of the prostate specific antigen (PSA), the majority of patients are diagnosed in early stages of disease, and currently more than 60% are classified as T1c (7). Thus, less frequently patients undergoing RP present involvement of seminal vesicles, and their resection may be unnecessary in more than 90% of cases (5).

Since the removal of the seminal vesicles can be technically difficult in some cases, increasing the surgical time and blood loss, and their removal can exert some influence on the erectile function and recovery of urinary continence, in many patients (3,8,9), the preoperative identification of cases with low risk of involvement of seminal vesicles might select cases for surgery with preservation of seminal vesicles, improving the quality of life of these patients following the surgery.

Since digital rectal examination of the prostate, imaging studies, and biopsy of the seminal vesicles fail to detect the involvement of seminal vesicles in patients with localized PCa (3), the preoperative prognostic factors more commonly used for predicting tumor extension are PSA, Gleason score and clinical staging (7). Recently, some authors proposed that in patients with PSA lower than 10.0 ng/mL, when the Gleason score was lower than 7 or less than 50% of fragments were involved, there would be a risk of involvement of seminal vesicles lower than 5%, and they could be preserved during RP (5).

In the present study, the objective was to assess the probability of involvement of seminal vesicles using preoperative PSA, Gleason score and the percentage of positive fragments on prostate biopsy.

**MATERIALS AND METHODS**

During the period from March 1991 to December 2002, we selected 960 patients undergoing RP for management of localized PCa at Syrian Lebanese Hospital, São Paulo, Brazil. The same surgeon performed all procedures and the same pathologist performed the pathologic analyses of the specimen.

Data from the 960 selected patients, as well as the number of fragments removed on biopsy, the number of fragments with cancer, Gleason score, PSA and the pathological study of the surgical specimen were retrieved from our database.

We excluded 54 patients who received neoadjuvant treatment and 7 who were diagnosed through endoscopic resection of the prostate or transvesical prostatectomy, leaving a total of 899 patients. All patients underwent clinical staging, using the TNM classification (AJCC, 1992), using diagnostic tests that included dosage of serum PSA, digital rectal examination, transrectal prostate biopsy, abdominal and pelvic computerized tomography, bone scintigraphy and chest radiography.

Preoperative variables analyzed were PSA, the percentage of positive fragments and Gleason score on biopsy. Preoperative PSA was categorized in scales from 0 to 4.0 ng/mL, 4.1 to 10 ng/mL, 10.1 to 20 ng/mL and > 20 ng/mL, and the Gleason score was divided in scales from 2 to 6, 7 and 8 to 10. The percentage of positive fragments was defined as the number of fragments with cancer divided by the total number of fragments on biopsy, divided in ranges from 0 to 25%, 25.1% to 50%, 50.1% to 75%, 75.1% to 100%. All these variables were related to the involvement of the seminal vesicles in the surgical specimen.

Mean age was 62.8 ± 7.4 years (ranging from 40 to 83 years). Mean PSA was 10.1 ± 7.7 ng/mL (ranging from 0.3 to 72 ng/mL). In relation to the clinical stage, 432 (48%) patients were classified as T1c, 219 (24%) as T2a, 173 (19.3%) as T2b, 68 (7.6%) as T2c and 7 (0.8%) as T3a. The mean percentage of affected fragments was 41% ± 24% (ranging from 5% to 100%). Mean Gleason score on biopsy was 5.8 ± 1.3, ranging from 2 to 9.

RP specimens (prostate, seminal vesicles and obturator lymph nodes) were fixed, in average during 6 hours, in 10% formalin and underwent a routine consisting of measurement and weighting of the gland in a digital balance sensitive to 2 decimal places. Thin transversal sections were made on the surgical margins relative to the bladder neck and prostate apex. Considering the urethra for reference, the remaining gland, after its margins had been stained with India
SEMINAL VESICLES INVOLVEMENT IN PROSTATE CA

Ink, were sequentially sliced at each 3 millimeters. Eight to 10 sections from each lobe were included for the histological study. The seminal vesicles were sectioned at the base, and were prepared for histological examination after longitudinal sectioning. The involvement of seminal vesicles was considered only when there was parenchymal invasion, without considering adventitial invasion.

Statistical assessment was performed through Pearson qui-square test and trend test for univariate analysis. For multivariate analysis, an approach of logistic regression was used. A significance level of 5% was adopted, thus, p values < 0.05 were considered statistically significant.

RESULTS

Of the 899 patients under study, approximately 11% (95% CI, 9% - 13%) had involvement of seminal vesicles. In relation to preoperative PSA, we observed that 9.3% (84) of the total of assessed patients presented levels lower or equal to 4.0 ng/mL. Table-1 shows the distribution of patients according to the involvement of seminal vesicles and preoperative PSA levels. The likelihood of presenting involvement of seminal vesicles increases according to the increase in preoperative serum PSA levels (p < 0.001).

Gleason score on biopsy showed association with the involvement of seminal vesicles as well (p < 0.001). Observing the Table-2 we verified that there is no statistically significant difference between the distribution of Gleason score 7 and 8 to 10 (p = 0.994), therefore we constructed a new category for scores between 7 to 10. According to the Table-3, approximately 8% of patients with Gleason score between 2 and 6 had involvement of seminal vesicles. On the other hand, among men with Gleason score between 7 and 10, 46 (19%) out of 245 had involvement of seminal vesicles.

The qui-square test showed a significant association between the percentage of affected fragments and involvement of seminal vesicles (p < 0.001). The Table-4 shows that as the percentage of affected fragments increase there is an increase in the

---

**Table 1 – Distribution of PSA levels according to the involvement of seminal vesicles (ISV).**

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>Patients N (%)</th>
<th>With ISV N (%)</th>
<th>Without ISV N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4.0</td>
<td>84 (9.3)</td>
<td>3 (3.6)</td>
<td>81 (96.4)</td>
</tr>
<tr>
<td>4.1 – 10.0</td>
<td>512 (57.0)</td>
<td>43 (8.4)</td>
<td>469 (91.6)</td>
</tr>
<tr>
<td>10.1 – 20.0</td>
<td>236 (26.3)</td>
<td>36 (15.2)</td>
<td>200 (84.8)</td>
</tr>
<tr>
<td>&gt; 20.0</td>
<td>67 (7.4)</td>
<td>14 (20.9)</td>
<td>53 (79.1)</td>
</tr>
<tr>
<td>Total</td>
<td>899 (100.0)</td>
<td>96 (10.7)</td>
<td>803 (89.3)</td>
</tr>
</tbody>
</table>

**Table 2 – Distribution of Gleason score according to the involvement of seminal vesicles (ISV).**

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Patients N (%)</th>
<th>With ISV N (%)</th>
<th>Without ISV N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 6</td>
<td>654 (72.8)</td>
<td>50 (7.6)</td>
<td>604 (92.4)</td>
</tr>
<tr>
<td>7</td>
<td>165 (18.3)</td>
<td>31 (18.8)</td>
<td>134 (81.2)</td>
</tr>
<tr>
<td>8 to 10</td>
<td>80 (8.9)</td>
<td>15 (18.7)</td>
<td>65 (81.3)</td>
</tr>
<tr>
<td>Total</td>
<td>899 (100.0)</td>
<td>96 (10.7)</td>
<td>803 (89.3)</td>
</tr>
</tbody>
</table>
proportion of patients with involvement of seminal vesicles ($p < 0.001$).

PSA levels, Gleason score and the percentage of positive fragments contributed significantly for predicting the involvement of seminal vesicles in logistic regression ($p < 0.001$). All second- and third-order interactions were tested and shown to be non significant ($p > 0.05$). Thus, the final model included only the main effects, which were shown to be independent prognostic factors for involvement of seminal vesicles.

The figures presented in each cell of Table-5 represent the probability of involvement of seminal vesicles based on logistic regression with PSA, Gleason score and percentage of affected fragments. For example, a man with PSA lower than or equal to 4.0 ng/mL, percentage of affected fragments up to 75% and Gleason score between 2 and 6 has a chance of less than 5% of presenting involvement of seminal vesicles. The same risk is observed for men with PSA lower than or equal to 10 ng/mL, more than 75% of affected fragments and Gleason score above 6 have a risk higher than 40% of presenting involvement of seminal vesicles.

### COMMENTS

In the present study, the authors demonstrated that in earlier cases, the involvement of seminal vesicles is uncommon, and this probability can be determined through the studied variables. Thus, in univariate analysis, when PSA is $\leq 4$, Gleason score is between 2 to 6 and less than 25% of biopsy fragments are involved, only 3.6%, 7.6% and 6.2% of patients respectively, will have involvement of seminal vesicles.

Among advantages reported in the literature concerning the preservation of seminal vesicles is the improvement in urinary continence and postoperative sexual potency (8,9). Additionally, some cases present technical difficulties during the resection, increasing surgical time and blood loss (3).

Rates of post-RP urinary continence decreased with the increasing anatomic knowledge on
neurovascular bundles. Moreover, better technical improvement, especially during dissection of the prostate apex, has enabled better preservation of the extrinsic sphincteric muscles (10). Despite these advances, urinary incontinence continues to impair the quality of life of some patients, and can reach 60% during the first 6 months after surgery (10).

Accurate surgical measures that influence post-RP urinary continence are not fully understood, and recent studies suggest that trigone innervation and posterior urethral sensitivity play an important role in continence during the immediate postoperative period (8). These nerve branches can be damaged during dissection of the prostate, posterior aspect of bladder and seminal vesicles, contributing for sphincteric incompetence (8). Thus, the preservation of seminal vesicles would prevent traction and damage to such structures, improving immediate postoperative continence.

Jonh et al. (8) studied the urinary continence in 20 patients undergoing RP with preservation of seminal vesicles and compared their results to other 34 patients undergoing classic RP. They observed that in the group with preservation of seminal vesicles, the continence rates at 6 weeks and 6 months following surgery were 60% and 95% respectively, versus 18% and 82% during the same periods for the group undergoing classic surgery.

The removal of seminal vesicles during RP is also partially implied as a cause of erectile dysfunction in many patients (3,8). Sexual function can be affected after RP despite the use of techniques that preserve the neurovascular bundles, showing that other mechanisms are involved in this process. The close relationship between the seminal vesicles and the lateral prostate pedicles, with penile blood supply and their own neurovascular bundles, suggest that the resection of the seminal vesicles can actually contribute for postoperative erectile dysfunction (5). Studies on sexual function with patients undergoing RP techniques with preservation of the seminal vesicles show a clear advantage when compared with patients undergoing classic RP. In a series of 191 patients that were prospectively assessed, the authors observed that sexual health in relation to the quality of life was significantly better in patients with preservation of seminal vesicles when compared with patients undergoing classic surgery (9).

In addition to these factors, the low frequency of PCa invasion to the seminal vesicles often makes their removal unnecessary. One study assessing the surgical specimens from 71 consecutive patients undergoing RP, found 12 cases (17%) of involvement of seminal vesicles, with 5 bilateral cases, but in none of these cases the tumor had spread to the distal 1 cm of seminal vesicles. The authors comment that in cases of technical difficulty, even if a small fragment of seminal vesicles is not removed, the patient’s prognosis probably will not change (11).

Thus, it is clear that preoperative identification of patients with involvement of seminal vesicles, in addition to being an important factor for staging and prognosis, can help to select cases for preservation of the seminal vesicles. In patients with localized PCa, imaging studies have limited accuracy and the biopsies of seminal vesicles have negative, posi-
tive predictive value and sensitivity of only 84 to 97%, 80% and 67% respectively (3). Thus it is necessary to identify risk factors for involvement of seminal vesicles, with main preoperative prognostic factors and serum PSA levels, Gleason score on biopsy and clinical staging (7).

The percentage of positive fragments on biopsy is associated with pathological characteristics, biochemical progression, distant metastases and overall survival in patients undergoing RP. Recent works show that this parameter must be used in preoperative models for predicting the prognosis (12). Peller et al. (13), while studying the usefulness of transrectal prostate biopsy for determining tumor extension of PCa in 102 patients undergoing RP, observed that the number of positive fragments was correlated with the involvement of seminal vesicles. Thus, when up to 50% or fragments were affected, only 10% presented involvement, versus 57% when more than 50% of fragments were affected (13). The present study demonstrated that similarly, when no more than 50% of fragments are affected, the risk of involvement of seminal vesicles is 10%, however when more than 50% of fragments are affected, such risk is superior to 28%.

The presence of positive fragments removed from the prostate base is also correlated with involvement of seminal vesicles. In a study with 763 patients with clinical stage T1c to T3 undergoing RP, 437 patients presented positive fragments at the base and 12.8% of those had involvement of seminal vesicles, versus only 1.2% of 326 patients without PCa at the base. On the multivariate analysis, serum PSA, primary Gleason grade, and the percentage of PCa at the base were the only prognostic factors implied in the involvement of seminal vesicles (3).

Zlotta et al. (5), in a retrospective study with 1238 patients, observed that when PSA was < 10.0 ng/mL, only 5.2% had involvement of seminal vesicles. On the multivariate analysis, the percentage of affected fragments on biopsy and Gleason score were predictive factors for involvement of seminal vesicles in this group of patients. Thus, in patients with PSA < 10.0 ng/mL, when the Gleason score was < 7 or less than 50% of the fragments were involved, there was a risk lower than 5% of involvement of seminal vesicles. In the present series, when the PSA was ≤ 10 ng/mL, we observed an 8.4% risk of involvement of seminal vesicles on univariate analysis. On the multivariate analysis we observed only 2 situations where the risk of involvement of seminal vesicles was lower than 5%, that is, PSA up to 4 ng/mL with a maximum of 75% of fragments affected by tumor and Gleason score lower than or equal to 6, and PSA under 10 ng/mL with up to 25% of fragments affected and Gleason score of 6 at a maximum. In no case with more than 75% of affected fragments or Gleason score higher than 6, there was a risk lower than 5% for involvement of seminal vesicles.

Since we still do not know the long-term effects of preserving the seminal vesicles, in the future this study could help to create study protocols that enable their preservation. The authors still recommend en-bloc removal of the seminal vesicles during RP however, in selected cases presenting the parameters mentioned above, non-removal of the entire seminal vesicles probably will not impair patients’ prognosis due to the low risk for their involvement.

Adriana Sañudo performed the statistical analysis

REFERENCES


6. Young HH: The early diagnosis and radical cure of carcinoma of the prostate. Being a study of 40 cases and presentation of a radical operation which was carried out in four cases. 1905. J Urol. 2002; 167: 939-46; discussion 947.


Received: September 13, 2004
Accepted after revision: October 27, 2004

Correspondence address:
Dr. Marcos F. Dall’Oglio
Rua Barata Ribeiro, 398 / 5o.
São Paulo, SP, 01308-000, Brazil
Fax: + 55 11 3159-3618
E-mail: marcosdallogliouro@terra.com.br
CONCURRENT VALIDITY, INTERNAL CONSISTENCY AND RESPONSIVENESS OF THE PORTUGUESE VERSION OF THE KING’S HEALTH QUESTIONNAIRE (KHQ) IN WOMEN AFTER STRESS URINARY INCONTINENCE SURGERY

JOSE T. N. TAMANINI, MIRIAM DAMBROS, CARLOS A. L. D’ANCONA, PAULO C. R. PALMA, NEURY J. BOTEGA, LUIS A. S. RIOS, CRISTIANO M. GOMES, FABIO BARACAT, CARLOS A. BEZERRA, NELSON R. NETTO JR

Division of Urology, School of Medicine, University of Campinas, Campinas; Department of Psychiatry and Psychology, School of Medicine, University of Campinas, Campinas; Division of Urology, Hospital do Servidor Publico Estadual de São Paulo; Department of Urology, University of São Paulo; and Division of Urology, ABC Medical School, São Paulo, Brazil

ABSTRACT

Objective: To evaluate the concurrent validity, internal consistency and responsiveness of King’s Health Questionnaire (KHQ) in patients who underwent sling procedures for the treatment of stress urinary incontinence.

Materials and Methods: We performed a prospective open label multicenter study in 4 tertiary referral centers. Sixty-eight female patients were enrolled with urodynamically diagnosed urinary stress incontinence. Patients were treated using surgical procedures, mostly (73%) with the synthetic sling procedure, which has been considered one of the gold standard methods for the treatment of urinary incontinence. The patients were assessed before and after one month of postoperative follow up, using the KHQ in its validated Portuguese version. Patients also underwent preoperative urodynamic test, Stamey incontinence grading, pad usage and the assessment of number of pads used per day. After surgery, patients underwent stress test, Stamey incontinence grading pad usage and the assessment of number of pads used per day.

Results: The concurrent validity showed good correlations in some domains of KHQ to clinical parameters. The internal consistency was higher after treatment compared to preoperative values. Objective parameters, such as pad usage and the assessment of number of pads used per day, had significant correlation with changes in post-treatment scores on KHQ. The responsiveness expressed in terms of standardized effect size (SES) and standardized response mean (SRM) was large.

Conclusion: The results showed moderate concurrent validity, strong internal consistency and high responsiveness for KHQ, indicating that it is suitable for measuring outcomes in clinical trials among female patients with stress urinary incontinence.

Key words: urinary incontinence; quality of life; questionnaire

INTRODUCTION

Quality of life is an abstract and highly subjective concept influenced by personal and cultural values, beliefs, self-concepts, goals, age and life expectancy. Its indicators have become an important outcome in clinical trials (1). These indicators are obtained by structured questionnaires. There is a wide
range of generic and disease-specific quality of life questionnaires covering different areas of life such as global quality of life, physical health, emotional functioning and social lifestyle among others. These questionnaires differ in length, varying from 3 or 4 to more than 100 items and are addressed for different goals in quality of life research. Short instruments are easier to administer and less burdensome to the patients, reaching high rate of complete responses. On the other hand, longer questionnaires are able to measure quality of life in different domains and thus, researchers can obtain more specific and detailed information from them (2).

Patient-reported outcomes including symptoms, functional status and perceived quality of life are increasingly used alongside objective clinical measurements to monitor the course of urinary incontinence (UI) and its treatment. Treatment outcomes, as perceived and reported by patients, complement clinical evidence and judgment of efficacy and effectiveness (3).

Well-designed and tested Quality of Life (QoL) scales for urinary incontinence exist and have been shown to be valid, reliable and internally consistent. A valid questionnaire measures what it is supposed to measure and if it is reliable, it can be reproduced (4). Apart from needing to be considered valid and reliable in this new context, such questionnaires should also be sensitive to changes in continence status after clinical or surgical treatment (responsiveness). According to Corcos et al. (5), the responsiveness of most quality of life questionnaires already published is either weak or has never been reported.

The King’s Health Questionnaire (KHQ) (6) and the International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF) (7) were recently translated into Portuguese and had their psychometric parameters such as validity and reliability assessed (8,9).

The aim of this study was to determine whether the above-mentioned instrument named King’s Health Questionnaire has good concurrent validity, internal consistency and also is sensitive to changes in continence status over time, with regard to internal and external responsiveness following surgery to treat genuine stress incontinence (GSI).

**MATERIALS AND METHODS**

A total of 68 consecutive female patients from 4 tertiary referral centers were included in this prospective open label study. The inclusion criteria were that patients should be aged ≥ 18 and have a complaint of GSI urodynamically diagnosed. Patients who were pregnant or breast-feeding, those who had past history of neurologic disease, actual urinary tract infection or who had clinically severe cognitive dysfunction were not enrolled in the study.

The study received prior approval from the Ethical Committee of the School of Medicine (# 82/2000).

Between January and December 2003, all new patients who underwent the sling procedure for the treatment of GSI were assessed by subjective and objective means, as well as by analysis of the (QoL) impact using the Portuguese version of King’s Health Questionnaire.

Before the surgery, patients were assessed using subjective parameters such as Stamey incontinence grading (10): 0 = cured, 1 = leakage with stressful activities - coughing, sneezing, 2 = leakage with minimally stressful activities - e.g. walking, 3 = leakage at all times, with any activity, and the QoL impact on patients’ lives by the Kings’ Health Questionnaire. The objective parameters were the urodynamic test, by means of Valsalva leak point pressure (VLPP), according to the standard protocol (11), and analysis of pad usage (yes/no). If pads were used, the frequency of their usage was recorded (0 = no use; 1 = 1-2 units/day; 2 = 3-4 u/d and 3 ≥ 4 u/d).

Objective outcome testing for stress incontinence surgery was conducted with the patient in the standing position with the physiological bladder filled to maximum vesical capacity (strong desire to void without urge sensation). Patients were asked to perform repeated coughing and Valsalva maneuvers. Any transurethral urine leakage (even drops), without detrusor contraction, was recorded as an objective failure of the surgical procedure. The patients were also asked to re-rate their QoL assessment according to the King’s Health Questionnaire after, at least one month of follow-up.
Quality of Life Questionnaire

The instrument known as the King’s Health Questionnaire (6) evaluates the impact of lower urinary tract symptoms on women’s quality of life. It comprises 21 questions divided into eight domains such as: general health perception, incontinence impact, role limitations, physical and social limitations, personal relationships, emotions, sleep/energy. Furthermore, it has 2 independent scales, which are severity measures and urinary symptoms. High scores in King’s Health Questionnaire represent a worse quality of life. King’s Health Questionnaire has already been submitted to the process of translation and cultural adaptation into Portuguese and is now available for use in clinical research in Brazil (8).

Reliability

The King’s Health Questionnaire reliability was calculated by means of internal consistency, using Standardized Cronbach’s Alpha coefficient and was based on the final scores from King’s Health Questionnaire filled out by patients before the procedure and after, at least, one-month follow up.

Concurrent Validity

The concurrent validity was evaluated by determining the capacity of the King’s Health Questionnaire to distinguish between different subgroups of patients with different clinical complaints, such as pad usage and frequency of changing pads per day. All of these parameters were obtained by means of anamnesis.

Responsiveness

Outcome measurements should be stable in stable subjects (reproducibility), but should also be able to detect changes in unstable subjects (responsiveness) (12). Focusing on this latter attribute, responsiveness is defined as the ability of an outcome instrument to detect clinically important changes in a specific condition. It has been shown that incontinence (13) and its impact on daily activities (14) decrease after treatment of urinary incontinence.

Internal responsiveness is the ability of a measurement to change over a particular pre-specified time frame. It can be assessed using a single-group repeated measurement design, in which patients are assessed before and after treatment that is known to be efficacious (e.g. the synthetic or fascial sling or Burch procedures). External responsiveness reflects the extent to which changes in a measurement over a specified time frame relate to corresponding changes in a reference measurement of health status (15).

Statistical Methods

The assessment of internal responsiveness involves statistical estimation of the size of the effect, i.e. an estimate of the magnitude of the change in health status (13). Standardized Effect Size (SES or ES I) and Standardized Response Mean (SRM or ES II) provide a standardized measurement of the change in score of an instrument. Both SES and SRM can be considered large (> 0.80), moderate (0.5 - 0.8) or small (< 0.5) (15,16).

To assess the reliability by means of internal consistency, standardized Cronbach’s Alpha was used. Wilcoxon’s signed rank test was used to compare the scores between follow-up and baseline. The McNemar test or Stuart-Maxwell test was used to assess significant changes between proportions. The Mann-Whitney U-test for independent groups was used to compare instrument scores and pad usage (external responsiveness and concurrent validity). Kruskal-Wallis test was used to compare mean scores and frequency of pad usage per day.

RESULTS

The sociodemographic characteristics of the sample population are displayed in Table-1. Forty-four (73.3%) of the patients underwent the synthetic sling procedure and 16 (26.7%) underwent classic (fascial) sling. The mean preoperative value of VLPP was 86.5 ± 40.3 cm H2O (mean ± SD). The mean (± SD) duration of follow-up was 4.7 (± 3.4) months.

A total of 27 out of 28 patients (96%; frequency missing = 40 cases) had a negative stress test after surgery.
Table 1 – Background data on all patients assessed using the King’s Health Questionnaire.

<table>
<thead>
<tr>
<th>Age (year, mean ± SD)</th>
<th>52 ± 10.3</th>
</tr>
</thead>
</table>

| Race (N)          | Caucasian | 43 (72.9%) |
|                  | Black     | 5 (8.5%)   |
|                  | Brown     | 10 (16.9%) |
|                  | Asiatic   | 1 (1.7%)   |
| Frequency missing | 9         |

| Literacy (N)               | Illiterate | 4 (6.7%) |
|                           | Incomplete elementary school | 25 (41.7%) |
|                           | Complete elementary school   | 19 (31.6%) |
|                           | High School                  | 7 (11.6%)  |
|                           | College                      | 5 (8.4%)   |
| Frequency missing         | 8         |

Clínica Outcomes

Reliability and Concurrent Validity Studies

The reliability of the King’s Health Questionnaire before and after treatment are shown in Table-2.

The study of the correlations between the scores of the King’s Health Questionnaire and the clinical variable categories (pad usage and frequency of changing pads per day) was unable to detect any significant differences in most of the domains but in role, physical and social limitations and severity measures, as shown in Table-3.

Stamey Grading of Incontinence

Although only 20 out of 39 patients (51.3%) considered themselves cured (frequency missing = 29 cases), the cure/improvement rate was 84.6% (p-value < 0.0001, by the Wilcoxon’s signed rank test).

Table 2 – Reliability assessed by means of standardized Cronbach’s alpha before and after treatment, in relation to King’s Health Questionnaire (N=68)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Standardized Cronbach’s Alpha Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>General King’s Health Questionnaire</td>
<td>0.82</td>
</tr>
<tr>
<td>General Health Perception</td>
<td>-</td>
</tr>
<tr>
<td>Incontinence Impact</td>
<td>-</td>
</tr>
<tr>
<td>Role Limitations</td>
<td>0.53</td>
</tr>
<tr>
<td>Personal Limitations</td>
<td>0.41</td>
</tr>
<tr>
<td>Social Limitations</td>
<td>0.71</td>
</tr>
<tr>
<td>Personal Relationship</td>
<td>0.90</td>
</tr>
<tr>
<td>Emotion</td>
<td>0.83</td>
</tr>
<tr>
<td>Sleep / Energy</td>
<td>0.61</td>
</tr>
<tr>
<td>Severity Measures</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Table 3 – Concurrent Validity: descriptive statistics of mean scores from each King’s Health Questionnaire domain and the clinical variables and respective comparisons among categories concerning to urinary incontinence.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>General Health Perception</th>
<th>Incontinence Impact</th>
<th>Role Limitations</th>
<th>Personal Limitations</th>
<th>Social Limitations</th>
<th>Personal Relationship</th>
<th>Emotion</th>
<th>Sleep/Energy</th>
<th>Severity Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pad usage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49</td>
<td>30.98</td>
<td>32.07</td>
<td>33.20</td>
<td>34.13</td>
<td>32.31</td>
<td>23.85</td>
<td>31.81</td>
<td>31.53</td>
<td>33.81</td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>28.36</td>
<td>23.50</td>
<td>18.45</td>
<td>14.32</td>
<td>22.45</td>
<td>22.06</td>
<td>24.68</td>
<td>25.91</td>
<td>15.77</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of pad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>14</td>
<td>26.04</td>
<td>20.07</td>
<td>27.14</td>
<td>23.61</td>
<td>19.18</td>
<td>19.32</td>
<td>22.93</td>
<td>24.50</td>
<td>21.18</td>
</tr>
<tr>
<td>3-4</td>
<td>20</td>
<td>22.30</td>
<td>26.38</td>
<td>21.02</td>
<td>25.02</td>
<td>23.40</td>
<td>16.41</td>
<td>24.13</td>
<td>22.80</td>
<td>22.35</td>
</tr>
<tr>
<td>&gt;4</td>
<td>15</td>
<td>27.63</td>
<td>27.77</td>
<td>28.30</td>
<td>26.27</td>
<td>32.57</td>
<td>22.80</td>
<td>28.10</td>
<td>28.40</td>
<td>32.10</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p = p < 0.05, * = Mann-Whitney test, * = Kruskal-Wallis test

Pad Usage

Assessing this clinical variable, 35 out of 39 patients (89.7%; frequency missing = 29 cases) used pads before treatment. After surgery, only 6 (15.4%) patients were still using them (p-value < 0.0001, by McNemar test).

Frequency of Changing Pads Per Day

Most of the patients before surgery (27 out of 39, or 69.3%; frequency missing = 29 cases) used at least 4 pad units per day. On the other hand, 33 out of 39 (84.6%) patients stopped using pads after the surgical treatment (p-value < 0.0001 by Stuart-Maxwell test).

Responsiveness Study

The internal responsiveness study is shown in Table-4. It was quantified using standardized effect size (SES) and standardized response mean (SRM), which demonstrated a large effect size by both means. Similar results were found from the study of external

Table 4 – Study of the internal responsiveness of King’s Health Questionnaire - KHQ (sensitivity to change), using Effect Size I or Standardized Effect Size (SES) and Effect Size II or Standardized Response Mean (SRM).

<table>
<thead>
<tr>
<th>KHQ Domains</th>
<th>N</th>
<th>p-value*</th>
<th>SES</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Health Perception</td>
<td>68</td>
<td></td>
<td>-0.76</td>
<td>-0.54</td>
</tr>
<tr>
<td>Impact of Incontinence</td>
<td>68</td>
<td></td>
<td>-1.94</td>
<td>-1.61</td>
</tr>
<tr>
<td>Role Limitations</td>
<td>68</td>
<td></td>
<td>-1.50</td>
<td>-1.27</td>
</tr>
<tr>
<td>Physical Limitations</td>
<td>67</td>
<td>0.0001</td>
<td>-1.49</td>
<td>-1.25</td>
</tr>
<tr>
<td>Social Limitations</td>
<td>68</td>
<td></td>
<td>-1.33</td>
<td>-1.28</td>
</tr>
<tr>
<td>Personal Relationships</td>
<td>62</td>
<td></td>
<td>-0.76</td>
<td>-0.61</td>
</tr>
<tr>
<td>Emotions</td>
<td>68</td>
<td></td>
<td>-1.44</td>
<td>-1.17</td>
</tr>
<tr>
<td>Sleep/Energy</td>
<td>68</td>
<td></td>
<td>-0.86</td>
<td>-0.70</td>
</tr>
<tr>
<td>Severity Measures</td>
<td>68</td>
<td></td>
<td>-2.40</td>
<td>-1.52</td>
</tr>
</tbody>
</table>

*p = Wilcoxon’s signed rank test
responsiveness, when the post-treatment scores were compared with an external variable such as pad usage and the frequency of changing pads per day (Table-5).

COMMENTS

Pubovaginal slings are considered the gold standard technique for the treatment of female stress urinary incontinence because of the excellent results after long-term follow-up (17). There is a consensus in the literature that urinary incontinence may adversely affect quality of life, with significant implications in many spheres, such as the psychological, social, physical, economic, personal relational and sexual domains (18). The standardization sub-committee of the International Continence Society (ICS) considers urinary incontinence to be “a complaint of any involuntary loss of urine”. This committee recommended, in 1997, that quality of life measurements should be included in all clinical research on urinary incontinence, as a complementary addition to the traditional clinical parameters (19).

Validity, reliability and responsiveness are psychometric properties that should be systematically tested in every questionnaire used in clinical research in order to allow scientific conclusions to be reached regarding the efficacy of the procedures. Reliability assessed after the surgical procedure showed results more homogeneous compared to the same results before treatment. This aspect shows a tendency of homogeneity from the answer of the patients when satisfied with the treatment as shown by the high-

Table 5 – Study of the external responsiveness of King’s Health Questionnaire, comparing post-treatment questionnaire scores and pad usage.

<table>
<thead>
<tr>
<th>Pad Usage</th>
<th>King’s Health Questionnaire Domain Score after Treatment</th>
<th>N</th>
<th>Mean ± SD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>General Health Perception</td>
<td>34</td>
<td>23.5 ± 16.2</td>
<td>0.1145</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>33.3 ± 12.9</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Incontinence Impact</td>
<td>34</td>
<td>10.8 ± 21.3</td>
<td>0.0022</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>55.6 ± 40.4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Role Limitations</td>
<td>34</td>
<td>9.3 ± 19.3</td>
<td>0.0829</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>36.1 ± 41.4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Physical Limitations</td>
<td>34</td>
<td>10.8 ± 21.7</td>
<td>0.2741</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>33.3 ± 45.9</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Social Limitations</td>
<td>34</td>
<td>2.6 ± 8.7</td>
<td>0.0221</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>18.5 ± 30.4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Personal Relationships</td>
<td>34</td>
<td>8.8 ± 25.4</td>
<td>0.0367</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>41.7 ± 49.2</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Emotions</td>
<td>34</td>
<td>11.8 ± 22.7</td>
<td>0.0396</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>53.7 ± 51.4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Sleep/Energy</td>
<td>34</td>
<td>18.2 ± 21.8</td>
<td>0.1434</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>44.4 ± 39.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Severity Measures</td>
<td>34</td>
<td>17.8 ± 20.1</td>
<td>0.0099</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>6</td>
<td>56.7 ± 35.2</td>
<td></td>
</tr>
</tbody>
</table>

* = Mann-Whitney test
standardized Cronbach’s alpha coefficient (Table-2). This means that most of patients had the same perception of improvement in quality of life after surgery. These findings are corroborated by objective results such as decrease in pad usage, stress test, and Stamey incontinence grading.

The King’s Health Questionnaire was able to distinguish between different subgroups of patients with different clinical complaints, which were diagnosed by means of anamnesis. Higher scores were associated to presence of pad usage and higher number of pad changes per day, showing positive correlation with these clinical parameters. These correlations were statistically significant in the domains role, physical, social limitations and severity measures, as shown in Table-3.

A common method for demonstrating the responsiveness of a health status measurement is to compare instrument scores before and after a specific treatment, that has known efficacy (16).

All the patients included in this prospective, multicentric, open label trial underwent sling procedure and King’s Health Questionnaire was applied before and after it. The results from the internal responsiveness study are shown in Table-4 and confirm that the Portuguese version of King’s Health Questionnaire captures changes over time. Responsiveness expressed in terms of the Standardized Effect Size (SES or ES I) and Standardized Response Mean (SRM or ES II) showed large values for effect size studies, for all the domains in King’s Health Questionnaire, except for the domains general health perception and sleep/energy, both with values under 0.8, which denotes only moderate responsiveness.

As shown in Table-5 (external responsiveness study), there was a good correlation between the King’s Health Questionnaire domain scores post-treatment regarding pad usage analysis. The King’s Health Questionnaire domain scores showed a significant difference when the 2 groups (yes/no) were compared after treatment (p value < 0.0002), especially those strictly related to incontinence, i.e. incontinence impact (p value < 0.0022) and severity measures (p value < 0.0099). Although individual incontinence symptoms may improve quickly after surgical treatment, alterations in lifestyle may take longer. Therefore, it would be interesting to explore remote effects of treatment in lifestyle (20). The Portuguese version of the King’s Health Questionnaire has now all the psychometric properties assessed including validity, reliability and responsiveness, being the first Quality of Life questionnaire related to female urinary incontinence ready for use clinical research in Portuguese language, as it has been recommended by ICS standardization sub-committee.

In conclusion, King’s Health Questionnaire demonstrated moderate concurrent validity and strong internal consistency, mainly after treatment. It also appears to capture changes, i.e. has good responsiveness in its multifaceted domains such as the social, emotional and personal domains, and in the domains strictly related to the incontinence symptom.

On the basis of our findings, we believe that King’s Health Questionnaire can be used for measuring the quality of life after the treatment of urinary incontinence. It is now available for use in national or international multicenter clinical trials, thus allowing scientific conclusions to be reached regarding the efficacy of such procedures.

REFERENCES

5. Corcos J, Beaullieu S, Donovan J, Naughton M, Gotoh M; Symptom Quality of Life Assesment Committee of


Received: July 26, 2004
Accepted after revision: November 20, 2004

Correspondence address:
Dr. Jose T. N. Tamanini
Rua Floriano Peixoto, 443
Jaú, SP, 17201-100, Brazil
Fax: +55 14 3621-3056
E-mail: tadeutamanini@jau.flash.tv.br
FEASIBILITY OF REFREEZING HUMAN SPERMATOZOA THROUGH THE TECHNIQUE OF LIQUID NITROGEN VAPOR

SIDNEY VERZA JR, SANDRO C. ESTEVES

Center for Male Infertility, ANDROFERT, Campinas, São Paulo, Brazil

ABSTRACT

Objective: To assess the feasibility of refreezing human semen using the technique of liquid nitrogen vapor with static phases.

Materials and Methods: Twenty samples from 16 subjects who required disposal of their cryopreserved semen were thawed, corresponding to 6 cancer patients and 10 participants in the assisted reproduction (AR) program. Samples were refrozen using the technique of liquid nitrogen vapor with static phases, identical to the one used for the initial freezing, and thawed again after 72 hours. We assessed the concentration of motile spermatozoa, total and progressive percent motility and spermatic vitality, according to criteria of the World Health Organization (WHO), as well as spermatic morphology according to the strict Kruger criterion, after the first and after the second thawing.

Results: We observed a significant decrease in all the parameters evaluated between the first and the second thawing. Median values for the concentration of motile spermatozoa decreased from $2.0 \times 10^6$/mL to $0.1 \times 10^6$/mL ($p < 0.01$); total percent motility from 42% to 22.5% ($p < 0.01$); progressive percent motility from 34% to 9.5% ($p < 0.01$); vitality from 45% to 20% ($p < 0.01$); and morphology from 5% to 5% ($p = 0.03$). There was no significant difference in the spermatic parameters between the cancer and assisted reproduction groups, both after the first and after the second thawing. We observed that in 100% of cases there was retrieval of motile spermatozoa after the second thawing.

Conclusion: Refreezing of human semen by the technique of liquid nitrogen vapor allows the retrieval of viable spermatozoa after thawing.

Key words: fertility; in vitro fertilization; sperm; freezing; nitrogen

INTRODUCTION

It is well known that the process of freezing and thawing human spermatozoa affects their fertile potential under several aspects, such as the decrease of spermatic motility (2), decreased penetration into the cervical mucus (3), changes in the plasmatic membrane (4), making it less fluid, as well as in the acrosomal integrity (5), in addition to changing the activity of protease acrosin (6). For these reasons, lowest fertilization and pregnancy rates are achieved when thawed spermatozoa are used for intra-uterine insemination (7) and conventional in-vitro fertilization.
REFREEZING OF HUMAN SPERMATOZOA

(8). However, after the development of intracytoplasmic sperm injection (ICSI), it has been shown that similar fertilization and pregnancy rates are achieved with this technique using both frozen-thawed and fresh motile spermatozoa (9).

The cryopreservation of spermatozoa is indicated in situations where there is risk of fertility loss and/or decrease in the future fertility. Moreover, the cryopreservation of human semen is used in assisted reproduction programs, both for preserving exceeding spermatozoa obtained from the testis or epididymis or in cases of azoospermia, and for cases where it is impossible to conciliate semen collection and aspiration of oocytes. Among indications for semen cryopreservation, the group of male cancer patients deserves special attention, and several works have alerted to the importance of semen cryopreservation in these individuals (10). Some types of cancer, such as testicular cancer, affect mainly men in reproductive age. Due to advancements in its management, currently cure and survival rates are quite high, sometimes reaching more than 90% (11).

The objective of the present study was to assess the feasibility of refreezing-thawing of human spermatozoa using the technique of liquid nitrogen vapor with static phases.

MATERIALS AND METHODS

Twenty semen samples were obtained from 16 individuals who required the disposal of cryopreserved semen that was stored in the therapeutic semen bank of a tertiary care institution.

Among those, 6 men with mean age 26.5 ± 7.2 years had their semen cryopreserved due to cancer, and other 10 men with mean age 39.6 ± 4.7 years had their semen cryopreserved for use in an assisted reproduction program involving in vitro fertilization. All individuals or their legally responsible person signed a document authorizing the disposal and the utilization of samples for performing this study, which was approved by the Institutional Research Ethics Committee. The reasons for disposal in the cancer group were death in 3 cases and successful treatment with subsequent recovery of spermatogenesis in the remaining three. In the assisted reproduction group, 6 individuals required disposal due to successful treatment (pregnancy), 1 due to financial difficulty for maintaining the cryopreserved samples, and 3 did not state the reason for disposal.

Cryopreservation Protocol

On the day of cryopreservation, samples were collected by masturbation in sterile vials, remaining on a heating plate (Labline, USA) for 30 minutes until complete liquefaction. An aliquot was reserved for performing complete seminal analysis, according to the WHO criteria (12). Next, freezing was performed under aseptic conditions in a biological safety cabinet (Veco, Brazil). In short, the procedure consisted in conditioning the liquefied semen inside a 15-mL conical tube (Falcon, USA), adding aliquots of cryoprotector medium, corresponding to 25% of the semen volume to be frozen, each 5 minutes. This procedure was repeated until equal volumes of diluent medium and ejaculate were obtained (proportion 1:1, v/v). The cryoprotector agent employed was a ready-to-use preparation, containing 20% yolk egg (v/v), 12% glycerol (v/v), 85 mM of Tris ([hydroximetyl] amino methane), 189 mM of TES (n-Tris [hydroximetyl] methyl-2-amino-etano-sulphonic acid), 11 mM of glucose, 0.25 mg/mL of streptomycin sulfate, 0.15 mg/mL of penicillin and pH = 7.5 (Test yolk-buffer, Irvine Scientific, Santa Ana, USA). The final mix was distributed in sterile plastic, cylindrical tubes with conical base, with capacity for conditioning 1.0 mL of mixture each (Nunc, Denmark). Cryopreservation was performed by the technique of liquid nitrogen vapor with static phases (5). Freezing itself consisted of 3 consecutive steps: 1) cooling phase – the metallic racks containing the cylindrical tubes with the sample were put inside a freezer, with temperature set to minus 20°C, on horizontal position, and were then maintained in this environment for 8 minutes, in order to reach a temperature of +4°C; 2) freezing phase – the metallic racks containing the cylindrical tubes were transferred to the tankard of the liquid nitrogen barrel (N₂L), with each rack vertically positioned, and the 2 cylindrical tubes located in upper positions. The tankard was then transferred to the barrel containing liquid nitrogen only at the base, so that the lower cylindrical tube
was located at 15 cm from the N₂L level and the upper tube at 18 cm. Temperature at the place occupied by the cylindrical tubes was around minus 79ºC, as measured by an appropriate thermometer, and those were maintained in this closed environment of N₂L vapor for a period 2 hours. Freezing rate during this phase is estimated in 10ºC / minute; 3) storage phase - after 2 hours in N₂L vapor, the metallic racks containing the cylindrical tubes were transferred to the storage barrel, and were then immersed in N₂L at -196ºC.

Thawing, Assessment and Refreezing of Samples

Samples were thawed by removing the cylindrical tubes from the storage barrel with liquid nitrogen, which were maintained at room temperature for 5 minutes (5). Next, the tubes were taken to water-bath (Fanem, Brazil) at 37ºC, where they remained for 20 minutes. Samples were then homogenized, and an aliquot was removed for assessing the following parameters: concentration of motile spermatozoa, percentage of motile spermatozoa, percentage of spermatozoa with progressive motility (grades A and B), vitality and spermatic morphology. The parameters were assessed in accordance to the instructions in the WHO procedure manual (12), with exception of spermatic morphology, which was assessed according to Kruger’s strict criteria (13). For the eosin-nigrosin test, a 1% eosin solution was used as spermatic stain and a 10% nigrosin solution was used as background stain, in order to make reading easier. For morphologic assessment, thin 5-µL smears of thawed semen were prepared on dry slides that were previously cleaned with 70% alcohol. The smears were dried on fresh air, and subsequently fixed and stained using an appropriate kit (Laborclin, PR, Brazil) as follows: the dry slide was immersed in fixation solution for 5 times during 1 second at each time, with a 1-second interval between each immersion. Once the slide was completely dry, it was immersed in the solution I, for 5 times during 1 second at each time, with a 1-second interval between immersions. Excessive stain was removed, and the slide was finally immersed in the solution II, for 2 times, during 1 second at each time, with a 1-second interval between immersions. The slide was rinsed with deionized water, in order to remove excessive staining, and was left to dry naturally. At least 200 spermatozoa were evaluated per smear in order to measure the percentage of live and morphologically normal spermatozoa, using bright field light microscopy under immersion with a magnification of 1000 times (Nikon Alphaphot, Japan).

The remaining sample of thawed semen was kept in the cylindrical tubes on the heating plate at 37ºC during the assessment of concentration and motility parameters, that is, approximately 1 hour, and underwent cryopreservation again, according to the method described above, however without adding the cryoprotector diluent, since it was not removed during thawing. After 72 hours, samples were thawed again and the same spermatic parameters were assessed according to the method described above.

Statistical Analysis

Kolmogorov-Smirnov test was used to verify the type of data distribution. Wilcoxon and Mann-Whitney non-parametric tests were used to compare the spermatic parameters after the first and the second thawing and to compare both subgroups of patients (cancer and assisted reproduction), respectively. Data were expressed in median and 25% and 75% percentile. P values < 0.05 were considered statistically significant. The statistical analysis was performed using the StatSoft software, Tulsa, United Kingdom.

RESULTS

The results for spermatic parameters after the first and the second thawing are expressed in Table-1. We observed a significant decrease between the first and the second thawing in the number of motile spermatozoa (from 2.0x10⁶/mL to 0.1x10⁶/mL, p < 0.01), in total motility (from 42% to 22.5%, p < 0.01) and progressive motility (from 34% to 9.5%, p < 0.01), in the percentage of live spermatozoa (from 45% to 20%, p < 0.01) and spermatozoa with normal morphology (median values of 5% for the first and the second thawing, but with p = 0.03). Nevertheless, despite the decrease in the quality of all the analyzed
parameters, live and motile spermatozoa were found after the second thawing in all cases.

We also compared the 2 subgroups of individuals, that is, those who had semen cryopreservation due to cancer and those who cryopreserved their semen for subsequent use in the assisted reproduction program, aiming to assess if there was any difference in the retrieval and survival rates relative to the reason for freezing. Deleterious effects of cryopreservation on spermatic parameters were observed in both groups between the first and the second thawing (Table-2), with no difference between them in the magnitude of changes (Table-3).

**COMMENTS**

Semen cryopreservation has allowed many men to guarantee their future fertility and generate their own children. Among them, cancer patients and those who will undergo chemotherapy and/or radiotherapy deserve special attention, since many are in their reproductive years and do not have children.

**Table 1** – Assessment of spermatic parameters after the first and the second thawing of 20 seminal samples. The values are expressed as median and 25 and 75 percentiles.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>After the First Thawing</th>
<th>After the Second Thawing</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of Motile spermatozoa (x 10^6/mL)</td>
<td>2 (0.1 - 11)</td>
<td>0.1 (0.05 - 3)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Total Motility (%)</td>
<td>42 (17.5 - 54)</td>
<td>22.5 (6.5 - 34.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Progressive Motility (grade A + B) (%)</td>
<td>34 (0.5 - 38)</td>
<td>9.5 (2 - 18)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Vitality (%)</td>
<td>45 (20 - 54)</td>
<td>20 (10 - 24)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Morphology (%)</td>
<td>5 (3 - 8)</td>
<td>5 (2.5 - 5)</td>
<td>= 0.03</td>
</tr>
</tbody>
</table>

**Table 2** – Spermatic parameters from 16 individuals divided into Assisted Reproduction and Cancer subgroups, after the first and the second thawing. The values are expressed as median and 25 and 75 percentiles.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Thawing</th>
<th>p value</th>
<th>Second Thawing</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of Motile Spermatozoa (x 10^6/mL)</td>
<td>4.7 (0.1 - 16)</td>
<td>NS</td>
<td>0.5 (0.01 - 4)</td>
<td>NS</td>
</tr>
<tr>
<td>Total Motility (%)</td>
<td>47 (26 - 56)</td>
<td>NS</td>
<td>23.5 (7 - 39)</td>
<td>NS</td>
</tr>
<tr>
<td>Progressive Motility (grade A + B) (%)</td>
<td>34 (19 - 51)</td>
<td>NS</td>
<td>14.5 (2 - 25)</td>
<td>NS</td>
</tr>
<tr>
<td>Vitality (%)</td>
<td>47.5 (42 - 55)</td>
<td>NS</td>
<td>20 (12 - 22)</td>
<td>NS</td>
</tr>
<tr>
<td>Morphology (%)</td>
<td>5 (4 - 8)</td>
<td>NS</td>
<td>5 (4 - 6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = non significant
Table 3 – Percent difference between the first and the second thawing on spermatic parameters from 16 individuals in the Assisted Reproduction and Cancer subgroups. The values are expressed as median and 25 and 75 percentiles.

<table>
<thead>
<tr>
<th></th>
<th>Assisted Reproduction (n = 10)</th>
<th>Cancer (n = 6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of Motile Spermatozoa (x 10^6/mL)</td>
<td>66.6 (41.2 – 80)</td>
<td>78.5 (70 – 96.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Total Motility (%)</td>
<td>48.5 (42.8 – 61.1)</td>
<td>50.0 (43.7 – 65)</td>
<td>NS</td>
</tr>
<tr>
<td>Progressive Motility (grades A + B) (%)</td>
<td>62.7 (49.1 – 80)</td>
<td>72.2 (56.7 – 81.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Vitality (%)</td>
<td>56.9 (27.3 – 64.5)</td>
<td>48.9 (43.2 – 66.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Morphology (%)</td>
<td>12.5 (-25 – 33)</td>
<td>28.5 (0.0 – 37.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = non significant

yet. Thanks to the advances in oncologic treatments, increasingly higher survival rates have been reached (11). However, treatment can lead to germinative aplasia, and it is impossible to predict which individuals will recover normal spermatogenesis. Consequently, a concern with future fertility arises, and many studies have alerted about the importance of semen cryopreservation before starting chemotherapy and/or radiotherapy (10,14). Probably due to the stress generated by the disease, in addition to the increase in the circulating levels of cytokines and tumoral markers, as well as orchiectomy in cases of testicular cancer, we observe that approximately 50% of individuals present a significant decrease in the quality of semen at the moment of freezing (14). This reduction in the initial quality, associated with the small number of collected samples due to the urgency in initiating treatment, can limit success at the moment when theses samples are used, especially when low-complexity techniques for assisted reproduction, such as intrauterine insemination, are used for obtaining pregnancy. However, with the advent of ICSI, just one single spermatozoon per oocyte is required to possibly obtain pregnancy. ICSI can be performed even with non-motile spermatozoa, provided they are alive, with good results (15), though the use of specific tests, such as the hypo-osmotic test for selecting live spermatozoa, even if non-motile, can optimize the process efficacy (16). Thus, even in very unfavorable conditions concerning number and quality of spermatozoa, it is possible to offer satisfactory chances of pregnancy, lying around 20-40% per treatment cycle (15). However, due to the limited success per trial that is inherent to the technique, multiple trials can be required in order to obtain pregnancy.

Cryopreserved spermatozoa are used in association with different techniques for assisted reproduction, depending on their number and quality after thawing. When techniques requiring few spermatozoa are employed, such as conventional in vitro fertilization or ICSI, commonly there are exceeding spermatozoa that are not used and thus are discarded. Refreezing of theses exceeding spermatozoa would enable new trials of assisted reproduction, increasing the chances of pregnancy, particularly for individuals who have only one or few cryopreserved samples. Studies focusing on this aspect have been developed, and results are as encouraging as those found in the present study are. Polcz et al. (17) demonstrated that human spermatozoa can resist to 5 repeated freezing-thawing cycles, though significant reductions in the spermatic parameters have been observed (decrease in motility from 70.1% before freezing to 24.4; 8.0; 3.5; 1.5 and
1.8% after each thawing, respectively), confirming our findings. Rofeim et al. (18) also demonstrated that human spermatozoa resist to refreezing, and suggest that they can be used for ICSI.

In this study, we assessed the feasibility of refreezing human spermatozoa as well, but using a simple and low-cost technique, instead of computerized protocols, which are more complex and expensive. Other studies indicate that there is no significant difference in spermatic survival when freezing by liquid nitrogen vapor with static phases is compared with automated techniques (19,20). Bandularatne & Bongso (20) assessed the fertilization rates obtained with refrozen and thawed spermatozoa through the ICSI test in hamster oocytes, which is a functional test designed to assess the fertile potential of human spermatozoon, and obtained similar rates when refrozen and fresh spermatozoa were compared (22.2 versus 27.3% respectively, non significant). These authors also assessed the survival of refrozen spermatozoa in relation to the type of samples from which they were derived, normozoospermic and oligozoospermic, and observed that there was no significant difference in survival rates and in the decrease of spermatic parameters between the 2 groups (20). Such fact motivated us to compare in the present study 2 subgroups of individuals that had their semen frozen for different reasons, aiming to assess if the subgroup of men who froze their semen due to cancer would have lower performance following refreezing and thawing, however no significant difference was observed. Such findings enable us to suggest that these individuals could benefit from refreezing as well.

Though the results from this and other mentioned studies are promising, other studies are required in order to assess the fertile potential of refrozen human semen in cycles of assisted reproduction, with emphasis not only on rates of term pregnancy, but also on rates of miscarriage, complications and malformations.

CONCLUSION

There was a significant reduction in all the spermatic parameters under evaluation between the first and the second freezing-thawing cycle. However, refreezing of human semen through the technique of liquid nitrogen vapor with static phases enables the recovery of viable spermatozoa. We observed that in 100% of cases there was retrieval of motile spermatozoa after the second thawing.

Work presented at the Meeting of the American Society for Reproductive Medicine, San Antonio, USA, September 2003.

REFERENCES

10. Hallak J, Kolettis PN, Sekhon VS, Thomas AJ Jr, Agarwal A: Cryopreservation of sperm from patients...
REFREEZING OF HUMAN SPERMATOZOA


Received: September 13, 2004
Accepted after revision: November 23, 2004

Correspondence address:
Dr. Sandro C. Esteves
Av. Dr. Heitor Penteado, 1464
Campinas, SP, 13075-460
Fax: + 55 19 3294-6992
E-mail: s.esteves@androfert.com.br
CHOLESTEATOMA OF THE UPPER URINARY TRACT

DANIEL X. LIMA, ELI A. S. RABELO, PAULO G. O. SALLES

General Hospital, School of Medicine, Federal University of Minas Gerais, UFMG, Belo Horizonte, Minas Gerais, Brazil

ABSTRACT

We report the case of a 57-year old patient with complex cystic image in right kidney. Following radical nephrectomy, the pathological study established the diagnosis of renal cholesteatoma. We discuss the frequency, pathogenesis, clinical presentation, propedeutics, histological findings and proposes for intervention observed in the literature.

Key words: kidney; cholesteatoma; cyst; disease, urinary tract


INTRODUCTION

Cholesteatoma (leukoplakia) of the upper urinary tract is a rare benign condition, with approximately 80 cases being described in the literature (1). The characteristic histopathological finding is squamous metaplasia of the urothelium associated with exuberant keratinization and desquamation of keratinized layers. The urinary elimination of horny material can lead to intermittent obstruction of the collector system and flank pain, which are the main clinical manifestations of the disease. Classically, the condition is treated by nephrectomy, though recently its malignant and recurrence potential has been questioned, warranting conservative approaches.

CASE REPORT

Male, 57-year old patient, previously healthy, reported infrequent episodes of right lumbar colic for approximately 6 months. The physical examination did not present significant alterations, as well as the exam of urinary sediment and urine culture. The ultrasound showed a pyelocaliceal cyst in right kidney, with calcification on its inferior wall. On the computerized tomography (Figure-1), the cyst showed to be hypodense, with heterogeneous content, septate, with captation of contrast medium and calcification in its wall (Bosniak III). Considering the finding of complex renal cyst, right radical nephrectomy was

Figure 1 – Abdominal computerized tomography, showing hypodense image in right kidney, with inner calcification, suggestive of cystic mass.
URINARY TRACT CHOLESTEATOMA

performed, due to the possibility of neoplasia. Surgical procedure evolved without intercurrences, as well as postoperative outcome.

The pathological examination showed a kidney measuring 11.6 x 5.8 cm and weighting 305 g, with a pyelocaliceal cyst measuring 4.6 cm in its larger diameter, with smooth and regular walls, filled by whitish, semi-solid and somewhat friable material, which compressed the adjacent renal parenchyma (Figure-2). On microscopy, the cyst was covered by urothelium with extensive squamous metaplasia, abundant keratinization and corneal-lamellar content, compatible with the diagnosis of cholesteatoma (leukoplakia) of the upper urinary tract. There was fibrosing chronic inflammation on the periphery of the cyst, focal chronic pyelonephritis and hyaline vascular nephrosclerosis. No neoplasia was observed.

COMMENTS

Desquamative keratinizing squamous metaplasia of the upper urinary tract, or cholesteatomatous leukoplakia most often is located in renal pelvis and adjacent calices, where sometimes it assumes cystic form. It shows a clear predominance in adult population (97.5% of described cases) and is slightly more common in males than in females (3:2 ratio). The process is more commonly considered as a reactive phenomenon related to chronic urothelial inflammation, though hypotheses of embryological anomaly or even spontaneous transformation of urothelium into squamous epithelium cannot be ruled out.

It is inconsistently correlated with squamous cell carcinoma, since the progression from metaplasia to neoplasia was never demonstrated (1). Conservative approaches, by percutaneous and transureteroscopic route, or even clinical follow-up have already been described (2,3). In the case of this patient, there was clinical and radiological suspicion of a malignant renal cyst, warranting radical surgery.

The most characteristic sign in renal cholesteatoma is the elimination of flake-like keratinized material in the urine, which becomes opaque. Such alteration is not always present, making pre-operative diagnosis difficult for this rare condition. Imaging exams such as excretory urography and retrograde pyelography can be helpful in suspected cases of renal cholesteatoma, though urothelial tumor must be always considered in differential diagnosis (1).

REFERENCES


Received: June 23, 2004
Accepted after revision: July 27, 2004

Correspondence address:
Dr. Eli Armando S. Rabelo
Section of Nephrology and Urology
General Hospital, School of Medicine, UFMG
Rua Piauí 933 / 501
30150-320, Belo Horizonte, MG, Brazil
URETERAL ENDOMETRIOSIS AND COEXISTENT URETHRAL LEIOMYOMA IN A POSTMENOPAUSAL WOMAN

ANDREW STRANG, SCOTT W. LISSON, STEVEN P. PETROU

Wake Forest School of Medicine, Winston Salem, North Carolina, and Department of Urology, Mayo Clinic, Jacksonville, Florida, USA

ABSTRACT

We report the case of a postmenopausal woman with a synchronous obstructing intrinsic endometrioma of the left ureter and a coexistent periurethral leiomyoma. Endometriosis in postmenopausal women is a rare clinical entity usually associated with exogenous estrogen use. Urethral leiomyomas are also rare, with only 40 cases reported in the literature. Ovarian hormones are believed to influence the growth of leiomyomas. We report the genitourinary presentation of 2 separate disease entities with known hormonal influence in a postmenopausal woman receiving estrogen replacement therapy. We believe the patient’s hormonal milieu affected the development of her concurrent pathology.

Key words: ureter; urethra; leiomyoma; endometriosis

Int Braz J Urol. 2004; 30: 496-8

INTRODUCTION

Endometriosis occurs rarely in postmenopausal women and is usually associated with exogenous estrogen use or excessive endogenous production by the adrenals or pituitary gland (1). Leiomyomas are benign tumors of smooth muscle origin and are infrequently found in the urinary tract, with only 40 cases of urethral leiomyoma reported in the literature (2,3). The growth of both endometriomas and leiomyomas may be hormonally related. We report the case of a postmenopausal woman with a synchronous obstructing intrinsic endometrioma of the left ureter and a coexistent periurethral leiomyoma.

CASE REPORT

A 65-year-old woman was evaluated for painless gross hematuria. She denied irritative voiding symptoms or a history of urolithiasis or urinary tract infections. The patient’s medications included conjugated estrogens and ramipril. Pelvic examination indicated a thickened urethra. Her laboratory test results were unremarkable. The patient had normal cystoscopic findings, and intravenous pyelography (IVP) revealed poorly opacified, dilated calices throughout the left intrarenal collecting system without visualization of the left distal ureter. Computed tomography (CT) noted a high-density mass within the left distal ureter. Ureteroscopic biopsy of the ureteral mass (Figure-1) indicated endometriosis. Magnetic resonance imaging of the urethra noted a 2.9×2.9×3 cm posterior periurethral mass (Figure-2) with signal characteristics suggestive of a leiomyoma.

The patient underwent pelvic exploratory surgery with left pelvic lymphadenectomy, left distal ureterectomy and ureteroneocystostomy. The periurethral lesion was transvaginally excised. Pathologic analysis confirmed a benign leiomyoma.
Endometriosis in postmenopausal women is a rarity usually associated with exogenous estrogen use or excessive endogenous production by the adrenals or pituitary gland (1). Endometriosis involving the genitourinary tract has been reported with an incidence of 1.2% and a mean age between 30 and 35 years (1). The ratio of occurrence in the bladder to ureter to urethra is 40:5:1 (1). On IVP, intrinsic endometriomas tend to produce filling defects and may mimic transitional cell carcinoma and radiolucent stones. Intrinsic lesions represent advanced disease and require resection of the involved segment.

Leiomyomas are benign tumors of smooth muscle origin found rarely in the urinary tract, with 40 cases reported in the literature (2,3). Leiomyomas are 3 times more common in women with an average age at presentation of 39 years (3). Common presenting symptoms include urinary tract infection, mass effect, voiding dysfunction, and dyspareunia. The most common site of urethral occurrence is the posterior wall (3). Excision is the treatment of choice.

Ovarian hormones are believed to influence the growth of leiomyomas (2). The incidence of these benign tumors increases after menarche. Estrogen and progesterone receptors have been demonstrated in uterine smooth muscle tumors and underscore the rationale for medical treatment of these lesions (3). Endometriomas are also hormone-sensitive lesions with their growth likely affected by ovarian steroids. Like leiomyoma, endometriosis is treated medically with hormonal agents aimed at suppressing the hypothalamic-pituitary-gonadal production of gonadotropins.

We report the genitourinary presentation of 2 separate disease entities with known hormonal influence in a postmenopausal woman receiving estrogen replacement therapy. We entertain the likelihood that the patient’s hormonal milieu affected the development of her concurrent pathology.

REFERENCES


**Correspondence address:**
Dr. Steven P. Petrou  
Department of Urology, Mayo Clinic  
4500 San Pablo Road  
Jacksonville, Florida, 32224, USA  
Phone: + 1 904 953-0413  
E-mail: petrou.steven@mayo.edu
NON-HODGKIN LYMPHOMA OF THE BLADDER

ALBERTO A. ANTUNES, LUCIANO J. NESRALLAH, MIGUEL SROUGI

Division of Urology, Paulista School of Medicine, Federal University of São Paulo, UNIFESP, São Paulo, SP, Brazil

ABSTRACT

Lymphomas of the bladder are rare lesions, representing approximately 0.2% of the primary neoplastic lesions and approximately 1.8% of the secondary lesions in this organ. The authors report the case of a 41-year old patient with secondary lymphoma of the bladder occurring 2 years after treatment for non-Hodgkin lymphoma, diagnosed by biopsy of cervical lymph node, and analyze the clinical and prognostic aspects of bladder lymphomas.

Key words: bladder; bladder neoplasms; lymphoma, non-Hodgkin


INTRODUCTION

Lymphomas of the bladder are rare lesions, representing approximately 0.2% of the primary neoplastic lesions and approximately 1.8% of the secondary lesions in this organ (1).

Patients with bladder lymphomas can be divided into 3 groups, according to their clinical presentation: 1) primary cases in bladder, 2) cases occurring in bladder as a manifestation of systemic disease, and 3) secondary cases, with clinical history of malignant lymphoma recurring in bladder. In the latter case, the main sites of primary involvement are peripheral lymph nodes, bone marrow and spleen (2).

The authors report the case of a 41-year old patient with secondary lymphoma of the bladder occurring 2 years after treatment for “non-Hodgkin” lymphoma, diagnosed by biopsy of cervical lymph node.

CASE REPORT

Male, 41-year old, asymptomatic patient was referred for urological evaluation with ultrasound revealing a tumor in the bladder lateral wall. There was a previous history of non-Hodgkin lymphoma, diagnosed through biopsy of cervical lymph node and treated with chemotherapy. Patient reported that the disease was in remission for 2 years.

An abdominal computerized tomography was performed (Figure-1), which confirmed the ultrasound

Figure 1 – Pelvic computerized tomography, showing tumor in right lateral wall of the bladder.
findings. He underwent a cystoscopy, which showed a bulging in the right lateral wall of the bladder, without involving the mucosal surface, which presented normal aspect. The ureteral meatus were normal.

We performed a transurethral resection of the lesion. The pathological examination revealed a lymphoproliferative process with follicular pattern, characterizing a non-Hodgkin lymphoma of the bladder (Figure-2). The immunohistochemical analysis was positive to CD20, characterizing B-lymphocytes (Figure-3), and to bcL-2 protein (Figure-4), characterizing a follicular lymphoma. The patient was referred for adjuvant chemotherapy.

**COMMENTS**

Among cases of bladder lymphoma, approximately 17% occur in primary form, 47% in non-localized form, and 36% in secondary form (2). MALT-type lymphomas (mucosa associated lymphoid tissue) are the most common form of primary involvement of the bladder. The prognosis of these cases is usually good, and most series do not report deaths associated with the disease. The disease is 6.5 times more frequent in women and predominates in patients with mean age of 64 years old (20 to 85) (3). Lesions can be single or multiple, and irritative bladder symptoms may occur. Approximately 20% may present a history of chronic cystitis (2).

Cases of non-localized bladder lymphoma predominate in men, and tend to present fewer symptoms relative to bladder involvement. These patients usually present abdominal pain. Approximately half the patients can present ureteral obstruction. Mean survival in these cases is 9 years (2).

The occurrence of secondary involvement of the bladder by a systemic lymphoma is more common than primary involvement. Necropsy studies show that approximately 10 to 20% of cases of systemic non-Hodgkin lymphoma can involve the bladder secondarily (1,3). Normally, such patients die due to disseminated disease, which frequently involves other urogenital sites or associated with massive pelvic involvement.

In the series by Kempton et al. (2), 10 of 13 patients presented symptoms related to involvement
of the urinary tract, and 30% presented associated ureteral obstruction. The mean interval between diagnosis and secondary involvement of the bladder was 4.5 years (0.3 to 12 years), and the initial site of lymphomas, in decreasing frequency, were peripheral lymph nodes, bone marrow, spleen, orbit, lungs and palate. The patient in the present case presented initial involvement of lymph nodes from the cervical region.

Usually, patients with secondary involvement of the bladder are treated with salvage chemotherapy, and mean survival can range from 5 days to 8 years (median 0.58 years), thus constituting the group with poorer prognosis (2).

REFERENCES


Received: May 25, 2004
Accepted after revision: August 9, 2004

Correspondence address:
Dr. Luciano J. Nesrallah
R. Barata Ribeiro 414 / 25
São Paulo, SP, 01308-000, Brazil
E-mail: nesrallahuro@uol.com.br
TESTICULAR SCHISTOSOMIASIS MIMICKING TUMOUR

NICOLA MORTATI NETO, JOÃO P. S. GRANDO, HORACIO A. MOREIRA

Professor Antonio Prudente Hospital, Cancer Institute, Londrina, Parana, Brazil

ABSTRACT

Schistosomiasis or bilharziasis is a disease caused by Schistosoma. When infecting men the most common parasites are Schistosoma mansoni, Schistosoma japonicum and Schistosoma haematobium. The Schistosoma mansoni is the only endemic parasite in Brazil. We present a case of testicular schistosomiasis simulating malignancy. The case was treated successfully by excisional biopsy and praziquantel therapy. A review of the literature is discussed.

Key words: testis; nodule; Schistosoma mansoni

CASE REPORT

A forty-year-old white man attended at the outpatient clinics of our hospital in May 2003, complaining about a nodule in his right testis. His wife recognized the nodule during a sexual intercourse. The physical examination revealed a painless 2-cm solid nodule in his right testicle. The laboratory data including beta-human chorionic gonadotropin (beta-hCG), lactic dehydrogenase (LDH), and alpha-feto protein (AFP) were normal. The scrotal ultrasonography depicted a 1.8 cm hypoechoic nodule in the right testis. The patient was submitted to a frozen excisional biopsy. It revealed a granulomatous lesion with schistosomal egg (Figure-1). The patient was further treated with 40 mg/kg of praziquantel at single dose and after 10 months of follow-up, there is no evidence of the disease.

COMMENTS

Patients who present a testicular nodule or mass are always suspicious of harboring cancer since 80% of such lesions are germ cell carcinoma (1). Most
of testicular tuberculosis and 2 cases of testicular histiocitosis.

Urogenital schistosomiasis is a rare condition. It can affect kidney, ureter, bladder, prostate, epididymis and testis. Schistosoma mansoni is the main responsible for the disease in Brazil (2). The reason why schistosomal eggs are found in the testis has been a controversial issue. Portal hypertension seems to be an important condition to the development of ectopic lesions. The presence of collateral circulation would disseminate the eggs to other organs. The eggs can cause allergic reactions in the testicle, which mimic a testicular neoplasia (3). Testicular schistosomiasis can also cause intermittent pain owing to chronic manifestation of the disease (2).

We perform excisional frozen biopsy before radical orchiectomy in patients who have a small periphery nodule (≤ 2 cm) and normal serum markers, owing to the possibility of benign lesion. Unfortunately, there are no reliable imaging methods for differentiating a testicular lesion precisely and many benign cases are treated by radical orchiectomy when frozen biopsy is inconclusive.

There are few reports of testicular schistosomiasis described in the literature owing to the rarity of this entity in this organ. It usually mimics a malignant lesion presenting with a painless small solid nodule (3,4,5). It should be part of differential diagnosis especially in endemic areas.

REFERENCES


Correspondence address:
Dr Nicola Mortati Neto
Rua Bandeirantes 460, Centro
86010-180, Londrina, Parana, Brazil
Phone: + 55 43 33371800
E-mail: nicolald@sercomtel.com.br

Received: May 10, 2004
Accepted after revision: July 20, 2004
FINDINGS IN CYSTOURETHROGRAPHY THAT SUGGEST LOWER URINARY TRACT DYSFUNCTION IN CHILDREN WITH VESICoureTERAL REFUX

UBIRAJARA BARROSO JR, ANTONIO J. VINHAES, MILTON BARROS, VIVIAN A. BARROSO, ADRIANO A. CALADO, MIGUEL ZERATI FILHO

Section of Pediatric Urology, San Rafael Hospital, and Federal University of Bahia, Salvador, Bahia, and Institute of Urology and Nephrology, São José do Rio Preto, São Paulo, Brazil

ABSTRACT

Purpose: Children with lower urinary tract dysfunction and vesicoureteral reflux, at cystography assessment, frequently present alterations in the lower urinary tract anatomy such as dilated posterior urethra, irregularity of the bladder wall and diverticula. However, the significance of these findings is unknown. The objective of this study is to evaluate the incidence of these findings, their time of disappearance and their correlation with the severity of the reflux.

Materials and Methods: 193 children with vesicoureteral reflux, considered simple, in the age group above 5 years at the moment of diagnosis, were analyzed. The recommendation for follow-up of these patients was one voiding cystoureterography (VCUG) each year. Only patients with a minimum of 2 VCUGs performed in a period of at least 6 months were considered. The VCUGs were classified as positive and negative in relation to findings that were characteristic of lower urinary tract dysfunction (LUTD).

Results: From the 193 children analyzed, 50 (26%) presented positive VCUG and 143 negative VCUG. From the patients without symptoms of lower urinary tract dysfunction (n = 135), 12 (9%) presented positive VCUG and 123 (91%) a negative VCUG. From the patients with negative VCUG, 68 (48%) presented unilateral reflux and 75 (52%) presented bilateral reflux. From those with positive VCUG, 26 (52%) had unilateral reflux and 24 bilateral reflux (48%). This difference was not statistically significant. A higher incidence of grade II reflux was more evident in patients with negative VCUG and degree III in patients with positive VCUG (p < 0.05).

Conclusions: Our study demonstrated that 64% of the patients with LUTD and reflux presented findings in the VCUG that suggest dysfunction.

Key words: bladder, neurogenic; vesicoureteral reflux; imaging studies; voiding dysfunction

Int Braz J Urol. 2004; 30: 504-7

INTRODUCTION

Usually, the first exam requested in the evaluation of vesicoureteral reflux is voiding cystoureterography (VCUG). It offers the advantage, in a first evaluation, of supplying information about the anatomy of the lower urinary tract, besides grading the reflux (1). The association of vesicoureteral reflux with bladder dysfunction is well established (2). The symptoms that indicate dysfunction of the lower urinary tract are voiding urgency, incontinence with or without urgency, and infrequent voiding (3,4). Children with these symptoms, at cystography assessment, frequently present alterations in the lower urin-
nary tract anatomy such as expanded posterior urethra, irregularity of the vesical wall that corresponds to trabeculations and thickening of the detrusor, besides the possibility of diverticula. However, the significance of these findings is unknown. The objective of this study is to evaluate the incidence of these findings, their time of disappearance and their correlation with the severity of the reflux.

MATERIALS AND METHODS

From January 1986 to June 1999, 193 children with vesicoureteral reflux, considered simple type, in the age group above 5 years at the moment of diagnosis were analyzed. The recommendation for follow-up of these patients was one voiding cystoureterography each year. Only patients with a minimum of 2 VCUGs performed in a period of at least 6 months were considered. The results of the VCUGs were evaluated by means of reports from the radiologist and pediatric urologists, which contained the information about bladder anatomy. When there was doubt in relation to the diagnosis we reassessed the images. When the images could not be duly characterized, the patients were excluded from the study. The vast majority of the X-rays were done by just one pediatrician radiologist.

The VCUGs were classified as positive and negative in relation to findings that were characteristic of lower urinary tract dysfunction (LUTD). They corresponded to dilation of the posterior portion of the urethra, irregularity of the vesical wall and diverticula of the bladder. The rate and time of resolution of the findings of the VCUG were studied, i.e., how many and when the positive VCUGs became normal (negative). The grades of reflux were registered, as well as if they were unilateral or bilateral. The children were treated with continuous antibiotic prophylaxis, at low doses, and those with symptoms of the lower urinary tract dysfunction were treated with anticholinergics.

The statistical analysis, to compare the proportions, was done by means of Fisher’s exact test or the chi-square test, or by Student’s t test for the continuous variables. We considered $p < 0.05$ as statistically significant.

RESULTS

From the 193 children analyzed, 50 (26%) presented positive VCUG and 143 negative VCUG. From 58 (30%) children that presented symptoms of lower urinary tract dysfunction, 37 (64%) had a positive VCUG and 21 (36%) a negative VCUG. From the patients without symptoms of lower urinary tract dysfunction ($n = 135$), 12 (9%) presented positive VCUG and 123 (91%) one negative VCUG. This difference was statistically significant.

In the group with positive VCUG, 49 were female and 1 male. In the group with negative VCUG, 123 were female and 20 were male. In the patients with LUTD symptoms 56 were female and 2 were male, while for those without LUTD these numbers were 19 and 39 respectively. The gender difference between these groups was statistically significant.

From the patients with negative VCUG, 68 (48%) presented unilateral reflux and 75 (52%) presented bilateral reflux. From those with positive VCUG, 26 (52%) had unilateral reflux and 24 bilateral reflux (48%). This difference was not statistically significant. The correlation between the findings of VCUG according with the grades of reflux is demonstrated on Table-1. A higher incidence of grade II reflux was more evident in patients with negative VCUG and degree III in patients with positive VCUG ($p < 0.05$). The resolution rate was evaluated for the findings of the VCUG. From the 50 positive VCUGs, 30 became negative at an average period of 49 months, varying from 6 to 125.

COMMENTS

Our data evidenced that around 25% of the children with vesicoureteral reflux presented findings that suggest LUTD in the VCUG, with dilation of the posterior urethra, trabeculation of the wall and vesicle diverticula. From the children with LUTD, 64% presented these findings. What is interesting is that 9% of the children without LUTD symptoms presented a VCUG that suggests dysfunction. An explanation for this event is that these children may have had neonatal reflux that is associated to LUTD in the large majority of cases (5). In this situation, the VCUG could
demonstrate alterations, still not presenting symptoms. Sillen et al. have demonstrated that many children who are diagnosed with LUTD at 3 or 4 years of age, may have had a neonatal reflux and the dysfunction may be vestiges from this period (6). Another hypothesis is that these findings in VCUG may not be specific of vesical instability. Batista et al. have made it evident that sensitivity, specificity and accuracy of VCUG findings that suggest instability, when detrusor instability is detected in the urodynamic study, correspond to 0.5, 0.62 and 0.52 respectively (7). Sillen et al. recently reported that VCUG was well correlated with the urodynamic study of children with neonatal reflux (8). Nevertheless this is a select group of patients, in an age group that is different from the one we have studied.

We have not found difference in relation to unilateral or bilateral reflux and the VCUG findings. Scholtmeijer & Nijman have demonstrated that children with urinary dysfunction more frequently present bilateral reflux than those with urgency syndrome (9). According to our data a VCUG that suggests urinary dysfunction is not predictive of bilateral reflux. Nevertheless, our study made it evident that children with positive VCUG more frequently have grade 3 reflux and those with negative VCUG more commonly have grade 2 reflux. The incidence of grades 1 and 4 reflux was similar between the 2 groups. The meaning of these findings is uncertain. One data that we considered important and that, to our knowledge, was not previously reported, is that the alterations of the VCUG tend to have resolution with time. The average was 49 months. This may reflect a clinical improvement that the patients have obtained with treatment, as well as it may be the result of neurophysiological maturation of the lower urinary tract.

CONCLUSIONS

Our study demonstrated that 64% of the patients with LUTD and reflux presented findings in the VCUG that suggest dysfunction. These findings were found in 9% of those without LUTD. In other words, the presence of elements found in the VCUG, such as dilated urethra and bladder trabeculation do not necessarily mean that the patients have LUTD symptoms, as they are only found in a little more than half of the patients with LUTD, demonstrating a low sensitivity. Nevertheless, not indicating bilateral reflux and severe reflux, as it may seem. When these findings are present, they tend to have resolution in 4 years period.

REFERENCES


Table 1 – Correlation between the voiding cystoureterography (VCUG) findings and reflux grade.

<table>
<thead>
<tr>
<th>Grade (total)</th>
<th>Positive VCUG (%)</th>
<th>Negative VCUG (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 (11)</td>
<td>21 (10)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>2</td>
<td>14 (19)</td>
<td>90 (41)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>3</td>
<td>39 (53)</td>
<td>78 (36)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>4</td>
<td>13 (17)</td>
<td>24 (11)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>0</td>
<td>1 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

Received: May 17, 2004
Accepted after revision: November 25, 2004
ADRIAMYCIN-INDUCED FETAL HYDRONEPHROSIS

ANDERSON GONÇALVES, WILLY G. FRANÇA, SUZANA G. MORAES, LUIS A.V. PEREIRA, LOURENÇO SBRAGIA

Institute of Biology and School of Medicine, State University of Campinas, UNICAMP, Campinas, São Paulo, Brazil

ABSTRACT

Introduction: At the end of pregnancy, the amniotic fluid (AF) depends basically on renal function, corresponding to fetal urine. Changes in AF, especially oligohydramnios, are reported in association with fetal hydronephrosis (FH). The experimental model using adriamycin in pregnant female rats has a teratogenic effect and has been classically employed to study esophageal atresia. Nevertheless, adriamycin promotes FH with high frequency as well. In the present study, using this animal model, we tried to identify the incidence and microscopic changes of FH, as well as its correlation with AF weight.

Materials and Methods: Eight Sprague-Dawley pregnant female rats received adriamycin 2.2 mg/kg on the 8th and 9th gestational days (considering term gestation = 22 days). Those fetuses that received adriamycin (Adriamycin Group) were compared with fetuses from 2 female rats (Control Group), which received 0.9% saline solution. On the 21.5 gestational day, the fetuses were collected by cesarean incision, sacrificed, and examined for macro and microscopic changes in kidneys and ureters. Fetuses with bilateral hydronephrosis formed the Hydronephrosis Group. AF weight was determined as well.

Results: Hydronephrosis occurred in 70 (95%) of the 74 fetuses in the adriamycin group against none of the 21 fetuses from the control group. The amniotic fluid weight was increased in the adriamycin group in relation to the control group (p < 0.001). The histomorphometric study revealed dilation of the renal pelvis and reduction of renal parenchyma in the hydronephrosis group in relation to the control group. Severe cortical atrophy, cortical tubular atrophy and medullar atrophy were observed in the hydronephrosis group.

Conclusions: Slight renal lesions were in agreement with changes in AF weight, since they suggest that there was production of urine with the maintenance of AF.

Key words: rats; amniotic fluid; fetus; adriamycin; hydronephrosis

INTRODUCTION

The amniotic fluid (AF) at the end of pregnancy depends basically on renal function, corresponding to the fetal urine (1). Changes in AF concerning volume, osmolarity and solute partition are reported in association with fetal hydronephrosis (FH) (2-4).

FH is characterized by prenatal dilation of the renal pelvis. Generally, it is associated with decreased urinary flow, structural changes in renal parenchyma and impairment of renal function (5,6). The clinical manifestation of FH is variable, presenting an unfavorable outcome when it is bilateral or is associated with decrease in AF (oligohydramnios) (2,7,8). Moreover, the prenatal assessment of AF has
a predictive value on the prognosis of the newborn (7,8).

The experimental model using adriamycin in pregnant female rats has a teratogenic effect and has been classically employed to study esophageal atresia. However, adriamycin promotes other fetal morphologic changes, with FH being the urinary anomaly that occurs with higher frequency (9-11). Much has been described about gastrointestinal changes in the adriamycin model (12), however, little has been studied about renal changes and their correlation with AF.

In the present study, we tried to identify the feasibility of using adriamycin for the microscopic study of FH, aiming to correlate renal microscopic changes with AF weight (AFw).

MATERIALS AND METHODS

Eight Sprague-Dawley pregnant female rats, weighting between 250 and 300 g, received intra-peritoneal adriamycin 2.2 mg/kg on the 8th and 9th gestational days (term = 22 days). The fetuses that received adriamycin (Adriamycin Group) were compared with fetuses from 2 female rats (Control Group) that had received 0.9% saline solution on the same gestational days.

On the day 21.5 of pregnancy, the rats underwent a cesarean incision and the amniotic sac was integrally extracted and weighted (ASw) in a precision balance. The amniotic sac was then excised and the fetus (Fw), the placenta and the amniochorionic membranes (PMw) were weighted separately. The AFw was obtained through the formula: AFw = ASw - (Fw + PMw) in grams.

Then the fetuses were collected, sacrificed and examined for macroscopic changes in kidneys and ureters, bladder changes, and presence of proximal digestive atresias. Fetuses from the adriamycin group with bilateral hydronephrosis formed the Hydronephrosis Group.

The abdominal region with the retroperitoneal cavity of fetuses, containing kidneys and ureters, was fixed in formaldehyde 4% and included in paraffin. Semi-serial coronal histological sections were obtained, measuring 5 µm, equidistant in 20 µm between the anterior and posterior renal limits. Sections were stained with hematoxylin and eosin.

Histomorphometric Study and Qualitative Microscopic Analysis

The fetal kidneys from the hydronephrosis group and the control group were compared under light microscopy. Images obtained by microscopy were transmitted to the computer via digital camera. Subsequently, they were dimensioned using Image-Pro Plus 4.1 software (Media Cybernetics 1999), which allows the gauging of linear measures and area after manually defining 2 points and the perimeter, respectively. The micrometric scale was previously defined by a calibration file, according to the microscope’s objective lens.

With a X20 magnification, the 3 consecutive sections of each left kidney were determined, where the diameters of the ureteropelvic junction were largest. In these sections, the diameter of the ureteropelvic junction, the mean parenchymal thickness, the area of the renal pelvis, and the area of renal parenchyma were measured, and the relationships between parenchyma and pelvis were established (Figure-1).

The histological changes of pelvic epithelium, proximal ureter and kidney (epithelial, mesenchymal, epithelial-mesenchymal, obstructive and inflammatory) were qualitatively analyzed according to what is described in the literature for the model of obstructive hydronephrosis (13,14).

Statistical Analysis

The statistical analysis of weights, with comparisons between the adriamycin and control groups, and the histomorphometric measures, with comparisons between the hydronephrosis and control groups, was performed through Mann-Whitney non-parametric test, considering the difference as significant for p < 0.05 and highly significant for p < 0.001.

RESULTS

Pregnancy was confirmed in 10 female rats, with 8 forming the adriamycin group and 2 the control group. A total of 81 fetuses were obtained in the
ADRIAMYCIN-INDUCED FETAL HYDRONEPHROSIS

adriamycin group, of which 74 (91%) were alive and 7 (9%) dead (4 were reabsorbed and 3 were hydromic). In the control group, 21 fetuses were obtained, all alive.

In the adriamycin group, hydronephrosis (Figure 2) was observed in 70 out of 74 fetuses (95%), in addition to other malformations. In the 21 fetuses from the control group, the malformations under study were not observed (Table 1).

ASw, Fw and PMw were decreased and AFw was increased in the adriamycin group in relation to the control group (p < 0.001) (Table 2).

The histomorphometric study revealed pelvic dilation and reduction of renal parenchyma in the hydronephrosis group when compared with the control group (p < 0.001) (Table 3).

The qualitative microscopic analysis of the kidneys in both groups demonstrated the capacity of distinguishing between medullar and cortical in a lower magnification (X20) and the existence of nephrogenic zone, composed by immature glomeruli (Figure 3). In the hydronephrosis group, we observed se-

Table 1 – Frequency of malformations in the adriamycin group.

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydronephrosis</td>
<td>70 (95)</td>
</tr>
<tr>
<td>- Bilateral</td>
<td>64 (87)</td>
</tr>
<tr>
<td>- Unilateral</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Duodenal Atresia</td>
<td>68 (92)</td>
</tr>
<tr>
<td>Esophageal Atresia</td>
<td>67 (91)</td>
</tr>
<tr>
<td>Bladder Hypoplasia</td>
<td>62 (84)</td>
</tr>
</tbody>
</table>

Table 2 – Comparison of weights. Mean, standard deviation and interval.

<table>
<thead>
<tr>
<th>Weights</th>
<th>Adriamycin Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASw (g)</td>
<td>5.23* (± 0.56); 0.38 – 6.51</td>
<td>5.96 (± 0.27); 5.27 – 6.63</td>
</tr>
<tr>
<td>Fw (g)</td>
<td>3.39* (± 0.43); 2.12 – 4.36</td>
<td>4.27 (± 0.18); 3.88 – 4.62</td>
</tr>
<tr>
<td>PMw (g)</td>
<td>0.95* (± 0.16); 0.35 – 1.62</td>
<td>1.11 (± 0.14); 0.67 – 1.50</td>
</tr>
<tr>
<td>AFw(g)</td>
<td>0.90* (± 0.33); 0.08 – 2.34</td>
<td>0.58 (± 0.18); 0.19 – 0.97</td>
</tr>
</tbody>
</table>

*p < 0.001; ASw = weight of amniotic sac; Fw = fetal weight; PMw = weight of placenta and amniotic membranes; AFw = weight of amniotic fluid.
vere cortical atrophy and tubular cortical atrophy; as well as moderate caliceal dilation, moderate to severe cystic tubular change and slight mesangial hyperplasia, whereas in the control group such changes were not observed (Figure-4).

The search for microscopic changes in pelvis and ureter revealed severe pelvic dilation with flattening of the epithelial cells, and dilation and tortuosity of the proximal ureter in the hydronephrosis group. On the other hand, no changes were observed in the ureteral epithelium, which was similar to the control group.

**COMMENTS**

Adriamycin acts on the S-phase of the cell cycle, inhibiting topoisomerase II and consequently DNA synthesis (15). This inhibition induces cell apoptosis, and is the potential molecular cause of the malformations detected, deriving mostly from a failure in the embryologic development of mesoderm (16).

The decrease in ASw, Fw and PMw in the adriamycin group in relation to the control group is due to the drug’s deleterious effects, either by its primary action, or by the repercussions from the malformations it induces (9,10).

The frequency of detected malformations was similar to those found by other authors who used adriamycin (9-11,17).

Fetuses with serious renal defects leading to intra-uterine urinary retention evolve with oligohy-

---

**Table 3** – Comparison of histomorphometric measures. Mean, standard deviation and interval.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Hydronephrosis Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal Thickness x UPJ Diameter</td>
<td>0.68 (± 0.25); 0.37 – 1.52</td>
<td>1.36 (± 0.30); 0.81 – 2.10</td>
</tr>
<tr>
<td>Parenchymal Area x Pelvic Area</td>
<td>1.83 (± 0.84); 0.83 – 4.35</td>
<td>5.83 (± 2.44); 2.81 – 12.13</td>
</tr>
</tbody>
</table>

*p < 0.001; UPJ = ureteropelvic junction*
dramnios, due to the relation between the production of fetal urine and a proper amount of AF (3,7). Despite bilateral FH occurring in 87% of fetuses in the adriamycin group, there was an increase in AFw in relation to the control group (p < 0.0001). However, a bilateral FH occurred in association with 100% of digestive atresias. Such atresias, especially proximal ones, impair the deglutition of AF, as well as its absorption in the gastrointestinal tract, and may lead to polyhydrarnnios (18).

The association between these anomalies, intestinal atresias and FH, which have a contrary effect on AFw, and other potential causes of oligohydrarnnios can make results controversial. However, the present study showed that the ability of forming urine, and consequently AF by the fetal kidney was preserved, since there was no decrease in the AFw. Hence, it is not important to say that AFw increased, but that it did not decrease, since little AF would indicate low production of fetal urine.

Merei et al. (2001) studied urinary malformations in the adriamycin model and concluded that the ureters would present a blind end, producing hydronephrotic fetal kidneys and altering the normal development of urinary bladder (11). In order to explain the increase in AF that occurs concomitantly in blind-ending ureters, extra-renal compensatory mechanisms would be required.

Liu & Hutson (2000), while studying urogenital malformations in the same model, concluded that the ureters might communicate with the urethra in male fetuses, and with the urogenital sinus in female fetuses, through an uretero-ureteral or uretero-urogenital fistula, respectively (19). Thus, urinary flow would occur, which would allow for a proper maintenance of AF amount. The occurrence of FH non-associated with oligohydrarnnios is suitable with the explanations proposed by Liu & Hutson (2000), since it may be the indirect result of passage of urine to the amniotic cavity (19).

In relation to bladder development, the occurrence of 84% of bladder hypoplasia observed in the present study could be explained both by the lack of filling due to fistula between ureter and urethra or urogenital sinus and by the presence of blind-ending ureter (11,19).

Liu et al. (1999) studied bladder development, using adriamycin and verified that the 7th gestational day is the critical time when the drug administration causes bladder agenesis. Bladder hypoplasia observed in the present study, considering that the drug was administered on the 8th and 9th days, must be consequent to ureteral defects or represent an effectively distinct anomaly from that observed by the same author (20).

The histomorphometric study revealed increase in the ureteropelvic junction (UPJ) diameter and in pelvic area, and decrease of parenchymal thickness and parenchymal area in the hydronephrosis group when compared with the control group. The parenchyma/pelvis relationships were decreased to half in the hydronephrosis group in relation to the control group, when we used linear measures decreased to one third, when area measurements were used. These results objectively confirm the pelvic dilation and decrease in renal parenchyma observed in kidneys with hydronephrosis.

In models of surgically created hydronephrosis, we detected epithelial, epithelial-mesenchymal, obstructive and inflammatory changes, including atrophy, dysplasia, fibrosis and changes in the renal development (3,13,14).

Microscopic findings in the present study are milder than the ones reported in those works, being restricted to the mechanical repercussion of urine retention, which is characterized by dilation of ureter, pelvis and ducts, and to secondary mass changes, such as atrophy of cortex and medulla. Moreover, no inflammatory or developmental changes were observed.

Other changes were expected in addition to dilation, since urine retention can be associated with renal damage and impair its normal differentiation (6,14). However, the microscopic findings are in agreement with other findings relative to AFw, which indirectly revealed production of fetal urine.

**CONCLUSION**

The experimental model of induction by adriamycin showed to be feasible for the microscopic study of fetal hydronephrosis. The microscopic
ADRIAMYCIN-INDUCED FETAL HYDRONEPHROSIS

changes, despite being milder than the lesions described for surgically produced fetal hydronephrosis, were in agreement with amniotic fluid weight, since they enabled the production of urine with maintenance of the amniotic fluid.

Anderson Gonçalves received scholarship for Scientific Initiation from CNPq, and Lourenço Sbragia Neto from FAPESP

REFERENCES


Received: August 23, 2004
Accepted after revision: November 17, 2004

Correspondence address:
Dr. Lourenço Sbragia Neto
Discipline of Pediatric Surgery, FCM, Unicamp
Rua Alexander Fleming, 181, Barão Geraldo
Campinas, SP, 13084-970, Brazil
Fax: + 55 19 3788-9473
E-mail: sbragia@fcm.unicamp.br
Rapid Communication: Relative effect of urinary calcium and oxalate on saturation of calcium oxalate

Pak CY, Adams-Huet B, Poindexter JR, Pearle MS, Peterson RD, Moe OW
Center for Mineral Metabolism and Clinical Research, The University of Texas Southwestern Medical Center, Dallas, Texas 75390-8571, USA

Background: The study compared the effect of urinary calcium with that of oxalate on urinary saturation [relative saturation ratio (RSR)] of calcium oxalate.

Methods: A retrospective data analysis was conducted on urinary stone risk analysis from 667 patients with predominantly calcium oxalate stones. Urinary RSR of calcium oxalate was individually calculated using Equil 2. A “theoretical” curve of the relationship between urinary RSR of calcium oxalate and concentration of calcium or oxalate was obtained at two stability constants for calcium oxalate complex, while varying calcium or oxalate and using group mean values for urinary constituents.

Results: At the stability constant of $7.07 \times 10^{3}$, the increase in RSR of calcium oxalate was less marked with calcium than with oxalate. However, at the stability constant of $2.746 \times 10^{3}$ from the Equil 2 that is considered the “gold standard,” calcium and oxalate were equally effective in increasing RSR of calcium oxalate. The above theoretical curves (relating RSR with calcium or oxalate) were closely approximated by the actual curves constructed with data from individual urine samples. Urinary saturation of calcium oxalate was equally dependent on urinary concentrations of calcium and oxalate ($r = 0.75$ unadjusted and $0.57$ adjusted for variables, and $P < 0.0001$ for calcium; $r = 0.73$ unadjusted and $0.60$ adjusted, $P < 0.0001$ for oxalate).

Conclusion: Among calcium oxalate stone-formers, urinary calcium is equally effective as urinary oxalate in increasing RSR of calcium oxalate.

Editorial Comment

It has long been held that urinary oxalate is a more important contributor to calcium oxalate stone formation than urinary calcium. This perception stems from work published in 1972 by Nordin, Peacock and Wilkinson (1) in which the relationship of urinary calcium and oxalate concentration on urinary saturation calcium oxalate was determined using the stability proposed by Robertson of $7.07 \times 10^{3}$. Their work showed that although urinary saturation of calcium oxalate initially increased with increasing urinary calcium concentration, saturation reached a plateau at moderate calcium concentration; in contrast, saturation of calcium oxalate continued to rise with increasing urinary oxalate concentration, thereby supporting a more pronounced effect of urinary oxalate than calcium on urinary saturation of calcium oxalate. Although Robertson later adjusted his stability constant, in line with a lower stability constant proposed by Finlayson (2), the relationships between urinary calcium and oxalate and urinary saturation of calcium oxalate were never re-assessed.

Pak and colleagues reexamined the relative contribution of urinary calcium and oxalate on urinary saturation of calcium oxalate using retrospective data from predominantly calcium oxalate stone formers in their stone registry. First, they constructed theoretical curves relating urinary calcium and oxalate concentrations to urinary saturation of calcium oxalate using average values for urinary analyses derived from the population of patients studied and varying the urinary calcium and oxalate concentrations from zero to 2 standard deviations above the mean of the patient-derived values. When the higher original Robertson stability constant was used, urinary saturation reached a plateau at relatively lower concentrations of urinary calcium than urinary oxalate. On the other hand, when the lower Finlayson stability constant was used (as is used in the Equil 2 computer program), urinary saturation continued to increase with increasing urinary oxalate concentration. However, the differences in the saturation curves were slight, and the conclusion remains the same: the effect of urinary oxalate on urinary saturation of calcium oxalate is more pronounced than that of urinary calcium.
Urological Survey

program, considered the gold standard for calculating saturation of stone-forming salts), saturation increased with both urinary calcium and oxalate concentrations, with the 2 curves departing only at high concentrations, at which point the curves reached a plateau at relatively lower calcium than oxalate concentrations. Furthermore, when actual urinary saturations were plotted against urinary calcium and oxalate concentrations for the patients in the database using the 2 stability constants, the “actual” values closely approximated the “theoretical” values derived using the lower Finlayson stability constant. Of significance, the calcium and oxalate curves were nearly superimposable.

These findings suggest that urinary calcium and oxalate contribute equally to the tendency toward calcium oxalate stone formation. As such, recent studies downplaying the role of dietary calcium in stone formation and advising against calcium restriction for stone prevention should be viewed cautiously. Indeed, urinary calcium, among stone risk factors, has most consistently been shown to be associated with risk of calcium stone formation. Although these findings in no way minimize the contribution of oxalate to calcium oxalate stone formation, both dietary calcium and oxalate should be taken into account when recommending dietary measures for stone prevention and efforts to reduce both levels in the urine may result in reduced stone formation rates.

References

Dr. Margaret S. Pearle
Associate Professor of Urology
University of Texas Southwestern Med Ctr
Dallas, Texas, USA

Fluid absorption during ureterorenoscopy
Cybulski P, Honey JD’A, Pace K
Division of Urology, St. Michael’s Hospital, Toronto, Ontario, Canada
*J Endourol*. 2004; 18: 739-42

Background and Purpose: Ureterorenoscopy (URS) is a common minimally invasive diagnostic and therapeutic modality for ureteral and renal pathology. Fluid absorption during routine URS has not been studied prospectively, despite the fact that fluid absorption during other endoscopic urologic procedures can be substantial.

Patients and Methods: During URS in 15 male and 8 female patients with a mean age of 54 years (range 19 - 81 years), volumetric balance was performed by measuring all fluids instilled into the urinary tract (irrigation fluid and contrast medium) and fluids collected from the urinary tract (irrigation fluid, contrast medium, and urine output) and by estimating urine output from creatinine concentration in the urine and in the fluids collected from the urinary tract. Fluids from the urinary tract were assessed by measuring drainage fluid and the preoperative and postoperative weights of the drapes and bedsheets. Of the procedures, 11 were right-sided and 12 were left-sided. The indications for URS were urolithiasis (N = 18) and diagnosis (hematuria in 2, ureteral or renal filling defect in 2, flank pain and hydronephrosis in 1).

Results: The mean total operative time was 55 minutes (range 20 - 95 minutes), and the mean URS time was 37 minutes (range 8 - 83 minutes). The mean volume of irrigation fluid used was 2531 mL (range 552 - 5580 mL). The mean estimated urine output during the procedure was 62 mL (range 7 - 201 mL). The mean estimated systemic fluid absorption during URS was 54 mL (range 4 - 137 mL). There were two intraoperative complications (ureteral perforations) but no postoperative complications.
Conclusions: Routine URS is associated with minimal systemic fluid absorption, even if ureteral perforation occurs. Estimated absorption of as much as 137 mL was seen; however, evaporative losses and unaccounted for losses of fluid likely account for a substantial portion of this fluid discrepancy. This result suggests that irrigation with fluids other than normal saline, such as sterile water, during URS is likely safe.

Editorial Comment

As ureteroscope design and instrumentation have improved, ureteroscopic procedures have become more ambitious; it is increasingly common to treat larger and more complex renal calculi with ureteroscopy, particularly as the limitations of shock wave lithotripsy have become better defined. However, with more complex ureteroscopic cases have come longer operative times and greater potential for complications. Among the potential problems with lengthy ureteroscopic cases are sepsis and systemic absorption of irrigation fluid similar to that seen in TURP syndrome and that reported in some PCNL cases.

Cybulski and colleagues attempted to quantitate systemic fluid absorption during routine ureteroscopy (both diagnostic and therapeutic) by applying volumetric balance studies of input and outflow fluids, estimating urine output by creatinine concentration measurement of the urine and outflow fluid. Among 18 ureteroscopic cases with a mean ureteroscopy time of 37 minutes, mean systemic fluid absorption was only 54 cc, which correlated strongly with actual ureteroscopy time. Among 2 cases of ureteral perforation, fluid absorption was approximately twice the average. The authors concluded that fluid absorption during routine ureteroscopy is minimal and use of sterile water irrigation fluid may be safe, but deserves further study.

This is an important study, the first of its kind to quantitate systemic fluid absorption during ureteroscopy and show that the risk of significant fluid absorption and the associated consequences are minimal during routine cases. However, it is important to keep in mind that the average ureteroscopy time in this series was quite short, only 37 minutes. Most of the more complex ureteroscopic procedures performed today (for stones as large as 2 cm or more), are associated with lengthier ureteroscopy times. It is not known if fluid absorption is a linear process, correlating directly with ureteroscopy time, or if the rate of absorption may accelerate with time. Second, in the current series, a ureteral access sheath was used in all cases. It has been shown in both a cadaver study (1) and in a clinical series (2) that use of a ureteral access sheath reduces intrarenal pressure, which in all likelihood will reduce the chance of fluid absorption from the collecting system. Whether fluid absorption is greater in cases performed without an access sheath remains to be seen, but the use of a ureteral access sheath may increase the margin of safety for lengthy ureteroscopic procedure for exactly this reason.

Having personally reviewed several medicolegal cases of deaths due to use of sterile water irrigation during prolonged ureteroscopic cases, I suggest that the advantage gained in visibility with the use of sterile water irrigation is not worth the risk.

References


Dr. Margaret S. Pearle
Associate Professor of Urology
University of Texas Southwestern Med Ctr
Dallas, Texas, USA
Laparoscopic transuterine fetal vesicostomy: a feasibility study
Ponsky LE, Cherullo EE, Banks KL, Ross JH
From the Section of Laparoscopic and Minimally Invasive Surgery and Pediatric Urology, Glickman
Urological Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA
J Urol. 2004; 172 (6 Pt 1): 2391-4

Purpose: We evaluate the feasibility of applying minimally invasive techniques for fetal vesicostomy. We also evaluate whether transuterine fetal vesicostomy can be performed laparoscopically.

Materials and Methods: A total of 25 pregnant ewes were time dated at approximately 90 days of gestation. With the animals under general anesthesia a low open abdominal incision was made and the uterus was brought out through the incision. With a 14 gauge needle the amniotic sac was filled with 1 to 2 L warm glycine. Three to 4, 5/12 blunt tip balloon trocars were placed in the uterus. Using laparoscopic techniques, a low transverse incision was made in the fetal abdomen, the bladder was opened at the dome and 2 running sutures were placed approximating the fetal abdominal wall to the edge of the fetal bladder. The trocar sites in the uterus were closed, and the maternal abdominal incision was closed.

Results: Of the 25 pregnant ewes the technique was developed in the initial 15. In the subsequent 10 animals the complete procedure was accomplished successfully. Following these 10 procedures 5 abortions occurred on postoperative day 2, and there was 1 intrauterine fetal demise. Three fetuses were alive and delivered by cesarean section on postoperative days 10, 30 and 31. In the first fetus in which we used an interrupted suture for the vesicostomy a large hernia was noted at the vesicostomy site. The other 2 fetuses had a patent, well healed vesicostomy and were alive at cesarean section delivery on postoperative days 10 and 31. The last fetus was allowed to deliver at term by standard vaginal delivery. The fetus was alive and well, and the vesicostomy had strictured down to a pinhole in size, which was not unexpected as it was not an obstructed model.

Conclusions: Although technically challenging, transuterine laparoscopic fetal vesicostomy is technically feasible in the ewe model. Continued evaluation of this technique should include intensive fetal monitoring and the use of tocolytics to decrease the incidence of spontaneous abortion.

Editorial Comment
Fetal bilateral hydronephrosis with oligohydramnios is an indication for evaluation and potential fetal intervention. Currently, when fetal lungs are immature with good renal function, vesical decompression can be performed in utero percutaneously with the placement of a shunt (stent) but the results are suboptimal due to malfunction of the stents often requiring manipulation or replacement.

The authors studied the feasibility of laparoscopic technique to perform transuterine fetal vesicostomy using an animal model.

Interesting technical aspects should be noted; i.e., the exchange of the amniotic fluid with warm glycine to optimize visualization and cauterization, the use of blunt tip balloon trocar to prevent fluid leakage through port sites and closure of port sites with endoscopic gastrointestinal anastomosis staplers. Clearly, the development of this technique required several steps including a significant number of animals culminating with 1 strictured and 2 well healed patent vesicostomies. The authors should be congratulated for the well designed and pioneering study.

Dr. Fernando J. Kim
Assistant Professor of Urology
University of Colorado Health Sciences Center
Denver, Colorado, USA
Transperitoneal or extraperitoneal laparoscopic radical prostatectomy: does the approach matter?

Eden CG, King D, Kooiman GG, Adams TH, Sullivan ME, Vass JA

From the Departments of Urology, North Hampshire Hospital, Basingstoke and Frimley Park Hospital, United Kingdom

*J Urol.* 2004; 172 (6 Pt 1): 2218-23

Purpose: The greater accuracy of apical dissection and reconstruction in our first 100 patients undergoing transperitoneal laparoscopic radical prostatectomy (TLRP) was not matched by a proportionate increase in the rate of return to normal continence compared with our prior open prostatectomy experience. We postulated that greater bladder dysfunction due to the almost total bladder dissection mandated by TLRP might be responsible and this might be rectified by the adoption of laparoscopic radical prostatectomy using an extraperitoneal approach (ELRP).

Materials and Methods: A total of 100 patients undergoing TLRP were compared with 100 undergoing ELRP. The groups were subdivided into halves to investigate the influence of any learning curve effect. All patients had clinical stage T3aN0M0 or less prostate cancer and they were operated on by a single surgeon.

Results: Mean operative time (238.9 vs. 190.6 minutes), blood loss (310.5 vs. 201.5 ml), postoperative hospitalization (3.8 vs. 2.6 nights) and catheterization duration (11.3 vs. 10.1 days) were significantly greater in the TLRP group. After the first 50 cases were excluded in each group statistical significance persisted only for operative time (218.3 vs. 184.2 minutes) and hospitalization (3.5 vs. 2.5 nights). The pad-free rate was significantly lower 3 months following ELRP (80% vs. 56%, p = 0.02). The overall 12-month pad-free rate for TLRP and ELRP was 90% and 96%, respectively. The overall 12-month erection rate for TLRP and ELRP was 61% and 82%, respectively.

Conclusions: ELRP is superior to TLRP with respect to operative time, hospitalization and early continence.

Editorial Comment

Since Guillonneau & Vallancien first described their successful series of transperitoneal laparoscopic radical prostatectomy this procedure disseminated world-wide.

Recently, few other centers developed the extraperitoneal technique mimicking the open approach. Although the anatomical features are more familiar to the surgeon the working operative space is more limited. Conversely, the ELRP can be performed with the patient in supine position and potentially decreases the incidence of ileus since the peritoneum is not violated.

Important points discussed in this manuscript: 1) LRP should be taught by a mentor/proctorship program, 2) Surgeons performing LRP must have enough experience with radical prostatectomies anatomical variations and its complications (more than 50 cases yearly), 3) According with the authors bladder mobilization in the TLRP group affected patients early urinary continence recovery compared to the ELRP. The authors tried to remove other factors out of the equation, i.e.; learning curve, prior obstructive problems and surgeries. The overall rate of positive margins were the same revealing that the dissection was performed uniformly in terms of technique but question remains if the last group of ELRP patients with higher clinical stage prostate cancer and higher positive margin rate had more incontinence than the rest. Certainly the observations are intriguing and provoking but better delineation of the pathophysiology is needed.

*Dr. Fernando J. Kim*

Assistant Professor of Urology

*University of Colorado Health Sciences Center*

*Denver, Colorado, USA*
Differentiation of renal clear cell carcinoma and renal papillary carcinoma using quantitative CT enhancement parameters

Ruppert-Kohlmayr AJ, Uggowitzer M, Meissnitzer T, Ruppert G
Department of Radiology, University Hospital Graz, Graz, Austria
AJR Am J Roentgenol. 2004; 183: 1387-91

Objective: The purpose of our study was to evaluate quantitative multiphasic CT enhancement patterns of malignant renal neoplasms to enable lesion differentiation by their enhancement characteristics. We used a new method to standardize enhancement measurement in lesions on multiphasic CT not being influenced by intrinsic factors like cardiac output.

Conclusion: The new correction method is a simple tool for excluding intrinsic influences on the enhancement of lesions. Quantitative enhancement evaluation with this method of the influence of intrinsic factors enables accurate differentiation between renal clear cell carcinoma and renal papillary carcinoma.

Editorial Comment
The authors present an interesting and standardized method of measurements of the attenuation of renal tumors on computed tomographic studies, which are designed to eliminate the influence of intrinsic factors on the measured attenuation values of these lesions. This method was able to differentiate the most common malignant renal tumors accurately and was performed using multiphasic CT (unenhanced, corticomedullary, and nephrographic phases). In this study, the author used an enhancement correcting method in the corticomedullary phase, which allowed them to differentiate renal clear cell carcinoma from renal papillary carcinoma with an accuracy rate of 95.7. In other words this study showed a high enhancement in the corticomedullary phase in renal clear cell carcinoma with a slight washout in the nephrographic phase; it showed a low enhancement in many renal papillary carcinomas - sometimes less than 12 H in the corticomedullary phase - but in the nephrographic phase, the enhancement of renal papillary carcinoma was clearly higher than 12 H.

Several recent papers have dealt with the CT capabilities of distinguishing the histological type of renal cell carcinoma. The reason for this effort is related to the potential effect of this differentiation in the preoperative and operative strategies. As we know the papillary sub-type of renal cell carcinoma has better prognosis than the clear cell carcinoma. This information might be useful in the management of patients with high surgical risks. Because renal papillary carcinoma are usually hypovascular they may also show less propensity for bleeding during surgical resection or during conservative treatments such radiofrequency ablation or cryotherapy.

Further studies, with larger number of patients, is necessary to confirm the CT capabilities to differentiate the histological sub-types of renal cell carcinoma.

Dr. Adilson Prando
Chief, Department of Radiology
Vera Cruz Hospital
Campinas, São Paulo, Brazil
Organ-confined prostate cancer: effect of prior transrectal biopsy on endorectal MRI and MR spectroscopic imaging
Qayyum A, Coakley FV, Lu Y, Olpin JD, Wu L, Yeh BM, Carroll PR, Kurhanewicz J
Department of Radiology, University of California, San Francisco, San Francisco, CA, USA
AJR Am J Roentgenol. 2004; 183: 1079-83

Objective: Our aim was to determine the effect of prior transrectal biopsy on endorectal MRI and MR spectroscopic imaging findings in patients with organ-confined prostate cancer.

Materials and Methods: Endorectal MRI and MR spectroscopic imaging were performed in 43 patients with biopsy-proven prostate cancer before radical prostatectomy confirming organ-confined disease. For each sextant, two independent reviewers scored the degree of hemorrhage on a scale from 1 to 5 and recorded the presence or absence of capsular irregularity. A spectroscopist recorded the number of spectrally degraded voxels in the peripheral zone. The outcome variables of capsular irregularity and spectral degradation were correlated with the predictor variables of time from biopsy and degree of hemorrhage after biopsy.

Results: Capsular irregularity was unrelated to time from biopsy or to degree of hemorrhage. Spectral degradation was inversely related to time from biopsy (p < 0.01); the mean percentage of degraded peripheral zone voxels was 18.5% within 8 weeks of biopsy compared with 7% after 8 weeks. Spectral degradation was unrelated to the degree of hemorrhage.

Conclusion: In organ-confined prostate cancer, capsular irregularity can be seen at any time after biopsy and is independent of the degree of hemorrhage, whereas spectral degradation is seen predominantly in the first 8 weeks after biopsy. MRI staging criteria and guidelines for scheduling studies after biopsy may require appropriate modification.

Editorial Comment
This study provides several important information related to the performance and interpretation of endorectal MR and MR spectroscopic imaging of the prostate after transrectal biopsy. As we know a thickened and irregular prostate capsule is an important MRI sign of extra-prostatic tumor extension. The authors suggests that these capsular changes are common in organ-confined prostate cancer and are unrelated to time from biopsy and extent of post-biopsy hemorrhage and that these changes may represent a normal variant rather than a biopsy artifact. Another interesting finding was related to the presence of spectral degradation on MR spectroscopic studies. This spectral curve degradation was significantly more frequent within the first 8 weeks after transrectal biopsy and was caused by post-biopsy changes. It is well known that post-biopsy hemorrhage usually precludes an optimal result in the conventional endorectal MRI study performed for local staging of prostate cancer. Since post-biopsy changes precludes also an optimal spectroscopic evaluation of the metabolites, the authors recommend that a period of 8 weeks after biopsy is necessary before submit the patient to a MRI and MR spectroscopic evaluation. This information is very important because recent studies have shown that the ideal MRI protocol for local staging of prostate cancer is obtained with the association of conventional endorectal MRI and 3D-MR-spectroscopic techniques. 3D-MR-spectroscopic imaging offers important additional information to the conventional endorectal MRI exam such as: estimative of tumor volume, better prediction of an extra-prostatic disease and information about tumor aggressiveness. As the authors pointed out, this optimized post-biopsy interval for an adequate MRI and MR spectroscopic imaging should be balanced against patient anxiety, although this interval is probably negligible in terms of the natural history of prostate cancer.

Dr. Adilson Prando
Chief, Department of Radiology
Vera Cruz Hospital
Campinas, São Paulo, Brazil
UROGENITAL TRAUMA

High-grade renal injuries in children - is conservative management possible?

Rogers CG, Knight V, MacUra KJ, Ziegfeld S, Paidas CN, Mathews RI
Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland, USA

Urology. 2004; 64: 574-9

Objectives: To review our experience with the management of high-grade (grade IV and V) renal injuries to clarify the role of conservative management.

Methods: From 1991 to 2003, 79 consecutive patients (age range 2 to 14 years) with renal injuries were treated in an urban level I pediatric trauma center. Twenty children were identified as having high-grade renal injury (grade IV, 10 children and grade V, 10 children). The mechanism of injury was blunt trauma in 17 patients (85%) and penetrating trauma in 3 (15%).

Results: Of the 10 patients with grade IV injury, 8 (80%) were successfully treated conservatively with bedrest and catheter drainage. Two patients with persistent urine leaks required ureteral stenting, and one subsequently required open operative repair. The initial radiographic findings in both patients demonstrated complete renal fracture with retained vasculature to both renal segments. All 10 patients with grade V injury required open operative management and only 3 (30%) achieved long-term renal salvage.

Conclusions: Most children with grade IV renal injury can be treated conservatively. Patients with complete renal fracture or significant urinary extravasation on initial radiographic imaging may be less likely to undergo spontaneous resolution. Patients with a persistent urinary leak can be successfully treated with internal drainage. Grade V injuries are associated with an increased risk of requiring open operative intervention, and the renal preservation rates are low.

Editorial Comment

Information on pediatric renal trauma has lagged behind information reported about adults. Now several excellent papers have been published which attempt to establish the “proper” amount of surgery for children with renal trauma.

The paper by Rogers et al. attempted conservative management even for Grade IV injury. Only 1 of their 10 patients required a stent and 1 required open repair. All 10 Grade V injury patients required surgery, and this was a nephrectomy in 7/10 patients. (It is not clear to me that the remaining 3 patients truly had a Grade V injury by the description of the injuries provided in the paper). Conservative management was not without its problems. Patients had to stay at bed rest an average of 13 days, and required urinary catheterization an average of 9 days, although significant complications such as death or iatrogenic nephrectomy was avoided. Interestingly, 3 out of 3 cases of attempted vascular repair failed, further bolstering the opinion of most experts that significant unilateral renal vessel injury should be treated with nephrectomy (as repair never seems to work).

The conclusions from this study are:

1) Conservative management of even high-grade renal injuries (Grade IV) in children can be attempted.
2) Conservative management will fail only in a small percentage of the population.
3) Ureteral stents will need to be used in a small percentage.
4) Even severe penetrating renal injury might be treated nonoperatively in children.
5) Grade V renal injuries will likely still need surgery, and that surgery will likely be a nephrectomy.

Dr. Richard A. Santucci
Assistant Professor of Urology
Wayne State University
Detroit, Michigan, USA
Pediatric renal injuries: management guidelines from a 25-year experience
Buckley JC, McAninch JW
Department of Urology, University of California School of Medicine and Urology Service, San Francisco General Hospital, USA
J Urol. 2004; 172: 687-90; discussion 690

Purpose: We defined the mechanism and cause of pediatric renal trauma, and developed guidelines for management based on the outcome analysis of operative vs. nonoperative management.

Materials and Methods: We retrospectively reviewed 374 pediatric renal injuries at San Francisco General Hospital, comparing operative vs. nonoperative management based on clinical presentation, type of renal injury, hemodynamic stability, associated injuries and the results of radiographic imaging.

Results: Blunt trauma accounted for 89% of pediatric renal trauma with a renal exploration rate of less than 2%. Penetrating trauma represented the remaining 11% with a renal exploration rate of 76%. Of grade IV renal injuries 41% were successfully managed nonoperatively based on computerized tomography and staging in hemodynamically stable children. Our overall renal salvage rate was greater than 99%.

Conclusions: Pediatric renal trauma is often minor and observation poses no significant danger to the child. In serious pediatric renal injuries early detection and staging based on clinical presentation and computerized tomography are critical for determining operative vs. nonoperative management. Regardless of the type of management the standard of care is renal preservation (less than 1% nephrectomy rate in this series).

Editorial Comment

The study by Buckley & McAninch is the largest pediatric renal trauma series ever reported. Although this center is now devoted to conservative management when appropriate, some of this series is 25 years old, and predates the time when conservative management was used widely by anyone. Interestingly, even though this series reports 374 patients, they had fewer Grade IV and V injuries than that reported in Roger’s et al. smaller series of 79 patients (Urology. 2004; 64: 574-9)! In this series, 8/9 blunt Grade IV renal trauma patients were managed nonoperatively. The overall rate of exploration was higher than that seen now, however, because of the policy of exploring all penetrating trauma patients with gross hematuria, and all patients who are taken immediately to the operating room “in whom renal staging (imaging) was incomplete”. To the credit of this group, only 1 patient (1%) got a nephrectomy.

The conclusions from this study are:
1) As has been reported elsewhere, blunt renal trauma patients can probably be imaged just like adults (that is, CT only with gross hematuria, major associated injuries, hypotension or deceleration).
2) Most pediatric renal injuries are minor and can be observed.
3) Major blunt renal injuries can be managed nonoperatively.
4) Nonoperative management of renal trauma may require a long hospitalization (average 14 days in McAninch and 13 days in Rogers).

Dr. Richard A. Santucci
Assistant Professor of Urology
Wayne State University
Detroit, Michigan, USA
Characterization of minute adenocarcinomas of prostate at radical prostatectomy

Truskinovsky AM, Sanderson H, Epstein JI
Department of Pathology, University of California, Davis, Medical Center, Sacramento, California, USA
Urology. 2004; 64: 733-7

Objectives: To characterize minute prostate cancer seen at radical prostatectomy. With aggressive screening and more extensive biopsy sampling, we have increasingly seen these cancers at radical prostatectomy.

Methods: We examined radical prostatectomy specimens submitted in total for minute cancer.

Results: During the past 1.5 years, 78 prostates (5.2%) had either no cancer (2 cases) or contained between one and six foci of organ-confined carcinoma (76 cases) measuring 6 mm or less, with a Gleason score of 6 or less. The mean prebiopsy serum prostate-specific antigen level was 5.8 ng/mL, and 84.6% of the patients had undergone biopsy because of an elevated prostate-specific antigen level. Of these patients, 40% had had either benign or atypical diagnoses on prior biopsies, and 43% had only minute (0.5 mm or less) foci of carcinoma on biopsy. The radical prostatectomy specimens had a mean of two cancer foci measuring, on average, 3 mm in the greatest dimension. In 85% of the cases, the side of the positive biopsy matched the side of the carcinoma found at radical prostatectomy; 81.5% of cases had high-grade prostatic intraepithelial neoplasia immediately adjacent to the cancer.

Conclusions: The incidence of minute carcinoma of the prostate has increased from 0.5% in 1988 to 5.2% in the current study. The patients often had moderately increased prostate-specific antigen levels and minute foci of carcinoma on biopsy. These small tumors at radical prostatectomy are usually discovered by fortuitous biopsy that is often preceded by other biopsies with noncancerous diagnoses. Patients with the above clinical and biopsy findings should be counseled about the possibility of finding only minute foci of carcinoma at radical prostatectomy and may want to consider watchful waiting.

Editorial Comment

The incidence of “minute” (minimal, insignificant) cancer at radical prostatectomies has substantially increased in the last years. The main reason is aggressive screening and more extensive biopsy sampling. It is important to note that “minute” (minimal, insignificant) cancer in radical prostatectomy does not mean “latent” (dormant, indolent) carcinoma. It represents a low volume (incipient) cancer that can progress either as a “latent” or a “clinical” cancer. It is important to counsel the patients about the possibility of finding only minute foci of carcinoma at radical prostatectomy including the possibility of not finding a tumor at all.

According to the authors of the study, patients having clinical and biopsy findings for minute cancers may want to consider watchful waiting. In this respect, urologists consider age an important variable but the cut point is controversial. Carter et al. (1) informed men older than 65 years that expectant management was a reasonable option for management of cancer regardless of the presence or absence of co-morbidity. The recommended follow-up for those men managed expectantly was semiannual total and free PSA measurement with digital rectal examination, and annual surveillance transrectal ultrasound directed prostate biopsies.

Reference

Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, São Paulo, Brazil
Background: The authors examined the cases of men who had undergone radical prostatectomy for low-volume clinical T1c prostate carcinoma that was judged to be “insignificant” on the basis of previously established preoperative clinicopathologic parameters. Pathologic findings subsequently were analyzed for correlations with extent of disease in an attempt to validate the contemporary usefulness of existing parameters for predicting the “significance” of prostate tumors.

Methods: A series of 237 men who had undergone radical prostatectomy for T1c disease between December 2000 and August 2003 was evaluated. Insignificant prostate carcinoma as assessed on biopsy was defined according to the 1994 Epstein criteria, which were as follows: prostate-specific antigen density < 0.15 ng/mL, Gleason score ≤ 6, fewer than 3 cores containing prostate carcinoma, and ≤ 50% involvement of any core with prostate carcinoma. Postsurgical pathologic findings were analyzed for potential correlations with the Epstein criteria.

Results: According to the Epstein needle biopsy criteria, organ-confined prostate carcinoma was detected in 91.6% of all patients, whereas the remaining 8.4% of patients were found to have non-organ-confined disease. Comparison of pathologic findings and Epstein biopsy criteria revealed that alteration of the original criteria did not improve the detection of non-organ-confined prostate carcinoma.

Conclusions: The findings made in the current study suggest that the majority of patients with T1c prostate carcinoma have insignificant disease. Furthermore, it was found that the Epstein criteria for identifying insignificant prostate carcinoma remained a useful tool in the making of treatment-related decisions.

Editorial Comment

Considering the aggressive screening and more extensive biopsy sampling resulting in higher frequency of stage T1c, criteria predicting “minute” (minimal, insignificant) tumor in radical prostatectomy are of utmost importance.

The Epstein criteria for identifying insignificant prostate carcinoma remain a useful tool in the making of treatment related decisions. In this study prostate-specific antigen density < 0.15ng/mL was included in the criteria. In another study Epstein et al. (1) found a positive predictive value of 94.4% using a free/total PSA of 0.15 or greater and favorable needle biopsy findings (less than 3 cores involved, none of the cores with greater than 50% tumor involvement and Gleason score less than 7).

The involvement of the cores in percentage is controversial. Other authors consider that the extension of the tumor is a better way of evaluation. Noguchi et al. (2) consider that the combination of 1 positive core with cancer length less than 3 mm. that contains no Gleason grade 4 or 5 is probably the best predictor of prostate cancer less than 0.5 cc in men with nonpalpable tumors (stage T1c). These authors also found that PSA or PSA density in combination with needle biopsy findings did not enhance prediction of tumor significance.

References

Androgen receptor expression is inversely correlated with pathologic tumor stage in bladder cancer
Boorjian S, Ugras S, Mongan NP, Gudas LJ, You X, Tickoo SK, Scherr DS
Department of Urology, New York Presbyterian Hospital-Weill-Cornell Medical Center, New York, New York, USA
Urology. 2004; 64: 383-8

Objectives: To evaluate the expression of the androgen receptor (AR) in transitional cell carcinoma (TCC) of the bladder, and to assess whether its expression correlated with pathologic tumor stage. TCC of the bladder is three times more common in males than in females. The origin of this sex difference in incidence is unknown.

Methods: We evaluated tumor specimens from 49 consecutive patients treated for TCC of the bladder at our institution between July 2002 and June 2003. Immunohistochemistry was performed using a monoclonal mouse anti-AR antibody on paraffin-embedded tissue sections of tumors obtained from transurethral resection, radical cystectomy, or resection of metastases. Specimens were assessed for AR expression, and, in tumors that demonstrated AR staining, the percentage of nuclei that stained positive was recorded.

Results: Of the 49 tumors, 26 (53.1%) expressed the AR. The percentage of tumors that expressed the AR decreased with increasing pathologic stage, from 88.9% of pTa lesions to 0% of pT3 tumors. Overall, 75% of superficial tumors (pTa + pT1 + carcinoma in situ) expressed the AR compared with 21.4% of invasive tumors (pT2 + pT3; P = 0.002). In addition, among AR-expressing tumors, the mean percentage of nuclei that stained positive for the AR was significantly greater in pTa tumors (62.5%) than in pT1 (31%) or pT2 (20%) tumors (P = 0.005).

Conclusions: We found a decrease in AR protein expression in tumors with increased pathologic stage. Our data suggest that the loss of AR expression is associated with invasive bladder cancer.

Editorial Comment
A previous study that considered smoking and occupational risks showed that the sex-related risk of bladder cancer for men persists independently of other risks (1). Some experimental studies in rats showed that the bladder tumors development is significantly grater in males than in females (2,3), although studies in humans are still scarce. A functional role for the AR in human bladder cancer has been suggested by a recent study that demonstrated that androgen treatment inhibited bacille Calmette-Guérin-induced interleukin-6 expression in bladder cancer cell lines that expressed the AR. The study also demonstrated that pharmacologic androgen deprivation restored bacille Calmette-Guérin-induced interleukin-6 expression (4).

In this present important contribution, Boorjian et al., after evaluating 49 tumor specimens, found a decrease in androgen receptors correspondent to increased pathologic stage. The authors suggest that as a...
potential therapeutic application, given the high percentage of superficial (particularly Ta) tumors that expressed the AR in the present study, together with the results of androgen deprivation therapy in animal studies, the potential exists to investigate the impact of androgen deprivation therapy in superficial bladder cancer.

References

Dr. Francisco J.B. Sampaio
Full-Professor and Chair, Urogenital Research Unit
State University of Rio de Janeiro
Rio de Janeiro, Brazil

Dendritic cell immunotherapy for urological cancers using cryopreserved allogeneic tumour lysate-pulsed cells: a phase I/II study
Pandha HS, John RJ, Hutchinson J, James N, Whelan M, Corbishley C, Dalgleish AG
Department of Histopathology, St George’s Hospital Medical School, Cranmer Terrace, London
BJU Int. 2004; 94: 412-8

Objective: To assess the feasibility, toxicity and immunogenicity of dendritic cell (DC)-based immunotherapy in patients with advanced urological cancers.

Patients and Methods: Patients with hormone-refractory prostate cancer (11) and metastatic renal cell carcinoma (five) received 1-3 x 10(6) intradermal allogeneic tumour lysate-pulsed DCs fortnightly for six vaccinations then monthly until disease progression. Intradermal keyhole limpet haemocyanin was injected near the DCs as the adjuvant. DC vaccine was prepared from buffy coats, then lysate-pulsed, cryopreserved in aliquots, and tested for phenotypic expression and activity in an allogeneic mixed lymphocyte reaction before clinical use.

Results: There was no evidence of significant toxicity from vaccine or adjuvant. Delayed-type hypersensitivity skin testing and biopsy revealed a cellular infiltrate to intradermal re-challenge to tumour lysate and adjuvant in almost all patients. In addition, there was increased expression of T helper type 1 cytokines, interferon-gamma-expressing T cell by ELISPOT analysis, but also interleukin-10 in a few patients. Vaccination resulted in a reduction in the level of prostate-specific antigen (PSA) in one patient, a reduction in PSA velocity in a further man and an increased PSA doubling time in six. Two of five patients with renal cell carcinoma had stabilization of disease.

Conclusion: The cryopreservation and repeated administration of DC vaccine was feasible and not toxic. There was evidence of induction of both humoral and cellular immunity to vaccine and adjuvant in most patients. The use of sequential aliquots of identical cryopreserved vaccine will ensure quality control and
greatly facilitate future clinical studies in terms of consistency of vaccine administered and the provision of primed DCs for in vitro assessment of response.

Editorial Comment

This is a very well done scientific research with immediate potential clinical implications. As the authors stated, one of the most significant limitations to current dendritic cell-based immunotherapy is the need to prepare fresh vaccine repeatedly. The ability to culture and cryopreserve numerous aliquots of identical dendritic cells from a single venesection would reduce hospital intervention for patients, and greatly facilitate clinical trials by allowing the manipulation of dendritic cells before or after freezing, and their subsequent use as sequential vaccines.

The authors demonstrated the feasibility of a potentially generic approach to cellular immunotherapy, and the preparation of identical aliquots of dendritic cell vaccine that were readily tested for safety and immunoreactivity before injecting into patients. Dendritic cell therapy resulted in significant in vitro immunological responses in patients even with very advanced disease. Also, in this study, dendritic cell vaccine showed to be safe and non-toxic

Dr. Francisco J.B. Sampaio
Full-Professor and Chair, Urogenital Research Unit
State University of Rio de Janeiro
Rio de Janeiro, Brazil

RECONSTRUCTIVE UROLOGY

Vaginal and penile reconstruction
Sievert KD
Department of Urology, University of Munster, Munster, Germany

Purpose of Review: Reconstructive surgery for patients with genital abnormalities or for patients who require reconstructive efforts is challenging. This review highlights those articles, which are outstanding among all those important papers, which have been published during the last year (2002-2003).

Recent Findings: A greater understanding of embryonal development improves the success of reconstructive surgery. Other factors, such as the patient’s sex, influence the surgical technique used and the degree of invasiveness or complexity. In the adult the pressure to shorten hospital stays has played a big part in the continual modification and enhancement of surgical techniques. In addition to modified techniques, new off-the-shelf materials are introduced to the clinic, which seem to have the potential to improve the surgical outcome and shorten hospital stays.

Summary: With the continued successful basic anatomy and basic research, reconstructive surgery brings higher success rates. Long-term results are still required to validate the reliability of these new surgical techniques and materials.

Editorial Comment

This paper nicely outlines the current status of reconstruction of male and female genitalia for a successful reconstruction in genital abnormalities a greater understanding of the embryonal development is advantages. Flap technology and prefabrication are the currently preferred methods for surgical success in transsexual
patients. However, here again we are awaiting the clinical application of tissue-engineered segments for both the penile autologous prosthesis and vaginal cavity.

Dr. Arnulf Stenzl
Professor and Chairman of Urology
Eberhard-Karls-University Tuebingen
Tuebingen, Germany

Orthotopic bladder substitution in women: nontraditional applications
Lee CT, Hafez KS, Sheffield JH, Joshi DP, Montie JE
Department of Urology, University of Michigan, Ann Arbor, Michigan, USA
J Urol. 2004; 171: 1585-8

Purpose: Orthotopic urinary diversion is a feasible and optimal technique for many women undergoing cystectomy. Although successful outcomes have been achieved, groups at most centers have strict selection criteria. We evaluated our experience with female orthotopic diversion in traditional and nontraditional candidates.

Materials and Methods: From September 1, 1995 to February 6, 2003 53 females with a mean age of 62 years underwent orthotopic bladder substitution. Median followup was 24 months. Clinicopathological parameters were evaluated in traditional and nontraditional patients. The nontraditional subset comprised 22 women older than 70 years (12) or had a history of pelvic radiation (2), neoadjuvant chemotherapy (6) or stress incontinence (2).

Results: The entire group had a mean operative time, blood loss and hospital stay of 6.2 hours, 1,135 ml and 8.2 days, respectively. Tumor was organ confined in 38 and extravesical in 14 patients with bladder cancer. Complications were detected in 20 patients, including 9 who were traditional (23%) and 11 who were nontraditional (50%). Daytime and nighttime continence was reported by 46 (87%) and 45 (85%) patients, respectively, of whom 11 (21%) required intermittent catheterization. Of the patients with cancer 42 were disease-free, 2 were alive with disease and 6 died of disease. The nontraditional subset was older (p < 0.0003) and had shorter followup (p = 0.05), a higher American Society of Anesthesiologists score (p = 0.01) and a shorter overall survival (p = 0.001) than the traditional group. Continence was seen in 19 of 22 nontraditional patients (86%) and 4 (18%) required intermittent catheterization.

Conclusions: Orthotopic neobladder diversion offers excellent clinical and functional results, and should be the diversion of choice in most women following cystectomy. A subset of less favorable candidates can also successfully undergo orthotopic substitution with a tolerable toxicity profile.

Editorial Comment
In this paper the authors confirm previous studies on a successful use of orthotopic neobladder in a wide range of female patients. Despite extravesical disease, an age older than 70 years, a history of pelvic radiation, neoadjuvant chemotherapy, or preoperative stress incontinence, these patients had a continence rate of 86% and an intermittent catheterization rate of 18%. None of the patients had a urethral recurrence after a median follow up of 24 months.

This study reinforces previous suggestions that an orthotopic bladder substitution in women undergoing radical cystectomy is not only feasible but also applicable to a majority with localized bladder tumors. Not everybody might agree with the technique of surgery by the authors, which might be the reason for a higher rate
of urinary retention compared to other reports, but undoubtedly this paper shows that unfavorable factors must
be a contraindication for an orthotopic neobladder.

Dr. Arnulf Stenzl
Professor and Chairman of Urology
Eberhard-Karls-University Tuebingen
Tuebingen, Germany

UROLOGICAL ONCOLOGY

Primary T1G3 bladder cancer: organ preserving approach or immediate cystectomy?
Thalmann GN, Markwalder R, Shahin O, Burkhard FC, Hochreiter WW, Studer UE
Department of Urology and Institute of Pathology, University of Bern, Inselspital, Bern, Switzerland

Purpose: In this retrospective nonrandomized study we compared the long-term outcome in patients
with newly diagnosed stage T1G3 bladder cancer treated with transurethral resection and bacillus Calmette-
Guerin or immediate cystectomy.

Materials and Methods: Of 121 patients with a median age of 67 years (range 36 to 88) diagnosed with
primary T1G3 bladder cancer between 1976 and 1999, 92 were treated by transureteral resection with additional
intravesical bacillus Calmette-Guerin and 29 were treated with immediate cystectomy.

Results: Of the 92 patients treated with an organ preserving approach 29 remained disease-free, local
recurrence developed in 33 (36%) and progression developed in 30 (33%) at a median followup of 6.9 years
(range 0.6 to 16.5). Of these 92 patients 27 (29%) underwent deferred cystectomy at a median of 12.9 months
(range 4.8 to 136), of whom 10 (37%) with a median postoperative followup of 19 months (range 2 to 173) died
of progressive disease with a median survival of 13 months (range 3 to 34) after cystectomy. The majority of
patients who died of progressive disease refused cystectomy, were referred too late for cystectomy, were
inoperable or had upper urinary tract disease. Six of the 29 patients (21%) undergoing immediate cystectomy
had progression at a median of 13.2 months (range 5.5 to 37). Overall and tumor specific survival at 5 years in
patients treated with an organ preserving approach was 69% and 80%, and in those treated with immediate
cystectomy it was 54% and 69%, respectively.

Conclusions: The results of this analysis demonstrate that the concept of an organ preserving approach
is acceptable and spares the bladder in approximately half of the patients with primary T1G3 bladder cancer. Of
the patients 30% require deferred cystectomy, making meticulous, close followup mandatory.

Editorial Comment

This paper is an non-randomized observation of patients with high risk bladder cancer treated either
with TUR-B and BCG or with immediate cystectomy.

The data suggest altogether that T1G3 bladder carcinoma is a dangerous disease but can be treated
effectively by TUR-B and BCG. Cystectomy may be prevented by this treatment, according to this conservative
estimate, in approximately 50%.

Interestingly, if patients were looked upon closely, median time to progression, overall mortality, and
all other outcome data were similar between two groups. In both groups around 15% showed positive lymph
nodes at lymphadenectomy.
Tumor specific survival at 5 years was 80% and 69%, respectively (not significant). In the group of patients treated with immediate cystectomy 48% died. Even more interestingly, for tumor specific survival the difference was significant in favor of deferred cystectomy (p = 0.02).

Dr. Andreas Bohle  
Professor of Urology  
HELIOS Agnes Karl Hospital  
Bad Schwartau, Germany

FEMALE UROLOGY

Mechanical properties of urogynecologic implant materials  
Dietz HP, Vancaillie P, Svehla M, Walsh W, Steensma AB, Vancaillie TG  
Royal Hospital for Women, New South Wales, Australia  
Int Urogynecol J Pelvic Floor Dysfunct. 2003; 14: 239-43

Synthetic suburethral slings have recently become popular despite the risk of erosion commonly associated with synthetic implants. Some of these materials seem to have unexpectedly low erosion rates. Based on the hypothesis that erosion is due, in part, to biomechanical properties, we undertook an in vitro study. The biomechanical properties of eight non-reabsorbable synthetic implant materials, stiffness (slope, N/mm) and peak load (N) were determined from load vs. displacement curves. Open-weave Prolene mesh showed unique biomechanical properties compared to other tested materials. The tension-free vaginal tape had the lowest initial stiffness (0.23 N/mm), i.e. low resistance to deformation at forces below the elastic limit, whereas the stiffest implant tested, a nylon tape, reached 6.83 N/mm. We concluded that the TVT and other wide-weave Prolene tapes have unique biomechanical characteristics. These properties may be at least partly responsible for the apparent clinical success of the implants.

Editorial Comment

The authors review the biomechanical properties of currently popular implant materials used in the treatment of female stress urinary incontinence and pelvic reconstruction. Materials reviewed included polypropylene as well as polyethylene terephthalate (mersilene), expanded polytetrafluoroethylene (Gortex) and nylon. Parameters quantified included initial stiffness (load needed before the material begins irreversible deformation) and the mean peak load at which time the material will rupture. Testing indicated that the tension free vaginal tape was the least stiff of the materials tested.

The authors utilized a testing system, which is valuable to review for future researchers in this area. It would have been of great value to the reader if the authors had been able to also test the reviewed materials at identical widths; they noted in the report that some specimens were of smaller width than others secondary to their commercial production. The discussion section raises some valuable points regarding the interaction of the graft material on the native tissues and the effect of a biomechanical difference between the two. Though this paper does not comment on the manner of weave and mesh pore size it makes for excellent reading for those interested in the physical properties of these popular synthetic graft materials.

Dr. Steven P. Petrou  
Associate Professor of Urology  
Mayo Clinic College of Medicine  
Jacksonville, Florida, USA
A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up
Ward KL, Hilton P; UK, and Ireland TVT Trial Group
Department of Obstetrics and Gynaecology, University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom

Objective: This study was undertaken to compare tension-free vaginal tape (TVT) with colposuspension as the primary treatment for stress incontinence.

Study Design: The trial was conducted in gynecology or urology departments in 14 centers in the United Kingdom and Ireland. Three hundred forty-four women with urodynamic stress incontinence were randomly assigned to groups: 175 to TVT and 169 to colposuspension. Patients were assessed using the Short Form-36 health status questionnaire, the Bristol Female Lower Urinary Tract Symptoms questionnaire, clinical examination, and a 1-hour perineal pad test. Unpaired and paired data were analyzed with the Wilcoxon rank sum and matched pairs tests, respectively, and proportions were compared with the Fisher exact test.

Results: When data were analyzed on an intention-to-treat basis, assuming patients with missing data to be treatment failures, 63% of the TVT group and 51% of the colposuspension group were objectively cured at 2 years (odds ratio 1.67, 95% CI 1.09-2.58).

Conclusion: The TVT procedure appears to be as effective as colposuspension for the treatment of urodynamic stress incontinence at 2 years.

Editorial Comment
The authors publish a follow up article to their six-month outcomes report between tension-free vaginal tape (TVT) and colposuspension (1). This is an excellent paper, which addresses surgical outcomes in patients who were randomized to one of the two anti-incontinence procedures. The paper’s strength lies in its strict measurement tools including validated questionnaires, clinical examinations and pad tests. The comments section holds an interesting discussion regarding the possible patient desire for minimally invasive surgery to explain the differentially higher withdrawal rate after randomization but before surgery in the colposuspension group as opposed to the TVT group. This preference has been previously noted (2).

References

Dr. Steven P. Petrou
Associate Professor of Urology
Mayo Clinic College of Medicine
Jacksonville, Florida, USA
Paternity after adolescent varicocele repair

Salzhauer EW, Sokol A, Glassberg KI
Department of Urology, State University of New York, Downstate Medical Center, Brooklyn, New York, USA

Pediatrics. 2004; 114: 1631-3

Objective: Varicocelectomy has long been a therapeutic modality used in the treatment of male infertility. In the past decade, adolescent varicocelectomy has become a frequent procedure to preserve testicular growth and to help prevent future infertility. Because our clinical population includes a large portion of orthodox Jews who traditionally marry early and are forbidden to use birth control by religious law, we thought that by studying our patients, we might be able to accelerate our follow-up regarding paternity. In addition, we wanted to learn whether adolescent varicocelectomy might have any negative impact.

Methods: Questionnaires inquiring as to the marital and paternity status, postoperative course, and complications were sent to 50 patients who had undergone a unilateral or bilateral varicocele repair during adolescence and who were at least 21 years old at the time of this review. In addition, a careful chart review was performed to examine the perioperative and postoperative parameters of each respondent.

Results: Of the 43 responses (86% response rate), 18 of 18 patients who had attempted to father a child were successful. The remaining 25 were not married or had never attempted to father a child. In the paternity group, 10 of the fathers had undergone an Ivanissevich repair; the remaining 8 had a Palomo repair. Sixteen of the 18 had unilateral varicocelectomies, and 2 underwent bilateral repairs. Of those with a unilateral varicocele, the indication for surgery in 10 was a grade 2 to 3 varicocele associated with a > 20% volume difference when compared with the right testicle. Three had 10% to 20% volume loss, whereas the remaining three had unusually large grade 3 varicoceles without concurrent volume difference.

Conclusions: Varicocelectomy in the adolescent population has been proposed as a therapeutic intervention to preserve both fertility and testicular growth. Although not showing a cause-and-effect relationship, it is our contention that varicocelectomy in adolescence at worst does no harm and at best preserves fertility.

Editorial Comment

The authors report on the follow-up of 50 patients who had undergone varicocele surgery and were at least 21 years old. 43 (86%) responded and of those, 18/18 who had attempted paternity had fathered a child. They conclude that “varicocelectomy in adolescence at worst does no harm and at best preserves fertility.”

This is a fascinating report by an excellent group. However, it is still best to remain skeptical about their conclusion. First, regarding the presumption that the surgery did not harm, there are several issues. 1) 7 patients did not respond. Can we presume that their results are the same as the responders? Probably not. 2) Three of the 18 had a recurrent varicocele and one of these required a second operation. 3) Similarly, three of the patients developed hydroceles (and again one required operative repair).

Regarding the suggestion that the patients benefited from the repair, there are also some issues. 1) Again, the non-responders may not have the same paternity as those that did respond. 2) There are no controls. We do not know the paternity rate of patients with the same varicoceles who are untreated. Indeed, we have no idea of the natural history of a varicocele in this population. 3) Eighteen of 18 is clearly a high rate of paternity (assuming the self-report is truly accurate), but this is a very small group. If there were a statistical comparison to a control group, a high rate of failed paternity would be needed to show a statistical difference. 4) Fifty patients were operated on, but we do not know how many adolescents with varicocele were seen. Presumably
these were the worst cases, but there are not data on presented. How many teens with normal fertility underwent unnecessary surgery?

Although we would all like to think that repair of adolescent varicoceles is beneficial in selected cases. However, a randomized prospective trial designed to prove its efficacy would be welcome.

**Dr. Barry A. Kogan**

*Chief and Professor of Urology and Pediatrics*

*Albany Medical College*

*Albany, New York, USA*

**The outcome of prenatally diagnosed renal tumors**

Leclair MD, El-Ghoneimi A, Audry G, Ravasse P, Moscovici J, Heloury Y; French Pediatric Urology Study Group

Department of Pediatric Urology, Hopital Mere-Enfant, Centre Hospitalier Universitaire de Nantes, Nantes, France

*J Urol. 2005; 173: 186-9*

Purpose: We assessed the incidence of perinatal morbidity and evaluated the outcome in children with prenatally diagnosed renal tumors in a retrospective multicenter study.

Materials and Methods: A review of the records of patients from 20 institutions identified 28 children with prenatally diagnosed renal tumors. Prenatal findings, clinical charts, and radiological, surgical and pathological reports were reviewed in this study.

Results: There were 26 congenital mesoblastic nephromas and 2 Wilms tumors. One or more complications were identified in 20 of the 28 cases (71%) during the perinatal period. Polyhydramnios was observed in 11 fetuses (39%), 2 presented with hydrops fetalis and 7 presented in acute fetal distress requiring emergency cesarean section, of which 1 died in utero before delivery. Median gestational age of the 27 neonates born alive was 35 weeks (range 29 to 39), including 13 (46%) who were pre-term (less than 34 weeks of gestation). Complications at birth included hemodynamic instability in 3 newborns, of whom 2 underwent emergency surgery, respiratory distress syndrome in 8 (30%) and hypertension in 6 (22%). Surgical complications occurred in 7 patients (26%), including tumor rupture in 1 and intraoperative bleeding with postoperative death in 1. At a median follow-up of 42 months (range 2 to 105) 26 of the 27 children were in complete remission.

Conclusions: Fetal renal tumors have an excellent oncological outcome but a high risk of perinatal complications. Prenatal diagnosis should allow planning the delivery at a pediatric tertiary care center to avoid a potentially life threatening condition in neonates in the first hours of life.

**Editorial Comment**

Although neonatal renal tumors are rare, the authors report the outcome of 28 cases diagnosed prenatally. These tumors are thought to be benign based on the limited post-natal experience. However, the authors note a strikingly high complication rate, especially prenatally. Forty-six percent were born premature and a large number had hemodynamic instability, hypertension or respiratory distress. There were 7 major surgical complications. Although 26 of the 28 are doing very well at a mean follow-up of 42 months, the authors emphasize that when diagnosed in fetal life, the course of these patients is anything but benign.

**Dr. Barry A. Kogan**

*Chief and Professor of Urology and Pediatrics*

*Albany Medical College*

*Albany, New York, USA*