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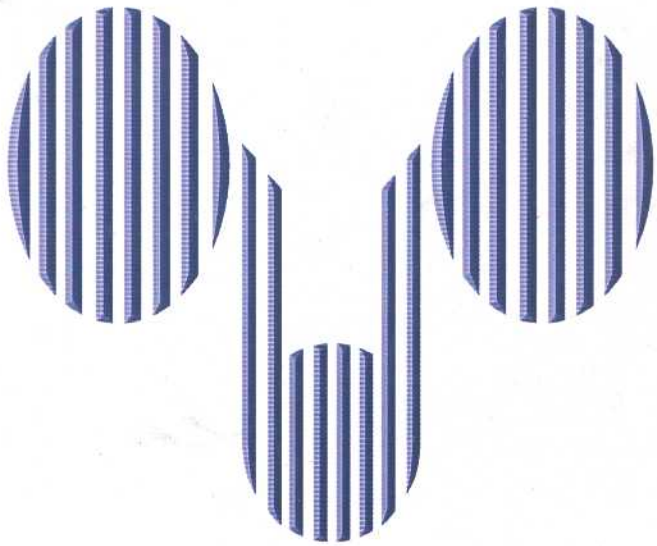

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EDITOR'S COMMENT

The May - June 2000 issue of the Brazilian Journal of Urology presents outstanding contributions from USA, Europe, Asia and Brazil.

Dr. Paul F. Schellhammer, Chairman of Urology at Eastern Virginia Medical School, Norfolk, and Dr. Kenneth Pienta, Professor of Clinical Oncology at University of Michigan, Ann Arbor, USA, authored an important and up-to-date article on therapy for advanced and hormone refractory cancer of the prostate (page 256). In this article, the authors present their own experience and also an extensive review of current modalities of therapy. The chemotherapy protocols and other strategies for hormone refractory prostatic cancer are discussed and the guidelines of the National Comprehensive Cancer Network for standard chemotherapy options are presented. A discussion on the state of the art in palliative radiotherapy as an alternative or adjunct to chemotherapy is also provided. New areas of research in advanced prostatic cancer, including vaccines, antibodies, gene therapy, anti-angiogenesis therapy, antisense therapy and blocking signal transduction are also updated.

Drs. Beduschi and Montie from University of Michigan, Ann Arbor, USA, presented the current indications and new possibilities for organ preservation in invasive carcinoma of the bladder (page 234). The currently available bladder preservation strategies are capable of eradicating invasive bladder tumors in some patients, nevertheless, tumor recurrence occurs in approximately 40% to 60% of patients participating in bladder-sparing regimens. While radical cistectomy with neobladders remains the preferred therapy for invasive bladder cancer, research into bladder preservation schemes, possibly using biomarkers to predict the outcome, should improve the results.

Drs. Stapp, Deitch and deVere-White from University of California Davis, Sacramento, USA, presented and discussed in deep the current schemes of intravesical therapy and follow-up of superficial transitional cell carcinoma of the bladder (page 242). The authors divided the intravesical therapy into chemotherapy and immunotherapy. Based on their own experience and on the urological literature, the authors propose the following practice: 1)- for patients at low risk of progression, only resection of the tumor; 2)- for patients at low risk of progression but with high grade tumors that are either at stage Ta or T1, they treat with an immediate single post-transurethral resection dose of 30 mg of thiotepa; 3)- for recurrent, low risk tumors, they treat with a course of thiotepa; 4)- for patients at a high risk for progression (e.g., those with high grade tumors and stage T1), they administer a 6-week course of BCG; 5)- for patients at high risk for progression, where the next tumor recurrence would require a cystectomy, they treat with a 6-week course of BCG followed by maintenance.

Drs. Figueiredo et al. from Coimbra University, Portugal, studied the relationship between the genes GSTM1 and CYP2D6 polymorphisms and exposure to risk factors, with the occurrence of bladder cancer (page 250). The authors found that GSTM1 null genotype seems to be associated with bladder tumor occurrence, particularly superficial tumors (Ta/T1). This association is stronger in individuals with exposure to tobacco smoke. CYP2D6 gene does not seem to play any significant role in bladder tumor development.

EDITOR'S COMMENT *- continued*

Drs. Ozyurt et al. from Ege University, Izmir, Turkey, studied the voiding dysfunction in patients with multiple sclerosis (page 315). They found that urinary symptoms frequently occurred into four years after diagnosis, and urgency was the most common manifestation. Cystometric alterations were present in 84% of the patients, and the most frequent abnormality was hyperactivity. The authors also found a positive relationship between bladder functional score and disease duration.

Drs. Arap and Mitre from State University of São Paulo, Brazil (page 304) contributed with a comprehensive discussion on penoscrotal hypospadia repair and presented their extensive experience with some surgical techniques.

Drs. Hering et al. from Federal University of São Paulo, Brazil, compared the effects of continuous and intermittent hormonal treatment in patients with advanced (stage D2) adenocarcinoma of the prostate (page 276). In the period studied, intermittent treatment was as effective as continuous treatment, but afforded a better quality of life. Also, 96% of the patients were potent during the intervals between the cycles.

Drs. Thorell et al., from Federal School of Medicine, Porto Alegre, Brazil, analyzed the frequency of positive reactions for p53 protein in localized prostate cancer and how they relate to clinical and histopathologic staging parameters. Their findings show that p53 protein was not an independent marker of prostatic cancer in the group studied (page 270).

Francisco J.B. Sampaio
Editor-in-Chief

BRAZILIAN JOURNAL OF
UROLOGY

COMENTÁRIO DO EDITOR

O número de Maio - Junho de 2000 do Brazilian Journal of Urology apresenta importantes contribuições dos EUA, Europa, Ásia e Brasil.

O Dr. Paul F. Schellhammer, chefe do departamento de urologia da Eastern Virginia Medical School, Norfolk, e o Dr. Kenneth Pienta, professor de oncologia clínica da University of Michigan, Ann Arbor, USA, publicam um artigo completo e atual sobre o tratamento do câncer de próstata avançado e hormônio resistente (pag. 256). Os autores apresentam sua própria experiência e também uma extensa revisão das modalidades terapêuticas atuais. São discutidos os protocolos de quimioterapia e outras estratégias para tratamento de câncer de próstata hormônio refratário e são apresentadas as diretrizes para quimioterapia do National Comprehensive Cancer Network. Também é apresentada uma atualização sobre radioterapia como uma alternativa ou um método complementar à quimioterapia. Os autores fornecem ainda uma atualização sobre novas áreas de pesquisa em câncer de próstata avançado, como: vacinas, anticorpos, terapia genética, terapia anti-angiogênese e bloqueio do sinal de transdução.

Os Drs. Beduschi e Montie da University of Michigan, Ann Arbor, USA, apresentam as indicações atuais e as novas possibilidades de preservação do órgão em carcinoma invasivo de bexiga (pag. 234). As estratégias disponíveis são capazes de erradicar tumores invasivos de bexiga em alguns pacientes, entretanto, a recorrência tumoral ocorre em aproximadamente 40 a 60% dos pacientes submetidos aos protocolos de preservação da bexiga. A cistectomia radical com confecção de neobexiga permanece como a terapia de eleição para câncer invasivo de bexiga. Entretanto, novas pesquisas sobre os protocolos de preservação do órgão, possivelmente com o uso de biomarcadores, poderiam melhorar os resultados.

Os Drs. Stapp, Deitch e deVere-White da University of California Davis, Sacramento, USA, apresentam e discutem em profundidade os esquemas atuais de terapia intra-vesical e de seguimento de pacientes com carcinoma superficial de células transicionais da bexiga (pag. 242). Os autores dividem a terapia intravesical em imunoterapia e quimioterapia. Baseados na sua própria experiência e na literatura urológica, os autores propõem a seguinte conduta: 1)- para pacientes com baixo risco de progressão, apenas ressecção do tumor; 2)- para pacientes com baixo risco de progressão mas com tumores de alto grau, tanto estádio Ta ou T1, tratar com uma dose de 30 mg de thiotepa imediatamente após a ressecção transuretral do tumor; 3)- para tumores recorrentes de baixo risco, tratar com um curso de thiotepa; 4)- pacientes com alto risco de progressão (tumores de alto grau e estádio T1), administrar um curso de 6 semanas de BCG; 5)- para pacientes com alto risco de progressão, nos quais a próxima recorrência tumoral irá levar à indicação de cistectomia, tratar com um curso de 6 semanas de BCG seguido por terapia de manutenção.

Os Drs. Figueiredo et al. da Universidade de Coimbra, Portugal, estudaram a relação entre o polimorfismos dos genes GSTM1 e CYP2D6 e a exposição a fatores de risco, com a ocorrência de câncer de bexiga (pag. 250). Os autores encontraram que a ausência do genótipo GSTM1 parece

estar associado com a ocorrência de tumores de bexiga, particularmente os tumores superficial (Ta/T1). Esta associação é mais forte em indivíduos expostos à fumaça de cigarro. O gene CYP2D6 parece não ter um papel significativo no desenvolvimento do tumor de bexiga.

Os Drs. Ozyurt et al. da Ege University, Izmir, Turkey, estudaram as disfunções miccionais em pacientes com esclerose múltipla (pag. 315). Os autores observaram que os sintomas urinários ocorrem geralmente dentro dos primeiros 4 anos após o diagnóstico, sendo a urgência a manifestação mais comum. As alterações cistométricas estavam presentes em 84% dos pacientes, e a anormalidade mais freqüente foi a hiperatividade. Os autores também encontraram uma correlação positiva entre o escore funcional da bexiga e o tempo de doença.

Os Drs. Arap e Mitre da USP, Brasil (pag. 304) contribuem com uma discussão profunda sobre o tratamento da hipospádia peno-escrotal e apresentam sua extensa experiência com algumas técnicas cirúrgicas.

Os Drs. Hering et al. da EPM-UNIFESP, Brasil, compararam os efeitos do tratamento hormonal intermitente e contínuo em pacientes com câncer avançado de próstata (estádio D2), pag. 276. No período estudado, o tratamento intermitente foi tão efetivo quanto o tratamento contínuo, e ofereceu uma melhor qualidade de vida. Além disso, 96% dos pacientes estavam potentes durante os intervalos entre os ciclos.

Os Drs. Thorell et al., da Faculdade Federal de Medicina, Porto Alegre, Brasil, analisaram a freqüência de reações positivas para proteína p53 no carcinoma localizado de próstata e tentaram estabelecer uma correlação com os parâmetros de estádio clínico-patológicos. Seus achados mostraram que a proteína p53 não é um marcador independente de câncer prostático no grupo estudado (pag. 270).

Francisco J.B. Sampaio
Editor-Chefe

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CURRENT INDICATIONS AND NEW POSSIBILITIES FOR ORGAN PRESERVATION IN CARCINOMA OF THE BLADDER

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ABSTRACT

Objective: To assess the efficacy of bladder-sparing strategies in the treatment of muscle-invasive bladder cancer.

Patient and Methods: This overview discusses the evolving role of transurethral resection of bladder tumors, radiation therapy, systemic chemotherapy, and combination therapy in the treatment of invasive bladder cancer. The pertinent literature was reviewed and the specific aspects of each modality were analyzed. The results of bladder-sparing strategies were compared with radical cystectomy.

Results: The bladder preservation strategies that are currently available are capable of eradicating invasive bladder tumors in some patients, but most patients are unlikely to be durably cured by any of these regimens. Tumor recurrence occurs in approximately 40% to 60% of patients participating in bladder-sparing regimens. Approximately half of these recurrences are muscle invasive, placing the patients at risk for metastasis. Pelvic recurrence rates after radical cystectomy range between 10% and 30%. The disease specific five-year survival rates in pathological stages T1/T2 are close to 70% to 80%; less than 50% for pathological stages T3b/T4. Decreasing morbidity post radical cystectomy and the advent of the orthotopic neobladder technique using either the small or the large bowel is capable of restoring urinary function, which lessens the qualitative benefits of any organ-sparing modality currently available.

Conclusion: While radical cystectomy with neobladders remains the preferred therapy for invasive bladder cancer, research into improved bladder preservation strategies, possibly using biomarkers to predict responsiveness to treatment, should continue.

Key words: bladder, carcinoma, invasive, organ preservation, radiotherapy, chemotherapy
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INTRODUCTION

Management of high-grade urothelial carcinoma of the bladder is one of the most challenging problems facing urologists today. Radical cystectomy is currently accepted as the most effective treatment for muscle invasive disease based on the fact that it provides excellent local control in the pelvis with a low perioperative mortality rate. Nevertheless, the morbidity related to this procedure is significant and issues of impotence and urinary incontinence remain. The negative impact on the quality of life of patients undergoing radical cystectomy fosters a search for alternative ways to treat invasive bladder cancer that would allow a patient to retain the natural organ. Alternative therapies would have to provide fewer complications without compromising control of the primary tumor or survival. Several options tested in clinical practice attempt to preserve the urinary bladder in patients with invasive bladder cancer using a combination of chemotherapy and radiation or bladder-sparing surgery.

The aim of this article is to review the existing bladder preservation strategies. It is our view that current bladder-sparing techniques are less effective than radical cystectomy for cancer control, and thus reserved for highly selected patients.

RATIONAL FOR BLADDER PRESERVATION

Eradication of a tumor without removal of the affected organ is the ideal treatment for any cancer. Therefore, for bladder cancer, the best treatment is the one capable of providing control of the primary tumor without compromising survival, thus avoiding the morbidity and adverse effect in quality of life associated with radical cystectomy. Several options have been tested in clinical practice, from transurethral resection alone to a combination of multiple therapies.

TRANSURETHRAL RESECTION OF BLADDER TUMOR (TURBT)

Transurethral resection is the mainstay of treatment for noninvasive (Ta) or minimally invasive (T1) bladder cancer. It is apparent that TURBT may also effectively cure some patients with higher stage disease (T2a). This is supported by 2 pieces of evidence: 1)- TURBT yields a prolonged disease-free survival in selected patients with T2 disease; and 2)- no residual tumor is found in the radical cystectomy specimens in approximately 10% of patients (pathological stage T0), indicating that the TURBT effectively removed the tumor (1-4). Early studies have shown that TURBT alone can provide a five-year survival rate close to 50% in selected patients, which is not substantially different from that of some large cystectomy series (1-4).

Treatment selection is clearly important. In a series of patients adversely selected by advanced age and poor surgical risk that underwent TURBT alone for muscle-invasive bladder cancer, the five-year survival was 14% (5). Although capable of controlling the cancer in some cases, TURBT alone will fail to cure most patients with high stage bladder cancer. TURBT as a primary treatment is more likely to be successful in patients with small volume tumors, who likely may have an even greater chance of cure by cystectomy. Circumstantial evidence to support this observation has also been reported. The five-year survival rate for patients with smaller T2 tumors, who underwent radical cystectomy, ranges from 60% to 80% as compared to the 50% rate observed after TUR alone (6-9). However, TURBT is an invaluable tool for evaluating bladder cancer therapy and staging after other modalities of bladder preservation (10). Patients who achieve a clinical T0 status on a transurethral resection of the primary tumor site are likely to respond better to further therapy (chemical or radiation) than those who do not achieve this condition (4).

PARTIAL CYSTECTOMY

Resection of only the cancerous portion of the bladder has some theoretical advantages over either TURBT or cystectomy in the management of invasive bladder cancer. It allows full-thickness resection of the bladder wall and more certain removal of the tumor confined to that segment compared to TURBT. It also preserves the patient's bladder and sexual function. The trade off is the risk of remaining or new cancer in the bladder, since the urothelium remains exposed to the same predisposing factors to bladder carcinoma. Approximately 50% to 70% of the patients who undergo partial cystectomy develop later tumors in the bladder; some of which will be muscle invasive and potentially lethal. The commonly reported five-year survival rates for partial cystectomy is approximately 50%, which is similar to TURBT alone (11). It ranges from 70% for early stages (T2 tumors) to 17% for more advances tumors (T3b and T4 tumors). Patient selection remains critical. Ideal patients for partial cystectomy have: 1)- a single tumor in space and time (no previous history of bladder cancer); 2)- the tumor located in a site favorable to resection (dome or high posterior wall of the bladder); and 3)- no carcinoma in situ (CIS). Patients with a urachal tumor or occasionally a tumor in a bladder diverticulum may be reasonable candidates for partial cystectomy. The number of patients meeting these criteria is extremely low, much less than 5% of the patients with stage T2a or higher disease. Good functional results with radical cystectomy and ileal neobladder formation have diminished considerably the role of partial cystectomy in patients with invasive bladder cancer. When indicated, it should be performed removing the overlying peritoneum along with the involved bladder and a 2 cm margin of nor-

mal bladder around the entire circumference of the bladder tumor. Biopsies around the resected area and elsewhere in the bladder are necessary to exclude concomitant CIS. The ill-advised partial cystectomy commonly turns into a nightmare and diminishes later success even with total cystectomy.

EXTERNAL RADIATION THERAPY

Ionizing radiation therapy has been extensively used in the treatment of invasive bladder cancer, particularly in Europe. In the United States, its role remains limited. Results with external radiation therapy (RT) in the U.S.A. have been consistently less optimistic than those from Europe.

In a large randomized European trial comparing pre-operative pelvic RT and radical cystectomy versus RT only for patients with T2b and T3 bladder cancer, the survival rate was not statistically different between the two groups. A five-year survival rate of 38% was reported for those who underwent radical cystectomy, compared to 29% for those treated with RT only (12). Similar results were reported in a more recent study (13). For those patients that underwent immediate surgery, a five-year survival rate of 29% was reported, versus 23% for the RT only group. In one of the largest series of patients treated with primary radiation therapy alone (cystectomy was reserved as salvage treatment), the complete clinical response rate was 45% for clinical stages T1 to T4. Fifty percent of the patients had locally recurrent tumors, with an overall five-year local control rate of 25% for stages T1 through T3 tumors. Those with clinical stage T4 achieved a five-year local control rate of only 16%. Patients with persistent tumors underwent radical cystectomy, with an overall five-year survival rate following surgery of approximately 45%. In this series, the overall survival rate for patients with deeply invasive tumors was approximately 25%; 69% for those with more superficial tumors (14).

As a single modality for the treatment of muscle invasive cancers, RT may provide local control in 30% to 50% of the cases at best, with a five-year overall survival rate ranging from 23% to 40% (15-18). Analyzing data from several trials of primary radiation therapy for T2 disease, an overall five-year survival rate of approximately 40% was reported, with a local control rate ranging between 40% and 50%. Primary recurrence was a serious concern in all studies (19-24). Patients with T3 disease had a five-year survival rate of only 20%, with 50% to 70% having local recurrence (19-24).

More recently, several drugs (radiosensitizers) have been investigated as a possible means of improving the efficacy of RT. Most interesting have been the studies investigating the concurrent use of RT and Cisplatin. One small randomized study that compared radiotherapy with and without the concurrent use of Cisplatin demonstrated a significant improvement in local control with the concurrent regimen, but it failed to show any benefit in terms of overall survival (25). A pilot trial is currently under way at the University of Michigan to evaluate the combination of gemcitabine and radiation therapy as a bladder preservation strategy. Gemcitabine is an antimetabolite that was initially synthesized as an antiviral drug. Further investigations demonstrate that the drug is a potent radiosensitizer and has significant activity against urothelial carcinoma as a single agent.

In summary, the results with RT for invasive bladder cancer in the U.S.A. have been systematically inferior to those of radical cystectomy, therefore RT is only exceptionally recommended as a primary option for invasive bladder cancer.

SYSTEMIC CHEMOTHERAPY

The search for an effective chemotherapy regimen for metastatic bladder cancer led to the evaluation of various cytotoxic agents in patients with disseminated disease. Cisplatin was found to be the most active single agent against urothelial cancer, but other agents such as 5-FU, methotrexate, vinblastine and doxorubicin have also been tested with partial success. Nevertheless, none of these agents was found to be solely effective. Combination regiments are more effective and capable of inducing a complete response in patients with metastatic bladder cancer (26). Several combination regiments were tested in clinical practice until the introduction of the MVAC

regiment (methotrexate, vinblastine, doxorubicin and cisplatin) at the Memorial Sloan Kettering Center. The first results of a phase-II trial were reported in 1985, and since then, MVAC has evolved into the preferred chemotherapy treatment for bladder cancer. An updated report from 1989 revealed that 121 patients had been enrolled in the clinical trial. An overall response rate of up to 70% was reported, but a durable disease-free survival was observed in only a small percentage of patients (27). The median survival duration for the entire group was 13.3 months; only 20% of the patients were long-term disease-free survivors. MVAC was subsequently compared to other systemic regiments and found to be the most effective. This relative success in treating metastatic disease led to the utilization of MVAC in bladder-sparing protocols at the same institution. In a series of patients treated with both TURBT and MVAC, 54% achieved an early T0 status (28). Unfortunately, additional studies revealed that only in a few patients was the response durable and complete (29). In addition, the toxicity of the regiment is substantial and another limitation. Even at a standard dosage, the side effects of MVAC were poorly tolerated by most patients.

The toxicity and limited efficacy of this regimen led to new investigational agents. Two of the most promising agents are paclitaxel and gemcitabine (30). Both have shown significant activity as single agents against urothelial carcinoma. In a one phase-II trial, 27% of the patients with metastatic bladder cancer that were treated with paclitaxel achieved a complete response (31). When combined with carboplatin, an overall response rate of 50% was achieved. This combination was well tolerated, with only moderate side effects (granulocytopenia and thrombocytopenia) (32,33).

The combination of gemcitabine and cisplatin also appears particularly promising. Longer follow-up and randomized trials are required to reveal if any of them will supplant MVAC as the standard therapy for metastatic urothelial carcinoma of the bladder. The diminished toxicity of these new regiments as compared to MVAC makes them attractive. Data on the efficacy on localized disease must be obtained to judge a role for this treatment for bladder preservation.

Currently, systemic chemotherapy fails to produces results comparable to radical cystectomy, and the results may be no better than TURBT or partial cystectomy alone. Until more effective and less toxic regiments are fully investigated, it should not be recommended as a primary treatment for invasive bladder cancer. Data using adjuvant or neoadjuvant chemotherapy combined with radical cystectomy is sparse, and thus far, no conclusive improvement in survival has been shown.

COMBINATION THERAPY

Combined approaches using all 3 modalities of therapy (TURBT, RT and chemotherapy) have also been investigated in organ preservation approaches with more encouraging results. A combination of maximal TURBT with initial chemotherapy (cisplatin, methotrexate and vinblastine), followed by RT with concurrent cisplatin was tested in a series of patients at Massachusetts General Hospital (34,35). Patients were evaluated after 4,000cGy and those with complete response received an additional 2,480cGy. For those who did not reach complete response, total cystectomy was recommended. After a median follow-up of four years, 53% of the patients had achieved complete response; bladder function was adequately preserved in 89% (34,35). In a recent update from the same institution with the same regimen, a complete response was observed in 76 of 106 patients enrolled in the study (66%). Twenty-one of the 76 patients developed Ta or T1 recurrence. Recurrence was controlled with TURBR and intravesical therapy in 15 of these patients; 13 patients presented with an invasive recurrence. After a median follow-up of five years, 54% of the enrolled patients had no cancer found in the bladder at their most recent evaluation (36). In other trials similar results were reported, with five-year survival with an intact bladder ranging from 39% to 45% (37-41). However, in another study, a disappointingly low rate of disease-free bladder preservation with no definitive improvement in survival was reported; only 18% of the enrolled population was alive with an intact bladder at the end of the study. The five-year survival rate of patients who had a cystectomy at some point

in the study was 65%, compared to 40% for those who had their bladder spared (41). The data from these studies suggests that the combined regimen is capable of preserving the bladder in some patients with muscle invasive disease; however, a significant number will have an incomplete response or will develop recurrent disease within the bladder, including some of these invading muscle tissue. Therefore, until new agents or more effective approaches become apparent, combinations of all 3 modalities remain as a secondary alternative for the management of invasive bladder cancer.

IMPROVING PATIENT SELECTION FOR BLADDER PRESERVATION

Not all patients with muscle invasive disease require radical cystectomy to eliminate the cancer in their pelvis. The dilemma is how to select which patients are appropriate candidates for bladder-sparing strategy. Most of the studies addressing bladder-sparing strategies are retrospective, and although capable of providing helpful information and some estimate of the efficacy of the different regiments, they are not appropriate to compare results achieved with cystectomy or for patient selection.

Tumor markers capable of predicting responsiveness to bladder-sparing strategies would be beneficial. Recent studies have identified several molecular markers important in the progression of urothelial carcinoma. Most of the attention has been focused on the p53 (42). p53 is a tumor suppressor gene that plays a significant role in determining cellular responses to DNA damage, leading to both cell cycle arrest and programmed cell death (42). Mutations of this gene and accumulation of the p53 protein are associated with the transition to an invasive phenotype of transitional cell malignancies (43). The gene may also influence the response to chemotherapy treatment, since most antineoplastic drugs act by promoting DNA damage. Several studies have now examined the proportion of invasive bladder cancer that express an abnormal p53 protein and how this finding would impact prognosis (44-48). According to these studies, from 43% to 66% of the invasive tumors expressed an abnormal p53 protein; an over expression of p53 was associated with a high recurrence rate and reduced survival. Conversely, patients with a tumor lacking p53 expression were more likely to have long-term survival, especially those with organ-confined T2 tumors. However, the influence of p53 on the response to treatment remains controversial. There is some evidence that patients with abnormal p53 may benefit from adjuvant chemotherapy (49). A recent report from the Memorial Sloan-Kettering Center suggests that long-term bladder preservation (up to ten years) is feasible in patients with T2 tumors who lack p53 if they respond completely to neoadjuvant chemotherapy with MVAC. Patients with T3 disease or T2 p53 expressing tumors are best treated with radical cystectomy (50). To better address the clinical usefulness of p53, a multi-center clinical trial is underway. Patients with organ-confined but invasive urothelial carcinoma of the bladder (T1 and T2) after cystectomy are randomized on the basis of their p53 status to receive adjuvant chemotherapy (MVAC) or observation with later chemotherapy.

Since not all muscle invasive cancer express p53, progression of the disease in the bladder must be regulated by pathways other than p53. Recent investigations have suggested that the retinoblastoma gene protein (pRb) may also play a role in this process (51-53). Studies have shown that deletion of the Rb gene is a negative prognostic factor for disease progression and overall survival. Whether or not Rb abnormalities affect response to chemotherapy in bladder cancer is yet to be determined. Several others tumor markers (histological and molecular markers) are currently under investigation (54). The development of molecular biomarkers will hopefully allow us to determine more appropriately which patients are suitable for bladder-sparing therapy.

CONCLUSION

It is clear that the strategies for bladder preservation currently available are capable of eradicating invasive bladder tumors in some patients, but most patients with muscle invasive bladder cancer are unlikely to be durably cured by any of these regimens.

Tumor recurrence occurs in approximately 60% of patients participating in bladder-sparing regimens, and approximately half of these recurrences are muscle invasive, placing the patients at a high risk for metastasis. Not all of these patients will be saved by salvage cystectomy. Patients with superficial recurrence require further treatment with intravesical treatment and long-term surveillance, since they are also at a high risk for progression of the disease. Bladder function is another concern, and may not be ideal in those receiving multiple TURBTs, intravesical therapy with BCG, and a high dose of RT. It is also evident that patients with high stage disease (T3 and T4), who are at highest risk for developing metastatic cancer, are the ones with the lowest chance for complete elimination of the local cancer. Twenty percent of these will have a complete response with bladder preservation therapy, a figure inferior to radical cystectomy that is capable of providing local control of the disease in 60% to 90% of the cases. Expanding the indications for organ preservation likely exposes a greater proportion of the patients to a higher risk of metastasis or local progression of the disease. Do the qualitative benefits warrant this risk?

In our opinion, radical cystectomy remains a preferred local therapy. The peri-operative mortality rate currently ranges between 1% and 3% (55). Under close monitoring and a good pre-operative evaluation, it can be performed safely on patients of all ages who are reasonably healthy (56). The therapeutic results of radical cystectomy are dependent on the clinical and pathological stage; most failures are due to distant metastasis. The pelvic recurrence rate after radical cystectomy ranges from 10% to 30%, with the higher rate for larger T3b tumors (palpable mass) (57,58). Disease-specific five-year survival rates in pathological stages T1/T2 are close to 70% to 80%, compared to less than 50% for pathological stages T3b/T4. High-grade cancers (as most invasive tumors are) tend to perform worse; lymph node involvement is also a strong predictor of relapse, but cure is possible with surgery alone even in the presence of positive lymph nodes (58,59).

Improved quality of life and decreasing morbidity post radical cystectomy are clearly evident in the last 5 to 10 years. Nerve-sparing cystoprostatectomy allows preservation of the autonomic innervation of the corpora cavernosa with preservation of erectile function in some patients. In a highly selected series, recovery of sexual function was seen in up to 62% of patients between 40 and 49 years of age, without compromising cancer control (60). Orthotopic neobladder, using either the small or large bowel, is capable of restoring urinary function, bringing it closer to that of a preserved bladder, and should be recommended as the first option for diversion in most of the patients undergoing radical cystectomy. External urinary diversion (ileal conduit) is recommended only for patients with poor general health, sedentary lifestyles, or decreased renal function.

Until better molecular tumor markers are available to predict patients that are likely to respond to either RT or chemotherapy, radical cystectomy with neobladders should remain as the preferred therapy for invasive bladder cancer.

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INTRAVESICAL THERAPY AND FOLLOW-UP OF SUPERFICIAL TRANSITIONAL CELL CARCINOMA OF THE BLADDER

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ABSTRACT

Intravesical therapy is commonly used for the treatment of superficial transitional cell carcinoma (TCC) of the bladder. There are 2 major categories of intravesical therapy; chemotherapy and immunotherapy. The 2 types have different indications and different mechanisms of action.

Chemotherapy: there is evidence that intravesical therapy fails to affect disease progression, nevertheless, chemotherapy in the form of thiotepa, mitomycin-C, doxorubicin or epirubicin has been recommended for those patients having low-grade, low-stage tumors (Ta, Grade 1-2) who have multiple tumors at presentation or whose recurrence rate on follow-up is unacceptable. While intravesical chemotherapy reduces the risk of recurrence during the first 3-6 month period after TUR, the difference in recurrence rates becomes less significant with increasing time after resection.

Immunotherapy: unlike chemotherapy, intravesical immunotherapy in the form of BCG has been shown to reduce tumor recurrence and prevent progression. Patients who are suitable candidates for intravesical BCG include those with carcinoma in situ (CIS), or with T1 lesions that have been completely or incompletely resected, as well as those patients who have failed intravesical chemotherapy for low-grade, low-stage tumors. BCG must never be given immediately after tumor resection due to the possibility of severe systemic infection.

To summarize, the authors practice regarding intravesical therapy for superficial bladder cancer, is the following: 1)- for patients at low risk of progression, we initially resect the tumor and do not treat with intravesical therapy; 2)- for patients at low risk of progression but with high risk of recurrence, (e.g., those with high grade TCC that are either stage Ta or stage T1), we treat with an immediate single post-TUR dose of thiotepa of 30 mg; 3)- for recurrent, low risk tumors, we treat with a course of thiotepa; 4)- for patients with a high risk for progression (e.g., those with high grade TCC and stage T1), we administer a 6-week course of BCG; 5)- for patients at high risk for progression, where the next tumor recurrence would indicate a cystectomy, we will treat with a 6-week course of BCG followed by maintenance.

Key words: bladder, transitional cell carcinoma, chemotherapy, immunotherapy
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INTRODUCTION

Intravesical therapy is commonly used for the treatment of superficial transitional cell carcinoma (TCC) of the bladder. However, there is considerable debate as to when to implement this therapy and which type of intravesical treatment is most appropriate. Moreover, even if the decision is made to adopt intravesical therapy, questions remain as to whether maintenance therapy should be undertaken and how often and when to follow these patients. These treatment decisions affect a substantial number of patients since more than 50,000 cases of transitional cell carcinoma of the bladder are diagnosed annually in the United States alone (1).

TCC is the most common histological type of bladder cancer seen throughout the world. In the United States, if one includes both the initial presentation and recurrences, 92% of cases are superficial TCC which are designated as either stage Ta or T1

Table 1 *- Impact of tumor stage and grade on disease progression in patients with superficial TCC*

Study	Patients	Follow-up	Rate of Progression
National Bladder Cancer Group Heney NM	207	Median 39 months	Grade 1 : 2% Grade 2 : 11% Grade 3 : 45% Stage Ta : 4% Stage T1 : 30%
Holmang et al.	176 (65 had definitive treatment)	At least 20 years or death	Stage Ta : 14% Stage T1 : 39%
EORTC-GU Group Kurth et al.	423 treated with TUR alone or TUR plus doxorubicin or ethoglucid	Median 10.7 years	Stage Ta : 9% Stage T1 : 22%

(Ta: confined to the epithelium; T1: penetrating the lamina propria but not into muscle). The primary treatment for Ta/T1 TCC is transurethral resection (TUR). In a compilation of data from 3,404 patients in 21 trials comparing TUR alone versus TUR plus intravesical chemotherapy, Lamm showed that only 49% of patients remained recurrence-free after TUR alone (2). That review advocates the use of intravesical therapy solely for those patients who are at high risk of tumor recurrence or disease progression. Even when all visible tumor is completely resected by TUR, the overall risk of recurrence remains approximately fifty percent. Recurrence is not in itself life threatening, unless the recurring tumors progress to a higher stage. There have been a number of studies showing that the progression rate for Ta lesions is very different from that for T1 lesions. For stage Ta disease, the progression rate is approximately 5-9%, while it is as high as 45% for stage T1 TCC. Moreover, the grade of the tumor also plays an important role in disease progression. While Ta lesions tend to be grade 1 or 2 and are rarely grade 3, T1 lesions can often be grade 3, putting these tumors in a much higher risk category (Table-1).

Thus, intravesical therapy is appropriately administered to those patients who are found to be at higher risk of recurrence after the initial TUR, based on their tumor characteristics (Table-2). When treating patients who have high-risk lesions, the clinical aim is to avoid the need for cystectomy and to decrease the potential chance of death from TCC. However, if intravesical therapy is employed for those having low risk lesions, the clinical goals are different. For the latter patients, the goal is to try to increase patient comfort and reduce health care costs by decreasing the need to intervene for recurrences.

There are 2 major categories of intravesical therapy, chemotherapy and immunotherapy. The 2 types have different indications and different mechanisms of action. In addition, there is some controversy

Table 2 *- Superficial bladder cancer tumor characteristics*

Low Risk or "Favorable"	Higher Risk or "Unfavorable"
Single tumor	Multiple tumors
Stage Ta	Stage T1
Low grade	High grade
No CIS*	CIS or cytological atypia or dysplasia
Diploid	Aneuploid
Negative cytology	Positive cytology

* *Carcinoma-in-situ defined as a high-grade intraepithelial lesion*

regarding the timing of administration of intravesical chemotherapy, i.e., is immediate adjuvant chemotherapy reasonable? We will explore these and other issues regarding intravesical therapy and will highlight key points about following patients with superficial bladder cancer.

INTRAVESICAL CHEMOTHERAPY

In general, after a bladder tumor has been resected and a bimanual examination has been performed, the histological characteristics of the tumor will dictate whether or not to use intravesical therapy. As discussed above, if a tumor belongs to the high-risk group, then intravesical treatment is reasonable to use in order to prevent cancer recurrences and, if possible, to halt progression to muscle-invasive disease. The former goal is often achieved, while the latter is more doubtful.

Why do superficial bladder tumors recur? In a recent review by Akaza et al., this question is addressed and possible explanations are given (3). These authors surmise that there are four reasons for recurrence that are not mutually exclusive: 1)- implantation ("seeding" or dispersion) of tumor cells in the epithelium during tumor resection, 2)- growth of co-existing microscopic lesions, 3)- an incomplete TUR resulting in tumor cells being left behind, and 4)- the emergence of a "second primary" or of new bladder tumors. It is the total of all these types of "recurrences" that we try to prevent by using intravesical therapy. Specifically, the use of intravesical chemotherapy has been shown to decrease the recurrence rate of low-grade, low-stage tumors. Some of the most compelling data on this subject comes from the Fourth International Consensus Conference on Bladder Cancer in 1993. This conference concluded that, compared to no adjuvant therapy, intravesical chemotherapy provided a 12-15% lower tumor recurrence rate. It is noteworthy that this conference also concluded that intravesical chemotherapy had no effect on progression to higher disease stages. Both of these observations are supported by the work of Lamm (2), who examined the long-term results of 1,938 bladder cancer patients treated with intravesical chemotherapy and compared them to 2,607 who did not receive adjuvant therapy. No significant survival or progression advantages were demonstrated for those receiving adjuvant intravesical therapy. Akaza et al. have offered a hypothesis explaining why reducing tumor recurrences does not influence disease progression (3). This group proposes that intravesical therapy has no effect on the subsequent emergence of second primary tumors, which may then be responsible for progression. However, they considered that intravesical therapy is effective against dispersion of the original tumor during TUR as well as against residual microscopic foci or otherwise incomplete resections. This theory seems plausible, and underscores the need for prevention of disease progression, which can ultimately lead to death.

Despite the above evidence that intravesical therapy fails to affect disease progression, chemotherapy in the form of thiotepa, mitomycin-C, doxorubicin or epirubicin has been recommended for those patients having low-grade, low-stage tumors (Ta, Grade 1-2) who have multiple tumors at presentation or whose recurrence rate on follow-up is unacceptable. Akaza et al. contention that intravesical therapy is not effective against the "second primary" tumor (3) is based on their data plotting the frequency of tumor recurrence at given timepoints after TUR. While intravesical chemotherapy reduces the risk of recurrence during the first 3-6 month period after TUR, the difference in recurrence rates becomes less significant with increasing time after resection. Their explanation for these observations is that recurrences due to implanted cells and microscopic tumor lesions are affected by the intravesical chemotherapy, but that the risk of "recurrence" due to the appearance of new primary tumors is not affected. Such tumors will become manifest considerably later after resection. While this explanation might lead one to question the value of using any intravesical chemotherapy, we believe that chemotherapy does have a role to play in the treatment of superficial bladder cancer. There is an obvious benefit to the patient if this therapy can reduce the number of recurrences or, at the least, lengthen the time between recurrences. However, it has become evident that maintenance therapy is needed to achieve

the full beneficial effects of intravesical chemotherapy. The National Bladder Cancer Cooperative Group (NBCCG) conducted a prospective randomized trial in which treatment with thiotepa delayed time to recurrence in most patients until after they had stopped a two-year course of monthly maintenance therapy.

In addition to the standard administration of intravesical chemotherapy (i.e., starting after a period of 1-2 weeks post-resection), there has been recent interest in using immediate post-surgery adjuvant intravesical chemotherapy. In a recent review by Schellhammer, the data resulting from this latter form of treatment is clearly outlined (4). The rationale for immediate post-resection adjuvant intravesical chemotherapy is based on the first mechanism of tumor recurrence cited above, namely the implantation or "seeding" of tumor at the time of resection. The concept is that a denuded epithelial bed exists secondary to transurethral resection. This, coupled with the concomitant release of tumor cells, may provide the fertile "soil and seed" for tumor regrowth. One of the most significant of the initial small trials of this early adjuvant chemotherapy was a prospective, randomized trial by Zincke et al. which compared immediate adjuvant treatment with thiotepa (60 mg) or doxorubicin (50 mg) versus saline (control). This study reported recurrences in only 30% of the group treated by intravesical thiotepa, 32% in those receiving doxorubicin, compared to 71% in the control group (4). Should we therefore conclude that the 40% reduction in recurrences resulted from prevention of tumor cell seeding? On the face of it, this appears to be highly unlikely. Furthermore, it seems improbable that a single dose of thiotepa could cure microscopic or residual disease. Part of the problem in interpreting these data is that the 71% recurrence rate in the control group is 20% higher than that reported by others. Nevertheless, whatever the reasons for these findings, other clinical trials have reported similar results. For example, the European Organization for Research on Treatment for Cancer (EORTC) conducted a study of 431 patients comparing a single dose of epirubicin (80 mg) to controls receiving intravesical water. This study demonstrated a clear advantage of immediate epirubicin therapy in reducing tumor recurrence. Schellhammer's paper (4) also raises the concept of combining immediate intravesical chemotherapy with a subsequent Bacillus Calmette-Guerin (BCG) induction course initiated 1-2 weeks later with subsequent maintenance of BCG treatment. We believe that such a combined chemo and immunotherapy approach may very well reduce both recurrence and progression. It is important to stress that BCG cannot be used immediately after resection due the potential for systemic absorption. If we are going to use a course of intravesical immunotherapy, we see no advantage to administering immediate chemotherapy.

For the patient with low risk of progression, we recommend instilling a single dose of thiotepa after resection as this will save the patient coming 6 weeks in a row to receive intravesical therapy. If the single dose fails to stop recurrence, it is highly unlikely that at the next visit and at 3 and 6 months post-resection that these patients will experience disease progression.

The available data on intravesical chemotherapy does not indicate that any single agent currently in use is clearly better than any other. Therefore, selection of a chemotherapy agent is usually based on cost, toxicity, and availability as well as on physician preference and experience. There is an advantage to using a limited number of agents so that standard protocols can be adopted, thereby reducing errors in drug administration.

We will consider 4 chemotherapy agents that have been used with some success in the adjuvant treatment of bladder cancer. Thiotepa is an alkylating agent of molecular weight 189.22 that inhibits nucleic acid synthesis. Typically, it is administered in an intravesical dose of 30-60 mg (1mg/ml in sterile saline or water), weekly for 6 weeks, then monthly for up to 1 year. While thiotepa is inexpensive, it can have serious side effects. In approximately 5% of patients, myelosuppression may result due to the low molecular weight of this compound, which permits systemic absorption to occur. Therefore, the white blood cell (WBC) count must be checked prior to giving the next dose. If the WBC counts are down, the dose is withheld. About 25% of the patients receiving

intravesical thiotepa report irritative voiding symptoms. However, this is clearly a lower rate than that found for patients receiving BCG. The efficacy of thiotepa varies in the literature, probably due to the variable doses and regimens that have been employed. Lamm reviewed 10 controlled studies with 1,009 patients treated with thiotepa and found that the recurrence rate was 45% in the thiotepa group as compared to 62% in the control group. However, in 5 out of the 10 series, statistical significance was not reached. Thiotepa is probably best reserved for those having stage Ta lesions. Indeed, this patient group is the one studied in the early thiotepa studies reported by Dr. Koontz.

Mitomycin C (MMC) is an alkylating agent that is cell-cycle nonspecific with a molecular weight of 329. The usual dose is 20-60 mg and side effects are minimal. This drug is not readily absorbed so systemic effects are rare. However, allergic reactions such as a palmar rash occur in approximately 10% of cases. A study conducted by the EORTC examined the use of MMC for existing papillary tumors and found a complete response rate of 43% (270 of 627). When used for carcinoma-in-situ (CIS), 58% of patients had resolution of disease. For prophylactic use, MMC has a relative advantage of 15% over no chemotherapy. The use of maintenance therapy after MMC is controversial but probably is not advantageous (2).

Doxorubicin is a high molecular weight (580) anthracycline antibiotic that acts as an intercalating agent and is most toxic to S-phase cells. It is usually given in a dose of 30-100 mg administered either weekly or every 3 weeks. Chemical cystitis with this agent can be severe, occurring in 25-50% of patients. This side effect is reversible with cessation of drug treatment. The success rate of doxorubicin as first line treatment is approximately 40% overall. It does not appear to have significant advantage over no additional treatment when used prophylactically (2). Maintenance therapy with this drug is without value. For all of the above reasons, we very seldom employ doxorubicin for treatment of TCC. A derivative of doxorubicin, epirubicin, has become increasingly used. It has fewer side effects with similar antitumor effects to doxorubicin. The dose of epirubicin is 30-80 mg in saline given daily for 3 days with a rest period followed by 3 more daily instillations.

Intravesical chemotherapy clearly reduces short-term recurrence in superficial bladder cancer when compared with no additional treatment. The relative advantages are 17% for thiotepa, 15% for mitomycin-C and 18% for doxorubicin (2). However, long-term reduction in tumor recurrence does not occur and intravesical chemotherapy does nothing to prevent tumor progression. Furthermore, there have been no documented survival advantages for adjuvant intravesical chemotherapy.

INTRAVESICAL IMMUNOTHERAPY

Unlike chemotherapy, intravesical immunotherapy in the form of BCG has been shown to reduce tumor recurrence and prevent progression. We consider it to be the most effective form of intravesical treatment for superficial bladder cancer. While BCG is an immune stimulant or modulator (5), the exact mechanism of action of BCG on TCC is unknown. BCG causes an inflammatory reaction in the bladder leading to production of cytokines (interleukins 1, 2 and 6, interferon gamma and tumor necrosis factor alpha). It is thought that, as a result of BCG treatment, macrophages and lymphocytes infiltrate the bladder and destroy tumor cells. There is some evidence that BCG instillation involves not only local immunological efforts but also systemic immune responses (6). BCG therapy has been shown to be superior to chemotherapy in reducing disease progression. Nseyo & Lamm have tabulated the results of 6 clinical studies comparing surgery alone with intravesical BCG immunotherapy and have shown that 5 out of the 6 studies demonstrate a significant advantage of BCG therapy (5). The 1 study that was not able to show a significant advantage had only 77 patients and had a fairly high recurrence rate for the controls of 42%.

Patients who are suitable candidates for intravesical BCG include those with CIS, or with T1 lesions that have been completely or incompletely resected, as well as those patients who have failed intravesical chemotherapy for low-grade, low-stage tumors (1). As mentioned previously, BCG must never be given immediately after tumor

resection due to the possibility of severe systemic infection.

Optimal BCG therapy depends on the appropriate use and understanding of the basic principals of this immune modulator. BCG must have direct contact with the tumor cells. Furthermore, the tumor burden should be minimized prior to therapy and an adequate number of viable bacteria must be used. Although complete response rates of 60% or more have been reported for BCG treatment of residual Ta or T1 TCC, it is best to resect as much tumor as possible before the onset of treatment (5). Toward this end, the use of vaportrodes to eradicate a large bulk of tumor is beneficial. The best dose of BCG has yet to be defined, however, there are current recommendations for the 2 commercially available preparations (TheraCys-Connaught, and TICE-Organon) (7). The usual doses advocated are 81 mg of TheraCys or 50 mg of TICE BCG in 50 cc normal saline instilled through a catheter. We typically wait 2 weeks after TUR before beginning treatment with BCG. Once the BCG has been instilled, we ask the patients to hold the instilled fluid in their bladders for approximately 2 hours, and have them change positions frequently in order to distribute the medication throughout the bladder. It is important to be sure that the patient can do this. We not infrequently see patients who say they have failed therapy using BCG but, by our standards, we believe that they have never been adequately treated.

To date, there is no completely accepted schedule of administration for BCG. It has, however, been shown that approximately 50% of patients will not be successfully treated by a single 6-week course of BCG. A Southwest Oncology Group (SWOG) study compared 2 treatment arms. Arm 1 consisted of an induction course of 6 weekly treatments with BCG. Arm 2 consisted of the same induction course followed by 3 months off-therapy, and a subsequent maintenance protocol in which BCG was administered once weekly for 3 weeks. This maintenance protocol was repeated every 6 months for 3 years. Comparing the 2 treatment arms, complete response was increased from 68% to 84% when a single maintenance regimen was utilized (5). Long-term disease-free status and, most important, patient survival were increased as well when the 3 weekly maintenance courses were employed (1). The largest response rate differences was apparent at month 3, at the time when the first maintenance treatment was administered.

The toxicity of this treatment must be considered when deciding on the best BCG schedule. In the SWOG study cited above, significant toxicity requiring cessation of therapy, decreased dose or administration of isoniazid (INH) therapy, occurred for 26% of patients receiving maintenance therapy as compared to only 9% of those receiving BCG induction alone ($p<0.0001$).

Taking the above information into consideration, it appears that some patients will benefit from maintenance BCG therapy. However, for patients who are receiving BCG due to “failed” intravesical chemotherapy for low-grade tumors, the increased risk of toxicity encountered using maintenance therapy may not be justified. In this population, it seems reasonable to use either a 6-week induction courses or a 6-week induction followed by a 3-weekly course at 3 months. However, if a patient has CIS and/or a T1 grade 3 tumor, maintenance should be attempted. This is especially true if the patient has tolerated the induction course without significant toxicity. Recently, the question of whether or not to biopsy at the 3-month period after the initial BCG treatment has been examined in detail. Routine biopsy was part of the SWOG study cited above and tends to be carried out in general practice. However, this procedure is uncomfortable for the patient and is very expensive. Dalbagni et al., from Memorial Sloan-Kettering reviewed 81 of their patients who had undergone routine biopsy at 3 months after BCG treatment (8). They found that 58% of these patients had a complete response (negative biopsy) at 3 months and that a negative cystoscopy correlated well with a negative biopsy. However, only 10% of patients who had erythematous lesions had a positive biopsy. Therefore, the authors advocate evaluating the need for biopsy combining the cystoscopic appearance of the bladder and the results from cytological examination. If the patient has a normal-appearing bladder or has erythema with a negative urine cytology, biopsy is deferred at the 3-month period. However, this group still biopsies all patients at 6 months. The question can thus be raised

about the usefulness of the biopsy at 6 months. It is necessary? Can one avoid biopsies altogether? At present no data exists to support not biopsying these patients. It is to be hoped that such data will be available soon to help us to identify those who can avoid a routine biopsy as part of follow-up.

Our current protocol for BCG treatment is as follows: For patients who do not have CIS and who do not have recurrent tumors at the first cystoscopy 3 month following resection, we do not perform biopsies and we follow these patients with standard 3-monthly cystoscopies. If however, the initial lesion was especially aggressive-appearing (Stage T1, Grade 3 multifocal lesions with or without CIS), or if there is concomitant CIS, we will obtain a biopsy. If that is negative, we wait 2 weeks and give a 3-week course of BCG. If the resected tumor was less aggressive, we administer a 3-weekly course of BCG that is initiated at the first 3-month cystoscopy following resection, providing that this first cystoscopy is clear of tumor. We then repeat cystoscopy at 6 months. If this is clear, we do not give BCG at this time, but wait for the 9-month cystoscopy and then repeat the 3-weekly course of BCG (Table-3).

We are presently reviewing all of our cases to try and develop reliable data to allow us to reduce the number of biopsies.

Treatment with BCG, one of the most effective agents against superficial bladder cancer, can result in a wide range of side effects, and the toxicity of this drug must be recognized. Some of the symptoms associated with the use of BCG are relatively minor and common, whereas others are more serious and must be treated promptly. For example, cystitis is the most frequent side effect of BCG therapy, and may be seen in up to 90% of patients. Dysuria and urinary frequency are also expected symptoms due to the inflammatory response to BCG therapy, but these symptoms are usually not present until the 3rd or 4th treatment. Most often, these latter symptoms will resolve within 24 hours and acetaminophen, pyridium and/or anticholinergic medication may be of some help. However, severe irritative voiding symptoms, or those lasting more than 72 hours can be treated with 300 mg per day of isoniazid (INH). This treatment can be continued for 1-2 weeks or until the symptoms have been resolved (7). It is however unnecessary to administer continuous treatment with INH. Some physicians advocate giving 300 mg INH one day prior to subsequent BCG instillations and continuing for 3 days after treatment with BCG (5). BCG treatment should not be repeated until all side effects from the previous treatments have resolved. This is especially true of hematuria, which can occur in approximately 20-35% of patients.

Other, non-life-threatening symptoms, which may occur in about 20% of patients, include malaise, fatigue, and lethargy. A low-grade fever of less than 101 degrees Fahrenheit can also be seen in approximately 10-15% of patients, but this usually is resolved within 24 hours. It is important to distinguish these less severe and short-lived side effects from the more serious symptoms of systemic infection.

Any patient who develops a fever of greater than 103 degrees Fahrenheit should be hospitalized and treated for BCG sepsis. Other symptoms include shaking chills and hypotension. Sepsis, although rare, can be fatal if not treated quickly. The current recommendations for treatment are INH 300 mg, rifampin 600 mg, and prednisone 40 mg, daily. Blood cultures need to be obtained and broad-spectrum antibiotics should be administered until the culture results are returned. Frequently, however, with BCG sepsis, blood cultures can be negative. Treatment with

Table 3 - *Schedule for BCG treatment*

Time period after initial tumor resection	Cystoscopy	BCG treatment
2 weeks	No	6-week induction
3 months	Yes, +/- biopsy	3-weekly maintenance
6 months	Yes	No
9 months	Yes	3-weekly maintenance

prednisone should be given until sepsis resolves and then the dose should be tapered for 1-2 weeks. The INH and rifampin are generally continued for 3-6 months. Patients who have experienced BCG sepsis should not receive BCG again.

INTERFERON

We will not discuss treatment with interferon due to its expense. Because of the relative ineffectiveness of this agent, we no longer employ it in the treatment of TCC.

CONCLUSIONS

To summarize our practice regarding intravesical therapy for superficial bladder cancer, we would like to stress the following points:

For patients at low risk of progression, we initially resect the tumor and do not treat with intravesical therapy.

For patients at low risk of progression but with high risk of recurrence, (e.g., those with high grade TCC that are either stage Ta or stage T1), we treat with an immediate single post-TUR dose of thiotepa of 30 mg (off protocol).

For recurrent, low risk tumors, we treat with a course of thiotepa.

For patients with a high risk for progression (e.g., those with high grade TCC and stage T1), we administer a 6-week course of BCG.

For patients at high risk for progression, where the next tumor recurrence would indicate a cystectomy, we will treat with a 6-week course of BCG followed by maintenance.

It is to be hoped that in the future molecular markers will better define the risk groups for recurrence and progression of TCC. Ideally, such markers will also serve to define the appropriate choice of intravesical therapy for this disease.

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GENETIC POLYMORPHISMS OF GENES GSTM1 AND CYP2D6 AND BLADDER CANCER

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ABSTRACT

Objective: To study the relationship between GSTM1 and CYP2D6 polymorphisms and exposure to risk factors, and the occurrence of bladder cancer.

Patients and Methods: The study included 77 patients with fully characterized transitional cell carcinoma of the bladder, from whom a complete history was taken, and 191 healthy individuals, who served as controls for the genetic assessment. Using a polymerase chain reaction technique, GSTM1 polymorphisms were studied in all patients and controls, and CYP2D6 polymorphisms were studied in 53 patients and 99 controls. Chi-squared test was used for statistical analysis.

Results: GSTM1 null genotype was detected in 75.3% of patients and in 57.1% of controls, and the difference was statistically significant ($\chi^2 = 7.79$; $p = 0.005$). This difference was due exclusively to individuals with tumors Ta/T1 (81.5% were GSTM1 deficient, $\chi^2 = 10.7$; $p = 0.001$). More smokers (85.7%) than non-smokers (62.8%) demonstrated the GSTM1 null phenotype ($\chi^2 = 5.36$; $p = 0.02$), and 95.8% of heavy smokers (> 40 pack-year) were GSTM1 null. Familial history of tumors was associated with GSTM1 null: 91.7% of patients with familial history versus 67.9% without such history showed the null phenotype ($\chi^2 = 5.01$; $p = 0.02$). Patients and controls were not significantly different in respect to frequency of CYP2D6 polymorphisms. Among patients, no significant association between CYP2D6 polymorphisms and tumor characteristics was found.

Conclusions: GSTM1 null genotype seems to be associated with bladder tumor occurrence, particularly "superficial" tumors (Ta/T1). This association is stronger in individuals with exposure to tobacco smoke. CYP2D6 gene does not seem to play any significant role in bladder tumor development.

Key words: bladder, bladder cancer, malignancy susceptibility, genetic polymorphisms, GSTM1, CYP2D6
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INTRODUCTION

Susceptibility to cancer is thought to depend on interplay between genetic factors and environmental chemical carcinogens. The xenobiotic-metabolising machinery includes oxidative enzymes (phase-I), which may inactivate carcinogens or, eventually, activate compounds to become carcinogenic, and phase-II conjugating enzymes, considered mainly protective since they detoxify a number of reactive chemical carcinogens (1).

Some enzymes involved in the metabolism of xenobiotics are polymorphically expressed on a Mendelian hereditary basis. Thus, different individuals (and different populations) may be differently affected by the exposure to risk factors. Recent works have addressed the issue that susceptibility to many cancers (including bladder cancer) may vary according to polymorphisms of the genes CYP2D6 and GSTM1. The gene CYP2D6 encodes for a phase I enzyme of the cytochrome P450 superfamily, the debrisoquine hydroxilase, whose substracts include aromatic amines and tobacco nitrosamines (2). Five to 10% of Caucasians are recessive homozygous, and are termed poor metabolizers (in opposition to extensive metabolizers, whom can be homozygous or heterozygous) as they are unable to metabolize various substances. The issue on the implications of

CYP2D6 polymorphisms, in bladder cancer is not settled. Some researchers did not find any relation between CYP2D6 polymorphisms and bladder cancer (3,4,5), others concluded for an increased risk of aggressive bladder cancer in extensive metabolizers (6), and others for an increased risk in extensive metabolizers who are simultaneously GSTM1 deficient (7). Glutathione-S-transferases (GSTs) are phase-II enzymes with many functions, including detoxification of polycyclic aromatic hydrocarbons from tobacco smoke and aromatic amines (8,9). Glutathione-S-transferase M1 (GSTM1), a member of the GSTs superfamily, is polymorphic in humans, and about 50% of Caucasians have the null genotype, and are devoid of GSTM1 enzymatic activity. Several studies have pointed out that individuals with the null phenotype are in greater risk of developing bladder cancer (3,7,10,11). However, this matter is still under debate, and other workers did not find such a relation (12,13).

In this study, GSTM1 and CYP2D6 polymorphisms in bladder cancer patients were studied, and results were compared with those found in a community-based sample of healthy volunteers.

PATIENTS AND METHODS

The study population comprised 77 patients (60 males, 17 females) with transitional cell cancer (TCC) of the bladder and 191 healthy volunteers, who served as controls for the genetic characterization. Patients and healthy volunteers were Caucasians from the center of Portugal. After giving informed consent, all patients answered a standardized questionnaire pertaining smoking habits (non-smoker / smoker / ex-smoker; number of pack-years smoked [one pack-year meaning 7300 cigarettes smoked]), alcohol consumption (considered excessive if superior to 100g per day), medications, exposition to known risk factors for bladder cancer (chemicals, motor exhaust, etc.), and history of tumors in first and second degree relatives. All relevant data about the disease, like age at diagnosis, T-category and grade of the tumor [UICC], occurrence of relapses and their characteristics, were transcribed into a data sheet. Peripheral blood samples were collected from all patients and healthy volunteers into tubes with Na_2EDTA at pH8, and genotyping of the GSTM1 locus (77 patients and 104 healthy volunteers) and of the CYP2D6 locus (53 patients and 99 healthy volunteers) was done using a polymerase chain reaction (PCR) technique in a Omnigene® equipment. DNA was extracted by standard manual methods (14-16). Three primers were used for GSTM1 (P1: 5´-CGCCATCTTG TGCTACATTGCCCG-3´; P2: 5´-ATCTTCTCCTC TTCTGTCTC-3´; P3: 5´-TTCTGGATTGTAGCAGA TCA-3´) (9). P1 and P3 amplify a 230 base pairs (bp) product specific for the GSTM1 gene. P1 and P2 can anneal to either GSTM1 or GSTM4 genes and originate a 157bp product used as internal control. Each PCR reaction mixture comprised approximately 50 ng of isolated DNA, 2.5 µl of 10x PCR buffer (final concentration: 50 mM KCl, 10 mM Tris-HCl pH 8.4, 1.5 mM $MgCl_2$), 0.2 mM of each nucleotide (dATP, dTTP, dGTP, dCTP), 1.25 ml of 5% DMSO, 25 ng of primers P1 and P2 and 50 ng of P3 and 0.5 U of Taq DNA polymerase, to a final volume of 25 ml. A total of 30 PCR cycles with denaturation at 94ºC for 60 sec, annealing at 52ºC for 60 sec and extension at 72ºC for 60 sec was performed. An initial DNA denaturation stage at 95ºC and a final stage with annealing at 52ºC and extension at 72ºC were performed for five min each. In order to detect the G→A transition at the junction of intron 3/exon 4 of the CYP2D6 gene, a 334bp fragment that encompasses that spot was obtained by PCR (17). Two primers were used (P1: exon 3: 5´-GCCTTCGCCAA-CCACTCCG-3´; P2: intron 4: 5´-AAATCCTGCTCTTCCGAGGC-3´). Reaction mixture was as described previously, but to a final volume of 50 ml. After an initial denaturation cycle of 10 min at 96ºC, 1 U of Taq DNA polymerase was added and 30 PCR cycles were performed consisting on DNA denaturation at 94ºC for 60 sec, annealing at 60ºC for 30 sec, and extension at 72ºC for 2 min. A final polymerization extension at 72ºC for 10 min was accomplished. The CYP2D6 products were digested at 60ºC over-night with BstNI restriction enzyme. PCR products were separated on an ethidium bromide stained 2% agarose gel for GSTM1, or on a 5% polyacrylamide gel followed by ethidium bromide staining for CYP2D6. Visualization was accomplished with an UV transiluminator. The CYP2D6 normal allele produces two fragments of 105 and 229 bp by

digestion. G→A transition affects the restriction sequence and a unique fragment of 334 bp is observed. Heterozygous individuals display two bands corresponding to the restricted normal allele and a third band from the mutated allele. GSTM1 genotype is termed active when a 230 bp and a 157 bp bands are present and null if the 230 bp is absent. The chi-squared (χ^2) test was used for statistical analyses.

RESULTS

Mean age of the patients at diagnosis was 66.7 years ± 10.6 (standard deviation, SD). Age extremes were 36 and 85, and 71.4% were older than 60 years. Fifty-four (70.1%) tumors were "superficial" (Ta-T1) and 23 (29.9%) were invasive (≥ T2). There were 23 (29.9%) well-differentiated tumors (G1), 37 (48%) moderately differentiated (G2), and 17 (22.1%) poorly differentiated (G3). Among the 54 patients with "superficial" tumors, there was no history of relapses in 32 (63%). Nine (16.7%) had had one relapse, and 11 (20.3%) two or more relapses. There was no case of evolution to invasive tumor at relapse. Thirty-five patients (45.4%) had never smoked, and 42 (54.6%) were currently (22; 28.6%) or had been (20; 26%) smokers. Among the 42 patients with smoking history, the mean pack-years smoked was 43.8 ± 36.6 SD (2-200). The majority (24; 57.2%) were heavy smokers (> 40 pack-year); ten (23.8%) had smoked < 20 pack-year, and 8 (19%) between 20 and 40 pack-year. Seven (9.1%) had history of contact with genotoxics, and 17 (22.1%) recalled excessive alcohol intake. Family history of tumors (1st - 2nd degree relatives) was present in 24 (31.2%) patients, in four cases (5.2%) the tumor being a bladder cancer. The GSTM1 null genotype was detected more commonly in the diseased population altogether (75.3%) than in the healthy individuals (57.1%), and this difference was statistically significant (Table-1). Among patients with invasive tumors, the distribution of the polymorphisms was similar to that of the control group (Table-2). On the other hand, 44 (81.5%) of the 54 patients with "superficial" tumors had the null genotype, an even higher difference to the control group ($\chi^2 = 10.7$, $p = 0.001$; Table-2). Sub-dividing the patients with "superficial" tumors into 2 groups (with and without relapses), the sub-group without relapses demonstrated a higher degree of statistical difference to the controls ($p = 0.005$) than the ones with history of relapses ($p = 0.047$; Table-2). The null genotype was detected in 69.5%, 78.4%, and 76.5% of the patients with tumors well, moderately, and poorly differentiated, respectively. However, statistically significant difference to the control group was achieved only by grouping patients with G2 and G3 tumors ($\chi^2 = 7.64$, $p = 0.006$; Table-2). Patients with "superficial" tumors and "invasive" tumors were marginally different to each other in respect to GSTM1 polymorphisms ($\chi^2 = 3.68$, $p = 0.054$). The comparison of GSTM1 polymorphisms in smokers (current and ex-smokers) and non-smokers revealed that there were more smokers than non-smokers with the null genotype, the difference being statistically significant (Table-3). Further, the sub-division of smokers in 2 groups showed that much more heavy smokers than light smokers had the null genotype

Table 1 *- Comparison of GSTM1 genotypes in patients and healthy individuals*

	GSTM1 +	GSTM1 -	χ^2	p
Control population	82	109	7.79	0.005
Patients	19	58		

Table 2 *- Comparison of GSTM1 genotypes in the control population and in sub-groups of patients, defined in accordance with tumor characteristics*

	GSTM1 +	GSTM1 -	χ^2	p
Control population	82	109		
Patient sub groups:				
Ta/T1 tumor	10	44	10.7	0.001
≥ T2 tumor	9	14	0.12	0.73
Ta/T1, relapsing	4	16	3.90	0.047
Ta/T1, no relapses	6	28	7.75	0.005
G 1	7	16	1.32	0.25
G 2/3	12	42	7.64	0.006

Table 3 - *Relationship between smoking habits and GSTM1 polymorphism*

	GSTM1 +	GSTM1 -	χ^2	p
Non-smokers	13	22	5.36	0.02
Smokers	6	36		
Smokers < 40 PY	5	13	4.68	0.03
Smokers ≥ 40 PY	1	23		

(Table-3). Patients with family history of tumors were significantly more prone to have the null phenotype than patients without ($\chi^2 = 5.01$, $p = 0.02$). CYP2D6 polymorphisms frequency in the patients was not significantly different from that of the control population (Table-4). No significant differences were

Table 4 - *Comparison of CYP2D6 genotypes in patients and healthy individuals*

	EM	HET	PM	χ^2	p
Control population	61	31	7	2.22	0.32
Patients	37	15	1		

EM = extensive metabolizer, HET = heterozygote, PM = poor metabolizer

detected even after sub-division of the diseased population in sub-groups according to tumor characteristics (Table-5). There was a strong positive association between invasiveness and poor

Table 5 - *Comparison of CYP2D6 genotypes in the control population and in sub-groups of patients, defined in accordance with tumor characteristics*

	EM	HET	PM	χ^2	p
Control population	61	31	7		
Patient sub groups:					
Ta/T1 tumor	24	8	-	3.25	0.19
≥ T2 tumor	11	4	1	0.85	0.30
Ta/T1, relapsing	12	3	-	2.30	0.31
Ta/T1, no relapses	12	5	-	1.40	0.49
G 1	12	4	-	1.70	0.42
G 2/3	23	8	1	1.33	0.51

EM = extensive metabolizer, HET = heterozygote, PM = poor metabolizer

differentiation of the tumor (4.3% of G1, 24.3% of G2 and 76.5% of G3 tumors were invasive; $\chi^2 = 25.32$, $p = 0.0001$). On the other hand, no significant association between tumor differentiation or tumor invasiveness and smoking habits was detected.

DISCUSSION

The results of the present study strongly suggest that lack of activity of the GSTM1 gene is associated with the occurrence of bladder cancer. These results were achieved by comparing the genetic polymorphisms detected by PCR in a diseased population and in a control population, matched for ethnic and geographic origin. This requisite is essential, as polymorphisms show inter-ethnic, and even inter regional variations (12). In this study, absence of GSTM1 activity was detected in 57.1% of our control population, a value higher than the reported in several other studies (3,7,9,10,13), although identical to others (3,18). Patients with invasive (≥ T2) tumors demonstrated a GSTM1 null genotype frequency similar to controls: 60.9% and 57.1%, respectively. Division of the patients with "superficial" tumors in those with and without history of relapses revealed a stronger statistically significant difference to controls in the no relapses group (Table-2). However, given that 80% of the patients with history of relapses showed the null phenotype versus only 57.1% of the control population, it is likely that it was the small number of patients with history of relapses that have prevented the achievement of a stronger statistical significance in this group. Okkels et al., in a case control study involving 234 patients, detected association between GSTM1 deficiency and bladder tumors only in the group with "prevalent benign" tumors (meaning Ta or Tis (in situ) tumors with a long evolution) (9). Although not directly comparable, in both studies the association of GSTM1 null genotype with bladder tumor was more apparent in the group with less aggressive tumors. This distinction between patients with more or less aggressive tumors may be in accordance with recent studies that demonstrated distinct molecular defects in these different types of tumor, and that point to

different genetic pathways in the evolution from normal epithelium to "superficial" or invasive tumors (19). Our study design precludes for estimating the odds of developing bladder tumor in individuals exposed to risk factors such as tobacco smoke or alcohol. However, once smokers demonstrated a significantly higher frequency of the GSTM1 null genotype than non-smokers, and that the heavier the smoking history was, the higher was the probability of being GSTM1 null (Table-3), our data agree with previous studies suggesting that the GSTM1 null genotype increases the risk for bladder cancer only in individuals who smoke (9). Like others (3,6,11), we observed that variability in CYP2D6 activity does not seem to be relevant in respect to bladder tumor development. Anwar et al. found that the extensive metabolizer genotype increased the risk further in individuals with the GSTM1 null genotype (7), but the combined analysis of our results does not sustain this conclusion.

CONCLUSION

The GSTM1 null genotype seems to be associated with bladder tumor occurrence, particularly "superficial" tumors (Ta/T1), and this association is stronger in individuals with exposure to tobacco smoke. CYP2D6 gene does not seem to play any significant role in bladder tumor development.

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THERAPY FOR ADVANCED AND HORMONE REFRACTORY CANCER OF THE PROSTATE

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ABSTRACT

Cancers of the prostate are categorized as follows: 1)- hormone-naive (never having previously received hormone manipulation); 2)- androgen-dependent (having received hormonal manipulation but a less than continuous application, i.e., intermittent androgen blockade or with an agent that does not produce a castrate testosterone level, i.e., antiandrogen); 3)- androgen independent (progressive disease when serum testosterone levels are in the castrate range) but still potentially responsive to other hormone therapy, i.e., second line hormone therapy; 4)- hormone-independent or hormone refractory (progressive disease when castrate serum testosterone levels have been documented and one or more further hormonal manipulations have failed).

Here in, we present an extensive review of current modalities of therapy for advanced and hormone refractory cancer of the prostate. This revision includes a discussion of how hormone therapy should be delivered, when hormone therapy should be delivered, and appropriate monitoring for response in androgen-independent disease.

The chemotherapy and other strategies for hormone refractory prostatic cancer are discussed and we present the guidelines of the National Comprehensive Cancer Network for standard chemotherapy options. A discussion on the state of the art palliative radiotherapy as an alternative or adjunct to chemotherapy is presented. Finally, we present the new areas of research in advanced prostatic cancer, including vaccines, antibodies, gene therapy, anti-angiogenesis therapy, antisense therapy and blocking signal transduction

Key words: prostate, prostate cancer, advanced, therapy, hormone refractory
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INTRODUCTION

The definition of advanced prostate cancer is in evolution. Classically, patients with advanced prostatic cancer are those with node (N1, M1a) or visceral (M1c) or bone metastases (M1b). However, clinical stage T3 and T4 disease at diagnosis and pathologic T3 (extra-capsular extension, seminal vesical extension) after radical prostatectomy could reasonably be included in the category of advanced prostate cancer. An argument could also be made for including patients with a pretreatment PSA > 20 ng/ml and / or a high Gleason sum (> 8), as they have a diminished probability of organ-confined prostate cancer and are at higher risk for eventual disease recurrence. PSA monitoring after therapy has further modified the definition of advanced disease to include patients with a rising PSA after androgen deprivation even among those patients where there is absence of clinical or radiological disease.

When discussing advanced carcinoma of the prostate and potential treatment options, it is important to categorize disease status accurately. An outline developed by Scher (1) is very useful in segregating the heterogeneous advanced prostate cancer population into subgroups that have clinical relevance with regard to treatment choice and treatment response. Cancers of the prostate are categorized as follows: 1)- hormone-naive (never having previously received hormone manipulation); 2)-

androgen-dependent (having received hormonal manipulation but a less than continuous application, i.e., intermittent androgen blockade or with an agent that does not produce a castrate testosterone level, i.e., antiandrogen); 3)- androgen independent (progressive disease when serum testosterone levels are in the castrate range) but still potentially responsive to other hormone therapy, i.e., second line hormone therapy (2); 4)- hormone-independent or hormone refractory (progressive disease when castrate serum testosterone levels have been documented and one or more further hormonal manipulations have failed). A rather intriguing and newly recognized circumstance documents that the initial hormonal regimen will, at times, determine the response to subsequent hormonal manipulations (3). As an example, patients who had failed combined androgen blockade with an LH-RH analogue and Flutamide responded more frequently to a trial of the antiandrogen Casodex (150 mg) than did a group of patients who had progressed after androgen deprivation with an LH-RH analogue alone.

HOW SHOULD HORMONE THERAPY BE DELIVERED?

In 1999, hormone naive patients with N+/M+ disease are usually treated by androgen deprivation by either combined androgen blockade or monotherapy to achieve castrate "T" levels. Two large clinical trials one from the EORTC (#30583) and one from the NCI (#036) reported a statistically significant survival benefit for combination therapy when compared to monotherapy (4,5). The rationale for blocking adrenal androgens is the potential for conversion of the large amounts of adrenal DHEA to DHT (6). A very important subsequent NCI trial (#0105) of more than 1,300 patients demonstrated that there was no statistically significant advantage in survival or time to progression between orchiectomy combined with the antiandrogen Flutamide versus orchiectomy + placebo (7).

The NCI INT-0105 trial was initiated in December 1989 (7). Accrual was completed in September 1994. It was a prospective study of the relative benefits of combined androgen blockade and monotherapy based on extent of disease for patients randomized to orchiectomy plus placebo or orchiectomy plus Flutamide. With 1,378 patients accrued, this trial represents the largest to date to study the benefits of combined androgen blockade. This trial was constructed to answer objections raised by the NCI INT-0036 trial. They were that daily subcutaneous injections of leuprolide might have driven a subclinical period of disease progression "flare", and that flutamide in the combination arm only served to block flare.

Based on the results of the NCI INT-0036 trial, the NCI INT-0105 trial was constructed to have a 90% power at a 0.05 level of significance (one sided) to detect a 25% improvement in survival from a median of 28.3 months (death hazard ratio of 1.25). Information regarding treatment benefits for the subgroup of patients with minimal disease was considered of vital importance as this subgroup of patients currently represents the majority of men with M1 disease as a result of the early complete radiologic evaluation triggered by a rising PSA profile.

For most physicians caring for patients with metastatic prostate cancer who based their treatment recommendations to employ complete androgen blockade on the results of NCI trial 0036 published in the New England Journal of Medicine in 1989 which showed a survival advantage to combined androgen blockade, the final publication of NCI 0105 trial 10 years later was quite startling, disturbing and confusing for urologist and patient alike. By the parameters used to construct the trial there was no statistical advantage to orchiectomy plus flutamide versus orchiectomy alone. While the trial did show an approximately 10% survival difference in favor of the combination, this did not reach statistical significance because the trial had been powered to demonstrate a 25% difference in survival between the two arms, a difference comparable to the 0036 trial published 10 years previously. However a difference as large as 20% between the two groups could be missed. NCI 0105 had been constructed to randomize patients by performance status and extent of disease to either monotherapy or combined therapy, to test the validity of the hypothesis that patients with minimal disease would derive the greatest advan-

tage from combined androgen blockade as had been noted in trial 0036. However, in NCI 0105 there was no statistically significant advantage to the combination for the good performance and minimal disease subgroups. Again this outcome illustrated the danger of extrapolating post trial sub analysis, no matter how logical or attractive, to standard practice without confirmation as a primary question in a subsequent randomized trial.

An interesting caveat to consider is the possible consequence of cross over to flutamide at the time of failure among patients taking placebo which was permitted by trial design. Could this have favorably modified the control arm survival outcome so as to reduce the difference between the 2 arms? The NCI 0105 trial analysis also provided critically important information about the biomarker prostate specific antigen. This was the first large trial to systematically include PSA as a marker of tumor status and response and to correlate its profile with survival endpoints. There was a statistically higher incidence of normalization to a PSA < 4.0 ($p = 0.018$) in the combination arm. This intuitively might lead to the prediction that a better clinical and survival outcome was assured. If PSA response were truly a surrogate for survival, then this statistically significant reduction in PSA in the combination arm would predict a survival benefit for this arm. This was not the case and therefore in the context of a large perspective randomized trial, which is the only mechanism for assigning surrogate endpoints, this discordance between PSA response and survival rendered PSA invalid as a surrogate endpoint. In fact the discussion of results contained the statement “PSA has no role as surrogate marker for survival in patients with metastatic prostate cancer”.

The NCI 0105 trial was also unique in the fact that it measured quality of life parameters and therefore was able to assess the incremental morbidity, if any, of combination therapy as compared to monotherapy. A separate publication analyzing quality of life issues has been reported (8). A sobering conclusion was reached. Patients on the combination arms suffered a statistically higher incidence of gastrointestinal effects, anemia, and abnormality of liver function tests. In this setting the patients receiving combination of orchiectomy and flutamide not only failed to achieve a response benefit, but also paid a price both economically, the additional cost of the antiandrogen, and qualitatively with depreciation in quality of life. The attention to quality of life in this clinical trial is especially important because hormonal treatment of metastatic disease can be considered largely palliative rather than curative. Since relief of symptoms may be brought about at the expense of some treatment related toxicity it is important that overall quality of life is maintained, namely the treatment will not worsen the patient’s current status. As was done in this trial, quality of life measurement should be gathered through patient reported instruments.

Metaanalysis is a methodology to investigate the overall conclusions that can be drawn from a number of trials addressing the same questions with disparate outcomes and/or a methodology to combine the results of a number of small trials to gain statistical power for determining differences that these small trials, individually, are unable to detect. There are several metaanalyses dealing with combined androgen blockade that warrant discussion. The largest was conducted by the Prostate Cancer Trialists collaborative group (9,10). Twenty-two of the 25 possible trials that could be included were subject to metaanalysis and the results were published in 1995. The NCI 0105 trial data was not included as it was in the process of accrual. Individual data for 5,710 patients, 87% of whom had metastatic disease were obtained. At the time of the study 52.7% of patients had expired. No statistical benefit to combined androgen blockade was recorded. The overall mortality among patients randomized to castration alone was 58.4% compared with 56.3% among those randomized to combined androgen blockade. When patients were grouped by type of castration or type of antiandrogen therapy, no significant difference between subgroups was detected. A separate analysis of patients with M0 and M1 disease did not alter the results.

The five-year survival estimates were 22.8% for castration alone versus 26.2% for combined androgen blockade. This absolute difference of 3.5% was not statistically significant. Although a large

improvement in survival among patients with advanced disease had been excluded by this study, the existence of a more moderate benefit was not. The Prostate Cancer Trialists Collaborative Group plans to update results with inclusion of new studies and extended follow-up of existing studies.

While the first cycle of the analysis in 1995 found that combined androgen blockade gave no survival advantage with the caveat of larger confidence limits which did not exclude the possibility of a small improvement the latest results effectively eliminate significant benefit from combined androgen blockade.

The Ontario Cancer Treatment Practice Guidelines Initiative suggested that the Prostate Cancer Collaborative Group metaanalysis had a series of methodological weaknesses (11,12) in data collection and statistical decisions. The Canadian group conducted a metaanalysis based only on published data (20 studies) and showed a clear benefit in 2-year survival with combined androgen blockade over castration alone.

Yet another metaanalysis evaluated the current outcome of nine clinical trials, which had in common the use of flutamide as the antiandrogen. This study also included the NCI 0105 trial. The analysis of 4,128 patients demonstrated a 10% difference between monotherapy and combined therapy and this effect size was statistically significant (13). It is of interest that the NCI 0105 trial indeed had found a 10% survival benefit with flutamide; however the NCI 1015 trial had been sized to detect a larger difference, 25%, parallel to the difference of the first NCI study. However with more subjects and more events the same difference was statistically significant in the combined androgen blockade with flutamide metaanalysis!

A recently updated European metaanalysis of trials using combined androgen blockade by orchiectomy ± showed that nilutamide added to orchidectomy significantly reduced the odds for disease progression by 17% and death from any cause by 16% compared with orchidectomy alone (14,15). Lastly, an Agency for Health Care Policy and Research report was completed in 1999 (16). It concluded that there is no statistically significant difference in survival at 2 years between patients treated with combined androgen blockade or monotherapy. However metaanalysis of the limited data available shows a statistically significant difference in survival at 5 years in favor of combined androgen blockade. The magnitude of this difference is of uncertain clinical significance.

An important question is, therefore, raised; namely, the choice between surgical castration as monotherapy or combination therapy by medical castration and an antiandrogen. Androgen deprivation will variably decrease the quality of life of the asymptomatic patients, e.g., hot flashes, lethargy, loss of vigor and interest and libido, weight redistribution. In some circumstances, these quality of life issues will lead to cessation of androgen deprivation or intermittent androgen deprivation as an alternative protocol. Using initial medical castration, which is reversible, permits this option. In addition to the unpleasant short-term side effects of androgen deprivation long-term morbidity, including osteoporotic fracture have been reported. The option for an intermittent androgen deprivation regimen and rather than surgical castration is a viable option. When employing medical castration to this purpose the results of the NCI 036 trial and the EORTC 30583 trial support the addition of an antiandrogen.

Intermittent androgen therapy has garnered interest recently based on the work of Bruchovsky et al. (17). They have demonstrated that quality of life is improved by cycling androgen deprivation and avoiding the continuous morbidity/side effects of the regimen. The effect of this strategy on overall survival outcome is unknown; however this question is being addressed by a Phase III prospective randomized trial by the Southwest Oncology Group (#9346). The trial randomizes patients who have achieved a normal serum level (< 4.0 ng/ml) of PSA after a seven month induction period of combined androgen blockade to either continuous androgen deprivation or to the withdrawal of androgen deprivation with repetitive recycling based on PSA defined trigger points. Another multigroup clinical trial will test continuous or intermittent androgen deprivation for patients with a rising PSA after external beam radiotherapy.

WHEN SHOULD HORMONE THERAPY BE DELIVERED?

The question of appropriate timing of hormonal therapy has witnessed pendulum swings since the sentinel work of Huggins & Hodges (18). Initially, based on comparison with historical series, before the recognition of the pitfalls of using historical controls, early hormone therapy was recommended. The VACURG trials changed this practice and the pendulum swing to the opposite direction; namely, deferring therapy until symptomatic progression. It is important to recognize that these trials, while randomized, were not designed to answer the specific question of timing of androgen deprivation and were influenced by the significant cardiovascular effects of the hormone therapy employed, DES 5 mg/day. Nevertheless, they directed opinion towards deferring therapy. It should be noted that Byar, the VACURG statistician, in his 1973 review stated that "these data support the concept that treatment can be delayed" (19). He did not state that the data irrefutably concluded that therapy should be delayed. A later review of the VACURG trials by Byar did raise the possibility that early hormone therapy could be beneficial (20). The current delivery of androgen deprivation therapy with pharmaceutical agents much less toxic than DES and which avoid the psychological impact of surgical castration has once again raised the issue of appropriate timing. To delay therapy assumes that the results of therapy can be initiated at a later date without any detrimental loss. The medical research council of Great Britain investigated this issue and the results are noteworthy. A large randomized trial accrued 938 patients (21). The pertinent findings were as follows: a)- progression from M0 to M1 disease was significantly delayed among patients who received initial treatment; b)- among patients with M1 disease, bone pain was delayed if initial treatment was given; c)- local progression was more rapid in the deferred than in the initially treated group and transurethral resection of the prostate was more frequently necessary in the deferred group; d)- a statistically significant increase in extraskeletal metastasis and ureteral obstruction was noted in the deferred group. These results are consistent with the anticipated ability of androgen deprivation to delay disease progression. Of major importance was the increased incidence of spinal cord compression among the patients whose therapy was deferred. Of specific interest was that 19 of the 23 patients who were randomized to deferred treatment developed spinal cord compression after hormonal therapy had been started for another indication. In other words, the event of spinal cord compression was not a result of failure to follow or recognize its presence, but a failure of delayed therapy to effectively prevent it. This finding challenges the premise that has been used to justify delayed androgen deprivation; namely, that delayed therapy in the long-term would produce results similar to initially administered therapy. Also, of major importance was the finding that both cause-specific and overall survival of those patients treated initially was superior to those receiving deferred therapy. The benefit was specifically important for those patients with M0 disease. Critiques of the study read as follows: a)- PSA monitoring was not employed and for those patients who wish to avoid initial therapy with androgen deprivation and the pace of disease activity could be assessed by a period of PSA monitoring to determine the need or wisdom of therapy, b)- a protocol of intermittent androgen deprivation could have been employed, c)- quality of life instruments were not measured, d)- approximately 10% of patients who died from prostate cancer did so before receiving hormone therapy. Rebuttal statements include the nonavailability of PSA at trial initiation and the fact that patients with initial androgen deprivation suffered fewer complications of spinal cord compression, pathologic fractures, and obstructive events intuitively translates to improved quality of life. Without the defined monitoring provided by a clinical trial protocol, the patients in routine practice who fail to receive necessary androgen deprivation are unknown. In fact this unfortunate circumstance might be best addressed by the earlier administration of androgen deprivation therapy.

MONITORING FOR RESPONSE IN ANDROGEN-INDEPENDENT DISEASE

In order to evaluate treatments for androgen-independent disease it is necessary to identify response by selection of measurable endpoints. The

well-recognized difficulty in assessing such a response with prostate cancer is the infrequency of measurable metastatic disease (and when such measurable soft tissue disease is present, the applicability of its response to a more common osseous disease is questionable). PSA remains the most consistently used benchmark for establishing a response to therapy. Observation of PSA declines clarified the Flutamide withdrawal syndrome and later the responses to withdrawal of other antiandrogens. The antiandrogen withdrawal (AAW) effect first described in 1993 is now an well-accepted phenomena (22) and AAW represents the first therapeutic option for any patient failing combined androgen blockade. These observations also reawakened the possibility that subsequent second and third line hormonal maneuvers could be successful. Therefore the following pathways are reasonable considerations: a)- if CAB has been the initial therapy then withdraw the antiandrogen, b)- if monotherapy has been the initial therapy then add an antiandrogen, c) if failure occurs while receiving one antiandrogen change to another antiandrogen. Antiandrogen withdrawal has already been discussed. Fowler has reported (23) the benefit of adding flutamide to patients failing monotherapy. Armed with this information, exploratory trials by Liebertz (24) and later Joyce (25) reported that patients who failed combined androgen blockade, had a response to Flutamide withdrawal and, subsequently, failed once again demonstrated another response to Casodex. It is clear that antiandrogens are not identical in their mechanism of action, although they belong to the same antiandrogen drug class, namely, nonsteroidal antiandrogens. Also, it seemed logical that with AAW, a certain number of androgen receptors might be again exposed to unblocked adrenal androgens and that the response to AAW could be enhanced by adding an agent to block adrenal androgens. Thus the addition of aminoglutethimide or Ketoconazole to antiandrogen withdrawal has demonstrated an increase in the overall PSA response to 50 to 60% compared to the 20 to 30% response with AAW alone (26). Ketoconazole, low dose prednisone and DES 1.0 mg daily are effective in reducing PSA and alleviating symptoms in some patients and are worthwhile second line hormonal therapies to apply in selected circumstances. A number of patients are taking PC SPES (P.C. = prostate cancer; spes = hope) either as primary or second line therapy. A recent publication analyzed the components of PC SPES and found it to contain a number of estrogenic compounds (27). Both its therapeutic effect (decrease in PSA levels) and its adverse effects (DVT, CHF, gynecomastia/dynia) are consistent with this finding.

The interest in second line hormonal therapy was obvious at the 1999 American Society of Clinical Oncology meeting where several abstracts describing hormone strategies were presented (28,29).

A great deal of activity has centered around the development of strategies for disease which no longer responds to hormonal manipulation and is classified as hormone refractory. Chemotherapeutic agents are being reinvestigated. Interest also has developed in cytostatic agents rather than cytotoxic therapy. These new strategies avoid cell destruction in favor of cell manipulation and redirection. Assuming that a cancer is a normal cell with a number of aberrant characteristics, pharmacological agents that can force the aberrant cell towards a more disciplined cell cycle are quite attractive. Recently significant insight into the biologic activity of single agent and combination cytotoxic therapy based on monitoring PSA have appeared.

CHEMOTHERAPY AND OTHER STRATEGIES

At University of Michigan we believe that a decrease of pretreatment PSA by 50% is a useful predictor for survival and disease response for most drugs, however, a Phase III trial to accurately answer this question is needed. We looked at the relationship between PSA response with soft tissue disease response in 115 androgen independent prostate cancer patients who had chemotherapy with oral estramustine and oral etoposide as part of a phase II trial and demonstrated a strong correlation between PSA response and shrinkage of measurable tumors as well as increased survival for patients who decreased their PSA by greater than 50% from their baseline value (30).

PSA response has also been researched as a possible marker of prognosis and survival, i.e., a prognostic factor. Researchers at Memorial Sloan

Kettering analyzed the PSA response in 110 patients at that institution (31). They found a longer average survival for patients who experienced at least a 50% decline in PSA. In fact, this greater than a 50% decrease in PSA was one of the most significant variables that could actually predict how long a patient could survive with androgen independent prostate cancer. Another study from the National Cancer Institute analyzed the PSA response in 50 androgen independent prostate cancer patients (32). They found that 15 patients experienced a greater than 75% decrease in PSA. The average survival for this group was about 21 months. This value was significantly different ($p = 0.003$) from the non-responders whose average survival was about 6.9 months. A clinical trial of suramin in androgen independent prostate cancer showed a 1-year survival rate of 80% in patients with a greater than 75% decrease in PSA versus 20% for those without this response. In a trial of estramustine phosphate and vinblastine, patients who experienced a PSA decrease of greater than 50% on three successive measurements at least two weeks apart were found to have a significantly prolonged overall and progression free survival (33). However, it is important to mention that not all studies have found the same association. In two phase I studies of suramin, a PSA decrease did not predict for increased survival (34).

It is important to note two other special points or misconceptions about PSA in the hormone refractory setting. First, each person's hormone refractory tumor makes a different amount of PSA. In early disease we can use a PSA of 4 ng/ml as an upper limit of normal to screen for cancer. This is not true in the androgen independent setting. Patients in the androgen independent setting may have a small amount of cancer and a high PSA or a large amount of cancer and a low PSA. This is also mirrored clinically, i.e., we have patients in our clinic with a PSA of < 10 who have many bone metastases and need narcotics to control their pain. We have other patients with PSAs of > 1000 who have no pain. Therefore, there is no absolute PSA level, which correlates with symptoms.

Several researchers have looked for other prognostic factors in an attempt to explain differences in survival. Factors associated with decreased survival have included: increasing age, presence of bone pain, decreasing performance status, increased levels of blood LDH and SGOT, decreased levels of blood albumin, and low hemoglobin. Currently, however, there is no exact pretreatment prognostic factor, which can be used to accurately predict survival or patient response to treatment. Though the treatment of hormone refractory prostate cancer has improved dramatically, there is still no therapy that has been demonstrated to improve survival. The first choice of treatment for patients with hormone refractory prostate cancer, therefore, is still a clinical trial.

CONTINUED ANDROGEN SUPPRESSION

A controversial area in the treatment of androgen independent prostate cancer has been the role of continued androgen ablation. A retrospective review of patients enrolled in chemotherapy trials for androgen independent disease concluded that continued androgen ablation was not a significant factor in patient survival (35). However, another review showed a modest survival advantage for patients with continued testicular androgen ablation. Also, many patients feel more secure staying on hormone therapy. It is reasonable in the evaluation of new therapies for hormone refractory prostate cancer that patients maintain androgen ablation including LH-RH agonists.

NCCN GUIDELINES (NATIONAL COMPREHENSIVE CANCER NETWORK) FOR STANDARD CHEMOTHERAPY OPTIONS

The NCCN, an organization of cancer centers from around the country committed to promoting the best interests of cancer patients, recently updated their practice guidelines for the treatment of androgen independent prostate cancer. The guidelines published by this organization are rapidly evolving to be the standards of care for cancer treatment. The guidelines for the relief or palliation of androgen independent prostate cancer, outside of experimental protocols, list three different areas of care: a)- Supportive care usually with prednisone and other drugs, b)- Local and/or systemic radiation, c)- Palliative chemotherapy (Table).

Table - *National Comprehensive Cancer Network (NCCN) practice guidelines: hormone refractory prostate cancer.*

REGIMEN	SCHEDULE
Supportive Care	
Prednisone	7.5 - 10 mg/d
Dexamethasone	0.75 mg/bid
Chemotherapy	
Ketoconazole	1200 mg/d
Doxorubicin	20 mg/m^2 IV over 24h each week
Vinblastine	4 mg/m^2/week/for 6 weeks
Estramustine	600 mg/m^2/d for 42 days
Etoposide	50 mg/m^2/d for 21 days
Estramustine	10 mg/kg/d for 21 days
Mitoxantrone	12 mg/m^2 IV every 21 days
Prednisone	10 mg/d
Paclitaxel	120 mg/m^2 IV over 96h every 3 weeks
Estramustine	600 mg/ m^2/d continuously
Radiotherapy	
Standard external-beam radiation	
Strontium 89	

Supportive Care and Steroids

Currently, no drug combination has been shown to increase survival for androgen independent prostate cancer in a randomized phase III trial. Therefore, supportive care is a reasonable and logical alternative to active treatment. This should involve: aggressive pain management, aggressive control of symptoms, and hospice care if desired.

Glucocorticoids like prednisone have been used frequently to manage symptoms in advanced prostate cancer patients and many studies have shown improved symptom control and increased quality of life in patients. In one study, 40% of patients given low dose prednisone (7.5 - 10 mg/day) experienced objective improvement in pain control and 20% experienced improvement in overall quality of life. Another study using low dose dexamethasone (0.75 mg twice a day) showed improved symptom control in 63% of patients (36).

Recently, the use of bisphosphonates, drugs which alter bone metabolism, have regained popularity in relieving bone pain for advanced prostate cancer. The use of these drugs will probably increase over the next few years.

Chemotherapy (Sometimes called "Palliative" Chemotherapy)

The NCCN guidelines recommend that two drugs be used in combination. The drugs suggested were chosen based on demonstrated anti-cancer activity and acceptable toxicity and include: ketoconazole and doxorubicin; estramustine and vinblastine; estramustine and etoposide; mitoxantrone and prednisone; estramustine and paclitaxel.

Ketoconazole (Nizoral) and Doxorubicin (Adriamycin)

The combination of doxorubicin and ketoconazole has been evaluated in a phase II trial (37). Thirty-nine patients who had progressed following initial hormone ablation therapy were treated with weekly infusions of doxorubicin (20 mg/M^2 over 24 hours) and daily ketoconazole (1,200 mg daily). Patients received hydrocortisone only at the time of developing clinical adrenal insufficiency; 63% required this intervention at some time during the therapy. A PSA decrease of more than 50% was seen in 21 of 38 (55%) patients. Seven of the 12 patients (58%) with bi-dimensionally measurable disease showed a partial response. Twenty-nine percent of the patients developed significant complications like acral erythema (redness of the hands and feet) and stomatitis (mouth sores). These symptoms resolved when the doxorubicin was stopped. The doxorubicin was started again and the symptom did not return. Also, 2 patients with a history of heart disease died suddenly while on this therapy. One other patient experienced congestive heart failure. Seventeen patients (45%) required hospitalization for complications.

Vinblastine (Velban) and Estramustine (Emcyt)

Vinblastine has shown little response as a single agent in androgen independent prostate cancer. Single agent estramustine phosphate in androgen independent prostate cancer has shown response rates of 0 - 20% and is an approved drug by the Food and Drug Administration for patients with hormone refractory prostate cancer. The combination of vinblastine and estramustine demonstrated enhanced tumor killing in preclinical models. Vinblastine (4 mg/ M^2) given weekly with estramustine phosphate (600 mg/ M^2 or 10 mg/kg) daily for 6 weeks followed by a 2 week rest period has been tested in clinical trials (4). Response rates of 14 - 40% were demonstrated for patients with bi-dimensionally measurable disease. PSA decreases of more than 50% were found in 54 - 61% of patients, and this therapy was well tolerated. One trial showed that patients who experienced a greater than 50% decline in PSA on 3 separate occasions had significantly increased overall and progression free survival (38).

Etoposide (VP - 16, VePesid) / Estramustine (Emcyt)

Both drugs were given orally (estramustine 15/mg/kg/daily in 4 divided doses and etoposide 50 mg/ M^2/daily in 2 divided doses) for 3 weeks with a 1-week rest period. Of the 18 patients with bi-dimensionally measurable disease, 50% had objective responses: 3 complete and 6 partial. A PSA decrease of greater than 50% was demonstrated in 55% of patients. Estramustine caused significant nausea in about 30% of patients and 2 patients had to withdraw from the study because of this problem. A second trial used a lower dose of estramustine (10 mg/ kg/daily). This trial had 62 patients and demonstrated a PSA decrease of greater than 50% in about 40% of the patients and objective partial responses in 8 of 15 (53%) patients with measurable disease. Less nausea, because of the decreased estramustine dose, was noted. Average survival was around 14 months. A third trial using an even lower dose of estramustine (140 mg, 3 times a day) with etoposide (50 mg/M^2/ day) in 56 patients demonstrated similar results, 45% of the 33 patients with bi-dimensionally measurable disease had an objective response: 5 complete and 10 partial responses. A PSA decrease of greater than 50% was seen in almost 60% of patients. Average survival was about 13 months. The combined results of the above 3 trials showed soft tissue responses in about 45 - 55% of patients, PSA decreases of greater than 50% in about 40 - 60%, and average survival of 52 - 56 weeks.

Currently, it is our practice to treat patients with 280-mg estramustine 3 times a day and etoposide 50 mg 2 times a day. Patients are told to take the estramustine with food while avoiding calcium rich products (milk, yogurt, ice cream, calcium containing antacids, and calcium supplements or other supplements and multivitamins with calcium can interfere with absorption of these drugs). This combination produces only mild nausea and is generally well tolerated.

Mitoxantrone (Novantrone) and Prednisone

Mitoxantrone is similar in its structure to doxorubicin. Early studies of mitoxantrone given alone demonstrated modest activity with the drug being well tolerated. A phase II study of 27 patients using mitoxantrone (12 mg/M^2 IV every 21 days) and prednisone (10 mg/day continuously) was started. The primary end points used were quality of life, pain levels, and analgesic or pain medication use. A complete response was the elimination of all disease-related symptoms. A partial response was defined to be a 50% decrease in pain medication (analgesic) use with no increase in pain, a decrease by 2 points in a six point pain scale with no increase in analgesic use. Progression was defined as either: an increase in analgesic use, an increase by one in the 6 point pain scale, or new bone pain requiring palliative radiotherapy. Using the above criteria, 36% of patients experienced a complete response, 44% experienced a partial response, and 20% had stable disease. Overall, there was a modest decrease in analgesic usage. Quality of life analyses showed decreases in pain throughout treatment and social functioning also improved. However, there was no improvement in global quality of life. Serious side effects was limited to neutropenia (a decrease in the number of a type of white blood cell that fights infection); however, no patients required hospitalization.

A larger, randomized Phase III trial using similar endpoints and definitions of response compared the combination of mitoxantrone (12 mg/M^2 every 21 days) and prednisone (10 mg/day continuously) to prednisone alone (39). In this trial of 161 men with androgen independent prostate cancer the primary endpoint was achieved in about 30% of the mitoxantrone/prednisone patients and 12% of the prednisone only patients. The average duration of response for the mitoxantrone/prednisone group was 43 weeks, which was significantly longer than the prednisone alone group (18 weeks). Patients who demonstrated a response had significant improvement in quality of life scales measuring global overall well being. This study and a similar Phase III study led to the approval of the combination of mitoxantrone/prednisone as a treatment for hormone refractory prostate cancer by the Food and Drug Administration.

Paclitaxel (Taxol) and Estramustine (Emcyt)

These 2 drugs have been shown to inhibit the way cancer cells divide. A phase II trial of paclitaxel alone in 24 patients with androgen independent disease demonstrated only one objective response. It is important to note that the combination of paclitaxel and estramustine phosphate has demonstrated tumor killing in both animal and human prostate cancer cell lines. One study looked at this combination in a trial using estramustine phosphate (600 mg/M^2/day continuously) and paclitaxel (120 mg/M^2 by 96 hr infusion every 21 days) in 34 patients. Four of nine (44%) of patients with measurable disease (2 of 3 patients or 66% had liver metastasis and 2 of 6 patients or 33% had lymph node disease) showed an objective response. A PSA decrease of more than 50% was achieved in 17 of 32 (53%) of patients. An average response time was about 37 weeks with an average survival time of about 69 weeks. The combination of paclitaxel and estramustine is now being tested in several other combinations. For example, Phase II trials where the paclitaxel is given every 3 weeks or even weekly have demonstrated early and promising results. These dosage schedules should make it to the clinic very rapidly.

PALLIATIVE RADIOTHERAPY AS AN ALTERNATIVE OR ADJUNCT TO CHEMOTHERAPY

Spot Radiation and Systemic Radiation with Strontium-89 (Metastron)

The majority of patients with hormone refractory disease do not have soft tissue disease. Rather, they develop metastasis to the bones. Autopsy studies done on patients with advanced prostate cancer have shown that the frequency of bone metastasis is between 65 - 100%. Skeletal metastasis can decrease a patient's quality of life in many ways.

External beam radiation therapy has been shown to be effective in controlling symptoms in a specific area. Strontium-89 (Metastron) follows the same path as calcium and so finds it's way to the bones where there is increased bone mineral production. This feature helps to minimize bone marrow suppression. In patients with advanced prostate cancer, partial relief of symptoms was demonstrated in 53 - 80% of patients. Complete pain relief was experienced in 10 - 22% of patients. In fact, the largest study of patients treated with strontium-89 showed not only symptom relief, but also decreased use of pain medication (analgesics), increased mobility and an improved quality of life (40). A randomized trial of palliative local radiotherapy with or without adjuvant strontium-89 showed a long-term benefit for combined therapy with strontium-89. Local symptom control was not improved; however, patients treated with strontium-89 had a significantly lower rate of developing new painful bone lesions (41% versus 66%) and those who developed new lesions had fewer of them. One potential side effect of strontium therapy is that it can lower the platelet count and, therefore, subsequent chemotherapy can be more toxic. Therefore we generally give strontium after our chemotherapy options have failed.

NEW CHEMOTHERAPY COMBINATIONS, CLINICAL TRIALS, AND AREAS OF RESEARCH OVER THE NEXT FIVE YEARS (41)

Estramustine (Emcyt) / Docetaxel (Taxotere)

Docetaxel is a similar drug to paclitaxel and the combination of estramustine and docetaxel has

been demonstrated to be very effective in preclinical models. In a recent study 33 patients were treated with estramustine 280 mg orally 3 times per day for 5 days and then with docetaxel, 60 - 80 mg/m^2 on day 2 every 21 days intravenously. Sixty three percent of the patients demonstrated a drop in their pretreatment PSA of > 50%. Five of 18 patients with soft tissue disease demonstrated a response to therapy. In another study of 12 patients treated with estramustine 280 mg orally 3 times per day for 5 days and 70 mg/M^2 on day 2 every 3 weeks, 92% of the patients demonstrated a response by PSA and 3 of 4 patients (75%) with soft tissue disease demonstrated a response. In a third study of 17 patients, 14 patients demonstrated a PSA response (82%). In all of these trials, toxicity was not extensive. The combination of estramustine and docetaxel will be studied in a Phase III trial comparing this regimen to the combination of prednisone and mitoxantrone.

Estramustine (Emcyt) / Etoposide (VP-16, Vepesid) / Paclitaxel (Taxol)

Since the combinations of estramustine and etoposide and estramustine and paclitaxel were so effective, there was good rationale to combine all three of these drugs into one regimen. In a phase II trial combining estramustine 280 mg orally 3 times per day for 14 days every 21 days and etoposide 50 mg/M^2 for 14 days every 21 days with paclitaxel (135 mg/M^2 over 3 hours on day 2), showed an improved response rate compared to the dual drug combinations: estramustine and etoposide alone. Of 40 patients, approximately 70% had a PSA decrease of greater than 50% and in the patients with measurable disease, 66% had a partial response. Toxicities included hair loss and decreased blood counts.

Cyclophosphamide (Cytoxan), Diethylstilbestrol (DES), and Prednisone

The combination of oral cyclophosphamide, diethylstilbestrol (DES), and prednisone was tested in 54 patients with hormone refractory disease at the University of Michigan. All of the patients had previously failed combined androgen ablation and had evidence of rising PSA following antiandrogen withdrawal. A decrease in pretreatment PSA by more than 50% was seen in almost 40% of patients; the average length of the response was 6 months. Two of 6 patients (33%) with measurable disease showed a partial response. This triple combination was well tolerated by patients. This combination appears to be an active and well tolerated combination against androgen independent prostate cancer.

Adriamycin (Doxorubicin) / Ketoconazole (Nizoral) alternating with Vinblastine (Velban) / Estramustine (Emcyt)

This regimen has been tested extensively at the M.D. Anderson Cancer Center and forms the backbone of many of their current clinical trials. The regimen is a bit difficult to follow because the treatment cycle is 56 days. This regimen was demonstrated to have a PSA response rate of 67% and a soft tissue response rate of 75%. Side effects were manageable, with 50% of the patients experiencing swelling in the legs and 18% DVT.

Suramin

Suramin was the first in a new class of drugs that inhibit growth factors (also called growth factor antagonists). It has been shown to inhibit the interaction between growth factors and their receptors to inhibit enzymes that help DNA to grow and replicate, inhibit angiogenesis, and inhibit growth in some prostate cancer cell lines. At least 6 clinical trials have already been published. These trials have demonstrated a response rate ranging between 10 – 50%. Recently suramin was rejected by the Food and Drug Administration as an agent for treatment for hormone refractory disease. The status of suramin for use in hormone refractory prostate cancer patients is unclear.

NEW AREAS OF RESEARCH

Vaccines, Antibodies and Gene Therapy

Lymphocytes fight infection from viruses and destroy cancer cells. They do this in 2 major ways. The first is through the T cells, which destroy cancer cells directly. A second is through the B cells, which, when they come across a foreign cell, produce antibodies. These antibodies attach to the cancer cell and activate another set of cells, the macrophages destroy

it. Since our B cells do not seem to recognize cancer very well, several researchers are trying to find prostate cancer specific antigens or proteins that are found on the surface of prostate cancer cells only. Gene therapy may enhance T and B cell activity.

Antibodies

Antibody trials will become more available over the next few years. Almost all of the current trials are by attaching a radioactive isotope to the antibody the prostate cancer cell and nearby cancer cells. Early phase trials usually test the antibody alone and later trials test the antibody with radioactivity.

Anti-Angiogenesis Therapy

All new tumors need new blood vessels to grow and no concept has more excited the scientific community and the public than anti-angiogenesis. Preclinical laboratory results with the drugs angiostatin and endostatin are provocative and although these drugs will not be ready for clinical trial soon, several trials of other anti-angiogenesis agents are already underway in the Phase I and Phase II trials.

Antisense Therapy

Proteins maintain the structural integrity of cells and organs and serve as catalysts for biological reactions (enzymes). The biological computer program that codes for proteins is contained within the nucleus of each cell in the deoxyribonucleic acid (DNA) molecule in the form of genes. Protein production takes place in 2 steps known as "transcription" and "translation". In the nucleus, a gene for a protein is copied or "transcribed" into an intermediary molecule termed messenger RNA (mRNA). mRNA travels to the cytoplasm of the cell where it is "translated" into amino acids, the basic building blocks of proteins. Cancer, like many diseases, is associated with inadequate or inappropriate production or performance of proteins. Antisense technology involves the use of synthetic segments of DNA or RNA called oligonucleotides to stop the production of such disease-related proteins. Antisense compounds block the transmission of genetic information between the nucleus and the protein production sites within a cell by binding specifically with the messenger RNA and effectively jamming its genetic signal, thereby preventing the production of disease-associated proteins. To do this, scientists synthesize a length of DNA with a sequence of bases complementary to the messenger RNA. The DNA is a mirror image (antisense) of a portion of the messenger RNA (sense). The antisense DNA is taken up by the cell. The DNA binds to the messenger RNA because its sequence is designed to be an exact complement of the target sequence. Once the 2 strands bind, the messenger RNA can no longer dictate the manufacture of disease-associated protein in the ribosome. It is also marked for rapid breakdown by the cell's enzymes, thereby freeing the antisense oligonucleotide to seek and disable another identical messenger strand of RNA.

Blocking Signal Transduction

Signal transduction pathways are the chemical pathways by which messages are transmitted into a cell, through its cytoplasm, to its nucleus. The nucleus then acts on the messages that those signals give it. Research over the past 20 years has reinforced the view that cancer is associated with the damage, loss, or amplification of specific genes. Of the numerous cancer related genes (oncogenes) identified to date, many appear to be abnormal versions of signaling pathway components, such as growth factors, tyrosine kinases (TKs), serine-threonine kinases (STKs), or molecules associated with the ras oncogene. Many scientists are trying to develop drugs and therapies based on blocking the abnormal signal transduction pathways of cancer.

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IMMUNOHISTOCHEMICAL STAINING FOR p53 PROTEIN IN PATIENTS WITH LOCALIZED PROSTATE CANCER

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ABSTRACT

Purpose: To assess the incidence of positive staining for p53 protein in localized prostate cancer and to relate these results to clinical and histopathologic staging parameters.

Material and Methods: The retrospective study was made using 72 samples of surgical material. Patients were screened in an outpatient basis and underwent radical prostatectomy after staging of localized prostate cancer. Protein p53 was detected by immunohistochemical staining. Patient average age was 64.2 years. PSA values varied from 1.8 to 5.7 ng/ml, and were over 4.0 ng/ml in 93% of the cases. Of the studied patients, 22.2% were in clinical stage T3, and 30.6% had a Gleason score equal or over 7.

Results: Positive nuclear reaction for p53 was detected in 6.9% of the cases, but none of them presented homogenous reactivity throughout the slide. Among the patients whose Gleason score was equal to or over 7, 13.6% showed positive reactivity for p53, while among the patients who had a Gleason score lower than 7, only 4% had positive reaction. However, these values had no significant statistical difference ($p = 0.386$, Fisher exact test). There were no significant statistical differences between positivity for p53 and the levels of pre-surgery PSA or the Gleason score values.

Conclusion: These results indicate that immunohistochemical positivity for p53 protein correlates poorly with prostatic cancer.

Key words: prostate, p53 protein, prostate cancer, prognosis, immunohistochemistry
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INTRODUÇÃO

O câncer de próstata tem recebido atenção especial por ser a neoplasia mais freqüente após os 50 anos de idade nos países ocidentais (1,2). A alta freqüência desta doença justifica os esforços na busca do aperfeiçoamento de métodos de detecção precoce e de marcadores prognósticos, com a conseqüente melhora no planejamento terapêutico. Como acontece com outras neoplasias, tem sido constatada a importância de mutações na carcinogênese e na progressão da doença. O acúmulo da proteína p53 no núcleo das células tumorais, tem sido apontado como mutação importante na carcinogênese e na progressão neoplásica. Este evento está fortemente associado a mutações puntiformes no gene TP53, sendo estas alterações as lesões genéticas mais freqüentemente observadas nos diferentes tipos de câncer, incluindo as neoplasias urológicas (3-6). Alterações no produto deste gene podem ser detectadas por técnica imuno-histoquímica, que se baseia na evidência de que a meia-vida da proteína p53 mutada está aumentada, podendo ser detectada nas células neoplásicas (7). Vários estudos apontam a expressão da proteína p53 alterada como um marcador independente na evolução dos carcinomas de mama, cólon, reto, pulmão e próstata (8).

O objetivo deste trabalho foi avaliar retrospectivamente a freqüência de reações imunohistoquímicas positivas para a proteína p53 em tumores de próstata, em pacientes submetidos à prostatectomia radical e examinar a relação com variáveis clínicopatológicas.

MATERIAL E MÉTODOS

Foram estudadas 72 peças cirúrgicas de prostatectomia radical, do arquivo de material do Instituto de Pesquisas Cito-Oncológicas da Fundação Faculdade Federal de Ciências Médicas Porto Alegre (FFFCMPA). Os pacientes foram atendidos no ambulatório do Serviço de Urologia do Complexo Hospitalar da Santa Casa de Misericórdia de Porto Alegre, no período compreendido entre 1993 e 1997, E submetidos à prostatectomia radical por adenocarcinoma da próstata, estádios T1N0M0 e T2N0M0.

Os espécimes cirúrgicos foram submetidos a cortes seriados, compreendendo fatias com 0,5 cm de espessura de toda a glândula, obedecendo à rotina e ao protocolo do Departamento de Patologia do Instituto de Pesquisas Cito-Oncológicas da FFFCMPA. O material foi previamente embebido em tinta nanquim para melhor identificação e avaliação das margens cirúrgicas. As fatias representativas dos cortes macroscópicos foram submetidas a inclusão em parafina para realização de cortes histológicos de 3 m de espessura e coradas pela hematoxilina-eosina. Uma vez estabelecido o diagnóstico pelo patologista, foram separados os blocos de parafina das áreas neoplásicas a serem estudadas.

A gradação histológica foi estabelecida segundo os critérios de Gleason (9). A reação imunohistoquímica para a detecção do acúmulo da proteína p53 obedeceu ao protocolo usado no Instituto de Pesquisas Cito-Oncológicas da FFFCMPA. Os cortes histológicos foram desparafinizados e hidratados em concentrações decrescentes de etanol e lavados em água destilada. O material foi colocado em uma solução de citrato (pH = 6,0) e levado ao forno de microondas em temperatura média-máxima por 15 minutos, sendo após retirado e deixado em repouso à temperatura ambiente por 15 minutos. Após adicionar sobre o material uma solução tampão PBS (pH = 7,6) procedeu-se ao bloqueio da peroxidase endógena, incubando-se os cortes em uma solução a 3% de peróxido de hidrogênio em metanol, por 30 minutos à temperatura ambiente. Em seguida, procedeu-se um ciclo de lavagem com água destilada e incubou-se o material por 30 minutos numa solução contendo 4% de soro normal em PBS. O anticorpo primário anti-p53 (DO-7, Dako A/s, Dinamarca), foi preparado a uma diluição 1:50 em PBS e incubado com os cortes durante 12 horas em câmara úmida. Após um novo ciclo de lavagens os cortes foram novamente colocados em câmara úmida para a incubação, por 30 minutos, com o anticorpo secundário biotinilado de camundongo anti-IgG (Vectastain, Vector Lab., CA, USA) diluído 1:600 em PBS. Após outro ciclo de lavagens, o material foi incubado em câmara úmida por 60 minutos com o complexo avidina/biotina (Strepto ABC, Vectastain, Vector Lab. CA, USA), com diluição 1:800 em PBS. A coloração da reação da imunoperoxidase foi realizada por meio da imersão, por 8 minutos, em uma solução contendo o cromógeno DAB (tetra-hidrocloreto de 3,5-diamino-benzidina) e peróxido de hidrogênio. Após lavar em água corrente foi realizada a contra coloração com hematoxilina de Harris (Merck, Darmstadt, Alemanha), por 2 minutos. A cada grupo de cortes submetidos à análise foram incluídos controles positivos e negativos. A leitura da reação foi feita em microscópio óptico e foram observados os critérios para positividade utilizados por outros autores, ou seja, um percentual mínimo de 5% de células coradas, por campo de grande aumento (X400) (7,10).

Os grupos de pacientes com reação positiva ou negativa ao antígeno p53 foram comparados quanto às variáveis estudadas por testes não paramétricos: U de Mann-Whitney e exato de Fisher. O nível de significância adotado foi de p = 0,05 e as análises foram executadas com o auxílio do programa SPSS V6.0.

RESULTADOS

A idade dos pacientes variou de 40 a 74 anos, com uma média de 64,2 anos. A distribuição dos níveis de PSA variou de 1,8 a 57,0 ng/ml, sendo que em 93 % dos casos o PSA foi superior a 4,0 ng/ml.

O estádio clínico T3 foi identificado em 22,2% (16/72) dos pacientes e o escore de Gleason, foi igual ou superior a 7 em 30,6% (22/72) dos casos. De maneira consistente com os dados da literatura, os estádios clínicos mais avançados foram acompanhados pelos valores da gradação histológica de Gleason mais elevados (Tabela-1).

***Tabela 1** - Distribuição dos dados de estádio clínico e da mediana do escore de Gleason dos 72 casos.*

Estádio	N	Mediana dos Escores de Gleason
T2a	17	3 (2 a 7)
T2b	13	5 (5 a 7)
T2c	26	5 (2 a 9)
T3a	2	8 (5 a 10)
T3c	14	7 (5 a 10)

Entre os 72 casos analisados, 6,9% (5/72) apresentaram reação nuclear positiva. Em nenhum destes casos a positividade foi homogênea em toda a lâmina (Figura-1). Embora 22 pacientes tivessem escore de Gleason maior ou igual a 7, apenas 13,6%

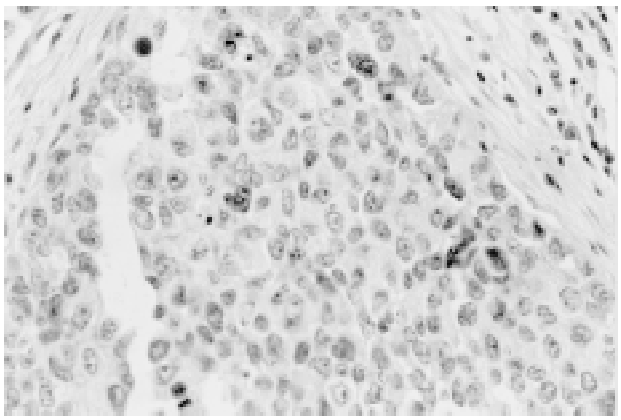

***Figura 1** – Núcleos de células neoplásicas, apresentando reação imuno-histoquímica positiva para a proteína p53, em áreas de pouca diferenciação (imunomarcação, X400).*

(3/22) apresentaram reação p53 positiva. Os pacientes com o escore menor que 7 tiveram apenas positividade de 4,0% (2/50) e estes índices não foram significativos (p = 0,386; teste exato de Fischer) (Tabela 2). Não foi observado associação significativa entre a positividade para o antígeno p53 e os níveis de PSA pré-cirúrgico (p = 0,515; Mann-Whitney) ou os valores do escore de Gleason (p = 0,137, Mann-Whitney) (Tabela-3).

***Tabela 2** - Freqüência dos casos com reação imuno-histoquímica positiva ou negativa para p53 em relação ao escore de Gleason.*

Escore de Gleason	Reação Imuno-histoquímica p53	
	Positiva	Negativa
≥7	13,6% (3/22)	86,4% (19/22)
< 7	4,0% (2/50)	96,0% (48/50)

p = 0,386

***Tabela 3** - Distribuição da mediana e da amplitude dos valores do PSA pré-cirúrgico (ng/ml) e dos valores da graduação histológica de Gleason dos casos com reação imuno-histoquímica positiva ou negativa para a proteína p53.*

Fatores	Reação Imuno-histoquímica p53		p
	Positiva	Negativa	
PSA	16,1 (7,9 - 45,3)	12,0 (1,8 - 57,0)	0,515
Gleason	5 (7 - 10)	3 (5 - 10)	0,137

DISCUSSÃO

A história natural do carcinoma de próstata mostra comportamento biológico heterogêneo, variando de uma forma indolente até uma forma agressiva com ocorrência de metástase precoce (1,11).

Os mecanismos que levam o tumor de próstata a se desenvolver ainda são pouco conhecidos. Os esforços na elucidação dos mecanismos moleculares do processo da carcinogênese prostática, não identificaram nenhum marcador biológico que esteja ligado aos estádios iniciais. Surge, por essa razão, a necessidade da realização de pesquisas para identificar um marcador que possa oferecer melhores informações prognósticas do que as rotineiramente usadas e que são baseadas na avaliação clínica e anatomopatológica.

Alguns autores descreveram uma associação significativa entre a alteração na expressão da proteína p53 nuclear e o câncer de próstata (10,12,13). Embora estes trabalhos tenham relacionado este fenômeno como um evento favorável no acompanhamento de pacientes com câncer de próstata submetidos a prostatectomia radical, existe um número significativo de outros estudos que não confirmam tais resultados (7,14-16). Por outro lado, são escassos os trabalhos desta natureza em nossa população.

Em nosso estudo observamos uma baixa freqüência de tumores apresentando acúmulo nuclear da

proteína p53 (6,9%). Esta observação está de acordo com diversos estudos que sugerem que a mutação do p53 é um evento tardio na carcinogênese prostática. A confirmação destes resultados, portanto, inviabiliza a utilização da detecção imuno-histoquímica desta proteína como um marcador independente, com propósitos prognósticos.

Entre as variáveis clinicopatologicas utilizadas na avaliação da evolução dos tumores, a gradação de Gleason é o parâmetro de melhor valor preditivo para definir o prognóstico de pacientes com adenocarcinoma de próstata. O escore igual ou maior que 7 indica pior prognóstico (17). Em nosso trabalho não pudemos demonstrar associação significativa entre a freqüência de reações imuno-histoquímicas positivas do p53 com esta variável (p = 0,137).

Apesar dos trabalhos publicados relacionando a proteína p53 e o câncer de próstata, o entusiasmo inicial, que adveio com a identificação do gene TP53, parece ter diminuído com o passar dos anos, arrefecendo a esperança de que este pudesse se tornar um marcador independente para evolução do carcinoma de próstata, pois a sua manifestação é de ocorrência tardia. O marcador ideal seria aquele que já demonstrasse positividade tecidual em estádios iniciais e assim pudesse prever o quadro evolutivo, melhor do que o fazem a graduação histológica pelo método de Gleason, o PSA, e o estadiamento TNM (18). Como a detecção imuno-histoquímica desta proteína mostra evidências de estar associada aos estádios avançados da doença, onde na maioria das vezes a graduação de Gleason é alta, o que sugere pior prognóstico, este evento perde o seu significado como um indicador preditivo independente de prognóstico.

Devemos assinalar, por outro lado, que a positividade pela imuno-histoquímica não indica necessariamente a presença de proteína mutada, já que ela pode acumular-se no núcleo por outras razões como, por exemplo, anormalidades em outros genes envolvidos no metabolismo e regulação do gene TP53 ou a presença de antígenos virais (19,20). Também, nem todos os tumores com mutação do gene TP53 serão detectados pela reação imuno-histoquímica. Alguns tipos de mutação podem resultar na expressão de uma proteína truncada que não apresentaria sítio antigênico para ser reconhecido pelos anticorpos comumente usados (20). Entretanto alguns estudos mostram que o acúmulo nuclear da proteína p53 correlaciona-se bem com a presença de mutações no gene TP53, sugerindo que esta técnica simples e rápida pode ser adequada a este tipo de estudo (21,22). Em nosso trabalho, foi realizada apenas a caracterização da positividade pela técnica imuno-histoquímica, não identificando-se a possível mutação.

Projeto de Pesquisa apoiado pela CAPES

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RESUMO

DETECÇÃO IMUNO-HISTOQUÍMICA DA PROTEÍNA P53 EM PACIENTES PORTADORES DE CARCINOMA LOCALIZADO DA PRÓSTATA

Objetivo: Avaliar a freqüência de reações positivas para a proteína p53, no câncer localizado de próstata e examinar a relação com os parâmetros de estadiamento clínico e anatomopatológicos.

Material e Métodos: Foram avaliadas retrospectivamente 72 peças cirúrgicas do arquivo de material do Instituto de Pesquisas Cito-Oncológias da Fundação Faculdade Federal de Ciências Médicas, de pacientes atendidos no ambulatório do Serviço de Urologia do Complexo Hospitalar da Santa Casa de Misericórdia de Porto Alegre e que foram submetidos à prostatectomia radical, tendo sido estagiados no pré-operatório como

portadores de carcinoma localizado. A detecção da proteína p53 foi realizada por meio de técnica imuno-histoquímica.

Resultados: A idade média dos pacientes foi de 64,2 anos. O valor do PSA foi superior a 4,0 ng/ml em 93% dos casos, apresentando uma amplitude de 1,8 a 57,0 ng/ml. Entre os pacientes da amostra, 22,2% estavam no estádio clínico T3 e 30,6% apresentaram escore de Gleason igual o superior a 7. A reação nuclear positiva para proteína p53 foi detectada em 6,9% dos casos, sendo que em nenhum deles a reatividade foi homogênea em toda a lâmina. Dentre os pacientes em que o escore de Gleason era igual ou superior a 7, 13,6 % manifestaram reatividade positiva para a proteína p53, enquanto que dos que tiveram o escore de Gleason inferior a 7, apenas 4 % demonstraram reação positiva. Estes valores, entretanto, não apresentaram diferenças estatisticamente significativas (p = 0,386, teste exato de Fisher). Da mesma forma não observamos diferenças estatisticamente significativas entre a positividade para a p53 e os níveis de PSA pré-cirúrgico ou os valores do escore de Gleason (p = 0,515 e p = 0,137, respectivamente, teste de Mann-Whitney).

Conclusão: Estes resultados mostram que a proteína p53, não é um marcador independente no câncer de próstata neste grupo de pacientes.

Unitermos: próstata, câncer de próstata, proteína p53, prognóstico, imuno-histoquímica
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METASTATIC ADENOCARCINOMA OF THE PROSTATE: COMPARISON BETWEEN CONTINUOUS AND INTERMITTENT HORMONAL TREATMENT

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ABSTRACT

Purpose: Continuous hormonal treatment is the standard procedure for stage D2 adenocarcinoma of the prostate. Experimental studies have shown that intermittent hormonal treatment (IHT) increases the response period to the treatment. However, few clinical studies have been carried out until now. In this study we compare the effects of continuous and intermittent hormonal treatment in patients with adenocarcinoma of the prostate.

Material and Methods: From 1994 to 1996, 43 patients with adenocarcinoma of the prostate were randomly divided into the following 2 groups: Group A, 18 patients submitted to continuous hormonal treatment (CHT); and Group B, 25 patients submitted to intermittent hormonal treatment (IHT). Both groups received 200 mg/day of cyproterone acetate. In the IHT group the cycle was suspended after reaching the PSA nadir, and was then restarted according to the initial PSA.

Results: In Group A, 11 patients (61.1%) completed the study. The average initial PSA was 32.3 ng/ml and the nadir was 0.4 ng/ml. Seven patients (38.8%) had side effects, 18 patients (100%) became sexually impotent, 7 (38.8%) became hormone resistant and 2 (11.1%) died. In Group B, 24 patients (96%) reached the 2nd cycle and 18 (72%) reached the 3rd. On average, each cycle lasted 10.2 months. Four patients (16%) became hormone resistant and 2 (8%) died. During the interval of the cycles, only one patient remained impotent.

Conclusion: In the period studied, IHT was as effective as continuous hormonal treatment but afforded a better quality of life and 96% of the patients were potent during the intervals between the cycles.

Key words: prostate, prostatic neoplasm, advanced disease, hormonal treatment
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INTRODUÇÃO

O tratamento de escolha para o adenocarcinoma de próstata metastático (estádio D) é o bloqueio hormonal (parcial ou completo). Além da orquiectomia, existem vários grupos de drogas que podem exercer a supressão hormonal, agindo tanto nos mecanismos centrais como nos periféricos, provocando a diminuição tumoral através do bloqueio da testosterona.

A maioria destas drogas tem efeitos colaterais importantes como o favorecimento dos fenômenos tromboembólicos, impotência sexual, distúrbios do trato gastrointestinal e respiratórios. Outro problema da hormônioterapia é que a grande parte dos tumores torna-se hormônio-resistente no período médio entre 18 e 36 meses, com progressão da doença e óbito em poucos meses (1,2).

Baseado em trabalhos experimentais e clínicos verificou-se que a inibição da apoptose é um dos mecanismos que torna a célula hormônio-resistente, além das possíveis alterações moleculares nos receptores de andrógenos, da clusterina, dos canais de cálcio e do bcl-2. O objetivo da terapia hormonal intermitente seria prolongar o tempo de resposta da célula tumoral ao hormônio (3-5).

Após a publicação do primeiro trabalho clínico sobre o tratamento hormonal intermitente (6),

poucos trabalhos clínicos subsequentes surgiram na urológica (7-12).

O objetivo desse estudo é comparar os resultados do tratamento e dos efeitos colaterais em pacientes submetidos à terapia hormonal contínua e intermitente, utilizando-se em ambos os grupos o acetato de ciproterona.

MATERIAL E MÉTODOS

Foram estudados prospectivamente entre 1994 e 1996, 43 pacientes com adenocarcinoma de próstata estádio D2, com idade entre 56 e 83 anos (mediana de 71,8 anos) e com atividade sexual. Os pacientes foram selecionados ao acaso, por sorteio, no momento do diagnóstico, em 2 grupos: grupo A com 18 pacientes submetidos a tratamento hormonal contínuo com acetato de ciproterona 200 mg/dia (2 comprimidos de 50 mg pela manhã, 1 comprimido à tarde e outro à noite); grupo B com 25 pacientes com tratamento hormonal intermitente, utilizando-se a mesma posologia do acetato de ciproterona.

Os pacientes incluídos no estudo não tinham realizado nenhum tratamento hormonal anterior e o tempo de observação para esse estudo foi de 48 meses ou até ocorrer escape hormonal. Todos os pacientes relataram atividade sexual no momento da anamnese de inclusão.

As características clínicas dos pacientes estudados encontram-se na Tabela-1.

Impotência sexual pré-tratamento e terapia hormonal anterior.

No momento do diagnóstico com comprovação de metástase óssea (mapeamento, radiografia, tomografia computadorizada ou ressonância nuclear magnética, foi introduzido o tratamento hormonal durante pelo menos 42 semanas, até atingir o nadir do PSA. O PSA e a testosterona total foram dosados de 2 em 2 meses.

Nos pacientes com PSA inicial £ 20 ng/ml a reintrodução do ciclo foi realizada quando o PSA atingiu o valor de 10 ng/ml, e em pacientes com PSA > 20 ng/ml o hormônio foi reintroduzido quando o PSA atingiu níveis próximos à metade do PSA inicial.

Quando o PSA aumentou em 3 medidas consecutivas com os níveis de testosterona baixos, foi considerado escape do tratamento hormonal empregado. O aparecimento de novas metástases ósseas também foi considerado como escape hormonal.

Tabela 1 – *Características clínicas dos pacientes submetidos a tratamento hormonal contínuo e intermitente*

	Contínuo	**Intermitente**
Número	18 pacientes	25 pacientes
Média de Idade	70,1 anos	72,4 anos
Estádio no início do tratamento		
T3 Nx M+	4 pacientes	10 pacientes
T3 N+ M+	2 pacientes	4 pacientes
T4 N+ M+	8 pacientes	9 pacientes
T4 Nx M+	4 pacientes	2 pacientes
Gleason		
4 - 6	9 pacientes	13 pacientes
7	6 pacientes	7 pacientes
8 - 10	3 pacientes	5 pacientes

Foram estudados os efeitos colaterais, impotência sexual, tempo de resposta e período em que o paciente se tornou hormônio-resistente.

Foi utilizado o teste exato de Fischer para comparar os parâmetros entre os 2 grupos.

RESULTADOS

No grupo A (tratamento contínuo), 11 pacientes (61,1%) chegaram ao final do protocolo (48 meses) e 7 pacientes (38,8%) tiveram escape hormonal (tempo médio de escape de 20,1 meses) e 2 (11,1%) foram a óbito (Tabela-2). A média do PSA inicial foi 32,3 ng/ml, variando de 11,2 a 110 ng/ml. O nadir do PSA foi 0,4 ng/ml, e o tempo médio de duração do nadir foi de 17,5 meses (Tabela-2). Cinco pacientes (27,7%) tiveram efeitos colaterais leves (gastrintestinais, ginecomastia e astenia) e 2 pacientes (11,1%) apresentaram efeitos colaterais importantes (gastrite com náusea e vômitos intensos e edema de membros inferiores). Dezoito pacientes (100%) tiveram impotência sexual (Tabela-2).

***Tabela 2** – Resumo dos pacientes submetidos a tratamento hormonal contínuo*

No. de pacientes	**18**
Média do PSA inicial (ng/ml)	32,3
Média do nadir do PSA (ng/ml)	0,4
Média do tempo do nadir do PSA (meses)	17,5
Média da testosterona inicial	435
Média do nadir da testosterona	43
Média do tempo de nadir da testosterona (meses)	15,2
No. de pacientes com escape hormonal	7
Tempo médio do escape hormonal (meses)	20,1
No. de pacientes com efeitos colaterais leves	5
No. de pacientes com efeitos colaterais importantes	2
Impotência sexual	18
Óbito relacionado à doença	2

No grupo B, 18 pacientes (72%) chegaram no 3o. ciclo, 4 pacientes (16%) tiveram escape hormonal, 2 pacientes (8%) foram a óbito pela doença e 1 paciente optou por orquiectomia no início do 3o. ciclo (Tabela-3). A média do PSA inicial foi de 30,9 ng/ml, variando de 10,9 a 138 ng/ml. A média do nadir do PSA foi 0,35 ng/ml e a média de duração de cada ciclo foi 8,3 meses e 9,2 meses no 1o. e 2o. ciclo respectivamente. A média de intervalo foi de 10,2 meses e 8,1 meses entre o 1o. e 2o. ciclo e entre o 2o. e 3o. ciclo respectivamente (Tabela-3). Os efeitos colaterais leves ocorreram em 2 pacientes (8%) e os importantes (digestivos) em 1 paciente (4%). Durante os ciclos, 18 pacientes (72%) apresentaram impotência sexual e apenas 1 paciente (4%) permaneceu impotente (Tabela-3).

Na comparação dos parâmetros entre os 2 grupos, apenas a função erétil apresentou diferença estatisticamente significante ($p < 0,0001$).

DISCUSSÃO

Embora o tratamento hormonal seja a terapia padrão para o adenocarcinoma avançado de próstata, mais de 80% dos tumores tornam-se hormônio-resistentes entre 18 e 36 meses (1,2). As razões ainda não são totalmente conhecidas, porem, alguns fatores estão sendo implicados nesse processo. Três mecanismos essenciais são importantes para o crescimento normal das células prostáticas: 1)- o estímulo positivo da síntese do DNA sobre a proliferação das células normais; 2)- o efeito inibitório que limita o número de células na próstata; e 3)- a apoptose, que é a forma programada do controle da morte celular.

***Tabela 3** – Resumo dos pacientes submetidos a tratamento hormonal intermitente*

	Ciclo 1	**Ciclo 2**	**Ciclo 3**
No. pacientes	25	24	18
Média do PSA inicial (ng/ml)	30,9	17,1	10,1
Média do nadir do PSA (ng/ml)	0,35	0,35	-
Média do tempo do nadir do PSA após suspensão do ciclo (meses)	6,9	6,4	-
Média da testosterona inicial	531	424	341
Média do nadir da testosterona (meses)	43	40	44
Média do tempo do nadir da testosterona após suspensão do ciclo (meses)	6,2	6,1	-
Média de duração dos ciclos (meses)	8,3	9,2	-
Média do intervalo entre os ciclos (meses)	10,2	8,1	-
No. de pacientes com escape hormonal	-	1	3
Tempo médio do escape hormonal (meses)	-	24	39
No. de pacientes com efeitos colaterais leves	1	-	1
No. de pacientes com efeitos colaterais importantes	-	-	-
Impotência Sexual após suspensão do ciclo	-	1	-
Óbito relacionado à doença	-	-	2

Estudos mostram que a dependência hormonal é a manifestação clínica da apoptose após a retirada do hormônio masculino, e ocorre tanto em células prostáticas normais quanto nas neoplásicas (7,13). Nos estágios precoces do câncer de próstata somente a forma de regulação androgênica que limita o número de células prostáticas é perdida. Devido a outros 2 mecanismos ainda funcionantes, a ablação androgênica tem o duplo efeito de deflagrar a apoptose e inibir a proliferação celular. Em células malignas a capacidade de resistir a apoptose é adquirida com a diferenciação celular sob o efeito dos andrógenos. Entretanto na ausência desses é impossível a divisão normal e diferenciação das células, que se tornam pré-apoptóticas novamente (7,23).

Estudos experimentais em linhagem de células hormônio-dependente SHIONOGI sugerem que a progressão para hormônio-resistente possa representar um processo no qual a deprivação hormonal está inclusa, alterando a taxa de diferenciação das "Stem Cells". Nesse estudo experimental foi demonstrado que o tratamento intermitente comparado com o contínuo, prolongam a progressão para independência androgênica de 50 para 150 dias (5).

Acredita-se que a independência androgênica surja em conseqüência da ativação de genes repressores de andrógenos e produção de fatores de crescimento autócrinos e parácrinos, capazes de substituir o andrógeno e manter a viabilidade das células tumorais.

Em condições experimentais, a apoptose pode ser de fato induzida múltiplas vezes em uma população de células tumorais através de repetidos ciclos de deprivação e reintrodução do hormônio (2,5,7,13).

Com o avanço da biologia molecular identificou-se proteínas envolvidas na morte ou na imortalidade das células neoplásicas como a clusterina que é uma proteína anticitolítica codificada no gene TRPM-2 (Testosterone Repressed Prostatic Message-2) e expresso em alta quantidade em células prostáticas submetidas a morte programada. Os níveis de clusterina aumentam após ablação androgênica (4).

O oncogen bcl-2 (B-cell Lymphoma-2) foi identificado no ponto de mutação da translocação do cromossomo t (14:18) associado ao linfoma folicular. Essa translocação resulta num aumento da expressão da proteína bcl-2 em células dos linfomas. No câncer de próstata ocorre um aumento da expressão do bcl-2 em células que perdem a capacidade de apoptose. Acredita-se que o bcl-2 possa prevenir danos oxidativos dos constituintes celulares, interfere com o fluxo de cálcio através do retículo endoplasmático e retirar no transporte nuclear de outras proteínas como, por exemplo, o p53 (7,14).

Baseados nesses dados, alguns trabalhos clínicos com tratamento hormonal intermitente para câncer de próstata vem surgindo nos últimos anos. O primeiro estudo clínico com tratamento hormonal intermitente foi publicado em 1986, onde os autores utilizaram flutamida e DES num período entre 2 e 70 meses. A suspensão do tratamento variou de 1 a 24 meses. A potência sexual retornou em 95% dos pacientes no período sem tratamento, e todos os pacientes responderam a reintrodução do medicamento (6).

Em nossa casuística apenas 1 paciente (4%) teve impotência sexual durante os ciclos no tratamento intermitente (grupo B), enquanto que no grupo A (tratamento contínuo) todos os pacientes tiveram impotência sexual. O nadir do PSA foi praticamente o mesmo nos 2 grupos, e a média do tempo do nadir do PSA no grupo B foi entre 8,2 e 8,9 meses, semelhante ao de outros estudos (9,10,12).

O critério de reintrodução do tratamento foi semelhante ao de Goldenberg et al. (7), porém outros trabalhos utilizam critérios diferentes como Higano et al. (8). Esses autores reintroduzem o tratamento quando o PSA atinge 4 ng/ml (se o inicial for ^{3} 10 ng/ml), se o PSA inicial for entre 11 e 100 ng/ml, reintroduzem quando atingir entre 10 e 20 ng/ml e se for maior que 100 ng/ml, só reintroduzem quando chegar entre 20 e 40 ng/ml. A média do nadir do PSA foi de 15 semanas. Ao nosso ver, a reintrodução do tratamento quando o PSA atinge o nível inicial é menos estressante para o paciente e não altera a evolução da doença. Alguns pacientes podem ter um rápido aumento do nível do PSA após a interrupção do tratamento, o

que pode coincidir com o aumento da testosterona. A maior sensibilidade da célula para a síntese do PSA e conseqüente proliferação celular pode exigir uma reintrodução mais precoce do tratamento. Por outro lado, alguns pacientes têm uma elevação muito lenta do PSA na ausência de detecção de progressão da doença e Gleason £ 7; nesses casos pode-se esperar até 2 anos para a reintrodução do ciclo. É importante nestes pacientes pesquisar a evolução da doença com PSA baixo.

Quanto à escolha do medicamento, alguns critérios têm de ser observados, como por exemplo: rápida supressão androgênica; rápida reversibilidade de sua ação; efeitos colaterais baixos; ausência de fogachos, fácil administração, baixo custo e fácil disponibilidade. Nas séries estudadas o bloqueio androgênico total não teve diferença sobre o bloqueio seletivo (4).

No nosso trabalho preferimos administrar o acetato de ciproterona por ser disponível gratuitamente no Sistema Único de Saúde (SUS) e, portanto de fácil acesso aos doentes institucionais, além de ter baixo índice de efeitos colaterais, fácil administração e ainda duplo mecanismo de ação, agindo tanto como anti-androgênico periférico como a nível central. A ausência do "flare" (aumento brusco e intenso no início do tratamento), da testosterona é um ponto importante na escolha, evitando-se assim a associação de drogas. Utilizamos 200 mg/dia, pois em nossa experiência prática é tão eficaz quanto a dose plena 300 mg/dia, diminuindo os efeitos colaterais e custos. Porém outras drogas podem ser utilizadas como o DÊS; análogos LHRH e outros anti-androgênicos periféricos.

O custo do tratamento dos pacientes que completaram os 48 meses foi bem menor no grupo com o THI. Baseado no preço médio de mercado (SP) do acetato de ciproterona em fevereiro de 2000 (embalagem com 20 comprimidos custa R$ 60,00 em média), os pacientes com THI que completaram o estudo (em média 3 ciclos de 9 meses), gastaram R$ 9.720,00, enquanto que os pacientes com THC gastaram R$ 17.280,00 em 48 meses.

Nossos resultados mostram que o tratamento intermitente no período estudado não foi inferior ao tratamento contínuo quanto à sobrevida e aparecimento da doença hormônio-resistente, além de ter uma melhor qualidade de vida devido ao período sem medicamento e, principalmente, por recobrar a potência sexual durante os ciclos, fato esse observado também por outros autores (9-12).

Para saber se existe real influência no aumento do período sem doença hormônio-resistente, protocolos multi-institucionais com elevado número de pacientes e observação por um tempo bem longo deverão ser instalados, assim como uma melhor seleção dos pacientes que serão beneficiados por essa modalidade terapêutica.

CONCLUSÕES

No período estudado, o THI foi tão eficaz quanto o THC, além de ter menor custo e melhor qualidade de vida sexual.

Séries maiores e períodos mais longos poderão mostrar se existe influência do THI no período de transformação de doença hormônio-sensível em doença hormônio-resistente.

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RESUMO

ADENOCARCINOMA DE PRÓSTATA METASTÁTICO: COMPARAÇÃO ENTRE TRATAMENTO HORMONAL CONTÍNUO E INTERMITENTE

Objetivo: O tratamento hormonal contínuo (THC) é o tratamento padrão para adenocarcinoma de próstata estádio D2. Trabalhos experimentais mostram que o tratamento hormonal intermitente (THI) pode aumentar o período de resposta ao tratamento, porém poucos estudos clínicos foram realizados até o momento. Esse trabalho é mostrar uma casuística clínica nacional comparando o THC com o THI.

Material e Métodos: Entre 1994 e 1998, 43 pacientes com adenocarcinoma de próstata foram divididos ao acaso em 2 grupos: grupo A, 18 pacientes submetidos a THC e grupo B, 25 pacientes com THI, ambos com Acetato de Ciproterona 200 mg/dia. No THI a suspensão do ciclo foi após atingir o nadir do PSA e a reintrodução de acordo com o PSA inicial.

Resultados: No grupo A, 11 pacientes (61,1%) completaram o estudo. A média do PSA inicial foi 32,3 ng/ml e do nadir 0,4 ng/ml. Sete pacientes (38,8%) tiveram efeitos colaterais, 18 pacientes (100%) ficaram com impotência sexual, 7 (38,8%) tornaram-se hormônio-resistente e 2 (11,1%) foram a óbito. No grupo B, 24 pacientes (96%) chegaram no 2º ciclo e 18 (72%) no 3º. A média do PSA inicial foi 30,9 ng/ml e a do nadir 0,35 ng/ml. Cada ciclo durou em média 10,2 meses. Quatro pacientes (16%) tornaram-se hormônio-resistente e 2 (8%) foram a óbito. No intervalo dos ciclos apenas 1 paciente permaneceu impotente.

Conclusões: No período estudado o THI foi tão eficaz quanto o THC com uma melhor qualidade de vida e, 96% dos pacientes potentes no intervalo entre os ciclos.

Unitermos: próstata, câncer de próstata, avançado, tratamento hormonal
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VESICOURETHRAL STRICTURES AFTER RADICAL PROSTATECTOMY: TREATMENT AND OUTCOME

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ABSTRACT

Objective: Stricture of the vesicourethral anastomosis is a complication after radical prostatectomy. Dilatation, stricture incision, or resection have been proposed as endoscopic treatment. The objective of this study was to report our experience with the management of the urethrovesical stricture.

Material and Methods: The sample consisted of 120 patients undergoing radical prostatectomy for localized prostatic carcinoma. The vesicourethral stricture was treated by endoscopic procedures in all patients. Stricture dilatation was performed in less severe cases, whereas cold knife transurethral incision or electrocautery resections were done whenever there was partial obliteration or when dilatation failed.

Results: In our sample, 16 patients (13%) had anastomotic stricture. The vesicourethral stricture was treated by dilatation, cold knife incision and electrocautery resection in 8, 6 and 2 patients, respectively. Recurrence after the first treatment of stricture occurred in 30% of the patients, but cure was achieved in all of the cases. Age, pre-operative PSA, histopathologic stage, and prior transurethral resection of the prostate were not predictive of this complication. No incontinence was found following treatment in a median follow-up of 23 months (4 months - 56 months).

Conclusion: The endoscopic treatment of the vesicourethral stricture presents a high rate of cure and a low incidence of incontinence.

Key words: prostate, carcinoma, radical prostatectomy, complications, urethral stricture
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INTRODUÇÃO

A estenose da anastomose uretrovesical é uma complicação da prostatectomia radical, ocorrendo em 0,8 a 20% dos casos (1,2). Apesar de não ser uma complicação infreqüente, os fatores de risco para a estenose ainda não estão bem definidos. O tratamento da estenose é endoscópico, havendo controvérsias quanto ao melhor método utilizado (dilatação, uretrotomia interna e ressecção da área estenosada) (1-5). O presente estudo tem por objetivo relatar a nossa experiência no tratamento da estenose uretrovesical pós-prostatectomia radical, examinando alguns possíveis fatores que poderiam influenciar na etiologia da estenose.

MATERIAL E MÉTODOS

Foram estudados 120 pacientes que foram submetidos a prostatectomia radical de julho de 1992 a junho de 1999 em nossa instituição. Os pacientes foram avaliados quanto a incidência, modo de apresentação, tratamento e complicações da estenose da anastomose uretrovesical.

A prostatectomia radical foi realizada por via retropúbica em todos os casos. A base prostática foi dissecada com tentativa de preservação do colo vesical. A mucosa vesical foi sempre evertida com sutura interrompida com categute simples 4-0. Quando necessário foi realizado redução do diâmetro da abertura vesical em "raquete", permitindo a passagem de um dedo indicador. Para a anastomose

uretrovesical, utilizou-se 4 pontos as 2, 5, 7 e 10 horas, com fio de poliglactina 2-0, sobre um cateter 20F. A sonda vesical foi mantida sem tração, por 21 dias em todos os pacientes, sem realização de uretrocistografia. Antibióticos profiláticos foram usados rotineiramente. O espaço perivesical foi drenado com penrose.

Os pacientes foram avaliados rotineiramente a cada 3 meses no primeiro ano de pós-operatório, a cada 6 meses no segundo ano e a seguir anualmente. Os pacientes que apresentaram sintomas urinários obstrutivos ou retenção urinária foram avaliados com cistoscopia. Os procedimentos terapêuticos para a estenose uretrovesical foram realizados sob anestesia peridural.

A estenose uretrovesical foi tratada com procedimentos endoscópicos em todos os casos. O tratamento endoscópico consistiu de dilatação para os casos menos severos. Nestes casos os pacientes eram submetidos a bloqueio anestésico e então era realizada dilatação progressiva promovendo ruptura do anel fibroso e permitindo a passagem de cistoscópio 24F.

A uretrotomia interna com faca fria ou ressecção da estenose foi realizada nos casos de estenose intensa, ou na falha da dilatação. A uretrotomia interna consistia de incisão profunda, realizada com a faca fria de Sachse, em toda extensão da área de estenose, havendo cautela com a musculatura esfincteriana. Ao final do procedimento, a área operada permitia, com facilidade, a passagem de um cistoscópio 24F.

Ao final do procedimento cirúrgico, todos os pacientes foram sondados, com Foley 20 ou 22F, e permaneceram com o cateter por um período de 3 a 5 dias.

RESULTADOS

Dezesseis pacientes (13%) apresentaram estenose da anastomose uretrovesical. A idade média dos pacientes foi de 63,2 anos, variando de 56 a 75 anos. O PSA médio pré-operatório foi de 14,3 ng/ml, variando de 1,3 a 38,2 ng/ml. Com relação ao estádio patológico tumoral, 7 pacientes apresentaram estádio T2, 8 T3 e em um esta informação não foi obtida.

Todos os pacientes com estenose apresentaram sintomas urinários obstrutivos, sendo que 2 evoluíram com retenção urinária. O intervalo médio e mediano entre a cirurgia e o diagnóstico de estenose foi de 3,9 e 3 meses, respectivamente, variando de 1 mês a 17 meses.

A distribuição dos pacientes de acordo com os tipos e os resultados do tratamento está demonstrada na Tabela-1. O índice geral de recidiva foi de 30%. Todos os pacientes tratados com dilatação endoscópica foram curados com um único procedimento. Metade dos pacientes tratados com uretrotomia interna e todos tratados com ressecção necessitaram de outro procedimento devido a ocorrência de re-estenose. Dos 5 pacientes que recidivaram ao primeiro tratamento, 4 foram curados com apenas um procedimento adicional (2 uretrotomias internas e 2 dilatações). Um paciente com estenose severa, tratado inicialmente com ressecção do tecido fibrótico, evoluiu com 7 recidivas após o primeiro tratamento. Estas re-estenoses foram tratadas com 2 novas ressecções, uma uretrotomia interna e 4 dilatações. Há 2 anos da última dilatação, o paciente encontra-se assintomático, apresentando bom jato urinário. Nenhum paciente evoluiu com incontinência urinária. O tempo médio de seguimento dos pacientes após o tratamento da estenose foi de 23 meses, variando de 4 a 56 meses.

Tabela 1 – *Correlação entre os tipos de tratamento e a recidiva da estenose uretrovesical*

Tipos de Tratamento	Número de Pacientes	Pacientes com Recidiva
Dilatação	8	0
Uretrotomia	6	3
Ressecção	2	2
Total	16	5

Estratificando-se o número de estenoses uretrovesicais de acordo com o número de prostatectomias radicais, encontrou-se uma taxa menor desta complicação após a sexagésima cirurgia, porém sem significância estatística (Tabela-2). A idade, o PSA pré-operatório, estádio patológico e antecedente de

RTU não foram fatores preditivos da estenose uretrovesical.

Tabela 2 – *Distribuição das estenoses uretrovesicais por número de cirurgias realizadas.*

Número de Prostatectomias Radicais	Número de Estenoses (%)
Primeiras 60 cirurgias	11 (18)
Últimas 45 cirurgias	5 (11)

p > 0,1

DISCUSSÃO

A anastomose uretrovesical durante a prostatectomia radical é uma das etapas cirúrgicas mais importantes. Várias foram as técnicas descritas para realização desta anastomose. Foi demonstrado que a técnica de Vest (6) obtém piores resultados em relação a anastomose direta (7,8). A importância da correta aposição mucosa-mucosa foi evidenciada em estudos experimentais e clínicos (9-11).

A incidência de estenose do presente estudo foi de 13%, o que condiz com a literatura (1,2,7,12). Encontramos uma taxa de cura de 69% com apenas um procedimento. Os demais foram curados com cirurgias adicionais. Apenas um paciente necessitou mais de 2 procedimentos; e nenhum dos nossos pacientes tornou-se incontinente após o procedimento. A taxa de cura da estenose uretrovesical é elevada de acordo com a literatura, variando de 88% a 100% (5,13), entretanto a incidência de incontinência após os procedimentos endoscópicos é variável. Popken et al. (5) relataram um sucesso de 100%, após ressecção endoscópica da estenose com 24 pacientes, para uma taxa de continência também de 100%, o que está de concordância com o nosso estudo, apesar dos métodos diferentes de tratamento. Srougi et al. (13) também obtiveram cura em 100% dos 13 pacientes tratados desta complicação. Em outro estudo, uma incidência de continência de 100% também foi referida após tratamento da estenose com uretrotomia interna (14). Surya et al. (1) analisaram 18 pacientes com estenose da anastomose uretrovesical pós-prostatectomia radical. Todos os pacientes foram submetidos inicialmente a dilatação. Treze pacientes falharam a este tipo de tratamento e foram tratados com uretrotomia interna com faca fria (n = 9) e ressecção da estenose com eletrocautério (n = 4). Entre os pacientes tratados com uretrotomia, 5 ficaram curados e os demais necessitaram de dilatações subseqüentes. Os pacientes tratados com ressecção ficaram curados da estenose, porém houve incontinência em todos os casos, sendo total em 3. Eles concluíram que, ao contrário dos resultados obtidos por Popken et al. (5), a ressecção com eletrocautério está contra-indicada nos casos de estenose uretrovesical, pela alta taxa de incontinência resultante. Em nosso estudo, apenas 2 pacientes foram tratados com ressecção o que não nos permite tecer conclusões sobre este método. A variação quanto aos índices de continência entre os estudos deve-se provavelmente a diferença entre os pacientes como idade e co-morbidades associadas; a diferença dos métodos utilizados; a preservação do esfíncter externo na prostatectomia radical e a habilidade técnica no procedimento endoscópico.

Nos parece que o principal fator de risco para incontinência urinária após o tratamento endoscópico da estenose é a preservação do esfíncter externo na prostatectomia radical e que o tipo de método utilizado tenha papel secundário. Os pacientes que recidivam após a dilatação ou nos casos de estenose acentuada, a uretrotomia interna ou a ressecção parecem ser procedimentos efetivos e seguros. Quando há obliteração completa, cirurgia aberta com excisão da estenose e re-anastomose uretrovesical pode ser aventada, apesar do alto índice de incontinência (15,16), ou, como proposto recentemente por Carr & Webster (17), o tratamento endoscópico, através de abordagem anterógrada e retrógrada.

De acordo com os nossos dados, idade, PSA pré-operatório, estádio patológico, peso da próstata, antecedente de RTU, não foram fatores de risco para a estenose uretrovesical. Como não realizamos cistouretrografia de rotina antes da retirada da sonda, o papel do extravasamento urinário perivesical não foi estudado como fator de risco de estenose. Entretanto há alguns trabalhos na literatura que abordam este tema(1,7,12). Surya et al. (1) relataram que dos 26 pacientes com extravasamento urinário pós-operatório, 14 evoluíram com estenose, enquanto que dos

130 sem extravasamento, apenas 4 tiveram esta complicação. Eles concluíram que independentemente do tempo de permanência da sonda uretral, a simples presença de extravasamento urinário perivesical acarreta uma maior incidência de estenose uretrovesical. Entretanto, 2 estudos não confirmaram estes achados (7,13). No estudo de Levy et al. (7) todos os 146 pacientes realizaram cistouretrografia miccional após a terceira semana pós-operatória e encontraram extravasamento em 14,1% dos pacientes, não apresentando diferença significativa de estenose no grupo com e sem extravasamento; o que sugere não haver correspondência entre o extravasamento urinário e a estenose da anastomose uretrovesical, desde que o cateter seja mantido até a resolução do problema.

CONCLUSÃO

O tratamento endoscópico da estenose uretrovesical a partir de dilatação, e reservando-se a uretrotomia interna e ressecção da estenose para os casos de falha, ou nos casos de obliteração acentuada, apresenta uma elevada taxa de cura, associando-se a uma baixa incidência de incontinência urinária. De acordo com os nossos dados, idade, PSA pré-operatório, estádio patológico, e antecedente de RTU não se constituíram em fatores de risco para a estenose uretrovesical pós-prostatectomia radical.

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RESUMO

EVOLUÇÃO E TRATAMENTO DA ESTENOSE DA ANASTOMOSE URETROVESICAL PÓS-PROSTATECTOMIA RADICAL

Objetivo: A estenose da anastomose uretrovesical é uma complicação pós-operatória freqüente da prostatectomia radical (PR). Há poucos relatos na literatura sobre a evolução dos pacientes acometidos por esta entidade clínica. O objetivo deste estudo foi avaliar a evolução dos pacientes acometidos por estenose uretrovesical pós-PR e as formas de tratamento desta complicação.

Material e Métodos: Foram analisados retrospectivamente 120 PR retropúbicas realizadas entre julho de 1992 e junho de 1999. Nestes pacientes foram analisados dados referentes ao procedimento cirúrgico, diagnóstico da estenose, tratamento, recidiva e evolução.

Resultados: Dezesseis pacientes (13%) evoluíram com estenose da anastomose uretrovesical. Os sintomas dos pacientes foram sugestivos de obstrução urinária em todos os casos. O intervalo entre a data da PR e o tratamento da estenose foi de 3,9 meses (1-17). A causa da estenose foi fibrose cicatricial em todos os casos. O tratamento da estenose foi primariamente dilatação endoscópica (n = 8). Nos casos de estenose acentuada, ou na impossibilidade de dilatação procedeu-se incisão endoscópica com faca fria (n = 6) ou ressecção endoscópica da estenose (n = 2). Recorrência da estenose foi evidenciada em 5 casos (31,2%), em um tempo médio de 2 meses após o tratamento. Todos os pacientes ficaram curados após procedimentos adicionais. Nenhum paciente evoluiu com incontinência urinária em um tempo médio de seguimento de 23 meses (4-56).

Conclusão: A estenose da anastomose uretrovesical é uma complicação freqüente da PR. O tratamento desta complicação por procedimentos endoscópicos é seguro e eficaz.

Unitermos: próstata, adenocarcinoma, prostatectomia radical, complicações, estenose de uretra
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THE USE OF ABSORBABLE MECHANICAL SUTURE IN ORTHOTOPIC ILEAL NEOBLADDER REPLACEMENT

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ABSTRACT

Purpose: For patients undergoing radical cystectomy with orthotopic bladder replacement, the process of detubulization and refashioning of the bowel into a neobladder is often time-consuming. We sought to determine whether using absorbable staples would be safer, more effective, and reduce surgical time.

Material and Methods: Radical cystectomy for bladder cancer and orthotopic ileal neobladder was performed in 22 patients using absorbable staples. We evaluated the method with regard to the operative time and inquiring the patients about urinary function.

Results: In all cases, the neobladder construction using absorbable staple was performed easily and rapidly. Use of staples reduced operative time by approximately 90 minutes. None of the patients had complications.

Conclusion: The use of absorbable staples for ileal neoblader construction reduces operative time. This technique should be considered for patients undergoing radical cystectomy with orthotopic intestinal neobladder.

Key words: bladder, urinary reservoirs, continent, staplers
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INTRODUÇÃO

A substituição vesical por segmentos intestinais detubulizados (1) e reconfigurados (2) de maneira a possuir características de neobexiga (capacidade volumétrica adequada e baixa pressão) tem sido utilizada como forma preferencial de derivação urinária nos pacientes com câncer infiltrativo de bexiga submetidos a cistectomia radical. Após os trabalhos pioneiros de Lilien & Camey (3), vários grupos desenvolveram técnicas, utilizando diversos segmentos do trato gastrointestinal (4). A reconfiguração intestinal em um reservatório requer tempo cirúrgico prolongado, devido principalmente às suturas manuais. Visando otimizar o tempo operatório na confecção de neobexigas, temos utilizado grampeadores absorvíveis. Relatamos nossa experiência com suturas mecânicas em adultos submetidos a cistectomia radical e neobexiga ileal ortotópica.

MATERIAL E MÉTODOS

Entre maio de 1997 e setembro de 1998, 22 pacientes (14 homens e 8 mulheres), com idade média de 62 anos (33 a 79), com diagnóstico de carcinoma infiltrativo de bexiga estágio clínico T2-T4aNxM0, foram submetidos a cistectomia radical.

Neobexiga ileal ortotópica realizada de acordo com técnica descrita anteriormente (5) e confeccionada com grampeadores absorvíveis foi a derivação utilizada em todos os pacientes.

Após a cistectomia radical, seleciona-se um segmento de íleo terminal de aproximadamente 40-45 cm. O trânsito intestinal é restabelecido com anastomose látero-lateral com stapler GIA 60.

Dispõe-se o segmento ileal isolado em "U" e no bordo antimesentérico do vértice desta alça faz-se pequena enterotomia, o suficiente para poder introduzir o aparato de sutura mecânica e corte, tipo Poligia 75 (US Surgical Corporation) com sutura absorvível

de poliglactina (Figura-1). Dessa maneira, realiza-se detubulização e sutura com uma só manobra, confeccionando a neobexiga em poucos minutos (Figura-2).

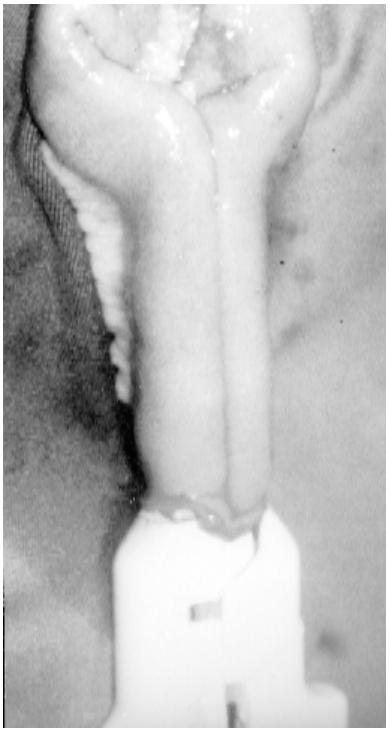

Figura 1 *- Detubulização e sutura da neobexiga ileal*

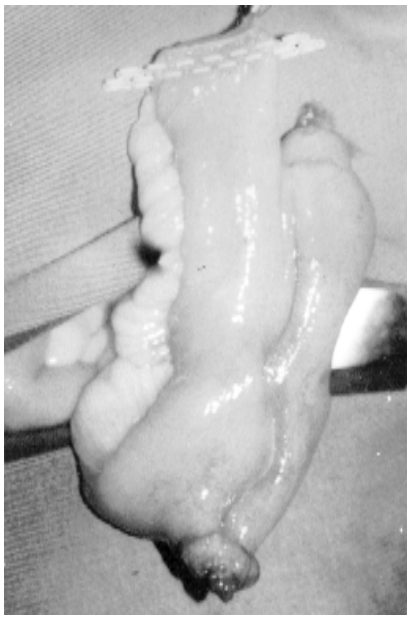

Figura 2 *- Neobexiga: aspecto final*

No final da confecção da neobexiga, permanecem 2 segmentos intestinais curtos, que passam a ser o segmento aferente para implantação dos ureteres pela técnica de "Le Duc". Splints ureterais são mantidos por 7 dias, sendo retirados após pielografia de controle. O tempo médio de internação foi de 10 dias (8 a 12 dias) e a sonda vesical pode ser retirada no vigéssimo primeiro dia de pós-operatório. Utiliza-se antibiótico de amplo espectro na primeira semana (cefalosporina de terceira geração) e a seguir, utiliza-se ácido pipemídico até a retirada da sonda de Foley. No seguimento ambulatorial, realizou-se urografia excretora em todos pacientes e estudo video-urodinâmico com fluoroscopia com aparelho Dantec UD 5500 MK2 a partir do sexto mês de pós-operatório em um subgrupo de 12 pacientes. O seguimento foi de 6 a 16 meses (mediana = 11 meses).

RESULTADOS

A confecção de neobexiga utilizando grampeadores absorvíveis foi rápida e de fácil execução. O tempo para se realizar a reconstrução do trânsito intestinal e para se confeccionar a neobexiga variou de 15 a 20 minutos, o que representa uma diminuição média de tempo de 90 minutos, quando comparada a sutura manual. O tempo atual para realização de cistectomia radical com neobexiga ileal ortotópica é de aproximadamente 5 horas. Antigamente com sutura manual era de 7 horas.

Não houve complicações relacionadas ao método. Após a retirada da sonda, no vigéssimo primeiro dia, as uroculturas foram negativas, porém leucocitúria em 50% dos pacientes foi um achado sem correlação clínica.

Todos as pacientes do sexo feminino apresentaram continência diurna e noturna imediata enquanto nos pacientes do sexo masculino enurese foi relatada em 11 dos 14 pacientes (78%).

No seguimento pós-operatório, o estudo radiológico do trato urinário (urografia excretora) no sexto mês de pós-operatório (Figura-3) mostrou preservação do trato urinário alto, com todas as unidades renais implantadas apresentando excreção normal. Na realização do exame vídeo-urodinâmico a capacidade do reservatório variou entre 380 e 650

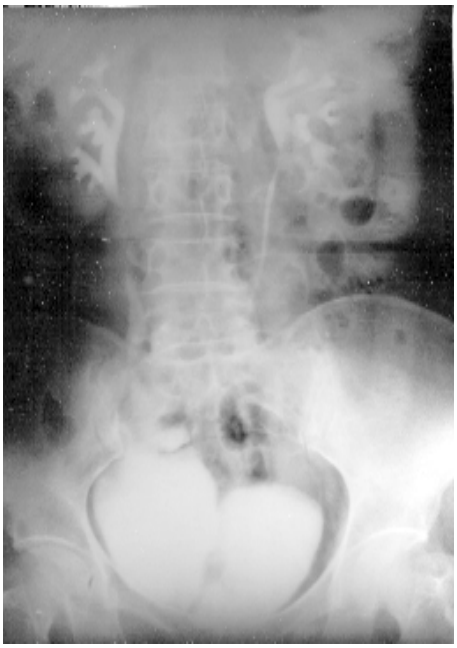

Figura 3 *- Urografia excretora*

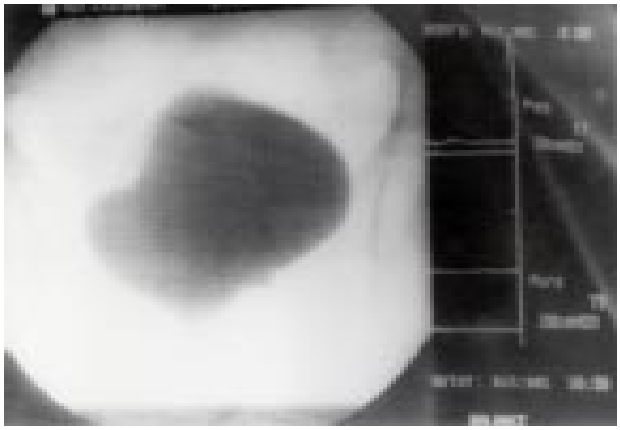

Figura 4 *- Exame vídeo-urodinâmico*

ml, com pressão final de enchimento entre 15 e 40 cm de H_2O. A observação de peristaltismo no reservatório foi um achado constante, porém sem provocar perdas urinárias ou alterações pressóricas durante o exame (Figura-4).

Cistoscopia realizada em 3 pacientes no terceiro mês de pós-operatório, não identificou a presença do material de sutura no interior da neobexiga, demonstrando que a absorção deste material (grampos de copolímero - lactomer) ocorre antes deste período.

DISCUSSÃO

Após comprovar-se a eficácia das suturas mecânicas metálicas e o avanço tecnológico que possibilitou a confecção de grampos absorvíveis em cirurgias do aparelho gastrointestinal (6), a cirurgia urológica passou a utilizar estes dispositivos na reconstrução do trato urinário inferior para confeccionar as neobexigas ileais (7), colônicas (8,9), ileocolônicas (10,11), de reservatório com tubo continente gástrico (12) e ileal (13) para cateterismo intermitente, ou para válvulas anti-refluxo nos reservatórios de Kock (14).

As neobexigas intestinais ortotópicas oferecem melhor qualidade de vida aos pacientes submetidos a cistectomia e a utilização de grampeadores oferece facilidade, rapidez e segurança ao procedimento cirúrgico, com bons resultados funcionais (8,9,15,16) e sem complicações relacionadas ao método (8,12,16), podendo ser utilizada também em pacientes pediátricos (8).

Com o emprego destes dispositivos, reduzimos nosso tempo cirúrgico em 90 minutos comparando com a sutura manual que era de 6 a 7 horas, resultados repetidos em muitas séries (8,10,13,15).

A continência urinária obtida e os resultados urodinâmicos encontrados, claramente confirmam o sucesso do método, com reservatórios de boa complacência, pressão inferior a 40 cm de H2O, capacidade de 380 a 650 ml possibilitando intervalos de micção entre 4 a 6 horas. Lytton (17) demonstrou resultados urodinâmicos semelhantes aos nossos e Kock (11), relata neobexigas com pressão limite de 40 cm de água. A presença de peristalse na neobexiga observada no estudo vídeo-urodinâmico foi muito freqüente, porém não houve repercussão pressórica na câmara ou perda urinárias. Nenhum dos nossos pacientes apresentaram complicações infecciosas ou litíase, que podem ser provocadas por suturas metálicas (15) e ocasionar infecção urinária crônica associada a falência do trato urinário superior (15).

Descompensação do reservatório confeccionado com grampeadores foi relatado, sendo a origem incerta. Presume-se que fibrose secundária a isquemia (7,15) e reação ao ácido poliglicólico (7) são causas de descompensação das neobexigas. Nes-

te material, não houve nenhum caso até o presente momento.

CONCLUSÃO

O uso de grampeadores absorvíveis para confecção da neobexiga ileal reduz significativamente o tempo cirúrgico, sendo seguro e de fácil manuseio, podendo ser considerada a utilização destes dispositivos nos pacientes submetidos a cistectomia radical com derivação urinária.

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RESUMO

UTILIZAÇÃO DE SUTURA MECÂNICA ABSORVÍVEL NA CONFECÇÃO DE NEOBEXIGA ILEAL ORTOTÓPICA

Objetivo: Nos pacientes submetidos a cistectomia radical por câncer, a confecção de neobexigas ortotópicas continentes tem proporcionado importantes avanços na qualidade de vida. Devido ao grande tempo

cirúrgico dispensado nestas cirurgias, a introdução de novos dispositivos técnicos como os staplers absorvíveis, reduziram dramaticamente o tempo operatório, com igual eficácia e segurança das suturas manuais.

Pacientes e Método: Foram realizadas 22 neobexigas ileais ortotópicas com sutura mecânica absorvível. O seguimento pós-operatório variou de 6 a 16 meses. Avaliamos o método com relação ao tempo cirúrgico e a função da neobexiga.

Resultados: Em todos os casos, a confecção da neobexiga utilizando grampeadores absorvíveis foi rápida e de fácil execução. O tempo cirúrgico diminuiu, que era de 6 horas em média, foi reduzido em 90 minutos. Houve preservação do trato urinário superior em todas as unidades renais re-implantadas e o resultado funcional foi confirmado através da avaliação urodinâmica.

Conclusão: O uso de grampeadores absorvíveis na confecção de neobexiga ileal reduz significativamente o tempo cirúrgico, demonstrando que o uso destes dispositivos é seguro, podendo ser considerado a utilização dos mesmos nas derivações urinárias.

Unitermos: bexiga, cistectomia, reservatório urinário, sutura mecânica
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Case Report

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METASTASIS OF BLADDER TRANSITIONAL CELL CARCINOMA EXCLUSIVELY TO ENDOMETRIUM

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ABSTRACT

Objectives: A case of solely endometrial metastasis from transitional cell carcinoma of the bladder is reported.

Material and Methods: The patient was referred to our institution after a transurethral bladder tumor resection (TURBT), with diagnosis of invasive transitional cell carcinoma of the bladder (high grade of Ash). The patient was submitted to a new TURBT on the site of the primary lesion and the diagnosis was confirmed. An anterior pelvic exenteration with a cutaneous ureteroileostomy were performed

Results: The pathologic examination of the surgical specimen revealed transitional cell carcinoma restricted to the bladder, with no lymphonodes or other pelvic organs involved by the neoplasia. At a single focal neoplasic area of an endometrial polyp, the immunohistochemical analysis confirmed a metastasis of the transitional bladder tumor (positive to: CEA, S- 100 protein and to cytokeratins 7,8,AE1-AE3, 34BE12 and negative to smooth muscle actin, desmin, HHF-35, HCG, AFP, vimentin.)

Comments: The hematogenic spreading of metastases to the uterus are rare. To our knowledge, this is the third case of transitional bladder cell carcinoma metastasis to the uterus in the literature and the first one with exclusive endometrial involvement.

Key words: bladder, endometrium, metastasis, uterus, transitional bladder cancer
Braz J Urol, 26: 293-294, 2000

INTRODUÇÃO

O útero, especialmente o endométrio, não é sítio habitual de metástases.

Os autores relatam um caso de carcinoma de células transicionais (CCT) invasivo de bexiga com metástase única para endométrio.

RELATO DO CASO

Paciente branca de 78 anos, há 18 meses apresentou hematúria macroscópica. A ultra-sonografia pélvica revelou lesão polipóide em parede lateral direita da bexiga de 3 cm e útero aumentado de volume (165 cm^3), com eco endometrial espessado (1 cm) e conteúdo líquido na cavidade uterina. Foi submetida à ressecção endoscópica transuretral (RTU) de bexiga e curetagem uterina, com diagnóstico histopatológico de CCT invadindo camada muscular da bexiga, grau III de Ash e coágulos no material de curetagem.

Há 4 meses foi admitida neste serviço, após ter sido submetida a radioterapia exclusiva para um carcinoma de laringe localizado, com resposta satisfatória. Realizou-se nova RTU no leito tumoral, que confirmou o diagnóstico de CCT da bexiga invasivo (alto grau). O exame físico geral foi normal e a investigação de metástases foi negativa.

Procedeu-se à exenteração pélvica anterior com uretero-ileostomia cutânea. O exame histopatológico revelou CCT de alto grau de Ash, infiltrando a muscular da bexiga. As margens cirúrgicas, os linfonodos pélvicos e os ovários não estavam comprometidos pela neoplasia. Foi encontrada leiomiomatose uterina e área neoplásica focal restrita ao endométrio em meio ao estroma de pólipo

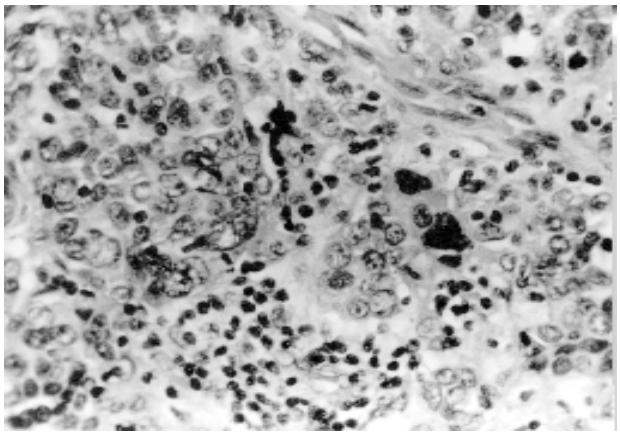

Figura – *Infiltração por neoplasia epitelial com acentuado pleomorfismo nuclear em meio a estroma endometrial com vasos proeminentes e discreto infiltrado linfocitário (HE, X200).*

endometrial (Figura). A imunohistoquímica foi positiva para CEA, proteína S-100 e as citoceratinas 7, 8, AE1-AE3 e 34BE12 e negativa para actina de músculo liso, HHF-35, desmina, HCG, alfa feto proteína, vimentina e citoceratina 20, com quadro imunohistoquímico compatível com CCT da bexiga metastático para endométrio.

DISCUSSÃO

Neoplasias pélvicas localmente avançadas podem envolver secundariamente o útero por contigüidade ou continuidade.

A disseminação hematogênica ou linfática para o útero é rara, geralmente secundária a neoplasias agressivas com múltiplos focos metastáticos. Nestes casos o colo uterino é afetado em 60,6% das vezes, o corpo em 21,2% e colo e corpo simultaneamente em 18,2% (1). Tumores metastáticos para o corpo uterino atingem somente o miométrio em 63% dos casos e apenas 3,8% acometem exclusivamente o endométrio. O presente caso apresentou metástase única de CCT, restrita ao endométrio, com tumor primário confinado a bexiga.

Kumar & Hart (1), revisando 63 casos de neoplasias extragenitais metastáticas para corpo uterino, encontraram 2 casos (3,2%) de tumores primários de bexiga. O sítio primário mais freqüente foi a mama (42,9%), seguida por pulmões, tireóide e pâncreas.

Metrorragia pode ser o primeiro sinal de metástase uterina (1,2). A paciente em discussão foi submetida à curetagem uterina para investigação de espessamento endometrial,

O presente caso também não apresentava comprometimento de linfonodos regionais ou de ovários, o que aumenta a probabilidade de metástase por via hematogênica exclusiva (3). A realização da primeira RTU vesical concomitante à manipulação uterina, poderia sugerir a possibilidade de implantação tumoral no endométrio cruento, porém vários autores têm demonstrado que ressecções endoscópicas vesicais não aumentam o risco de implantação tumoral à distância (3). Talvez, por ser portadora de 2 tumores primários (bexiga e laringe) a paciente apresente alguma instabilidade genômica, que tenha facilitado a disseminação anômala da doença.

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Case Report

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PENILE FRACTURE WITH URETHRAL INJURY

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ABSTRACT

Penile fracture or traumatic rupture of the corpus cavernosum is a relatively uncommon injury that occurs as a result of trauma to the erect penis. Associated urethral injury is present in 10% of patients with penile fracture. Most cases of penile fracture reported are a result of sexual intercourse. Some anecdotal cases have been associated with masturbation or during sleep. A case of penile fracture with urethral injury is documented in a 41-year-old white man with a history of bending his penis during intercourse. A surgical exploration was successfully performed through a classic subcoronal incision. The tears of the tunica and urethra were identified and repaired with non-absorbable sutures. A urethral catheter was left indwelling for 4 days and a cistostomy for 2 weeks. At 16 months of follow-up the patient is asymptomatic, without voiding symptoms. The erectile function was preserved and there is no penile curvature. The case herein reported emphasizes the importance of immediate surgical repair to preserve both sexual and voiding functions.

Key words: penis, injury, fracture, intercourse
Braz J Urol, 26: 295-297, 2000

INTRODUÇÃO

A fratura de pênis é uma emergência urológica rara. A lesão é caracterizada pela rotura da túnica albugínea, freqüentemente associada a coito ou manipulação (1). Clinicamente, identifica-se a formação de hematoma, seguida de deformidade. A fratura de pênis seguida de lesão uretral ocorre em 10% dos casos (2,3).

A seguir descrevemos um caso de fratura peniana associada com lesão uretral tratado através de cirurgia.

RELATO DO CASO

Paciente de 41 anos do sexo masculino, branco, deu entrada no Pronto Socorro com quadro de edema peniano seguido de dor intensa. Relatou que 2 horas antes, durante relação sexual, dobrou violentamente o pênis e ouviu um estalido, seguido de dor instantânea.

Ao exame físico apresentava volumoso hematoma peniano e uretrorragia (Figura-1). Com hipótese diagnóstica de fratura peniana e com provável rotura de corpo esponjoso, foi levado ao centro cirúrgico para exploração.

Não foi realizada a uretrografia pré-operatória porque conseguimos inserir sem dificuldade um cateter uretral, conseguindo identificar o sítio da lesão com facilidade (Figura-2). Como o paciente apresentava-se com dor local intensa e muita agitação foi realizado o cateterismo uretral sob sedação.

O paciente foi então submetido a uma incisão subcoronal e exposição de todo o pênis. Na superfície ventral do corpo cavernoso esquerdo, próximo a base, foi identificado uma lesão da túnica albugínea. A uretra apresentava lesão de 0,5 cm adjacente à lesão do corpo cavernoso, bem evidente após tentativa de cateterismo uretral (Figura-2). Foi realizado esvaziamento dos coágulos e síntese da túnica albugínea com fio absorvível de poliglactina 2-0 pontos separados e fio poliglactina 5-0 na lesão uretral. A introdução do cateter auxiliou, também, no reparo da lesão servindo como "molde". Deixado uma sonda uretral 18F por 4 dias e uma cistostomia por 14 dias.

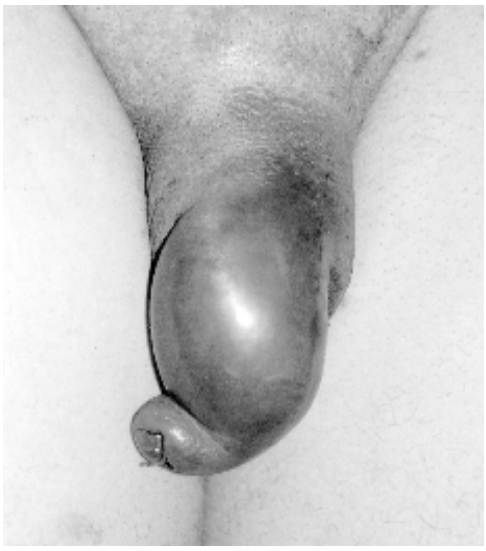

***Figura 1** – Observa-se volumoso hematoma peno-escrotal e saída de sangue pelo meato uretral externo.*

O paciente, atualmente, encontra-se totalmente assintomático, decorridos 16 meses da cirurgia. Apresenta micção espontânea sem nenhum sintoma obstrutivo e função erétil preservada.

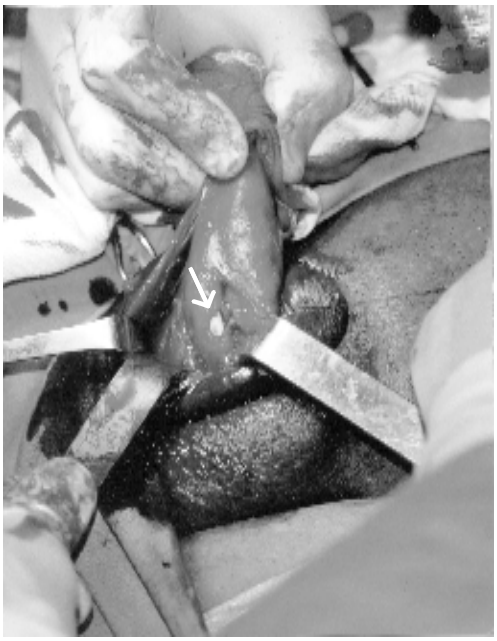

***Figura 2** – Durante exploração cirúrgica identifica-se a sonda de Foley caracterizando uma solução de continuidade na uretra.*

DISCUSSÃO

A fratura de pênis ou rotura de corpo cavernoso é um trauma genital raro, sendo descrito, aproximadamente, 200 casos (2,3). De acordo com um estudo recente, apenas 100 casos teriam sido publicados até 1988 (3). A lesão uretral associada é ainda mais infreqüente, ocorrendo em 10% dos casos (2,3). Acreditamos que muitos pacientes com fratura de pênis sequer procuram auxílio médico por constrangimento ou medo.

Esta lesão está sempre associada ao pênis no estado ereto, provavelmente devido a rigidez e ao adelgaçamento da túnica albugínea durante a ereção, de 2 mm para 0,5 mm (2). A lesão apresenta-se como um estalido com rápida detumescência seguida de dor, edema peno-escrotal e equimose. Nos casos com lesão de uretra associada, geralmente, está presente sangue no meato uretral externo e dificuldade para urinar (Figura-1).

O tratamento ideal da fratura peniana tem sido controverso. Até meados deste século, defendia-se a utilização de gelo, analgésicos e antibióticos (3). Aproximadamente 10% dos pacientes tratados desta maneira conservadora evoluíam com curvatura peniana importante. No entanto, a maioria dos trabalhos mais atuais advoga a exploração cirúrgica o mais breve possível (1,2). As vantagens da cirurgia reparadora são: curto período de internação hospitalar, menor índice de infecção e menor chance de desenvolver deformidade peniana. Nos casos com lesão de uretra a maioria dos autores sugere a correção cirúrgica imediata, através da re-anastomose ou da sutura com pontos absorvíveis. No caso acima descrito, a rotura da uretra não foi completa e, por isso, mais fácil de reparar. A exploração imediata com sutura da lesão uretral com fio absorvível proporcionou uma perfeita cicatrização sem seqüelas urinárias em longo prazo.

O caso aqui descrito reitera a importância no diagnóstico da fratura de corpo cavernoso quando associado a lesão da uretra peniana. Para um adequado restabelecimento da função erétil sem seqüelas é necessária a intervenção cirúrgica o mais precoce possível.

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Surgical Technique

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ALTERNATIVE FOR THE USE OF PROSTATIC RETRACTORS IN RADICAL PERINEAL PROSTATECTOMY

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ABSTRACT

The performance of perineal radical prostatectomy often required the use of high cost retractors (Young or Lowsley). An alternative option that was formerly employed by one of the authors is the use of a 22 or 24F Foley catheter passed through the urethra into the bladder and then, filling the balloon with about 20 cc of saline solution. By pulling strongly the catheter made possible to bring the prostate more close to the perineal incision. This maneuver, make possible our first 12 radical perineal prostatectomies. However, even making the procedure possible, this maneuver would exert tension over the penis and urethra. Therefore, to facilitate the procedure and to spare the penis and urethra from excessive tension, the authors designed a simple and low cost retractor.

The retractor is made by using a 24F Foley catheter with a 26 or 28F Beniqué dilator inside. The Beniqué is introduced passing trough a cut made two-thirds from the extremity of the Foley. This unit is then introduced through the urethra inside the bladder and the balloon is inflated. Afterwards, moving the Beniqué over the abdomen allows the surgeon to retract the prostate towards the perineal incision, making though the radical perineal prostatectomy feasible.

With this simple device, the authors have so far successfully performed over 50 radical perineal prostatectomies.

Key words: prostate, prostate cancer, radical perineal prostatectomy, retractor
Braz J Urol, 26: 298-300, 2000

INTRODUÇÃO

Recentemente a prostatectomia radical perineal ressurgiu como alternativa para o tratamento cirúrgico do câncer de próstata localizado. O acesso perineal data de 400 AC, para retirada de cálculos vesicais por Ammonius Lithotomus. Em 25 DC, Celsus descreveu a incisão curvilínea no períneo. Covillard, em 1639, removeu um lobo mediano durante uma litotomia perineal. Porém, foi Billroth quem primeiro realizou uma prostatectomia perineal para carcinoma prostático, em 1867 (1).

O uso do acesso perineal para cirurgias prostáticas levou ao desenvolvimento de inúmeros instrumentos para facilitar a exposição da glândula masculina, tais como tratores prostáticos, afastadores perineais e mesas cirúrgicas especiais.

Em 1900, Syms desenvolveu um balão para ser inflado na bexiga e tracionar a próstata para fora do períneo. Proust, em 1901, idealizou um trator prostático e uma mesa apropriada para cirurgias perineais (1).

No ano de 1904, o Dr. Hugh Hampton Young, considerado o "pai da prostatectomia perineal", realizou sua primeira cirurgia para carcinoma prostático no Johns Hopkins Hospital, Baltimore, USA, vindo o paciente a desenvolver litíase na linha de sutura e falecer na cirurgia para retirada dos cálculos. Em outras 128 prostatectomias perineais consecutivas ocorreram apenas 3 mortes (2). Young desenvolveu seu próprio trator prostático e mesa de cirurgia. O instrumento original por ele idealizado possuía apenas uma lâmina. Mais tarde, acrescentou-lhe outra, devido às

freqüentes saídas do mesmo nos momentos principais da cirurgia (1).

Mesmo com todas as modificações e facilidades atuais, a prostatectomia radical perineal é praticada em poucos centros em todo o mundo. Os autores apresentam sua experiência com o uso de um dispositivo adaptado para a realização desta cirurgia.

TÉCNICA CIRÚRGICA

Durante a dissecção apical na prostatectomia radical perineal, a tração da glândula é de primordial importância para que não ocorra uma dissecção em plano errado com conseqüente risco de lesão retal. O instrumento que utilizamos para exposição prostática consiste de um Beniqué 26 ou 28F e um cateter de Foley 22 ou 24F com duas vias. O Beniqué é introduzido por dentro do cateter através de uma incisão lateral, tendo-se o cuidado de não romper o fino conduto paralelo que leva ao balão (Figuras-1 e 2).

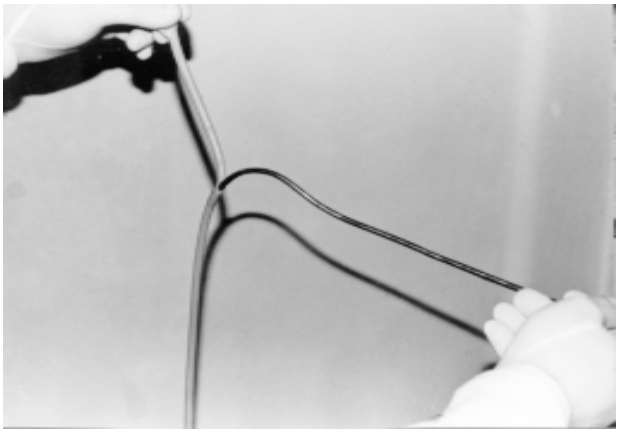

Figura 1 – *Passagem do Beniqué por dentro da sonda de Foley.*

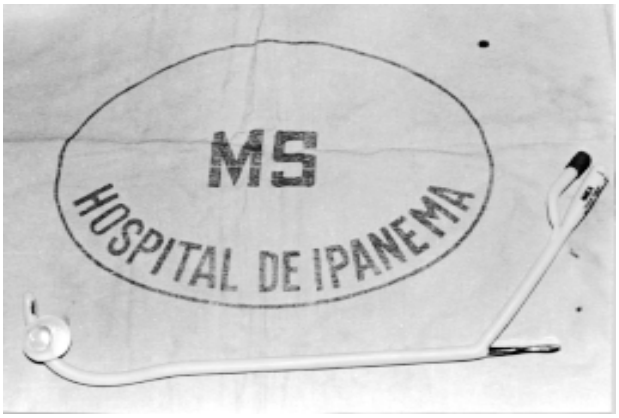

Figura 2 – *Trator pronto para o uso, evidenciando-se a integridade do balão.*

O conjunto é introduzido pela uretra até a bexiga e o balão inflado para permitir a tração da próstata e sua exposição durante o ato operatório (Figura-3).

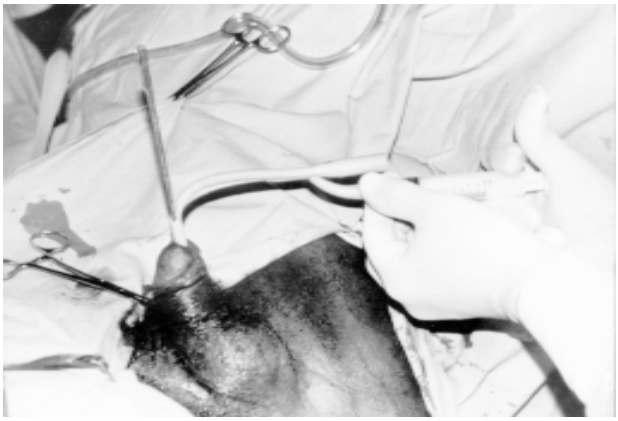

Figura 3 – *Posicionamento peroperatório do trator.*

A cirurgia é realizada de forma clássica e após a secção da uretra, o conjunto é retirado e utiliza-se um outro cateter de Foley introduzido na bexiga ou uma pinça de Allis, para ajudar a dissecar a próstata do colo vesical e a retirar as vesículas seminais.

COMENTÁRIOS

A realização de cirurgias perineais muitas vezes necessita de mesas cirúrgicas, afastadores perineais e retratores prostáticos especiais. No passado, a prostatectomia perineal era realizada em muitos centros e desenvolveram-se inúmeros tratores para a apresentação da próstata durante o ato operatório, sendo os mais conhecidos os de Young e de Lowsley.

Este tipo de instrumento passou a fazer parte novamente do armamentário do urologista após o ressurgimento da prostatectomia radical perineal para tratamento do câncer de próstata localizado. Porém, trata-se de material de custo elevado e a realização do procedimento em serviços onde não se pode contar com tais tratores, só poderia ser realizada com desconforto e tempo cirúrgico elevado.

Com a finalidade de viabilizar a realização da prostatectomia radical perineal em nossa instituição, adotamos o uso de um trator confeccionado a partir de material de baixo custo e amplamente disponível. Utilizamos uma pequena variação da técnica descrita por Nieh (2), com o uso de um Beniqué ao invés da sonda de Van Buren. Em nossa experiência de mais de 50 casos de prostatectomia radical perineal, este dispositivo permitiu uma boa exposição prostática durante todo o ato cirúrgico, com tração atraumática.

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SPERMATOZOA AND SPERMATIDS RETRIEVAL: MULTIPLE TESTICULAR BIOPSY TECHNIQUE

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ABSTRACT

Mature spermatozoa, as well as elongated or round spermatids, may be recovered from testicular tissue of non-obstructive azoospermic patients. These sperm cells have fertilizing capability when the intracytoplasmic sperm injection (ICSI) procedure is used. Thus, genetic offspring is possible in a population of individuals who were advised to use donated spermatozoa.

Failure of testicular sperm cell extraction (TESE) may occur in up to 57% of the attempts in patients with non-obstructive azoospermia. Currently, there are no means of predicting the presence of spermatogenesis, which may be focal. TESE has been a blind procedure that does not identify focal sperm-producing areas. Therefore, these areas may not be extracted by testicular percutaneous puncture or conventional testicular biopsy.

The approach of planned biopsy and cryopreservation before an in vitro fertilization (IVF) cycle can avoid the need of ovarian stimulation in cases where no spermatozoa or spermatids are recovered with biopsy.

Several approaches have been described for the isolation of rare spermatozoa present in the testes of individuals with complete azoospermia and limited sperm production.

We describe a technique for extracting testicular spermatozoa or spermatids by means of multiple testicular biopsies, rather than using a single testicular sample, which contributes to obtaining spermatozoa and spermatids in amounts sufficient for fertilization and cryopreservation from non-obstructive, azoospermic patients, with minimum trauma.

Key words: azoospermia, non-obstructive, sperm extraction, biopsy, male infertility, testis
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INTRODUÇÃO

Um paciente portador de azoospermia não-obstrutiva pode ser pai genético através da pesquisa minuciosa no interior do testículo para encontrar espermatozóides para serem utilizados na técnica de ICSI (intracytoplasmic sperm injection) (1,2). Tesarik et al. (3) utilizaram com sucesso células imaturas, espermátides, obtidas diretamente do testículo. Contudo, 50% dos pacientes com quadro de azoospermia não-obstrutiva apresentam espermatozóides ou espermátides no interior do testículo. Assim, diversos métodos têm sido preconizados: a biópsia testicular convencional e a punção aspirativa são os mais utilizados.

Todavia, esses 2 procedimentos são realizados totalmente às cegas, seguindo apenas o princípio de amostragem. Portanto, existe a possibilidade de áreas focais com túbulos seminíferos produtores de espermatozóides ou espermátides não serem extraídas pelos métodos supracitados. A técnica de extração de espermatozóides ou espermátides testiculares através das múltiplas biópsias testiculares, descrita a seguir, objetiva sobrepujar esta dificuldade com mínimo trauma.

TÉCNICA CIRÚRGICA

O paciente é colocado em posição supina sob anestesia geral ou local. O auxiliar apreende um dos

testículos para secção da pele que reveste o eixo transversal do testículo na extensão de 1,0 cm (Figura-1). Abre-se cuidadosamente a musculatura do dartos, mantendo-se a túnica vaginal fechada. Recomendamos realizar uma minuciosa hemostasia.

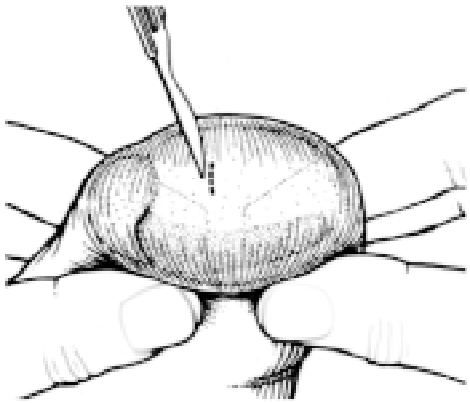

Figura 1 *– Incisão do hemiescroto na extensão de 1,0 cm.*

Utilizando-se uma tesoura de íris e uma pinça de Adilson, a musculatura do dartos é aberta cuidadosamente. Terminada a secção do dartos, um segundo campo cirúrgico, impermeável e com uma pequena abertura central é sobreposto sobre a incisão. Este campo é preparado a partir de luva estéril sem talco e objetiva impedir o umedecimento dos campos cirúrgicos circunjacentes e diminuir a contaminação do material que será colhido posteriormente.

Uma vez apreendida a túnica vaginal, o auxiliar libera o testículo e o cirurgião traciona essa túnica através do orifício do segundo campo. Abre-se a túnica vaginal e após repará-la, aspira-se o líquido intravaginal, identificando-se com facilidade a túnica albugínea. O testículo é imobilizado, sendo possível expor desde o segmento cefálico do epidídimo até o pólo inferior do testículo. Com o auxílio do microscópio cirúrgico, os vasos subcapsulares da túnica albugínea do testículo são perfeitamente reconhecidos e evitados, possibilitando-se assim, juntamente com a mobilização do órgão, a identificação de áreas avasculares. Desta forma, com um bisturi de lâmina 11, múltiplas microincisões atingindo apenas a albugínea podem ser realizadas, praticamente sem sangramento, e os túbulos seminíferos ficam assim expostos (Figura-2). Com duas pinças apropriadas para microcirurgia, os túbulos seminíferos são extraídos com delicadeza e segurança. A primeira amostra é fixada no líquido de Bouin para o diagnóstico histológico e os outros fragmentos extraídos são introduzidos em tubos estéreis contendo meio de cultura e encaminhados ao laboratório.

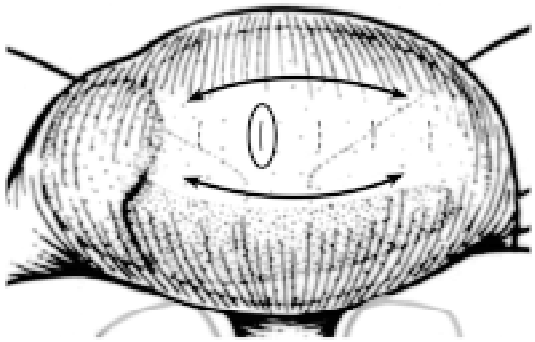

Figura 2 *– Múltiplas incisões na albugínea.*

No laboratório, cada fragmento é retirado do tubo e transferido com o auxílio de uma micropipeta para uma placa sob o estereomicroscópio. Empregando-se agora duas pinças apropriadas, os túbulos seminíferos são estirados e espremidos ao mesmo tempo, favorecendo-se assim a remoção das células germinativas do interior dos túbulos. Em seguida, esta suspensão composta de meio de cultura e células germinativas é transferida para o microscópio invertido. Nesta etapa, vários campos microscópicos são examinados com a finalidade de identificar os diferentes elementos germinativos presentes no material obtido.

Em se tratando de testículo, freqüentemente são encontrados espermatozóides imóveis e vários agrupamentos celulares, especialmente de espermátides. Em alguns campos é possível, o encontro de espermatozóides com algum movimento.

Após a obtenção do gameta masculino, a cirurgia encerra-se com o fechamento da túnica albugínea, da túnica vaginal, da musculatura do dartos e da pele. O paciente recebe alta no mesmo dia.

O procedimento entra agora na sua última fase, onde o elemento germinativo mais avançado é retirado da suspensão celular e transferido para uma

solução contendo polivinilpirrolidona (PVP). Em se tratando de espermatozóide, ele será o primeiro imobilizado e depois aspirado, estando pronto assim para a injeção intracitoplasmática em oócito (ICSI).

COMENTÁRIOS

Esta técnica de extração testicular (TESE-testicular sperm extraction) maximiza a colheita de espermatozóide ou espermátides para os procedimentos de reprodução assistida, principalmente nos casos de azoospermia não-obstrutiva, no qual, a possibilidade do insucesso é maior como nas técnicas de aspiração por punção testicular percutânea ou biópsia testicular convencional.

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PENOSCROTAL HYPOSPADIAS

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ABSTRACT

Proximal hypospadias include proximal penile, penoscrotal, scrotal and perineal types in which the site of the urethral meatus is respectively the proximal third of the penis, root of penis, scrotum or between the genital swellings and below the genital swellings. Proximal hypospadias cause micturition problems besides limiting sexual intercourse and fertility, and require correction.

Newborn children with proximal hypospadias bearing ambiguous genitalia characteristics or associated with cryptorchidism must be better studied from the standpoint of sexual development prior to gender assignment and before the birth certificate is obtained. This evaluation should be multidisciplinary, consisting of tests such as sexual chromatin investigation, karyotype, stimulation test using chorionic gonadotrophin, pelvic sonographic screening and retrograde and urinary urethrocystography, and eventually biopsy of the gonad. In the remaining cases, parents should be assured of the neonate's gender, and the only medical concern while awaiting surgical repair is to make sure that no stricture of the urethral meatus exists that may cause micturition difficulties.

Optimal age for hypospadias repair is between eight and 12 months of age. At that stage, the size of the penis is almost equivalent to that of a three year old child, and the trophic conditions of the skin allow a high degree of safety during operation.

Multiple principles rule the techniques used in hypospadias correction. This article will describe these principles and the authors' experience with some techniques for penoscrotal hypospadias repair.

Key words: hypospadia, penoscrotal hypospadias, indications, surgical techniques
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INTRODUCTION

Male hypospadias is a congenital anomaly, which affect different structures of the penis and eventually the scrotum and perineum. A wide range of types of hypospadias can be observed according to the original site of the opening of the urethral meatus and to other associated deformities. They are found in varying configurations that range from an aspect of ambiguous genitalia to a well-formed penis with a superficial defect.

Hypospadias is a common congenital anomaly and its incidence in Brazil has been calculated as 1:565 live male birth (1).

Some penile anomalies, often associated with hypospadias, are related to cosmetic and functional aspects of the penis (2). When in erection it is considered a significant ventral curvature of the penis (chordee) a deflection angle of the shaft of the penis greater than 20 degrees (3). In proximal hypospadias, the ventral curvature is often caused by fibrous chordee. Chordee is formed by residual fibrous tissue of the corpus spongiosum and is located on the ventral urethra, distal to the urethral meatus, in close contact with the tunica albuginea. Other significant causes of the ventral curvature began to be better defined with the introduction of the artificial erection technique (3). The cutaneous chordee arising out of the asymmetric distribution of the skin around the penis can originate some degree of curvature both in distal and in proximal hypospadias. Also, there can be an asymmetry of the tunica albuginea, which accounts for the permanence of the curvature despite the excision of the entire fibrous chordee (4). Other

uncommon cause of penile curvature is the growth differential between the corpora cavernosa and the corpus spongiosum.

In proximal hypospadias, the prepuce is asymmetric, accumulating on the dorsum of the penis and being deficient on the ventral segment. The prepuce may be normal in distal hypospadias in up to 7% of cases. Urethral meatus stenosis is less frequent in proximal hypospadias, where it is observed in about 15% of cases. Axial kicking of the shaft of the penis occurs in 14% of patients, and is not dependent on the degree of hypospadias.

Proximal hypospadias are a less common occurrence and correspond to 20% of total hypospadias. Proximal hypospadias are usually associated with scrotal malformations, such as penoscrotal synaechia, hypoplasia, bifid scrotum and high scrotum implantation.

The most commonly used classification of hypospadias is Barcat's, and it is based on the location of the urethral meatus after correction of the associated curvature of the penis. Proximal hypospadias include proximal penile, penoscrotal, scrotal and perineal types in which the site of the urethral meatus is respectively the proximal third of the penis, root of penis, scrotum or between the genital swellings and below the genital swellings.

Proximal hypospadias cause micturition problems besides limiting sexual intercourse and fertility, and require correction. Moreover, non-treated hypospadias put the patients at risk emotionally, regarding acceptance of their own body image, through the transference of parents' anxiety or the acknowledgement of the condition by friends or a sexual partner, which leads to embarrassing situations (5).

PATIENT PREPARATION

Newborn children with proximal hypospadias bearing ambiguous genitalia characteristics or associated with cryptorchidism must be better studied from the standpoint of sexual development prior to gender assignment and before the birth certificate is obtained. This evaluation should be multidisciplinary, consisting of tests such as sexual chromatin investigation, karyotype, stimulation test using chorionic gonadotrophin, pelvic sonographic screening and retrograde and urinary urethrocystography, and eventually biopsy of the gonad.

In the remaining cases, parents should be assured of the neonate's gender, and the only medical concern while awaiting surgical repair is to make sure that no stricture of the urethral meatus exists that may cause micturition difficulties. Exceptionally, a meatotomy may be necessary.

Optimal age for hypospadias repair is between 8 and 12 months of age. At that stage, the size of the penis is almost equivalent to that of a 3 year old child, and the trophic conditions of the skin allow a high degree of safety during operation. Children at that age suffer much less emotionally during the postoperative period than do older children and, as a consequence, parents' anxiety is also alleviated (2). During that period children are still in diapers and have not been exposed to other people's observation. Still more important, in case of complications that require reintervention further correction can be carried out sometime before the second year. At about this time the genital awareness begins and the child becomes more prone to psychological problems.

POSTINFORMED CONSENT

Parents must be informed with regard to prospects of success, care and inconvenient that involve the postoperative period, occurrence of complications associated with the repair of hypospadias and its treatment. In countries where this is customary the information should be provided to parents in written and contain the respective signatures of consent.

PREOPERATIVE PREPARATION

Preoperative laboratory tests are the basic required for this type of surgery. An ultrasonographic screening of the urinary tract is essential to rule out associated anomalies.

Preparation of the skin is obtained by washing it extensively with an iodized germicide solution (1%

active iodine) and saline, from some centimeters above de umbilical scar to the knees, including the entire perineum. The germicide solution is removed with pads and the desinfection is concluded with the topical use of the same solution.

INSTRUMENTATION

The suture material employed should be atraumatic; monofilament sutures are preferable (PDS or Vycril 6-0). The surgical material consists of the delicate instruments used in plastic surgery. Often a loupe is utilized with magnification at 2.5 power and a large focal length, which offers a detailed field of vision during surgery. The glans is fixed with nylon 5-0 suture to facilitate presentation of the penis throughout surgery.

DESCRIPTION OF SURGICAL PROCEDURES

Multiple principles rule the techniques used in hypospadias correction. We will indicate some examples, since it is impossible to mention here all the techniques described. The first reports of hypospadias surgery date back to the second century. Techniques proposing neourethroplasty via a dermal graft, extending from the urethral meatus to the glans, date from 1836, when Dieffenbach, and, later, Duplay, with 2 lateral incisions brought together the edges of the urethral floor to form a new urethra. In spite of initial failures, for the first time valid principles of the hypospadias surgery were employed (6).

At that period the correction of the ventral curvature by excision of the fibrous chordee began to be recognized. The concept of treating the ventral curvature at an initial and isolated stage (orthophaloplasty) became a dogma for all degrees of hypospadias (7).

Smith (8), in 1973, modified Duplay's technique proposing the coverage of the neourethra with a de-epithelialized skin flap, thus considerably reducing the incidence of urethrocutaneous fistula (9).

Devine & Horton (6) used a preputial skin graft after release of the fibrous chordee in a single procedure and reported good results with one-stage repairs. Hodgson (3) and, later, Asopa & Asopa (11) utilized the prepuce in the construction of the neourethra and to bridge the cutaneous defect of the urethral ventrum. Although the graft of the mucosal surface had the shape of an island its pedicle was not dissected but was brought along with the cutaneous surface of the prepuce onto the urethral ventrum. The advantage of this technique over the technique previously described lies in that the blood supply to the same tissues does not suffer interruption.

Duckett (12) suggested the use of a preputial island flap, where the preputial mucosa used to form the new urethra has a well-individualized pedicle containing superficial dorsal penile vessels and, when dissected to a certain extent, allows the neourethra to be advanced to the urethral plate without traction of the pedicle (Figure-1). With this technique the cutaneous surface of the prepuce becomes less vascularized and the tailoring of the skin around the penis using the Blair-Byars technique is more difficult.

Asopa & Asopa (11) devised the double-faced preputial island flap which consists of an adjacent skin flap covering the mucosal flap which serves as the new urethra, both being maintained by the same pedicle. The cutaneous surface graft is thus very well vascularized and when advanced along with the neourethra to the urethral ventrum permits a uniform distribution of the skin around the penis.

Considering hypospadias globally, to the present more than 300 original techniques and their variations have been described for its correction. The ultimate goal of hypospadiology is to achieve a normal penis regarding both function and morphology.

In the 1980s distal hypospadias began to be repaired in one procedure. At a later period, one-stage techniques were adopted for the correction of more complex hypospadias (13). In 1984 we began to use the Double Preputial Island Flap procedure (DIF) in substitution to the Preputial Island Flap as this technique ensures a better vascularization of the skin flap employed in the coverage of the ventral raw surface and allows a more homogeneous skin distribution around the penis.

The utilization of one-stage techniques became more popular as surgeons gained experience

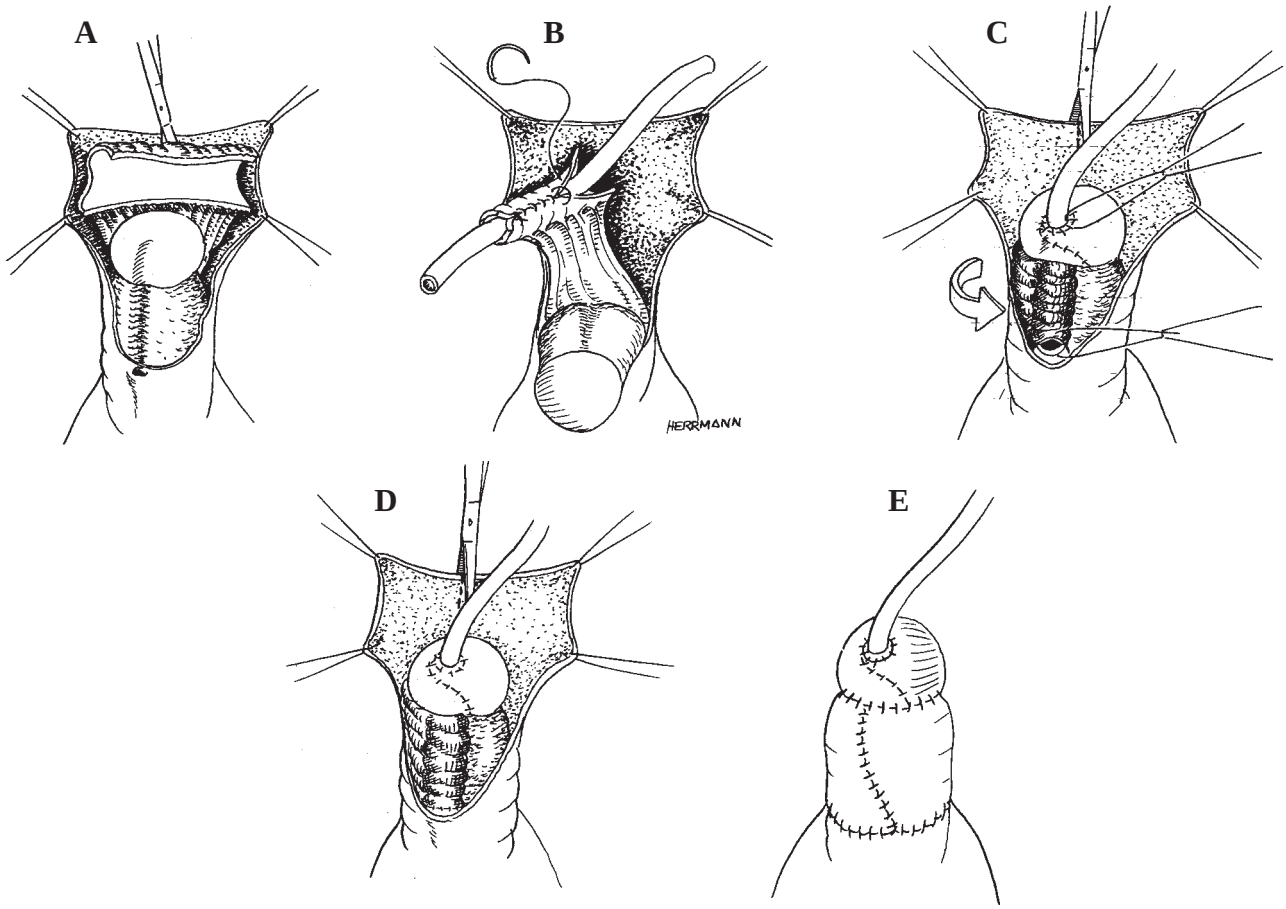

Figure 1 *- Schematic representation of island flap procedure.*

with these procedures, and the results obtained proved to be satisfactory. Familiarity with these methods represented an additional resource for electing the procedure that best applies in each individual case.

In March 1985 we began to perform on the cutaneous aspect of the preputial island double-flap (14,15), similar to the technique used by Smith (8), the de-epithelization of two rectangular strips close to the proximal and contralateral edges of the pedicle. Another tissue plane was created to offer a better protection against the formation of urethrocutaneous fistulas (Figure-2). With this method we were also able to avoid the depression that may occur between the neourethra and the corpus cavernous on the opposite side of the pedicle. Besides, it was possible to use the redundant skin from the cutaneous portion of the double island flap. After the modification introduced by us, this procedure is now called the Modified Preputial Island Double-Flap operation (MDIF). Later on, the application of the MDIF surgery was extended to include scrotal and perineal hypospadias, and the technique was further developed by adding to it the tubularization of the urethral plate up to the base of the penis, according to Duplay's technique (Figure-3).

More recently, due to the incidence of stenosis at the level of the anastomoses, and to the occurrence of urethrocutaneous fistulas, we have focused our attention on the preservation of the urethral plate. Despite the presence of 2 suture lines, the flaps are fixed to the spongiosum, which is a very well vascularized tissue and ensures a much lower incidence of fistulas. At the same time, circular sutures no longer exist at the level of the anastomoses, minimizing the risks of scar retraction and of meatal stenosis or proximal anastomotic strictures. Moreover,

the neourethra stands well rectified which makes easier an eventual catheterization.

The preservation of the urethral plate applies to hypospadias: 1)- without penile bend; 2)- with penile curvatures caused by cutaneous chordee; 3)- with mild penile curvatures by fibrous chordee which can be excised below the urethral plate; 4)- with moderate curvatures or residual bends caused by fibrous chordee or by asymmetry of the tunica albuginea where the contralateral plication does not significantly reduce the size of the penis. If necessary, the surgeon should not hesitate to discard the urethral plate in order not to shorten excessively the penis. Concerning this decision it is important to emphasize that performing the artificial erection is essential not only at the beginning of the procedure but especially during surgery.

Often, the tip of the hypospadic urethra is hypoplastic, which only conceals a more severe degree of hypospadia. Since this is a poorly vascularized tissue, not fitted for the anastomosis, it should be discarded and the urethra cut back to good spongiosum.

For more than one decade and a half we have being repairing all types of hypospadias, regardless of their degree in one operation. Techniques in 2 or 3 stages are reserved to patients previously submitted to surgery in whom the preputial hood is not available and that require us to adapt to existing conditions.

Operative Act for Correction of Proximal Hypospadias without Preservation of the Urethral Plate (Figures-2 and 3)

A circular incision is made distally to the urethral meatus, approximately 3-mm from the glans neck, and the fibrous chordee is excised on the urethral plate obtaining a progressive straightening of the penis. If a significant curvature still persists, by asymmetry of the tunica albuginea we proceed to plicate it on the dorsum of the penis, thus achieving the straightening of the organ. With the assistance of stitches, we present and outline with stain a horizontal rectangle on the mucosal surface of the prepuce which will constitute the neourethra with a length that will extend from the new position of the urethral meatus to the apex of the glans and whose caliber will equal that of the normal urethra. Superficial incisions are made following the previously drawn lines, deep enough to allow tubularization of the new urethra. The neourethra is created over a 6F plastic catheter. Several interrupted sutures are used on the edges of the neourethra; care must be taken to leave them spatulated. The neourethra is completed using a continuous suture. Afterwards, a rectangle is outlined on the cutaneous portion of the prepuce keeping the same direction as the coverage of the neourethra and raw surface of the urethral plate. As a reference we use the glans neck which represents the inferior side of the rectangular flap. After incising the skin, we proceed to dissect the pedicle responsible for the vascularization of the preputial island double-flap immediately below the superficial fascia, towards the base of the penis. The other dissection plane of the pedicle is right above de deep fascia of the penis, close to the tunica albuginea of the corpora cavernosa. The pedicle thus defined and which contains the penile superficial dorsal vessels is dissected to a sufficient extent permitting the preputial island double-flap to pass without any tension to the urethral plate, parallel to the shaft of the penis. Then the proximal anastomosis is made between the neourethra and the urethra, both espatulated, using interrupted sutures over a urethral catheter. Next, the distal anastomosis is made between the neourethra and the glans. The technique proposed by Devine & Horton is preferred; according to this method, 3 flaps are created originating from the V or Y-incision of the glans; the distal flap is incorporated to the distal end of the neourethra and the other 2, lateral, cover it. In the MDIF technique 2 strips of approximately 4 mm are outlined with stain on the inferior portion of the preputial island double-flap and on the margin contralateral to the passage of the pedicle relatively to the shaft of the penis. Both segments are de-epithelialized with a scalpel and/or iris scissors and then sutured laterally to the deeper fascia of the penis and proximally to the subcutaneous cellular tissue covering the anastomosis. Then the skin is closed and sutured to the mucosa of the glans neck at the correspondent points.

In patients with scrotal and perineal hypospadias, a Duplay-type neourethroplasty is

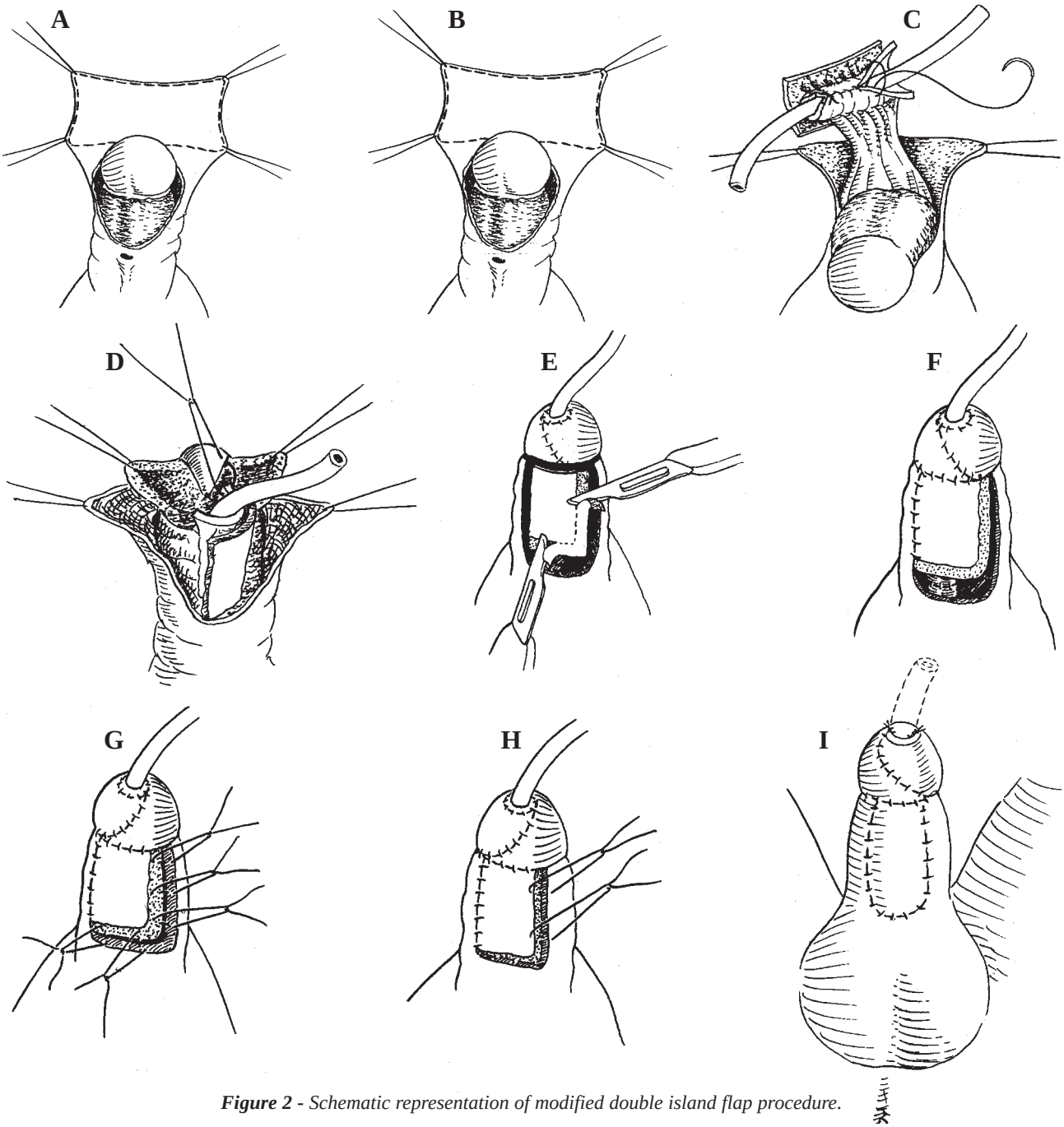

Figure 2 - *Schematic representation of modified double island flap procedure.*

performed, beginning at the urethral meatus and extending up to the base of the penis, thus allowing the neourethra made using the preputial mucosa graft to be sufficiently long to reach the tip of the glans. In these cases, the proximal anastomosis is made between two neourethras.

Operative Act with Preservation of the Urethral Plate (Figure-4)

We will point out only the aspects that distinguish this procedure from the method previously described.

The incision of the skin is circular and made on its dorsal and lateral aspects 3 mm from the glans neck. It is U-shaped on the urethral plate and surrounds the urethral floor. In order to avoid any accidental lesion to the urethra, next to the meatus, we recommend injection of normal saline using a fine needle (insulin needle) to achieve separation of adherent skin from the urethra. If exists a curvature caused by cutaneous chordee this is corrected after the incision of the skin. When the bend is moderate, regardless of the cause, it can be eliminated by plicating the dorsal tunica albuginea on each side relatively to the neurovascular bundle. When fibrous chordee is responsible for the curvature it can be excised laterally and inferiorly to the urethral plate. If a slight bend caused by fibrous chordee or asymmetry of the corpora cavernosa still persists the dorsal plication may be associated. However, when the remaining curvature is significant and due to the urethral plate, the latter should not be preserved and the technique previously described above is utilized.

Next, the preputial mucosal island flap is delimited and once it has been sutured to the mucosal plate it will form the neourethra. For this reason, it has the same length as the urethral plate but is narrower. The width of the flap associated with the width of the urethral plate should offer a neourethra whose diameter is the same as that of the normal urethra. The preputial skin island flap is delimited and the dissection of the pedicle is carried out as previously described.

After bringing the preputial island flaps to the urethral plate and placing the pedicle alongside the shaft of the penis, the mucosal flap is incorporated to the urethral plate with continuous sutures beginning at the urethral meatus and initially lying on the same side of the pedicle. The next steps are identical to what has been already described.

POSTOPERATIVE CARE

Postoperative care is mainly related to drainage of urine and to dressing.

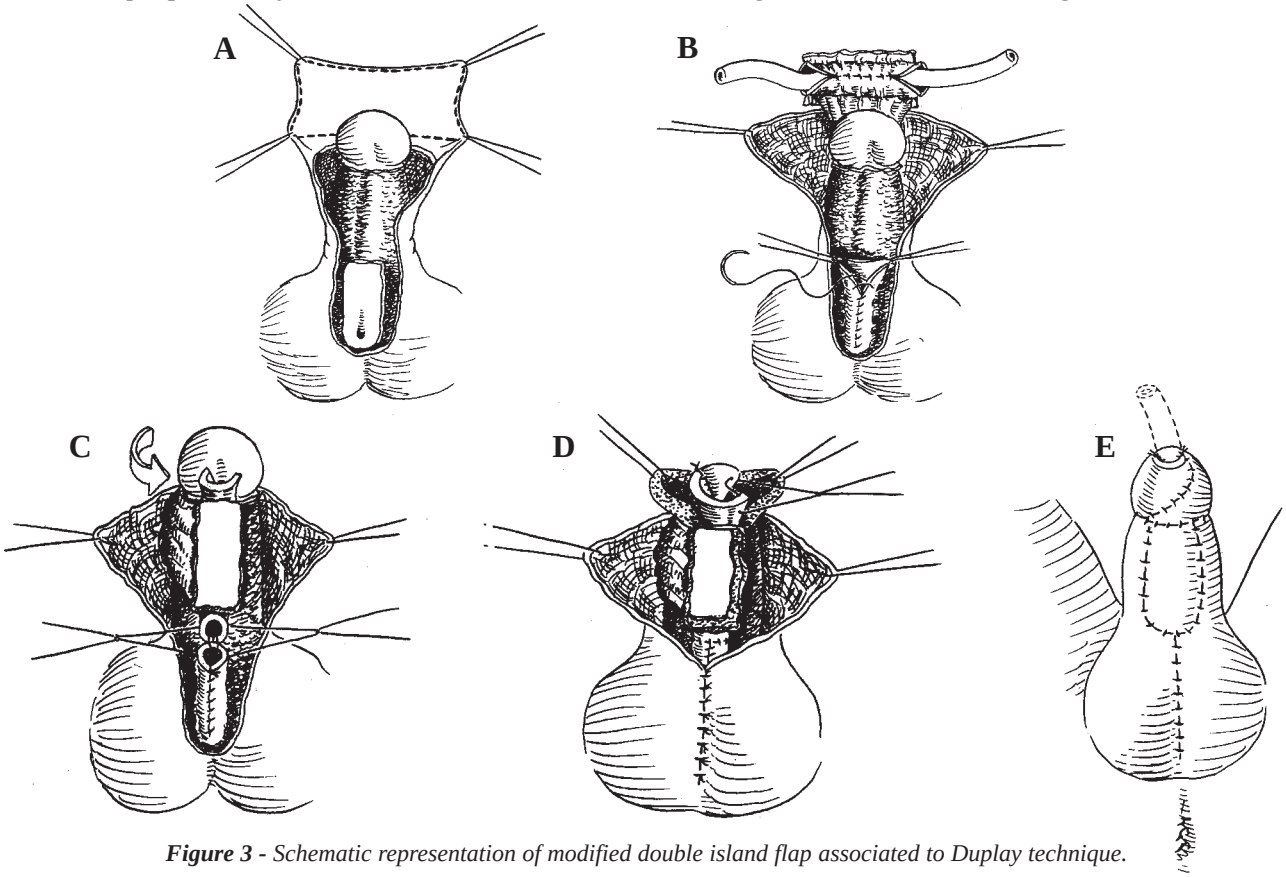

Figure 3 *- Schematic representation of modified double island flap associated to Duplay technique.*

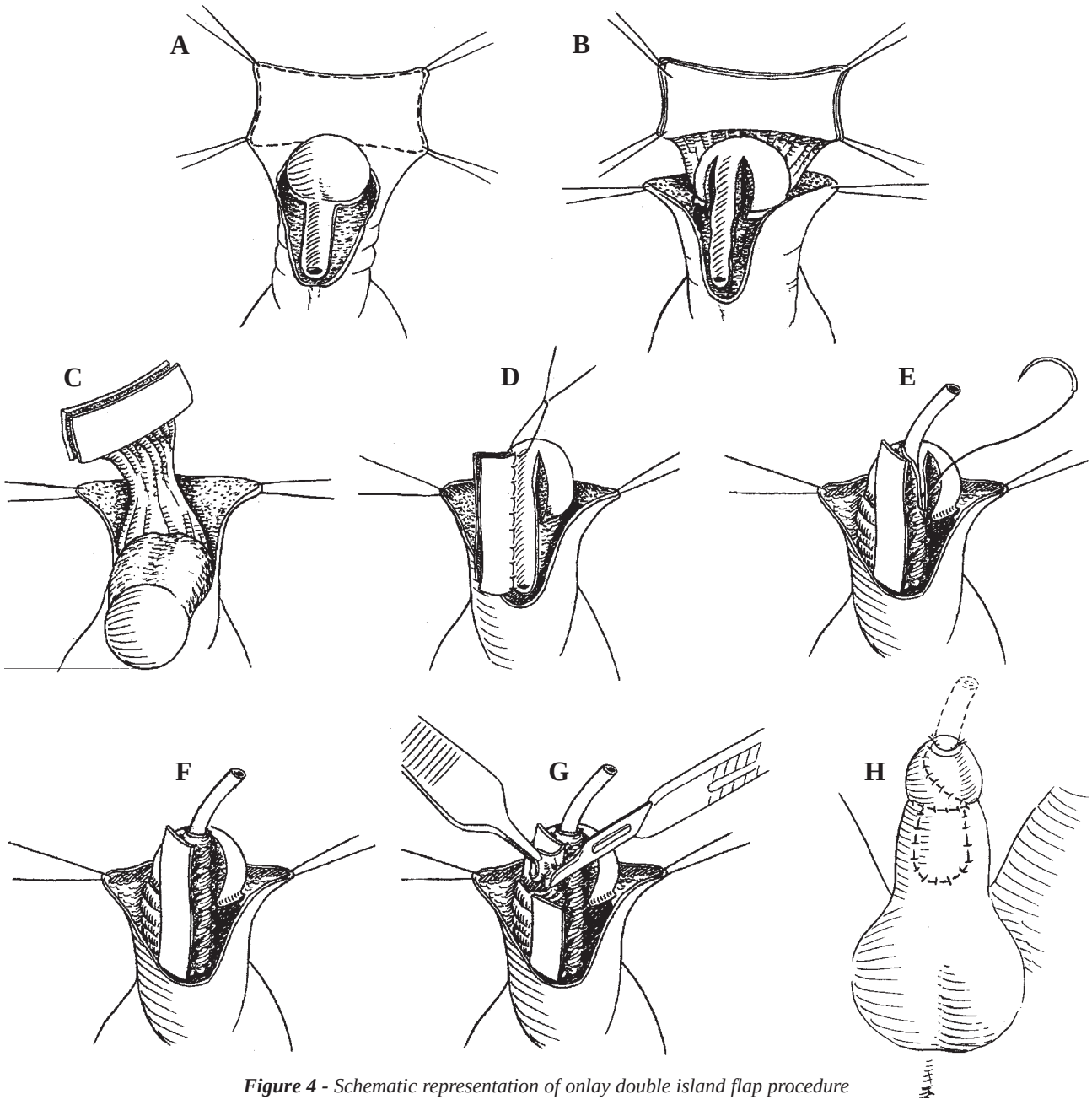

Figure 4 *- Schematic representation of onlay double island flap procedure*

In proximal hypospadias urinary drainage is necessary. The most commonly employed methods of urinary drainage are the urethral catheter, either continent or incontinent, and the suprapubic catheter (Figure-5).

In children still in diapers we prefer to leave the internal end of the urethral catheter in the bladder and to section the external end, fixing it to the glans. The urine drips continuously into the diaper. Another common alternative used by other surgeons is to leave the external end longer and allow it to drain between 2 diapers.

In older children, that no longer use diapers, the internal end can be left in the bulbous urethra in order to maintain the child continent, and the urine is eliminated through the catheter only during mictu-

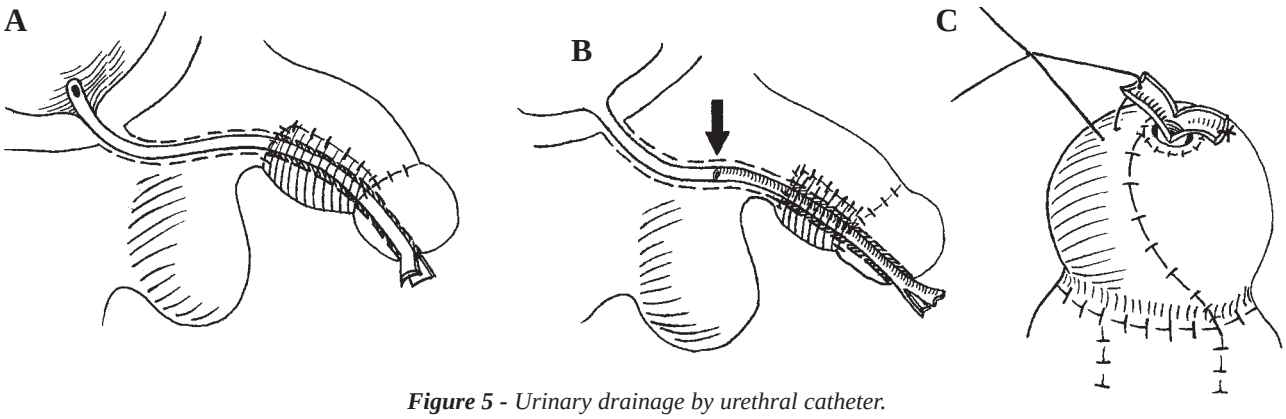

Figure 5 - *Urinary drainage by urethral catheter.*
A) *incontinent urinary drainage*
B) *continent urinary drainage*
C) *Both in continent and incontinent drainage, the end of the catheter is opened and fixed bilaterally to the glans with stitches*

rition. The urethral stenting avoids excess pressure inside the neourethra and ensures the drainage of eventual secretions.

The suprapubic catheter method is also often used and permits the introduction of larger caliber stents than it is possible via the urethra. However, with relative frequency it can cause spasms and undesirable urethral micturitions. In fact, the choice depends on the surgeon's preference.

Dressings should provide more immobilization than compression. If an incontinent urethral catheter is used, the best option is a bio-occlusive dressing that provides a good aeration but protects the surgical wound from permeation of bacteria or urine. This dressing is transparent and the surgical wound remains visible. With the suprapubic catheter a dressing with a layer of rayon or vaselinated gauze may be used with Coban (autostatic elastic dressing) to maintain it in position.

The surgical wound must be kept clean to prevent infections and gauze dressings should be changed every 2 to 4 days or simply be removed after a week in the case of a plastic dressing.

RESULTS

Cosmetic and functional results of one-stage repairs of proximal hypospadias are better than the results obtained with multistage corrections. Moreover, single-stage operations represent less physical and psychological discomfort for the patients who can have their problem solved with only one surgery. To parents it means fewer days of leave from work to accompany their child during the treatment. Consequently, costs of treatment are likely to be lower. Secondary procedures considered, we obtained good final plastic and functional results, in respectively 89.5 and 94.7% of patients with a surgery ratio of 1.7 per patient, using the DIF and MDIF techniques, either associated or not with a Duplay-type urethroplasty for the scrotal or perineal segments. The preservation of the urethral plate added to a significant improvement of results.

COMPLICATIONS

The incidence of complications of proximal hypospadias repair is far larger than with distal hypospadias. Perhaps for this reason proximal hypospadias should be corrected only by experienced surgeons in the treatment of hypospadias.

Generally, complication rates of penile, scrotal and perineal hypospadias correction have been similar. Therefore, the addition of the DIF or MDIF techniques for the penile segment to the Duplay-type urethroplasty for the scrotal and perineal segments did not contribute to an increase of complication rates. The incidence of urethrocutaneous fistulas and of stenosis of the anastomoses observed with the preservation of the urethral plate was considerably lower than with

tubular neourethras. In spite of the existence of two suture lines these are between well-vascularized tissues and a circular suture of the anastomoses is absent; the anastomoses, although left espatulated, tend to suffer scar retraction and stenosis.

Vascularization of the island flap was considered adequate in 92% of cases, and when considered inadequate in none of the cases the outcome was total necrosis of the island flap. However, it may occur and it is a most feared possibility as it eliminates the best source of tissue there is for the correction of hypospadias.

Necrosis of the dorsal and lateral skin occurred in 4% of cases and was probably due to the dissection of the superficial plane of the pedicle too close to the skin, compromising the intradermic vascularization and resulting in suffering of the blood supply.

Difference in results between the DIF and the MDIF methods was mainly the decrease in the incidence of urethrocutaneous fistulas by 50% (from 58 to 29%). Almost all urethrocutaneous fistulas could be repaired through fistulorrhaphy using the Smith-Belman technique, with insertion of a de-epithelialized cutaneous flap and creation of an intermediate plane, which minimizes the risk of fistula recurrence. The fistulorrhaphies were performed on an outpatient basis without necessity for postoperative bladder drainage.

Stenoses are a more serious complication than fistulas for depending on their degree they may affect the bladder and the upper urinary tract if their treatment is delayed. The incidence rate of stenosis of the anastomosis found with both the DIF and the MDIF methods was 9%. When possible, the stenosis may be treated by internal ureterotomy or using the Mickulicz technique (longitudinal incision and transversal suture). However, without a logical explanation, there was a 30% incidence of neomeatus stenosis with the MDIF technique against 9% for the DIF technique. Dilation of the urethral neomeatus can be initially tried but recurrence rates are high. The treatment we favor as a routine procedure is the meatoplasty, which can be distal and/or proximal. One should not hesitate when it comes to treatment of neomeatus stenosis because besides a larger incidence of urethrocutaneous fistulas it can cause dilation of the neourethra and allow its ballooning.

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