ORGAN CONSERVATION IN INVASIVE BLADDER CANCER BY TRANSURETHRAL RESECTION, CHEMOTHERAPY AND RADIATION: RESULTS OF A URODYNAMIC AND QUALITY OF LIFE STUDY ON LONG-TERM SURVIVORS

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ABSTRACT

Purpose: Transurethral resection, chemotherapy and radiation with salvage cystectomy may be used as alternatives to immediate radical cystectomy in the management of invasive bladder cancer. Concern exists about the function of the retained bladder after such therapy.

Materials and Methods: Of 221 patients with clinical T2–4a bladder cancer treated at Massachusetts General Hospital from 1986 to 2000 with trimodality therapy, 71 were alive with native bladders and disease-free in 2001. These patients were asked to undergo a urodynamic study and to complete a quality of life questionnaire. A total of 69% participated in some component of this study with a median time from trimodality therapy of 6.3 years (range 1.6 to 14.9).

Results: Of 32 patients 24 had normally functioning bladders by urodynamic study. Decreased bladder compliance was seen in 7. Bladder hypersensitivity, involuntary detrusor contractions and incontinence were present in 2 women. The questionnaire showed that flow symptoms occurred in 6%, urgency in 15% and control problems in 19%. Of all women 11% wore pads. Distress from urinary symptoms was half as common as prevalence. Bowel symptoms occurred in 22% with 14% recording any level of distress. The majority of men retained sexual function. Global health related quality of life was high.

Conclusions: The majority of patients treated with trimodality therapy retain good bladder function. A fifth have evidence of bowel dysfunction.

KEY WORDS: bladder neoplasms, drug therapy, radiation, quality of life, urodynamics

Organ conservation has been judged an effective and desirable alternative to radical surgery for many cancers, most notably breast, anus and larynx. Good functional or cosmetic results have been obtained at these sites without compromising survival.¹–³ Organ conservation in muscle invading bladder cancer has been a more contentious issue.⁴,⁵ Several groups using the combination of radiation with cisplatin based chemotheraphy and an aggressive transurethral resection of the tumor (TURBT) have documented high rates of local control and cure.⁴,⁶–⁸

Despite these satisfactory cancer outcomes, concern remains among physicians about the long-term function of a conserved, irradiated bladder, the collateral consequences for bowel and, in men, erectile function. The major series report low capacity bladder (less than 1%) and 2 series suggest low levels of patient reported symptoms.⁹,¹⁰ However, the issue of bladder function has not been evaluated in a comprehensive fashion. This study redresses this deficiency in the bladder sparing literature. We asked long-term survivors from our 1986 to 2000 protocols to return for a formal urodynamic evaluation and to complete a validated quality of life questionnaire.

MATERIALS AND METHODS

Patient population. Between 1986 and 2000, 197 patients with invasive bladder cancer (clinical stages T2–4a) were entered on 5 successive prospective protocols using TURBT, chemotherapy, and radiation.⁴,⁷,⁸,¹¹,¹² An additional 24 with T2–4a tumors and good medical status were treated with TURBT and chemoradiation but off protocol because of specific exclusions such as a language barrier or another recent malignancy.

Protocol designs. All protocols selected patients for bladder conservation on the basis of initial response to trimodality therapy (TMT). Bladder conservation was reserved for those who had a complete clinical response when evaluated at a midpoint in therapy. These patients, approximately two thirds of the total, then received further chemotherapy and radiation to a total tumor dose of 64 to 65 Gy. Patients whose invasive tumors persisted or recurred were advised to undergo salvage cystectomy. In these phase II and III protocols different schedules of radiation or drugs were tested.⁴,⁸,¹¹,¹² All patients received cisplatin, 98 methotrexate and vinblastine, 29, 5-fluouracil, and 29 received twice a day radiation.

Patients recalled for study. The fate of the bladders of the 221 patients treated from 1986 to 2000 is shown in the figure. A total of 62 had incomplete responses to induction therapy and were encouraged to undergo cystectomy, though 17 re-
fused or had become medically unfit. Of the 159 complete responders 25 subsequently underwent cystectomy for invasive or multiple superficial recurrences. Of the 151 patients not treated with cystectomy 39 died of metastatic disease and 38 of other medical conditions. Three are alive but have metastatic disease at the time of this study. A total of 71 potential participants were left for the current study. Of these, 32 returned for urodynamic study (UDS) (45%) and 48 completed questionnaires (68%).

Median patient age at original treatment was 62.1 years (range 49 to 80). Median followup from original treatment to the current study was 6.3 years (range 1.6 to 14.9). A record was kept of the reasons given by patients who declined to participate in the study.

**Urodynamic evaluation.** A uroflow study provided the voiding pattern, voided volume, and maximum and average urinary flow rates. Post-void residual volume was obtained by catheter before cystometry. A rectal catheter measured abdominal pressure. A cystometrogram (CMG) was performed as well as video urodynamics. The volume at first sensation, volume at first and maximal urge, bladder compliance during filling and the presence or absence of involuntary contractions were recorded. CMG results determined the extent to which bladder function was preserved. A pressure flow study determined maximum detrusor pressure and flow during voiding. Cystourethrography determined bladder contour and, in women, the presence of stress incontinence and/or prolapse.

**Quality of life evaluation.** Self-administered questionnaires were given. No published English language survey instrument directly addresses the quality of life of patients with bladder cancer treated with organ conservation. Therefore, we used items from scales validated in patients with prostate cancer and adapted additional items assessing long-term complications of pelvic radiation therapy. We assessed sexual function in men with items from our prostate cancer instrument and in women with the 9 items from the Brief Index of Sexual Functioning for Women. Global health related functional status and well-being were assessed with the general health perceptions and physical functioning scales of the Medical Outcomes Study Short Form Health Survey (SF-36). Measures of body awareness were also used.

**RESULTS**

**Responses.** During the study period (from March 2001 to May 2002) there were 71 potentially available patients alive and with their native bladders (see figure). Of these patients 49 (69%) participated in some aspect of the study (table 1). A total of 31 patients came for a UDS and completed a questionnaire, 17 completed a questionnaire alone and 1 presented for only the UDS. Those only answering the questionnaire or not participating at all gave reasons which are summarized in table 2. The most common reasons were distance, other active medical problems and fear of a catheter. Three who lived abroad or entered nursing homes could not be contacted. Those who did not participate in the study were no more likely to have had bacillus Calmette-Guerin (BCG) or to have had more than 3 TURBTs, factors which might be

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**Table 1. Patient characteristics and comparison of participants and nonparticipants**

<table>
<thead>
<tr>
<th></th>
<th>All Participants</th>
<th>UDS</th>
<th>Nonparticipants</th>
<th>Nonparticipants Vs Other Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>49</td>
<td>32</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Median age at TMT</td>
<td>62.1</td>
<td>62.3</td>
<td>66.9</td>
<td>Nonparticipants older than UDS/all participants 0.04</td>
</tr>
<tr>
<td>Current median age</td>
<td>68.9</td>
<td>70.9</td>
<td>77.5</td>
<td>Nonparticipants older than all participants/UDS &lt;0.01</td>
</tr>
<tr>
<td>% T3–4a</td>
<td>31.9</td>
<td>28.1</td>
<td>25.0</td>
<td>Not significant</td>
</tr>
<tr>
<td>% Any BCG</td>
<td>37.0</td>
<td>32.3</td>
<td>50.0</td>
<td>Not significant</td>
</tr>
<tr>
<td>% 3 or More TURBTs</td>
<td>23.8</td>
<td>14.3</td>
<td>15.8</td>
<td>Not significant</td>
</tr>
<tr>
<td>% External beam radiation therapy bid</td>
<td>55.3</td>
<td>50.0</td>
<td>45.8</td>
<td>Not significant</td>
</tr>
<tr>
<td>% Women</td>
<td>25.5</td>
<td>31.3</td>
<td>25.0</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
expected to predict a worse functional outcome. Nonparticipants were significantly older at the time of study (76.5 vs 67.9 years). Those consenting to the UDS were more likely to live in Massachusetts than those who consented only to a questionnaire (75% vs 53%).

Urodynamic studies. Median age of the studied females was 67 years and the males 72. The UDS was performed a median of 7.0 years after chemoradiation. One patient was currently using finasteride and 4 diuretics. None were using either α-blocker or anticholinergic medication. After urodynamic and clinical evaluation 24 of 32 patients were judged to have normally functioning bladders. Although some of the 24 normal patients had one or another abnormal urodynamic parameter the overall diagnostic impression was that of a normally functioning bladder. Details of the UDS are shown in table 3.

Uroflow: Median voided volume was 284 cc with a range of 125 to 630 cc. Of the 18 males with uroflow data, 5 ages 51, 66, 72, 77 and 85 had a maximum urine flow rate (Qmax) less than 15 ml per second, the lower limit of normal in men. The pressure flow study 8 had a sustained detrusor pressure greater than 40 cm H2O and a flow rate less than 12 ml per second. Of the 8 women completing the pressure flow study 1 had a voiding pressure greater than 100 cm H2O with a flow rate of 4 ml per second.

Video Study: In male patients with pressure flow studies suggesting bladder outlet obstruction, 3 had an impression of a median lobe on video study. Unilateral reflux was demonstrated in 3 males, diverticuli in 1 and trabeculi in 1. An incontinent woman had a cystocele with pelvic floor prolapse.

Quality of life questionnaire. Urinary Function: Urinary symptoms reflected gender differences found in the general population. Women reported urinary incontinence and difficulty controlling urine more often, while men more often reported symptoms of obstruction/irritation (tables 4 and 5). A fifth of patients reported some degree of incontinence within the preceding 7 days, with incontinence more than twice as frequent in women. None reported dysuria. Hematuria was reported by 5 patients during the preceding 6 months. Distress levels reported by men and women were less than the objective reporting of symptoms. No patient reported even moderate distress regarding urgency or leaking. The questionnaire responses of the 7 with decreased bladder compliance by UDS were studied. There was no leakage of urine in 5 and only 1 reported slight distress from symptoms. These 7 were no more likely than the remaining patients to have had 3 or more TURBTs or BCG.

Bowel Function: Bowel symptoms were evident in some patients. Difficulty in bowel control at any time in the last week was reported in 7 men (20%) and 3 women (27%), and 6 men (17%) and 5 women (21%) reported abdominal cramping or pain with bowel movements. On a grade scale of 1 to 5 those reporting these symptoms stated that they occurred at either a grade 2 or 3 level (“occasional” or “moderately/fairly frequently”). No patients reported that any of the itemized bowel symptoms occurred either “very frequently” or with a severity of “extremely”.

Sexual Function: Only 2 women completed the sexual function items, so we report only male responses. Although 39% of men reported no erections in the last 4 weeks, 36% reported full erections and another 18% less firm erections, but sufficient for vaginal penetration. A total of 54% were capable of orgasm and 50% of ejaculation. Only 8% of men reported sensitivity (first sensation at a volume less than 30 cc, and involuntary contractions resulting in leakage).

Pressure Flow Study: Of the 15 men who were able to void for the pressure flow study 8 had a sustained detrusor pressure greater than 40 cm H2O and a flow rate less than 12 ml per second. Of the 8 women completing the pressure flow study 1 had a voiding pressure greater than 100 cm H2O with a flow rate of 4 ml per second.

<table>
<thead>
<tr>
<th>Table 3. Urodynamic findings</th>
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<tbody>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Total No. pts</td>
</tr>
<tr>
<td>Uroflow parameters:</td>
</tr>
<tr>
<td>No. pts</td>
</tr>
<tr>
<td>Mean ml/sec Qmax (range)</td>
</tr>
<tr>
<td>Mean ml/sec av urine flow</td>
</tr>
<tr>
<td>(range)</td>
</tr>
<tr>
<td>Mean cc post-void residual urine vol (range)</td>
</tr>
<tr>
<td>CMG:</td>
</tr>
<tr>
<td>No. pts</td>
</tr>
<tr>
<td>Mean cm H2O resting pressure</td>
</tr>
<tr>
<td>(range)</td>
</tr>
<tr>
<td>Mean cc first sensation (range)</td>
</tr>
<tr>
<td>Mean cc capacity (range)</td>
</tr>
<tr>
<td>No. impaired compliance</td>
</tr>
<tr>
<td>No. involuntary contractions</td>
</tr>
<tr>
<td>Pressure flow study:</td>
</tr>
<tr>
<td>No. pts</td>
</tr>
<tr>
<td>Mean ml/sec Qmax with void</td>
</tr>
<tr>
<td>(range)</td>
</tr>
<tr>
<td>Mean cm H2O maximal detrusor pressure with void (range)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Prevalence of symptoms in patients who underwent bladder sparing protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Urinary:*</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Tenderness</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Abdominal cramping</td>
</tr>
<tr>
<td>Mucus passed from rectum</td>
</tr>
<tr>
<td>Tenesmus</td>
</tr>
<tr>
<td>Difficult control</td>
</tr>
<tr>
<td>Surprised by sudden need</td>
</tr>
<tr>
<td>Diarrhea†</td>
</tr>
<tr>
<td>Tenderness†</td>
</tr>
<tr>
<td>Bleeding†</td>
</tr>
<tr>
<td>Abdominal cramping†</td>
</tr>
<tr>
<td>Mucus passed from rectum†</td>
</tr>
<tr>
<td>Tenesmus†</td>
</tr>
<tr>
<td>Difficult control†</td>
</tr>
<tr>
<td>Surprised by sudden movement†</td>
</tr>
</tbody>
</table>

* Unaffected by urinary symptoms defined as no or only occasional urinary symptoms during the last week.
† Unaffected by bowel symptoms defined as no symptoms at all during the last week.
patients reported good urinary function.9, 10 The urodynamic Swedish cross-sectional studies in which more than 74% of this study are similar to those recorded in the Italian and participation. It makes it more likely that practical considerations prevented motion although high median age and current distant location of life study on cystectomy only 61% gave consent for a available for this study and show that a high proportion did consent. Sildenafil was used by 5 (16%).

Global Health related Quality of Life: Physical functioning was excellent in this group with an overall mean of 89. General health perceptions were lower with a mean of 74. Comparable means for men and women age 65 to 74 in the United States population are 69.4 for Physical Functioning and 62.6 for General Health Perceptions.17

Body Awareness: The study population had high levels of awareness of internal body sensations as measured by the Body Awareness scale. The mean score was 58 with 30% of patients indicating a strong tendency to attend closely to body sensations.

**DISCUSSION**

Our evaluation shows that at a median of 6 years after TMT the majority of conserved bladders function normally. Evidence of prior irradiation was found in some and seen as decreased bladder compliance, detectable levels of urinary incontinence in women, and a greater than normal frequency of bowel urgency and control issues among both sexes. However, other urinary and bowel symptoms were uncommon and few patients reported significant levels of distress. Overall, the level of bladder, bowel and general functioning was acceptable for most patients. Although quality of life information had been previously obtained for patients undergoing bladder conserving therapy, to our knowledge this study is the first to capture urodynamic data in parallel.9, 10

We were concerned about selection bias in our study population. The figure and table 2 trace the patients potentially available for this study and show that a high proportion did consent to return for a relatively unpleasant study that did not offer any obvious personal gain. In a comparable quality of life study on cystectomy only 61% gave consent for a questionnaire alone without any parallel invasive study.1,8 Questionnaire studies from Italy and Sweden, again without UDS, have had response rates of 66% and 82%, respectively. Those not returning for UDS may have worse urinary function although high median age and current distant location make it more likely that practical considerations prevented participation.

The questionnaire results for urinary function reported in this study are similar to those recorded in the Italian and Swedish cross-sectional studies in which more than 74% of patients reported good urinary function.9, 10 The urodynamic studies showed that the majority of patients were within the

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. Moderate or Greater Distress in Last Wk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Urinary:</td>
<td></td>
</tr>
<tr>
<td>Difficult flow</td>
<td>3</td>
</tr>
<tr>
<td>Painful or burning</td>
<td>0</td>
</tr>
<tr>
<td>Urgency</td>
<td>0</td>
</tr>
<tr>
<td>Frequency</td>
<td>4</td>
</tr>
<tr>
<td>Leaking</td>
<td>1</td>
</tr>
<tr>
<td>Nocturia</td>
<td>12</td>
</tr>
<tr>
<td>Worry about not reaching bathroom</td>
<td>0</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>2</td>
</tr>
<tr>
<td>Bowel:</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
</tr>
<tr>
<td>Tenderness</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td>0</td>
</tr>
<tr>
<td>Mucus passed from rectum</td>
<td>0</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>0</td>
</tr>
<tr>
<td>Urgency</td>
<td>7</td>
</tr>
</tbody>
</table>

* The remaining patients reported that they were either not at all or only slightly distressed.


