Preservation of the Bladder in Patients With Rhabdomyosarcoma

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Purpose: **To review the pathologic findings from children with gross residual rhabdomyosarcoma (RMS) of the bladder and compare the treatment outcome of those who underwent cystectomy with those who did not.**

Patients and Methods: **Primary and follow-up records and pathology specimens for 28 patients with gross residual disease entered onto the Intergroup Rhabdomyosarcoma Study (IRS) III were reviewed. These patients were assigned to receive 20 weeks of multiagent induction chemotherapy and 4 weeks of radiotherapy. Future therapy decisions were based on clinical and histologic evaluation at 20 weeks.**

Results: **All patients had a clinical and histologic response. Thirteen patients underwent cystectomy at intervals that ranged from 1.5 to 38 months after the start of therapy. All but one patient are alive and well without recurrence. Reasons for cystectomy included presumed evidence of tumor growth from imaging studies, findings at cystoscopy, or histologic interpretation of biopsies. In 12 of 14 specimens from 15 patients who retained their bladder, no tumor cells were seen at first or second evaluation. In cystectomy specimens, tumor cellularity was markedly reduced and all tumor cells were in varying degrees of cellular maturation. Review of primary tumor specimens showed a greater degree of cellular maturation in patients with retained bladders than in those who underwent cystectomy.**

Conclusion: **Bladder RMS is responsive to chemotherapy and radiotherapy. Twelve of 26 patients showed complete loss of tumor cells after induction therapy. Cystectomy specimens showed diminished tumor cells with varying degrees of cellular maturation. It is hypothesized that these tumors may have shown further maturation and ultimate loss of matured cells with continuing therapy.**

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THE GOAL OF THE Intergroup Rhabdomyosarcoma Study (IRS) for patients with primary bladder or bladder/prostate rhabdomyosarcoma (RMS) is not only survival, but survival with an intact and functioning bladder.[1-3] Retention of the bladder may also minimize some of the long-term problems of sexual dysfunction associated with cystectomy. The use of partial cystectomy has been fostered to attain this goal, but is applicable in a relatively limited number of cases.[4,5] Among patients in IRS III with gross residual disease after biopsy, subsequent cystectomies were performed most frequently in patients with intravesical primary tumors (43%), less often in those with prostatic primary tumors (36%), and least often in those with extravesical primary tumors that did not extend through the bladder wall (14%).

Because more cystectomies were performed for intravesical primary tumors and subsequent biopsies more readily obtained at cystoscopy, this group was chosen for review. Pathologic review of primary and follow-up specimens was made, comparing findings between those patients who retained the bladder and those who underwent cystectomy.

PATIENTS AND METHODS

Patient Selection

One hundred three patients were entered onto IRS III with primary tumors that involved the bladder between November 1984 and September 1988. There were 35 patients with positive biopsies from intravesical bladder sites, 24 with abdominal or pelvic masses with bladder attachment, and 44 with prostatic or bladder/prostate involvement. Among the 35 intravesical tumors, four were group I cases (no gross or microscopic residual disease after initial surgery) and all are living and well following partial cystectomy and chemotherapy. A single group II patient (microscopic residual disease) underwent cystectomy as primary therapy for an intravesical tumor that extended through the bladder wall to an abdominal mass. This patient died of pneumonia after 8 months of chemotherapy and radiotherapy. Two of 30 patients with group III disease died following 2 and 3 weeks of therapy from toxicity related to chemotherapy. The remaining 28 group III patients comprise the current study.

Treatment

After initial biopsy, patients with gross residual disease (group III) were scheduled to be treated with 20 weeks of induction chemo-

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therapy, which consisted of the following: 14 doses of vincristine; doxorubicin for 2 days at weeks 0, 3, and 12; cyclophosphamide for 3 days at weeks 0, 12, and 16; cisplatin for 1 day at weeks 0, 3, 6, and 9; and dactinomycin for 5 days at week 16. Radiotherapy to the primary tumor site was begun at week 6 with the prescribed dose of 45 Gy. At 20 weeks (10 weeks after completing radiotherapy), evaluation with imaging studies, cystoscopy, and either biopsy or definitive surgery was to be performed. Patients who were considered in complete remission at 20 weeks were to continue maintenance therapy with alternating courses of vincristine, doxorubicin, and cyclophosphamide (VAdrC) and vincristine, dactinomycin, and cyclophosphamide (VAC) for 1 year. From year 1 to 2, VAC was to be given every 4 weeks. Patients who had partial remissions at week 20 received two courses of dactinomycin and etoposide at weeks 20 and 23 and were reevaluated at week 26. If a complete or partial remission was present due to either chemotherapy, radiation therapy, and/or definitive surgery, maintenance chemotherapy as outlined earlier was to begin. For patients with a mixed or no response at 20 weeks, cystectomy or other chemotherapy was to be considered. There was central review of surgery, chemotherapy, and radiation therapy.

Pathology Evaluation

Since many of these patients had several biopsies following initial therapy, specimens from the initial biopsy and subsequent cystoscopies, laparotomies, or cystectomy were reviewed centrally. Evaluation was performed on hematoxylin and eosin–stained sections from either paraffin blocks or slides provided by the local institutions. The parameters of evaluation included (1) estimation of the percentage of tumor cells compared with reactive or inflammatory cells, and (2) documentation of the percentage of tumor cells that showed no, minimal, moderate, or marked maturation. Definitions of these criteria are listed in Table 1. Supporting matrix, which consisted of reactive cells (myofibroblasts or fibroblasts) or inflammatory cells, was present in the specimens to a variable degree. Pathology specimens were submitted for review on 14 of 15 patients who retained the bladder and 12 of 13 of those who underwent cystectomy. All slides were reviewed on three occasions by the pathologists (W.A.N. and A.H.).

Table 1. Criteria for Tumor-Cell Maturation of Initial and Subsequent Specimens Evaluated on Hematoxylin and Eosin–Stained Sections

Maturation	Description
None	Tumor cells consist almost entirely of a round to oval vesicular nucleus that contains finely granular chromatin in amounts that produce hyperchromasia, and little or no obvious cytoplasm.
Minimal	Early myoblastic differentiation with scanty eosinophilic cytoplasm, nuclei little changed from cells with no differentiation, nuclear/cytoplasmic ratio > 1.
Moderate	More prominent amounts of eosinophilic cytoplasm, nucleus often eccentric and showing less hyperchromasia, nuclear/cytoplasmic ratio < 1.
Marked	Abundant eosinophilic cytoplasm with normal myofibers; nuclei less hyperchromic and often lobed rather than round or oval.

RESULTS

Among the 28 group III patients, 15 retained the bladder and 13 underwent cystectomy. Two patients were lost to follow-up evaluation at 3 and 4 years after starting therapy, but were well at last contact. All others have been monitored for more than 5 years (median, 6.5 years; range, 5 to 8).

Of 15 patients who retained their bladder (Table 2), four had a partial resection of tumor via resectoscope at the time of initial cystoscopy to remove gross tumor that was readily available at the proximal urethra or bladder neck, or within the bladder. Attempts were not made to remove all of the tumor or to provide tissue for margins, and most specimens consisted of multiple fragments. In the same group, four patients had laparotomies, two after completing induction therapy and two when there was new tissue prolapse during therapy. One of the latter (patient no. 8) underwent a successful partial cystectomy at that time, and the resected specimen showed no tumor. The patient had received 10.8 Gy radiotherapy before prolapse occurred. Among 13 patients who ultimately underwent cystectomy (Table 3), two had a partial resection at initial cystoscopy and a third had both cystoscopy and laparotomy at diagnosis, with the latter probably because of tumor obstruction at the neck. At laparotomy, the bladder was opened and multiple polyps removed.

All patients who retained their bladder received the scheduled 20 weeks of induction chemotherapy, and all received 45 Gy of radiotherapy, except for patient no. 8, who received 10.8 Gy. Three patients with a retained bladder were evaluated before radiotherapy. All were evaluated at variable intervals after radiotherapy completion (median, 2.5 months) and a median 5.75 months (range, 1.25 to 11.5) after therapy onset. A single patient (no. 13) in this group had no further cystoscopic examinations after the initial biopsy. On follow-up examination, inspection of the bladder at cystoscopy was felt to be abnormal in eight of 14 patients based on mass effect due to prolapsed tissue, nodular areas, tissue fronds or projections, or the appearance of edematous tissue.

The characteristics of the patients who underwent cystectomy (Table 3) are similar to those in the first group. Eleven of 13 patients received 20 weeks of induction chemotherapy and 45 Gy of radiation therapy. Patient no. 20 received no radiation therapy and a cystectomy was performed 6 weeks after starting chemotherapy. Patient no. 25 received only 9 weeks of chemotherapy because of toxicity. Patient no. 27 was lost to follow-up evaluation after 21 months, having completed a course of radiation therapy and 19 months of chemotherapy. When he was

Table 2. Patients With Group III RMS Who Retained Their Bladders

Patient No	Age*/Sex	Procedure	Time From Therapy Start/ End of RT†	Bladder Appearance	Pathology					
						Subsequent Specimens				
						% Tumor Cells to Evaluate	% Cellular Maturation			
					At Dx		None	Minimal	Moderate	Marked
1	3/M	C/PR	—	—	EB		40	50	10	
		C/B	6 m/2.5 m	Normal		0				
		C	9 m/6 m	Normal		—				
2	20 m/M	C/B	—	—	EB			30	60	10
		C/B	4 m/2 wk	Tumor urethra, neck		10			80	20
		Lap/B	6.5 m/3 m			0				
3	22 m/M	C/B	—	—	E			80	20	
		C/B	5.5 m/2 5 m	Pedunculated tissue prostatic fossa		10		100		
4	21 m/F	C/B	—	—	E		60	40		
		C/PR	7 wk/2 wk	Residual tumor		20				100
		C	6 m/3 m	Normal		—				
5	4/F	C/B	—	—	E			30	60	10
		Lap/B	4.5 m/2 m	Edematous tumor		10			50	50
		C/B	6 m/4 m	Piling of mucosa		0				
6	21 m/M	C/PR	—	—	EB		90	10		
		C/B	6 m/3 m	Normal, B of Prostate		0				
7	2/M	C/B	—	—	EB			80	20	
		C/PR	5.5 m/1.3 m	Mass in prostate, bladder wall		0				
		C/B	10 m/7 m	Wall thickened		0				
8	3/F	C/PR	—	—	E			100		
		Lap/P Cyst	1.3 m/2 d	Prolapse of tumor after 6 d RT		0				
9	1/M	C/B	—	—	E			100		
		C/B	5 m/2 m	Nodular densities in neck		0				
		C	1 2 y	Normal		—				
10	1/M	C/B	—	—	EB		10	80	10	
		C/B	7.5 m/2.5 m	Mass in dome, urethra		0				
		C/B	1.7 y	1.5 cm mass at neck		0				
11	2/F	C/B	—	—	E			40	50	10
		C/B	6 m/−6 wk	Lesions in neck, wall		0				
		Lap/B	7 m/−2 wk	Nodules in neck		0				
12	8 m/M	C/B	—	—	E			90	10	
		C/B	6 m/3 m	Normal		0				
13	4/M	C/PR	—		EB		30	60	10	
		None				—				
14	6 m/M	C/B	—	—	E			50	50	
		C	6 5 m/3.5 m	Normal		—				
		C/B	11.5 m/8 m	Small frond urethra		0				
15	6/F	C/B	—	—	EB			70	20	10
		C/B	6 wk/−2 wk	Tumor of wall, neck		0				
		C/B	5.4 m/2.5 m	Mass in wall		0				
		C/B	10 5 m/7 5 m	"Fern" lesions, neck		0				
		C/B	16 m/13 m	Small mass, neck		0				

Abbreviations: m, months; wk, weeks, M, male; F, female, RT, radiotherapy, Dx, diagnosis; C, cystoscopy; B, biopsy, PR, partial resection, Lap, laparotomy; P Cyst, partial cystectomy; E, embryonal; EB, embryonal botyroid.

*Age is given in years unless otherwise noted as months.

†All patients received 20 weeks of chemotherapy induction plus RT; patient no. 8 received only 10.8 Gy, while others received 45 Gy.

seen again a year later, he had gross recurrence obstructing the urethra. He was given a different chemotherapeutic regimen followed by cystectomy 4 months later. Six months later, he was noted to have metastatic disease and died 49 months after diagnosis. Although 12 of 13 patients were felt to have an abnormal bladder appearance at cystoscopy, the descriptions did not differ from the noncystectomy group. Cystectomy was performed at a

Table 3. Patients With Group III RMS Who Underwent Cystectomy

Patient No	Age/Sex	Proc	Time From Therapy Start/ End of RT†	Bladder Appearance	Pathology				
						Subsequent Specimens % Cellular Maturation			
					At Dx	None	Minimal	Moderate	Marked
16	3/M	C/PR			E	90	10		
		Lap/Cyst	6 m/2 5	Tumor neck				10	90
17	1/M	C/B			E	90	10		
		C/B	7 m/3 5 m	Polyps in neck				80	20
		C/B	9 m/6 5 m	Nodule in neck				20	80
		Lap/Cyst	10 m/7 m	Nodule in neck				20	80
18	6 m/F	C/B			E	90	10		
		Lap/Cyst	6.5 m/3 5 m	Mass in neck					100
19	18/F	C/PR			E		30	40	30
		Lap/Cyst	8 m/5 m	Tumor in wall				50	50
20	1/F	C/B			EB	20	60	20	
		Lap/Cyst	6 wk/no RT	Tumor smaller				100	
21	1/F	C/B			EB	10	60	30	
		C/B	5.5 m/2 5 m	1.5 cm tumor on wall			30	70	
		C/B	7 m/3.7 m	2 mm lesions neck and wall			50	50	
		Lap/Cyst	7.2 m/4 m					100	
22	1/M	C/B			EB	30	50	20	
		Lap/Cyst	3.5 m/3 wk	Mass in wall				40	60
23	9/M	C/B			E	90	10		
		C	5 m/2 m	Mass wall urethra					
		Lap/Cyst	5 m/2 m	No gross tumor				100	
24	2/M	C/Lap/B			EB	30	50	20	
		C	6 m/2 5 m	No obvious tumor					
		Lap/Cyst	6 m/2.5 m	Soft tumor neck			10	90	
25	4/M	C/B			EA		30	60	10
		Lap/Cyst	4 m/2 wk	Tumor at base				30	70
26	3/F	C/B			E	60	10	30	
		Lap/Cyst	6 m/3 5 m	Normal				80	20
27	18/M	C/B			E		30	60	10
		C/B	5 m/2 5 m	Tumor at neck			90		10
		C/B	10 m/7.5 m	Mass in urethra				100	
		C/B	17 m/14 m	No obvious tumor				50	50
		C/B	21 m/18 m	—				90	10
		C/B	34 m/31 m	Tumor obstructs urethra		30	60	10	
		Lap/Cyst	38 m/35 m	Tumor extends to pelvic floor			10	30	60
28	3/F	C/B			EB	No slides for review			
		C/B	3 m/2 wk	Polyp neck and urethra		No slides for review			
		Lap/Cyst	5 m/3 m	Fronds neck, trigone		No slides for review			

Abbreviation: EA, embryonal alveolar.

*Age given in years unless noted as months.

†Patient no. 20 received 6 weeks of chemotherapy and no RT; patient no. 25 received nine wks of chemotherapy and RT; the remainder received 20 weeks of chemotherapy and 45 Gy RT.

median of 6 months following onset of therapy (range, 1.5 to 38). From the data available, the reason for cystectomy in all but one patient involved residual tumor by imaging studies, cystoscopic examination, or histologic findings on biopsy specimens. Among the six female patients who underwent cystectomy, three also underwent hysterectomy and, in one patient, bilateral oophorectomy; four had a portion of the anterior vaginal wall removed. There was no tumor involvement outside the bladder in any of these resected specimens.

In comparing the degree of tumor-cell maturation in the primary tumors at diagnosis, 10 of 15 in the retained bladder group had 100% of cells showing minimal to moderate or marked maturation. Of the five with some cells showing no maturation, only two had more than half the cells without maturation. In contrast, in the primary

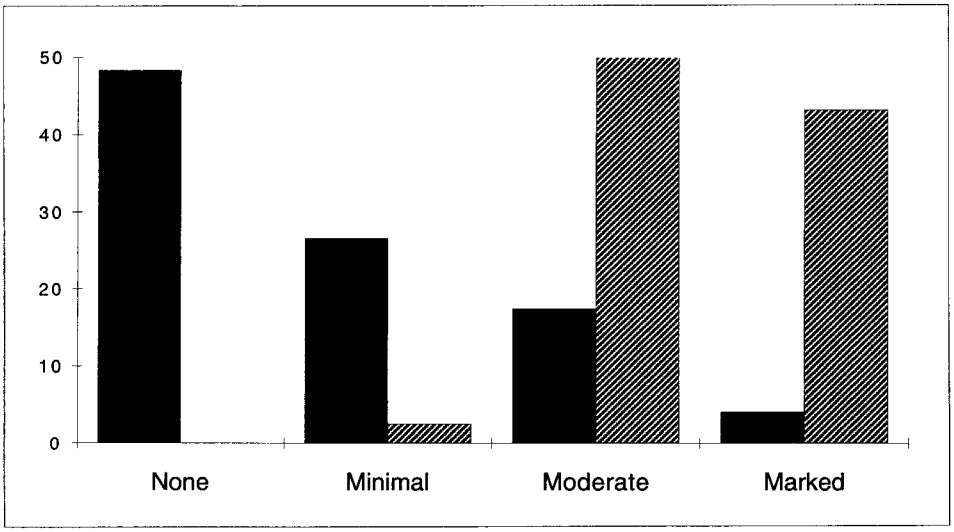

Fig 1. Tumor-cell maturation pretreatment (■) and posttreatment (▨) in 12 cystectomy patients. Bars represent the mean percent of the degree of maturation.

tumors of cystectomy patients, nine of 12 had some cells showing no maturation, and in five of the nine, they represented 60% to 90% of the total. Only three patients had all cells showing minimal to moderate or marked maturation.

Follow-up specimens from 12 of 14 retained bladders showed no tumor cells in either the first or second follow-up specimens. In two patients (no. 3 and 4) whose bladder was not removed, residual maturing tumor cells were present in the last biopsy specimen. Neither of these patients developed subsequent evidence of tumor. The bladders from the cystectomy group showed a persistence of residual tumor cells, but all showed maturation beyond that of the primary tumor. The degree of change is illustrated in Fig 1, which shows the mean maximum degree of maturation achieved following induction therapy compared with the mean degree of maturation present in the primary tumors.

DISCUSSION

The primary goal of this study was to determine whether more children with intravesical RMS with gross residual disease could retain their bladders and avoid cystectomy. A review of the clinical and pathologic data in these patients showed several findings that may be helpful in the management of this disease.

Imaging studies following chemotherapy and radiotherapy are not necessarily reliable in evaluating tumor size or viability. Several patients in both groups had either ultrasound, computed tomographic (CT) scan, or intravenous pyelogram that suggested increased tumor mass or poor response to therapy; yet, in all cases, the only evidence of tumor was that of maturing cells on histologic review. A similar discrepancy between CT scanning and surgical or biopsy findings was reported recently in a review of pelvic RMS in children.[6] Edema or tissue prolapse, particularly in the postradiotherapy period, can suggest an increase in tumor size, but does not establish actual tumor growth. As these tumors respond to therapy, it is common to see prolapse, particularly with bladder neck or urethral involvement. Abnormal-appearing tissue at cystoscopy likewise may not equate to tumor growth or viability. In three fourths of these patients, continuing cystoscopic abnormalities of mass effect, roughened or uneven mucosal surface, nodular-appearing lesions, or frond-like projections from the mucosal surface were reported, yet tumor cells were present in only half of the biopsy specimens, and these were in various stages of rhabdomyoblast maturation.

The sequence of histologic changes following therapy suggests a rapid diminution in the degree of cellularity and number of tumor cells followed by an interval wherein remaining tumor cells show evidence of maturation or tumor-cell degeneration. Among patients who retained bladders, 10 had a complete absence of tumor cells after they completed induction therapy. An additional two patients had no tumor cells in specimens following only 5 and 6 weeks of chemotherapy, respectively. Among cystectomy patients, 11 of 12 showed a reduction in cellularity, and in nine of 12, the percentage of tumor cells was reduced by $\geq$ 50%. All of the remaining tumor cells showed evidence of enhanced maturation. The decision to perform a cystectomy in this group of patients was based on tumor presence as shown by either imaging studies, cystoscopic findings, or the finding of tumor cells

on biopsy. The latter were often described as showing myogenic maturation at the institutional level. Quite expectedly, bladders were not removed when follow-up biopsies contained no tumor cells or a small number of maturing cells.

Primary RMS has long been known to show variable cellular patterns that simulate myogenic maturation. The review of primary specimens from the current group of patients showed a greater degree of tumor-cell maturation in the tumors of patients who retained the bladder than in those who did not. However, the numbers involved are too small for statistical analysis, but there is a trend to suggest that tumors with a greater degree of maturation at diagnosis may respond more favorably to induction chemotherapy and radiotherapy.

In the present study, patients whose primary tumor had a majority of cells showing no maturation did show maturation following treatment. These observations differ somewhat from an earlier report with respect to poorly differentiated RMS following therapy.[7] In that study, the primary tumors that consisted of moderately or well-differentiated rhabdomyoblasts showed a progression of their pretreatment level of differentiation; those whose tumor cells were all poorly differentiated showed only loss of tumor cells. These patients were treated in an earlier time period, perhaps less aggressively than in the present study. Chemotherapy varied as to the drugs used, and about half of the patients had not received radiation therapy.

A pathology review of cases from Italian RMS studies also showed marked maturation in a small number of biopsy specimens taken after only 6 weeks of chemotherapy, which led the investigators to conclude that chemotherapy of RMS tumors causes tumor-cell maturation that follows the pathways of normal muscle-cell development.[8]

Others have observed patients who did not develop further evidence of tumor when posttreatment biopsies contained maturing tumor cells, and when residual tissue was not removed.[6] In that report, one patient who had no tumor underwent cystectomy and another three patients have retained bladders and are well without further treatment.

The demographic characteristics of the two groups of patients presented here show minor differences. The older age of two patients in the cystectomy group might have been a factor in their course, since older age has been shown to have poor prognostic significance for outcome.[9,10] In the noncystectomy group, all patients completed 20 weeks of chemotherapy and local radiotherapy. In the cystectomy group, two patients had the bladder removed after 6 (no. 20) and 9 weeks (no. 25) of chemotherapy, and the former received no radiotherapy. The latter patients had decreased tumor cells and moderate to marked maturation in the cystectomy specimens.

As documented by this study, primary bladder RMS appears to be remarkably responsive to chemotherapy and radiotherapy, and survival is generally excellent. However, clearly, one group of patients responded more rapidly and completely to induction therapy. Whether the greater degree of cellular maturation in their primary tumors related to the good response cannot be answered by this study. One can hypothesize that given adequate time, tumor cells that show increased maturation following therapy will further mature and ultimately disappear. Answers to these questions will await a prospective study in which the more slowly responding tumors are carefully monitored with biopsies for their progress. Support for maturing cells that represent a nonproliferative group includes the findings in two patients in this study and those reported elsewhere who have had no recurrence of tumor when such cells have been present in the final biopsies taken.[6] In addition, these cells were not seen in biopsies taken at intervals following a year or more of therapy.

Cystoscopy specimens provide the only way to evaluate actual tumor response at any given interval. If the primary tumor mass is decreasing in size, and if histologic review of the biopsy specimens shows a decrease in cellularity, absence or reduction in tumor cells, presence of benign tissue (fibrosis, necrosis, or edema), or maturing rhabdomyoblasts, we suggest that treatment be continued with cystoscopic exams at 1- or 2-month intervals. These favorable histologic findings at 6 months of therapy or later are consistent with a good long-term outcome or cure with a retained bladder. If cystectomy is warranted based on documented persistence of tumor by imaging studies or examination and verified by histologic sections, structures outside the bladder, particularly in the female, should not be removed unless directly invaded by the tumor itself.

Based on the favorable initial response of every patient in this review to cytotoxic therapy, the use of histologic means to complement imaging studies for tumor regression should allow few bladders to be removed unnecessarily, and few patients to escape tumor control without a needed surgical resection.

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