Role of Surgery for Nonmetastatic Abdominal Rhabdomyosarcomas

A Report from the Italian and German Soft Tissue Cooperative Groups Studies

Giovanni Cecchetto, M.D.[1]
Gianni Bisogno, M.D.[2]
Jorn Treuner, M.D.[3]
Andrea Ferrari, M.D.[4]
Adrian Mattke, M.D.[3]
Michela Casanova, M.D.[4]
Patrizia Dall'Igna, M.D.[1]
Ilaria Zanetti, Ph.D.[2]
Sandra Volpato, Ph.D.[2]
Fortunato Siracusa, M.D.[5]
Gianni Scarzello, M.D.[6]
Camillo Boglino, M.D.[7]
Modesto Carli, M.D.[2]

[1] Department of Pediatrics, Division of Pediatric Surgery, University of Padua, Padua, Italy.

[2] Department of Pediatrics, Division of Oncology, University of Padua, Padua, Italy.

[3] Pediatric Oncology Division, Olga Hospital of Stuttgart, Stuttgart, Germany.

[4] Pediatric Oncology Unit, Istituto Tumori, Milan, Italy.

[5] Department of Pediatric Surgery, Istituto Materno Infantile, Palermo, Italy.

[6] Division of Radiation Therapy, General Hospital of Padua, Padua, Italy.

[7] Division of Pediatric Surgery, Bambin Gesù Pediatric Hospital, Rome, Italy.

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Address for reprints: Giovanni Cecchetto, M.D., Department of Pediatrics, Division of Pediatric Surgery, University of Padua, Via Giustiniani 3, 35128 Padua, Italy; Fax: (011) 39 049 8211781; E-Mail: cecchett@pediatria.unipd.it

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BACKGROUND. In the current study, the authors aim to evaluate clinical features and treatment results observed in patients from the German and Italian studies who had nonmetastatic abdominal rhabdomyosarcomas (RMS).

METHODS. One hundred sixty-one patients were observed; 78 registered in the German studies between October 1980 and August 1995, and 83 registered in the Italian studies between April 1975 and December 1995. The age range of the patients was 0–18 years (median, 4 yrs). The distribution of tumor sites was as follows: 32 intraperitoneal, 42 retroperitoneal, 75 pelvic, and 12 not otherwise specified (NOS). Most patients had a large and invasive primary mass (26 T1b, 114 T2b). The breakdown in histology was as follows: 116 embryonal, 34 alveolar, and 11 other (leiomyomatous, pleomorphic, and NOS); all cases were staged according to the Intergroup Rhabdomyosarcoma Studies (IRS) system. Nine Group I patients were treated after surgery with chemotherapy (CT) (radiotherapy [RT] was delivered to treat alveolar RMS in the 1991 German and 1988 Italian studies); 19 Group II patients received CT + RT (40–44 Gy); 133 Group III patients underwent neoadjuvant CT ± surgery and/or RT (54 Gy) + CT. Different CT regimens (based primarily on the administration of vincristine, dactinomycin, doxorubicin, and cyclophosphamide or ifosfamide) were adopted. RT was not recommended for patients age < 3 years.

RESULTS. The 10-year overall survival (OS) and progression-free survival (PFS) were 47.2% and 43.9%, respectively. The OS was related significantly to the following variables: histology (alveolar, 29.4% vs. nonalveolar, 52.1% [$P = 0.0156$]), tumor size (> 5 cm, 42.1% vs. < 5 cm, 81% [$P = 0.005$]), age (< 10 yrs, 51.4% vs. ≥ 10 yrs, 27.8% [$P = 0.02$]), complete surgery at diagnosis or after CT (±RT) (70.4% vs. 34.4% without it [$P = 0.0015$]). Most patients who achieved the delayed local control had responded well to neoadjuvant CT.

CONCLUSIONS. Tumor size, histology, age, and initial or delayed achievement of local control were important prognostic factors. Most relapsed patients had unfavorable outcomes. ***Cancer* 2003;97:1974–80.** © *2003 American Cancer Society.*
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Rhabdomyosarcomas (RMS) are the most common soft tissue sarcomas (STS) in pediatric age; they account for 6–8% of all pediatric malignancies.[1] RMS may appear anywhere in the body, from various organs or tissues. Abdominal RMS include tumors arising in the intestinal tract and its annexes, the retroperitoneum, and pelvic sites excluding the genitourinary organs. Approximately 10–12% of all RMS are abdominal. In this localization, tumors often are locally advanced or metastatic at the time of diagnosis, making it difficult in

some cases to determine the precise intra-abdominal organ of origin. Symptoms depend on the location of the primary mass but may be vague and indefinite—abdominal pain and distension, constipation, and weight loss are common features. Obstructive jaundice is the most frequent symptom when RMS appear in the biliary tree. Abdominal RMS sometimes present acutely because of intestinal or urinary tract obstruction. The outcome for children affected by abdominal RMS remains less satisfactory than for children affected by RMS in other sites, despite the growing trend of using intensive multimodal therapy. Local treatment is challenging due to the extent and local spread of the disease at presentation, the difficulty or impossibility of resection, and the severe toxicity associated with radiotherapy.

Only a few papers have reported groups of pediatric patients with STS appearing in selected intra-abdominal sites: retroperitoneum, gastrointestinal tract, and biliary tract.[2–4] The purpose of this report is to evaluate the clinical findings and the treatment results observed in a large group of patients with non-metastatic intraabdominal RMS who are registered in the Italian and German STS studies, with an emphasis on the role of surgery. Clinical features and therapeutic approaches were analyzed to evaluate prognostic factors.

MATERIALS AND METHODS

Two hundred eight patients affected by previously untreated abdominal RMS were observed between 1979 and 1995. One hundred sixty-one had localized disease and 47 had distant metastases at presentation. Only patients with localized RMS (88 males and 73 females) were analyzed. Seventy-eight patients were registered in the German studies (1981, 1986, and 1991). Eighty-three patients were enrolled in Italy, with 49 in the Italian Cooperative RMS Studies (1979 and 1988) and 34 in the Istituto Nazionale Tumori of Milan study. The median age at diagnosis was 4 years (range, 0–18 yrs). Twenty-two patients were age < 1 year, 111 were age 1–10 years, and 28 were age > 10 years. Data were collected prospectively, but for the purposes of this study, clinical and operative records were searched to obtain more precise information regarding the characteristics of the tumor and the abdominal localization. The study considered three main intra-abdominal sites: retroperitoneal, pelvic nongenitourinary (nGU), and intraperitoneal, which included tumors appearing in the intestinal tract, liver, and biliary tree. Treatment results and outcome were analyzed with a follow-up, which, in February 2002, ranged from 61 to 267 months (median, 159 mos).

Patients were classified according to the TNM pretreatment staging system, on the basis of the features of the tumor, the involvement of regional nodes, and the presence of distant metastases. Tumors were considered T1 if they were confined to the organ or tissue of origin, whereas T2 masses involved contiguous structures. T1 and T2 lesions were further divided into substages *a* (tumor size < 5 cm) and *b* (tumor size > 5 cm). After initial surgery, all patients were grouped according to the Intergroup Rhabdomyosarcoma Staging (IRS) system as follows: Group I, initial complete resection; Group II, initial excision with microscopic residuals and with or without regional lymph node involvement; Group III, initial biopsy or resection with macroscopic residuals. All histologic specimens were reviewed by the national panels of pathologists.

The therapeutic guidelines of the Italian and German studies for nonmetastatic RMS remained similar over the years. Surgery was the initial approach in all cases. Primary excision was recommended when a radical nonmutilating resection could be achieved on the basis of clinical and imaging evaluation; otherwise a diagnostic biopsy was requested. Patients who had initial biopsy or resection with macroscopic residuals were considered for a delayed excision, after neoadjuvant chemotherapy (CT), if it was feasible. Anatomic or functional mutilating procedures (pelvic exenteration and permanent urinary or intestinal diversions) were accepted only if there was no response to CT and/or radiotherapy (RT), or if the disease progressed.

Radiotherapy was recommended only for patients age > 3 years because of the high risk of late sequelae in patients age < 3 years. External beam irradiation was used when patients experienced microscopic disease after primary surgery (total dose, 40–44.8 Gy) and when delayed surgery was not radical or not possible (total dose, 45–54 Gy). Alveolar Group III RMS patients also received RT (44.8 Gy) when a complete delayed resection was obtained and, in the 1988 Italian and 1991 German studies, when they experienced initial complete excision. The radiation target volume included the initial mass plus 2-cm margins. Since 1988 in Italy and 1986 in Germany, accelerated and hyperfractionated irradiation has been used instead of conventional fractionation.

All patients received CT under different regimens, according to IRS group and ongoing protocol. Vincristine, dactinomycin, and cyclophoshamide; vincristine, adriamycin, and cyclophosphamide (VAC/CAV); or vincristine, dactinomycin ± ifosfamide (VA/IVA) was the recommended regimen for patients in Groups I and II. Neoadjuvant CT with VAC or vincristine, dactinomycin, ifosfamide, and doxorubicin (VAIA) was

given to Group III patients. For Group III patients, maintenance CT with VAC/CAV or IVA was administered after delayed local treatment.

Response to treatment was defined as follows: complete remission (CR) = no evidence of disease at imaging; partial remission (PR) = reduction to > 50% of the initial tumor volume; objective remission (OR) = reduction to > 25% of initial volume; stable disease (SD) = reduction to < 25% of initial tumor volume; progression of disease (PD) = increase in tumor volume or appearance of new lesions. The first evaluation of response to CT in Group III cases was performed after the initial 3 cycles of CT (9 wks) and was based on the decrease in the dimensions of the tumor mass.

The Kaplan–Meier method was used to estimate prognosis according to overall survival (OS) and progression-free survival (PFS) rates. The OS was defined as the time from the date of diagnosis to death by any cause, and the PFS was defined as the time from the date of diagnosis to disease progression or relapse. The log rank test was used for univariate comparison of survival levels and for defining the potential value of prognostic factors. The Cox proportional hazards model was employed to analyze the independent value of patient characteristics and treatment modalities in predicting outcome.

RESULTS

Adequate clinical data and treatment results were available for all 161 patients. The most common symptoms at presentation were pain and/or abdominal distension with signs of intestinal or urinary obstruction; indefinite tenderness and edema at one or both lower extremities were quite common in cases with retroperitoneal primary mass. General symptoms, such as fever and weight loss, were common in patients with locally advanced disease. Tumor site was intraperitoneal for 32 patients (20%), retroperitoneal for 42 (26%), and pelvic for 75 (46%). For 12 patients (8%), tumor site was not identified precisely. Tumor size was reported for 157 patients and was < 5 cm for 17 and > 5 cm for 140. Tumor classification was T1 for 34 patients, T2 for 125, and unknown for 2. Regional lymph nodes were involved for 27 patients at clinical or histologic evaluation, and information regarding regional lymph nodes was not available for 13 patients. The embryonal histologic subtype of RMS was found in 116 patients (72%), the alveolar subtype in 34 (21%), and the pleomorphic and leiomyomatous subtypes in 1 and 3, respectively; in 8 cases the histologic subtype of RMS was not recognized. The nonalveolar subtypes were found in 113 patients age < 10 years and in 14 patients age > 10 years, whereas the alveolar subtype was recognized in 20 patients age < 10 years and in 14 patients age > 10 years.

TABLE 1
Abdominal RMS: Events and Deaths According to IRS Group

Group	No. of patients	LR	Met.	LR + Met.	PD	Total
I	9	4 (3)[a]		1 (1)		5 (4)
II	19	8 (8)	2 (2)			10 (10)
III	133	36 (29)	9 (9)	10 (10)	18 (18)	73 (68[b])
Total	161	48 (40)	11 (11)	11 (11)	18 (18)	88 (82[b])

RMS: rhabdomyosarcdmas; IRS: Intergroup Rhabdomyosarioma Studies; LR: local relapse; Met.: metastases; PD: progression of disease.

[a] No. of deaths in parentheses.

[b] Two patients died because of treatment toxicity.

Treatment results and patient outcomes by IRS Group are described as follows (Table 1).

In Group I, nine patients achieved a complete tumor resection and then were treated with CT. The site was intraperitoneal in five patients (three T1b, two T2b), retroperitoneal (T1a) and pelvic (T1b) in one each, and unknown in two (T1b). Four maintained their first CR. A local relapse (LR) occurred in four T1b patients (three intraperitoneal, one pelvic), and only the patient with pelvic RMS achieved a second CR. One patient with intraperitoneal T2b RMS experienced local and distant recurrences and died of the disease (DOD) despite receiving further therapy. The 10-year OS and PFS rates were 73.2% and 56.4%, respectively.

In Group II, 19 patients had a primary excision with microscopic residuals. Regional lymph nodes were involved for one of these patients. All Group II patients received CT. RT was administered to 8 of 19 patients. Three patients who underwent RT are in first CR (two T1a, one T1b), and five DOD (two T1b, three T2b) after a LR (four patients) or metastases (one patient). Of the 11 patients who did not undergo RT, 6 are in first CR (3 T1b, 3 T2b), and 5 DOD (2 T1b, 3 T2b) after a LR (4 patients) or metastases (1 patient). The 10-year OS and PFS rates are 44.6% and 47.7%, respectively.

In Group III, 133 patients underwent initial resection with macroscopic disease (37 patients) or open biopsy (96 patients). The response to neoadjuvant CT could be evaluated in 111 Group III patients. CR was observed in 30 patients, PR was observed in 36, OR was observed in 32, and SD and PD were observed in 7 and 6 patients, respectively. Information regarding local treatment was available for 121 patients (another 6 died before local treatment due to PD). Twenty-nine patients underwent complete excision of the residual

TABLE 2
Abdominal-IRS Group III RMS: 10-Year PFS Rates by Local Treatment

Local treatment	No. of patients	Events	PFS (%)	
Complete excision				
With RT	15	3	73.3	
Without RT	14	5	46.7	$P = 0.2$
Incomplete excision				
With RT	24	12	40.5	
Without RT	6	6	—	$P < 0.01$
No excision				
With RT	42	26	40.4	
Without RT	24	12	47.8	$P = 0.41$

IRS: Intergroup Rhabdomyosarcoma Studies; RMS: rhabdomyosarcomas; PFS: progression-free survival; RT: radiotherapy.

mass (15 of these patients also received RT), 30 underwent partial excision of the tumor (24 of these patients were given RT), 42 received only RT, and 24 received no local treatment. The role of local treatment in Group III patients was evaluated by comparing the PFS of patients according to the treatment that they received (Table 2). Patients who underwent radical excision with RT had the best PFS (73%), whereas patients who underwent incomplete surgery with RT and patients who were treated locally with RT alone had similar, unsatisfactory outcomes (PFS, 40.5% and 40.4%, respectively). A group of 24 patients (21 of whom had nonalveolar RMS) did not receive local treatment due to the patient's age being < 3 years (15) or due to the histologically confirmed achievement of CR (9). The overall PFS for this group of 24 patients was 47.8% (46.6% and 50% for the age < 3 yrs and histologically confirmed CR subgroups, respectively).

The OS and PFS for the 133 Group III patients were 45.4% and 45.7%, respectively. Fifty-seven patients (42.8%) currently are alive in first CR. Eighteen patients (13.5%) did not respond to therapy and died of PD. Fifty-five patients (41.5%) relapsed after diagnosis (range, 4–108 mos after diagnosis; median, 16 mos); 36 relapsed locally, 9 relapsed with metastatic disease, and 10 relapsed with local disease and distant metastases. Of the 36 patients with LR, 29 died, and 7 responded to multimodality treatment and survived. All patients with metastatic spread died despite receiving further therapy. Two patients died because of treatment toxicity, and 2 other patients had a second tumor (1 bilateral benign epithelial ovarian tumor and 1 osteosarcoma of the right limb, 7 and 3 yrs after the end of therapy, respectively).

Data regarding the quality of surgical excision performed both at diagnosis and after neoadjuvant CT were available for 153 of 161 patients and demonstrated the favorable impact of radical surgery on outcome. Patients with a completely resected tumor either initially or after CT had better PFS and OS results ($P = 0.04$ and $P = 0.008$, respectively) than those who did not (Table 3). The impact of complete surgery at diagnosis could not be evaluated due to the limited number of patients (nine) in this group.

TABLE 3
Abdominal RMS: 10-Year PFS and OS Rates by Clinical and Treatment Factors

Clinical/treatment factors	No. of patients	PFS (%)	OS (%)
Age		$P = 0.024$	$P = 0.023$
< 10 yrs	133	48.7	51.4
> 10 yrs	28	21.4	27.8
Histology		$P = 0.10$	$P = 0.015$
Alveolar	34	34.9	29.4
Nonalveolar	127	48.6	52.1
Tumor site ($n = 149$)		$P = 0.3$	$P = 0.4$
Intraperitoneal	32	43.1	49.5
Retroperitoneal	42	54	54.7
Pelvic	75	39.3	40.1
Tumor size ($n = 157$)		$P = 0.003$	$P = 0.005$
< 5 cm	17	81.3	81.4
> 5 cm	140	40.1	42.1
T status ($n = 159$)		$P = 0.03$	$P = 0.07$
T1	34	59,8	63
T2	125	38.6	42
Regional LNF ($n = 148$)		$P = 0.2$	$P = 0.52$
uninvolved	121	49	44
involved	27	33	38.5
IRS group		$P = 0.8$	$P = 0.7$
I	9	44.4	76.2
II	19	47.7	44.6
III	133	45.7	45.4
Excision (initial or delayed)		$P = 0.04$	$P = 0.008$
Complete	38	56.4	73.2
Incomplete	49	38	33.8
Not performed	66	38.2	43.5
IRS Group III patients ($n = 111$)		$P = 0.001$	$P = 0.001$
Nine week response to CT			
CR	30	40.6	39.7
PR	36	62.2	60.7
OR	32	33.6	39.5
SD	7	28.6	14.3
PD	6	16.7	0

RMS: rhabdomyosarcomas; PFS: progression-free survival; OS: overall survival; IRS: Intergroup Rhabdomyosarcoma Studies; CT: chemotherapy; CR: complete remission; PR: partial remission; OR: objective remission; SD: stable disease; PD: progression of disease; LNF: lymph nodes.

The role of initial surgery for 94 patients with embryonal Group III RMS was also evaluated. A biopsy was performed for 57 patients, whereas an excision with macroscopic residuals (debulking procedure) was performed for 37 patients. The prognosis for patients with an initial debulking (PFS, 50%; OS, 56.3%) was slightly better than for patients who had received

a biopsy only (PFS, 41.2%; OS, 41.9%), but the difference was not statistically significant ($P = 0.7$ and $P = 0.35$ for PFS and OS, respectively).

Twelve patients had RMS of the biliary tree (age range, 14–78 mos; median, 58 mos). All tumors were embryonal at histologic evaluation. Three patients were in Group IIa and nine were in Group III. Eight patients received RT, which was the only local treatment for five Group III patients. Nine patients are alive in first CR (three from Group II and six from Group III). Two Group III patients experienced LR, one of which occurred after CR achieved by CT alone and the other after conservative surgery (one DOD). Another Group III patient suffered metastatic recurrence after local treatment with RT (one DOD).

For the group of 161 patients, the 5- and 10-year PFS rates were calculated to be 45.6% and 43.9%, respectively; the 5- and 10-year OS rates were 49.8% and 47.2%, respectively. In univariate analysis, the outcome at 10 years was correlated to the following clinical features (Table 3): 1) *age at diagnosis:* children age $<$ 10 years exhibited more favorable PFS and OS than children age $>$ 10 years; 2) *histology:* alveolar histology was linked to better OS than alveolar histology; 3) *tumor size:* tumors $<$ 5 cm were associated with better PFS and OS than tumors $>$ 5 cm; 4) *T status:* patients with T1 RMS showed better PFS than those with T2 RMS. Regarding the response to neoadjuvant CT after 9 weeks, the best outcome was linked to patients with PR (PFS, 62.2 %; OS. 60.7%). No significant difference related to regional lymph node involvement (N0 vs. N1) or intra-abdominal site was found, but pelvic nGU RMS was associated with a slightly worse outcome than retroperitoneal or intraperitoneal RMS.

Considering the long period of recruitment, we compared the outcomes of patients registered before 1988 and 1990 in the Italian and German studies, respectively, with the outcomes of patients treated subsequently. Patients treated after 1988 had a better 10-year OS (60.7%); however, this result was not statistically different from the OS (48.6%) of patients treated previously.

In the multivariate analysis, the most important factor in predicting OS and PFS was tumor size. Other significant variables were patient age and complete tumor resection (Table 4).

TABLE 4
Abdominal RMS: Cox Regression Analysis

	PFS		OS	
Prognostic variable	**RR**	***P***	**RR**	***P***
Age		0.0175		0.0141
≤ 10 yrs	1		1	
> 10 yrs	1.892		1.943	
Tumor size		0.005		0.0117
≤ 5 cm	1		1	
> 5 cm	4.286		3.718	
Tumor resection		0.054		0.0079
Complete	1		1	
Incomplete	1.902		2.692	
Not performed	1.998		2.640	

[a] RMS: rhabdomysarcomas; PFS: progression-free survival; OS: overall survival; RR: risk ratio.

DISCUSSION

Abdominal RMS are usually locally advanced or metastatic at the time of presentation due to intracavitary site and the relatively late onset of symptoms. As a consequence, many of these tumors are not resectable at diagnosis because the procedure would be either highly mutilating or otherwise prohibitively technically difficult.[2] Raney et al. examined 64 patients with nonmetastatic RMS and undifferentiated sarcoma of the retroperitoneum/pelvis treated in IRS Stage IV. Sixty of these patients had tumors that were unresectable at diagnosis. Sixty-one of 64 patients had a tumor mass whose dimension was $>$ 5 cm, and 55 of 64 patients had a tumor that was classified T2.[5]

In our group of 161 patients, 133 (83%) had an inoperable tumor at diagnosis. Most tumors were large and invasive (95.5%). Only 73 of 161 patients achieved and maintained the first CR, and most of those who suffered a recurrence died of the disease (80 of 88 patients). Irrespective of IRS Group, local relapses were the most frequent cause of treatment failure (48 of 88 patients); all patients who presented with distant recurrence or combined local and metastatic recurrence died of the disease. This unfavorable outcome for relapsed patients is comparable to the outcome reported for gastrointestinal and retroperitoneal sarcomas in adults.[6]

The cure rate for this cohort of patients was similar to those reported by other authors. In a group of 101 patients described by Crist, 44% and 42% of patients with localized or metastatic retroperitoneal sarcomas remained relapse-free 2 and 3 years after follow-up, respectively;[4] overall, about 40% of these patients subsequently developed relapses. Blakely et al. reported that the outcome was slightly better for 94 patients with advanced-stage retroperitoneal RMS. The overall 4-year failure-free survival rate for these patients was 50%, and the overall survival was 60%.[7]

Complete tumor resection at diagnosis or after initial CT was a favorable prognostic factor. However, IRS group was not a significant variable—the small number of Group I patients had an OS (76.2%) that

was better than that of Group II and Group III patients (44.6% and 45.4%, respectively), but the difference was not statistically significant.

In our experience, an initial complete and nondestructive excision of the tumor was rarely feasible because of the tumor's invasion or encasement of vital structures. Nevertheless, patients in whom the initial excision left microscopic residue had an unsatisfactory prognosis, despite the administration of RT to some patients; the outcome for this group of patients was not better than for patients who were initially biopsied or in whom excision left macroscopic residue.

Among Group III patients, 66 of 111 achieved CR or PR after neoadjuvant CT, whereas 45 did not respond satisfactorily. Patients who underwent a complete delayed surgical excision followed by RT had a PFS = 73.3%, which was better than the PFS of patients treated with complete surgery alone. The benefit of RT as an adjunct to complete delayed excision to improve local control also is reported in a series of adult sarcomas; after surgery, irradiation might be expected to sterilize subclinical deposits or seedings near the primary mass.[6] Patients who had an incomplete resection ± RT or only RT as local treatment had unstisfactory outcomes.

It is noteworthy that the 24 Group III patients (most of whom had an embryonal tumor) who did not receive local treatment had a PFS = 47.8%.

RMS of the biliary tree are the most frequently reported lesions in the current intra-abdominal RMS literature.[8–10] Biliary tree RMS represent less than 1% of all RMS but constitute the most common malignancy of this site in pediatric age. Boys are more frequently affected than girls at the typical age of 4–5 years. Despite accurate imaging evaluation, diagnosis often is not possible until surgery. It is widely accepted that CT should be the first therapeutic step after biopsy and adequate bile drainage, but some authors have reported cases in which neoadjuvant CT produced no response.[11] The most frequent histologic subtype is embryonal. In our experience, RMS of the biliary tract represented approximately 7.5% of all intra-abdominal RMS and occurred in young patients; the histology was embryonal in all cases. Nine patients were initially treated with CT and then received local treatment, whereas three patients underwent an initial excision with microscopic residuals. The outcome for the biliary tract RMS group was better than for the whole intra-abdominal RMS group: 10 of the 12 patients in the biliary tract group are alive and in CR (1 patient in second CR).

In a group of 64 patients with advanced-stage retroperitoneal embryonal RMS, Blakely et al. report the efficacy of initial debulking procedures versus initial biopsies in further improving outcome—the 4-year progression-free survival (PFS) rate of 25 patients whose tumors were debulked was 72%, whereas in 39 patients who underwent an initial biopsy, the EFS rate was 48% ($P = 0.03$).[6] In our group of 94 patients with embryonal Group III RMS, the prognosis for the 37 patients who had undergone an initial debulking procedure (PFS, 50%; OS, 56.3%) was slightly better than for the 57 patients who had undergone an initial biopsy (PFS, 41.2%; OS, 41.9%), but the difference was not statistically significant ($P = 0.7$ and $P = 0.35$ for PFS and OS, respectively).

CONCLUSIONS

In our experience, the prognosis for patients with abdominal RMS has not improved significantly over the last 20 years, and abdominal RMS currently constitute a therapeutic challenge. The intracavitary nature of these tumors and the relatively late onset of symptoms often lead to advanced stage at presentation and difficulties in treatment. Patient age, tumor size, and histologic subtype have been identified as important clinical variables that influence patient outcome. Only patients who underwent initial complete excision or delayed complete excision plus irradiation had satisfactory outcomes, and RT was probably effective in sterilizing microscopic intracavitary residue after CT and surgery. Microscopic positive margins after initial excisions negatively influenced the prognosis despite the administration of multimodal therapy. Almost all relapsed patients died of disease.

Future efforts should be aimed at improving the achievement of local control with accurate surgery and RT.

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