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Prognostic factors in children undergoing salvage surgery for bladder/prostate rhabdomyosarcoma

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Summary

Background
Prognostic factors have been studied in patients with rhabdomyosarcoma in general, but little is known about prognostic factors in the subgroup of patients with bladder/prostate rhabdomyosarcoma (BP-RMS) requiring salvage surgery after failure of chemotherapy ± radiotherapy to achieve local control. We reviewed the 28-year Italian experience with BP-RMS requiring salvage surgery after failure of nonsurgical management indicated by evidence of disease persistence after chemotherapy ± radiotherapy. Our hypothesis was that the same variables identified as prognostic factors in the general population with RMS could have prognostic value in this subgroup.

Method
Between 1986 and 2014, 108 patients with a histological diagnosis of BP-RMS were registered into three consecutive protocols. Patients undergoing salvage surgery after failure of chemotherapy ± radiotherapy and follow-up >5 years were considered for study. Variables related to the patient, to treatment, and to the surgical specimen were compared using the log-rank test in patients who achieved and failed to achieve 5-year progression-free survival (5-yr PFS). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for significant variables.

Results
Of the 108 patients enrolled in the protocols, 33 (30.6%) underwent salvage surgery and 26 matched study criteria. Seventeen patients were disease-free after a median follow-up of 125 months (range 65.5–311.7 months), 5-yr PFS 65.4%. Nine events were registered after a median follow-up of 5.4 months (range 1.9–27.5 months). Among the variables assessed (Table), only an undifferentiated histology proved to be significantly associated with a poorer 5-yr PFS, whereas a tumor size above 5 cm in the removed specimen approached significance. The OR (95% CI) for failure of 5-yr PFS was 28 (2.4–326.8) and 8.3 (1.03–67.1), respectively.

Conclusion
5-yr PFS proved unrelated to excision margins of the surgical specimen, that is on whether there was evidence of microscopic residues left behind during surgery. These data suggest that the outcome is more influenced by the biological properties of the tumor. If small foci of differentiated cells are left behind, these probably do not compromise final prognosis. In our patients requiring salvage bladder-prostate surgery after failure of chemotherapy ± radiotherapy, long-term progression-free survival seemed unrelated to patient/tumor characteristics at presentation and preoperative management. Regarding the characteristics of the removed specimen, instead, an undifferentiated tumor histology and a diameter of the removed tumor >5 cm negatively influenced prognosis, whereas the presence of positive excision margins did not.

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			PFS >5 years n/N (%)	p
Variables at diagnosis	Age at diagnosis	<5 years	14/20 (70)	0.4
		>5 years	3/6 (50)	
	Gender	Male	12/20 (60)	0.3
		Female	5/6 (83)	
	Histology on initial biopsy	Embryonal	9/16 (56)	0.1
		Botryoid	8/9 (89)	
	Tumor location	Prostate	4/7 (57)	0.6
		Bladder	11/15 (73)	
		Bladder-prostate	2/4 (50)	
	Tumor size	<5 cm	5/7 (71)	0.7
		>5 cm	12/19 (63)	
	T-stage	T1	7/10 (70)	0.7
		T2	10/16 (62.5)	
Treatment variables	Treatment protocol	RMS 88	5/7 (71.5)	0.5
		RMS 96	4/8 (50)	
		RMS 2005	6/8 (75)	
	Tumor response at 9 weeks	Complete response (CR)	0/1 (0)	0.4
		Partial response (PR) > 2/3	9/13 (69)	
		Minor response (MR) > 1/3 but < 2/3	4/7 (57)	
		No response or stable disease (SD) < 1/3	4/4 (100)	
	Preoperative radiotherapy	No	8/12 (67)	1
		Yes	9/14 (64)	
Pathology variables	Tumor location on surgical specimen	Prostate	5/8 (62.5)	0.1
		Bladder	11/14 (78.5)	
		Bladder-prostate	1/4 (25)	
	Surgical margins	Negative	7/12 (58)	0.1
		Positive	7/8 (87.5)	
	Diameter of tumor at the surgical specimen	<5 cm	10/12 (83)	0.06
		>5 cm	3/8 (37)	
	Histological differentiation	Differentiated	11/13 (84.5)	0.002
		Undifferentiated	1/7 (14)	
		Myxoid	3/4 (75)	

Introduction

In recent decades, multicentric trials have promoted an organ-sparing approach to bladder/prostate rhabdomyosarcoma (BP-RMS) in children with the aim of preserving bladder function [1—4]. Accordingly, surgery is initially limited to biopsy for diagnosis and staging, whereas radiotherapy (RT) is favored, on top of systemic chemotherapy (CHT), to achieve local control [5]. Ablative surgery is restricted, as salvage procedure, to cases showing unsatisfactory response to CHT and RT. Reportedly, 10-year overall survival in latest protocols exceeds 70% [6] and progression-free survival seems to reach a plateau in the sixth year of follow-up [7].

In the whole population of RMS patients, accepted adverse prognostic factors include patient age at diagnosis under 1 year or above 10 years, tumor size >5 cm, alveolar or undifferentiated histology, unfavorable tumor site (patrameningeal, extremities, bladder/prostate), higher risk group according to IRS grouping system, and older treatment protocols [7,8]. For BP-RMS in particular, instead, prostate involvement was identified as a negative prognostic factor, whereas tumor size was suggested to have no prognostic value [9].

Little is known on prognostic factors in the subgroup of patients with BP-RMS requiring salvage surgery after failure of CHT and RT. In these patients, it is not even clear whether the presence of microscopic remnants, that is positive excision margins, jeopardizes the outcome. A better knowledge of these parameters might help identifying patients requiring closer follow-up or additional adjuvant treatment after salvage surgery.

To evaluate prognostic factors in children undergoing salvage surgery, we reviewed the 28-year Italian experience in the treatment of BP-RMS. Our hypothesis was that the same variables identified as prognostic factors in the general