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Primary Renal Sarcomas in the Intergroup Rhabdomyosarcoma Study Group (IRSG) Experience, 1972–2005: A Report from the Children's Oncology Group

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Abstract

Purpose—To describe clinical and pathologic characteristics and outcome of patients with renal sarcomas.

Patients/Methods—The IRSG database includes newly diagnosed patients <21 years old with rhabdomyosarcoma (RMS) or undifferentiated sarcoma (UDS). We identified patients with renal sarcoma and reviewed their charts.

Results—Ten of the 5,746 eligible IRSG patients enrolled from 1972–2005 had primary renal embryonal RMS (N=6) or UDS (N=4). Anaplasia was present in six (60%) of the tumors. Patients' ages ranged from 2.6–17.8 years. Tumor diameters ranged from 7–15 cm (median, 12 cm). At diagnosis, seven patients had localized disease: four underwent complete removal of tumor (Group I), two had microscopic residual (Group II), and one had gross residual tumor (Group III). Three

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patients had distant metastases (Group IV) in lungs and bone. Nine patients received vincristine, actinomycin D and cyclophosphamide (VAC). Two Group I patients received no radiation therapy (XRT); others received XRT to the primary tumor and to some metastatic sites. Nine patients achieved complete disappearance of tumor, six due to the initial operation. Tumors recurred in lung (N=2) or brain (N=1) in Group IV patients; each died within 16 months. The Group III patient died of *Aspergillus* pneumonia. The six Group I and II patients survive, continuously disease-free, at 2.7 to 17.3 years (median, 4.7 years).

Conclusions—Patients with renal sarcomas often present with large tumors, many of them containing anaplastic features. Removing all gross disease at diagnosis, if feasible, is a critical component of treatment to curing patients with renal sarcoma.

Keywords

Renal Sarcomas; Children/Adolescents; IRS Group Experience

INTRODUCTION

The most frequent primary renal cancer in the first two decades of life is Wilms tumor. Since the National Wilms Tumor Study Group (NWTSG) began in the USA (1969), other types of renal tumors have been described, especially malignant rhabdoid tumor and clear-cell sarcoma of the kidney.[1–3] The commonest kidney malignancy in adults, renal cell carcinoma, can occur in children.[4] True sarcomas of the kidney are unusual at any age.[5–10]

The most frequent variety of soft-tissue sarcoma in children is rhabdomyosarcoma.[11] Since the Intergroup Rhabdomyosarcoma Study Group (IRSG) began in 1972, we have learned much about the diversity of this disease.[12] The IRSG, recently renamed the Soft-Tissue Sarcoma Committee of the Children's Oncology Group, has enrolled nearly 6,000 patients with rhabdomyosarcoma (RMS) and undifferentiated sarcoma (UDS) on IRS-I through-V protocols.[13–24] The purposes of this article are to ascertain the clinical and pathologic characteristics of patients with primary renal RMS and UDS and to describe their treatment and outcome.

PATIENTS AND METHODS

The University of Nebraska database was searched to determine the number of patients registered on consecutive IRSG protocols from November 1972 to September 2005, including those with primary sarcoma of the kidney. The cut-off date was selected to allow for ≥ 2 years of follow-up information on the recently entered patients. Twelve patients were identified with renal tumors. After examination of the pathologic materials by members of the IRSG and also by Drs. Bruce Beckwith and Elizabeth Perlman, primary pathology reviewers for the NWTSG, two patients were excluded from this review because of a consensus diagnosis of Wilms tumor or clear-cell sarcoma of the kidney. Thus ten patients with renal RMS/UDS were reviewed. Eligibility criteria included recently diagnosed, previously untreated patients < 21 years who underwent physical, laboratory, and radiographic examinations to establish the extent of the disease.[13–24] Pathologic materials were submitted to the Pathology Center in Columbus, OH. Pathology diagnosis and presence or absence of anaplasia (focal or diffuse) were defined according to well-established criteria.[25] Immunostains for MyoD1, myogenin, and desmin were performed as previously described.[26] For diagnosing undifferentiated sarcoma, other immunostains such as muscle specific actin, S-100 protein, myoglobin, neuron specific enolase, leukocyte common antigen, wide spectrum keratin, and epithelial membrane antigen were employed in

all cases in which adequate tissue was available. [27] In addition, translocations for cellular mesoblastic nephroma, monophasic synovial sarcoma, Ewing sarcoma and alveolar RMS were tested by the reverse transcriptase-polymerase chain reaction (RT-PCR), whenever the technology and adequate tissue were available. Patients were classified into one of four surgico-pathologic Groups during 1972–1991 [12,Table 1]. Afterward, patients were also categorized into one of four pre-treatment TNM Stages [12,Table 2]. Treatment details were reviewed, as already published.[13–24]

RESULTS

Table I summarizes clinicopathologic data. Treatment, response, and outcome data are displayed in Table II.

Patients

Patients were enrolled on IRS-1 (N=2), IRS-IV (N=3), IRS-V Pilot (N=2) and IRS-V (N=3) protocols, respectively, comprising 0.17% of 5,746 eligible patients enrolled on all IRSG studies from 1972–2005. Ages ranged from 2.6 to 17.8 years (median, 6.35 years); six were females and four males (Table 1).

Tumors

Eight tumors arose in the left and two in the right kidney. The tumor's widest diameter and its perpendicular ranged from 7 cm X 5.5 cm to 15 cm X 11 cm (median, 12 cm). Three tumors were non-invasive (T1); two were invasive (T2). A photograph of a recent six-year-old patient's gross specimen is shown in Figure 1. (The patient is not included in this series because of inadequate follow-up.) This embryonal RMS replaced the upper pole of the left kidney and measured 10.5 cm X 10.5 cm X 8.5 cm. The tumor plus kidney weighed 535 grams; the remaining normal kidney alone weighed 64 gm.

Pathology

Pathologic types were embryonal RMS (ERMS) in six patients and UDS in four. Eight tumor specimens (including that in Figure 1) were reviewed by Drs. Beckwith or Perlman and confirmed as RMS or UDS. Anaplasia was prominent, found in 4/6 ERMS patients (67%) and 2/4 UDS patients (50%; added together, 60%). The incidence of anaplasia exceeded the rates of 11%–14% in Wilms tumor [28,29] and 13% in RMS overall.[30] Figures 2 and 3 illustrate focal anaplasia in scattered nuclei of a renal ERMS; diffuse anaplasia would show these cytologic nuclear features in one cluster or nest of every five to six nuclei in RMS.[25] We have also not previously identified anaplasia in UDS in IRSG studies.[27] All cases of ERMS were strongly immunopositive for MyoD1, myogenin, and desmin; all UDS cases were immunonegative for these markers.[26] We found no case of renal alveolar RMS.

Initial Operative Management and Surgico-Pathologic Grouping

Initial operations were radical nephrectomy (N=9) and incisional biopsy (N=1) (Table II). Eight patients underwent regional lymph node dissection (N=2) or biopsy (N=6): seven patients had 2–15 uninvolved lymph nodes (N0) and one (Group IV patient 8) had 2 tumor-involved lymph nodes (N1). Seven patients (numbers 1–7) had localized tumors at diagnosis and were in Group I (tumor completely resected, N=4), Group II (microscopic residual, N=2) or Group III (gross residual, N=1). Three other patients had metastases (Group IV) in lung and bone, as well as in the pleura (patient 9). The primary tumors in these patients were resected with local microresidual disease (patient 8) and no residual local disease (patient 10); patient 9 had only a biopsy with gross local residual disease.

Chemotherapy

Patient 5 received vincristine and actinomycin D; the other nine patients also received cyclophosphamide (collectively called VAC) according to their protocol, modified as needed for toxicity. Patient 8 also received doxorubicin, and patients 9 and 10 also received topotecan.[24]

Radiation Therapy (XRT)

Eight patients received post-operative XRT to the primary tumor (including three to metastases), including two Group I patients and all six with more extensive disease (patients 5 through 10).

Response

Nine patients achieved a complete response (no tumor detectible), six due to initial surgical removal of the tumor. Patient 9 had incisional biopsy; at second-look operation (week 28) residual viable tumor was removed with clear margins, rendering her disease-free. Patient 10 never became disease-free.

Compliance

Chemotherapy. Drug doses received were computed as the percentage of doses expected to be given per protocol according to weight or body surface area. Eight patients received $\geq 78\%$ of scheduled vincristine; two others received 45% or 67%, respectively (patients 1, 9). Nine patients received $\geq 78\%$ of scheduled actinomycin D; the other received 70% (patient 4). Eight patients received $\geq 91\%$ of scheduled cyclophosphamide; the other received 70% (patient 1). Patients given doxorubicin or topotecan received 100% of those medications. Radiation Therapy (XRT). Two Group I patients received no postoperative XRT, per protocol. Patients 3 and 4 received 36 Gray (Gy). Group II patients 5 and 6 received 36 Gy per protocol; patient 5 had a close inferior margin (protocol deviation). Group III patient 7 received 45 Gy per protocol. Group IV patient 10 received appropriate doses to the primary tumor, 41.4 Gy, plus 14.4 Gy to both lungs and 50.4 Gy to a solitary bone metastasis. The other Group IV patients received appropriate doses, 45–46 Gy, to the primary tumor, but one lung (patient 9) or both lungs (patient 8) were not irradiated (protocol deviation), and the dose to a bone metastasis in patient 9 was low (30 Gy).

Recurrence

Each Group IV patient developed recurrent disease within 13 months after enrollment. All three patients had had lung metastases initially, and in two of them the disease recurred in the lung. One (patient 8) had received no lung radiation. Patient 9 developed metastases in the brain and meninges just beyond one year on study and died shortly afterwards.

Survival

Patients with recurrence died of tumor within 16 months from study enrollment. Patient 7 died with *Aspergillus* pneumonia following prolonged neutropenia without detectible tumor recurrence. Thus the six patients who survived the disease were those with the best initial outlook; each had initially undergone grossly complete resection of localized tumor. Their failure-free and overall survival intervals were 2.7⁺, 2.8⁺, 3.8⁺, 5.6⁺, 7.6⁺, and 17.3⁺ years from the date of study enrollment.

DISCUSSION

Pathology

Rhabdomyosarcoma of the kidney occurs rarely in adults and has a poor prognosis.[5,6] Suggested criteria for making the diagnosis include the following: the patient must not have or previously had a sarcoma elsewhere, the gross appearance should be indicative of origin within renal parenchyma (see Figure 1) rather than spreading there from a retroperitoneal primary site, and sarcomatoid renal cell carcinoma must be excluded.[8]

The pathology literature about renal sarcomas in children is quite limited. A new type of renal tumor, cystic embryonal sarcoma, was described in 25 patients reviewed by the NWTSG Pathology Center in 1995 and summarized in 1998.[31] Tumors consisted predominantly of undifferentiated malignant mesenchymal cells with foci of suggested smooth muscle or pericytes, and cysts with epithelial cells. All 16 tumors studied were positive immunohistochemically for vimentin, as were seven for actin and six for desmin. The prognosis was poor, with five tumor-related deaths and evidence of metastases in 11 of 17 cases with follow-up information. The disease was considered distinguishable from RMS, malignant rhabdoid tumor, and clear cell sarcoma of the kidney.[31]

Anaplasia does not appear to be a feature of the cystic embryonal renal sarcomas described above. Our cases also lacked the cystic epithelial features of that entity. Our series describes ten immunohistochemically-confirmed cases of ERMS or UDS in the kidney with a 60% incidence of anaplasia. Anaplastic Wilms tumors are uncommon, known to be resistant to standard Wilms chemotherapy programs, and appear to require complete surgical removal for cure.[28,29] By analogy, RMS or UDS of the kidney with anaplasia may have a similar evolution wherein aggressive surgical management of the primary tumor is necessary. A well-documented case of renal RMS was reported in a six-year-old boy with a bone metastasis. His tumor contained rhabdomyoblasts, some with cross-striations; the bone lesion and tumor-involved lymph nodes exhibited similar features of what was then called pleomorphic rhabdomyosarcoma. He died of progressive disease 13 months after diagnosis. [32] Pleomorphic RMS in children is now identified as anaplastic RMS.[33]

Clinical Characteristics and Outcome

The results of this series of young patients with primary RMS or UDS of the kidney indicate that children with this disease present with large tumors and may have metastases. Small numbers of patients make it unwise to draw broad conclusions, but when possible, we believe that the primary tumor should be removed completely, especially when the disease is localized. Regional lymph-node biopsy/dissection is indicated, because some may be tumor-involved, which would affect the radiation therapy volume. The role of local radiation therapy is not clearly defined in these patients, but local control was apparently achieved in the six surviving patients, including two in Group I who were not irradiated. The relatively short time to death from recurrence or infection might have obscured the issue about local control, however. Chemotherapy failed to prevent the recurrence of distant disease in lungs initially involved with metastases, even with the addition of whole-lung irradiation in one patient. Neither of the two patients with ERMS and metastases who were <10 years old at diagnosis had long-term control of the disease.[23]

In summary, we believe that until further data are available, patients with localized renal RMS should be treated as having a form of unfavorable-site rhabdomyosarcoma and classified in Stage 2 or 3 (depending on diameter, with or without tumor in regional lymph nodes), because patients with renal sarcomas may not have the relatively favorable outlook of patients with localized orbital, non-parameningeal head/neck, paratesticular and vulvovaginal/uterine RMS. In IRS-IV, patients with localized tumors arising in those

“favorable” sites were classified in Stage 1 and had failure-free survival rates at three years of 86%, regardless of tumor diameter.[20] Patients with undifferentiated renal sarcoma should be treated on protocols appropriate for that histology, and those with metastatic disease should be treated on Stage 4 protocols. Finally, the role of anaplasia in patients with renal sarcoma needs to be explored further.

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Figure 1.

This embryonal RMS with focal anaplasia was recently removed from a six-year-old patient. It had a discrete margin separating it from the kidney (arrows). The epicenter was in the kidney with secondary adrenal gland involvement. The pale, nodular, white gelatinous tumor with multiple foci of necrosis and central cystic change (arrow heads) was not typical of Wilms tumor.

Figure 2. Focal anaplasia in a renal embryonal RMS with large, atypical mitotic figures (arrows) (H & E stain, X400).

Figure 3. Focal anaplasia in a renal embryonal RMS with large, pleomorphic nuclei (arrows), three to four times the size of neighboring nuclei (H & E stain, X400).

TABLE I

PATIENTS AND TUMORS*

Pt. No.	Age (Yrs.), Gender	Tumor Site	Size, cm	Pathology; Anaplasia	Clinical Group, Lymph Nodes	Sites of Metastases
1	2.6, F	Upper Left	12 x 8	ERMS; none	I, 8 Neg. LNs	None
2	4.6, F	Left	8	UDS; focal	I, T1, 15 Neg. LNs	None
3	3.3, M	Left	11 x 8.5	UDS; diffuse	I, T2, 2 Neg. LNs	None
4	6.4, M	Left	7 x 5.5	UDS; none	I, T2, 6 Neg. LNs	None
5	7.7, M	Left	15 x 11	ERMS; diffuse	IIA, T1, 4 Neg. LNs	None
6	17.8, F	Right	12 x 11	ERMS; diffuse	IIA, T1, 3 Neg. LNs	None
7	12.0, F	Left	15 x 11	ERMS; focal	III, 7 Neg. LNs	None
8	6.1, M	Lower Left	8 x 7	ERMS; diffuse	IV, 2 Pos. LNs	Lung, Bone
9	5.8, F	Left	14 x 12	ERMS; none	IV	Lung, Bone, Pleura
10	10.8, F	Lower Right	11 x 10	UDS; none	IV	Lung, Bone

* Abbreviations: Pt. No. = Patient Number; Yrs. = years, cm = centimeters, ERMS = embryonal rhabdomyosarcoma, UDS = undifferentiated sarcoma, none = no anaplasia, T1 = non-invasive, T2 = invasive, Neg. = not involved by tumor, Pos. = involved by tumor, LNs = regional lymph nodes

TABLE II

TREATMENT, RESPONSE, AND OUTCOME*

Pt. No.	Operative Management	Study; Group, Regimen	Response	Site of Recurrence	Failure-Free Survival, Yr.	Survival, Years	Cause, if Dead
1	Radical Nephrectomy, LN Dissection	IRS-I; I, VAC	Complete	None	17.3+	17.3+	Alive
2	Radical Nephrectomy, LN Dissection	IRS-IV; I, VAC	Complete	None	7.61+	7.61+	Alive
3	Radical Nephrectomy, LN Biopsy	IRS-V; I, VAC + RT	Complete	None	3.83+	3.83+	Alive
4	Radical Nephrectomy, LN Biopsy	IRS-V; I, VAC + RT	Complete	None	2.7+	2.7+	Alive
5	Radical Nephrectomy, LN Biopsy	IRS-IV; IIA, VA + RT	Complete	None	2.82+	2.82+	Alive
6	Radical Nephrectomy, LN Biopsy	IRS-V; IIA, VAC + RT	Complete	None	5.6+	5.6+	Alive
7	Radical Nephrectomy, LN Biopsy	IRS-IV; III, VAC + RT	Complete	None	0.47	0.47	Infection
8	Radical Nephrectomy, LN Biopsy	IRS-I; IV, VAC, Dox., + RT	Complete	Lung	0.37	1.02	Tumor
9	Incisional Biopsy; SLO at week 28	IRS-V Pilot; IV, VAC, Topo., + RT	Complete	Brain and Leptomeninges	1.03	1.07	Tumor
10	Radical Nephrectomy	IRS-V Pilot; IV, VAC, Topo., + RT	Less than 50%	Lung	0.67	1.3	Tumor

* Pt. No. = Patient Number; Yr. = years; LN = regional lymph nodes; SLO = Second-Look Operation; VAC = vincristine, actinomycin D, cyclophosphamide; Dox. = doxorubicin; RT = radiotherapy; Topo. = topotecan