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Local Lymph Node Involvement in Pediatric Renal Cell Carcinoma: A Report From the Italian TREP Project

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Background. One of the most important adverse prognostic factors for adult renal cell carcinoma (RCC) is the retroperitoneal lymph node involvement. The aim of this article is to study the prognostic significance of local lymph node involvement in pediatric RCC and the role of retroperitoneal lymph node dissection (RLND) at diagnosis. ***Procedure.*** The series included 16 patients with RCC and lymph nodes involvement registered in the Italian Rare Tumors Pediatric Age (TREP) project, accounting for 26.2% of 61 pediatric RCC observed at AIEOP centers. ***Results.*** A radical nephrectomy was performed in all cases: at diagnosis in 12 cases, after preoperative chemotherapy (CT) in 4 cases. As a part of the same procedure 9 patients underwent RLND, and 7 received a more limited lymph nodes resection. Five (31.2%) developed disease recurrence 2–34 months after diagnosis (median, 6 months) plus 1 developed progression; 6 patients died, 1 of them from secondary leukemia. Among the nine patients receiving RLND, eight are alive and disease free. This compares with only one patient surviving among the seven receiving a more limited lymph nodes resection. The estimated 25-year PFS and OS rates for all patients were 61.4% (95% CI 33.2–80.5) and 50.8% (95% CI 16.5–77.5), respectively. ***Conclusions.*** Lymph node involvement is an unfavorable prognostic factor in children with RCC. RLND appears to be a critical factor to improve the outcome. However, when compared to similar adult patients, the outcome in children appears to be better, suggesting that pediatric RCC, or the host, may be critical differences. Pediatr Blood Cancer 2008;51:475–478. © 2008 Wiley-Liss, Inc.

Key words: lymph node involvement; rare childhood cancer; renal cell carcinoma

INTRODUCTION

Renal cell carcinoma (RCC) in childhood is rare. As in adults, children with RCC tend to have a worse prognosis with increasing stage, with 88.9% OS when the tumor is limited to the kidney and completely resected [1] and 5–10% OS when distant metastasis are present [2]. A direct comparison between adult and pediatric data, however, is difficult to perform because different stage classifications are applied. One of the most important adverse prognostic factors for adult RCC is the regional lymph node involvement with 5-year survival estimates of approximately 20% [3,4]. For this reason the role of lymph node dissection has been investigated extensively in adults [5,6]. Recently, the experience at Saint Jude Children Research Hospital and an extensive review of the literature have suggested that children with lymph node positive RCC had a relatively favorable long-term prognosis, with survival rates of 70%, nearly triple those of adult historical controls [7].

To gain more knowledge about this problem, we reviewed the experience of patients affected by RCC with local lymph node involvement.

PATIENTS AND METHODS

In 2002 the AIEOP Committee for rare tumors launched a project dedicated to children with very rare tumor (the TREP project) including patients with RCC. Children and adolescents up to 18 years were identified retrospectively from 1973 to 2002 and afterwards registered prospectively in the TREP database. Since 2002, specific diagnostic and therapeutic guidelines have existed for children with RCC and nephrectomy with retroperitoneal lymph node dissection (RLND) is recommended at diagnosis for children with pathologically lymph nodes positive RCC. Data were also checked against the registry of all newly diagnosed primitive renal tumors coordinated by the Wilms Tumor Italian Study. From January 1973 to April 2007 61 patients with RCC were observed in 18 AIEOP centers. Clinical data, surgical notes, pathologic findings and summaries of treatment patients with nodal involvement, as data recorded from the pathology reports, were reviewed for the purpose of this analysis. Pathologic material from all patients was reviewed by one of the authors (P.C.). Informed consent for data registration was obtained from the patients' guardians at the time of patient registration in the TREP project.

Pathology Methods

Tumors were classified according to the 2004 WHO classification [8].

Staging and Clinical Data

Pathological staging was performed according to the modified Robson staging classification system [2]. For the purpose of the present analysis only patients classifying as having stage 3B were considered. According to the classification, stage 3B disease (T_x N_{1-2} M_0) represents localized disease with invasion of local

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lymph nodes. The extent of surgical lymph node resection was estimated after detailed review of surgical and histopathologic notes, as elsewhere published [1], and for the purpose of the analysis this surgical procedure was divided in three categories as follows:

(1) Retroperitoneal lymph node dissection (RLND) included for the left-sided tumors ipsilateral hilar, periaortic, and common iliac lymph node dissection; for the right RCC hilar, intercavoaortic, retro-paracaval, and ipsilateral common iliac lymph node dissection.
(2) Para-aortic lymph node dissection: removal of para-aortic lymph node.
(3) Renal hilum lymphadenectomy: removal of the lymph nodes at the hilum of renal vessels.

STATISTICAL METHODS

Fisher exact test was used for analyzing association between RLND and progression or death. Overall survival (OS) and progression free survival (PFS) were estimated using the Kaplan–Meier method [9]. Survival was calculated for all patients from the date of surgery to the date of death or last follow-up, if alive. PFS was calculated from the date of surgery to the date of disease recurrence, death or date of last follow-up, if alive in complete remission. Twenty-five-year OS and PFS were estimated with their 95% confidence interval (95% CI). All *P* values are two-sided and values less than 0.05 were considered statistically significant. The SAS package (v 9.1.3; SAS Institute, Cary, NC) was used for data analysis. The data were analyzed as of June 2007.

RESULTS

Patient Characteristics

Sixteen patients (nine females) with lymph nodes involvement were included in this study. The age of patients ranged from 18 to 215 months (median 120 months), at diagnosis, was consistent with other series of pediatric RCC [1,7]. Clinical characteristics and outcome are presented in Table I.

The most frequent symptoms at presentation included hematuria (43% of patients), a palpable mass (25%), and abdominal pain in one patient. The classic clinical triad of a palpable mass, flank pain, and hematuria, typical in adults patient, was never reported. One patient had urolithiasis as an underlying disease. RCC were classified as clear cell subtype in 12 cases, papillary in 3 and collecting duct in 1 case. All papillary RCC patients were females. According to the TNM classification, 7 (43.7%) patients were N1 and 9 (56.2%) were N2; T1: n = 5; T2: n = 3; T3: n = 6; Tx: n = 2.

Treatment

Nephrectomy was performed at diagnosis in 12 cases and after preoperative chemotherapy in 4. At the same time as primary tumor resection, 9 patients underwent RLND, 4 had the para-aortic lymph node removal, and 3 had the renal hilum lymph nodes removal. A second surgery to perform RLND was never carried out in the group of patients with limited lymph node resection. Six patients (37.5%) received chemotherapy according to different institutional choices. Four patients received pre-operative chemotherapy (vincristine and actinomycin D) according to the SIOP nephroblastoma protocols because of the clinical diagnosis of Wilms

TABLE I. Clinicopathologic Features, and Outcome

Patients	Age (months)	Sex	Side	Extent of surgery	Histology	Site(s) of recurrence/II neoplasia	Time to recurrence (months)	Therapy	Outcome	Follow-up (months)
1. S.S.	97	F	Left	RLND	Papillary	None	Na	RT + IFN	NED	68
2. M.G.	156	F	Left	RLND	Papillary	Progression	Na	IL2 + IFN	DOD	6
3. M.M.	215	M	Left	RLND	Clear cell	None	Na	CT pre + IFN	NED	216
4. P.C.	109	M	Left	Nephrectomy + para-aortic LN	Clear cell	Med. LN	17	CT pre + RT	LOST	43
5. T.S.	94	F	Left	RLND	Clear cell	None	Na	RT	NED	311
6. Z.L.	18	M	Left	Nephrectomy + renal hilum LN	Clear cell	Liver	2	CT pre	DOD	3
7. S.M.	172	M	Left	RLND	Clear cell	None	Na	CT post + IFN	NED	201
8. R.B.	131	F	Left	Nephrectomy + renal hilum LN	Clear cell	ANLL	27	CT post + IFN	DOD	39
9. D'A.M.	95	F	Right	RLND	Papillary	None	Na	IL-2	NED	86
10. F.F.	27	F	Right	Nephrectomy + renal hilum LN	Clear cell	Liver, lung	34	CT pre + CT post	DOD	115
11. R.A.	138	M	Right	RLND	Clear cell	None	Na	IL-2	NED	45
12. R.C.	151	F	Right	RLND	Clear cell	None	Na	IFN	NED	55
13. A.C.	180	M	Left	Nephrectomy + para-aortic LN	Clear cell	None	Na	IFN	NED	61
14. B.A.	80	F	Left	Nephrectomy + para-aortic LN	Clear cell	Local + metastatic	6	IL-2 + TMO	DOD	33
15. I.I.	137	M	Right	Nephrectomy + para-aortic LN	Duct collecting	Liver, lung, bone, med.	3	IL-2	DOD	5
16. B.R.	30	M	Left	RLND	Clear cell	None	Na	IL-2	NED	9

M, male; F, female RLND, retroperitoneal lymph node dissection; LN, lymph node; med, mediastinum; ANLL, acute non-lymphoblastic leukemia; CT, chemotherapy; pre, preoperatory; post, postoperatory; IFN, interferon; IL-2, interleukin 2; RT, radiotherapy; NED, no evidence of disease; DOD, dead of disease

tumor. In three patients the responsible physician decided to give postoperative chemotherapy (vinblastine and epirubicin in two cases, carboplatin and etoposide in one case). Adjuvant therapy was administered to 12 patients with interleukin-2 (6 cases) or interferon (6 cases). Three patients received radiotherapy to the primary tumor site as part of their initial treatment with doses ranging from 30 to 40 Gy.

Outcome

After a median follow-up of 68 months (range 9–311 months), 9 patients are alive and disease free, 6 patients died, and 1 patient was lost to follow-up with evidence of disease. The estimated 25-year PFS and OS rates for all patients were 61.4% (95% CI 33.2–80.5) and 50.8% (95% CI 16.5–77.5), respectively (Fig. 1A,B). This compare with 88.9% 25-year EFS obtained in 30 patients with localized disease without lymph nodes involvement (stages 1–2) registered in the TREP project over the same period of time. Five patients (31.2%) developed metastatic disease, one of them combined with local relapse, 2 to 34 months after diagnosis (median 6 months). In these patients radical nephrectomy and the para-aortic or the renal hilum lymph nodes removal were performed at diagnosis. Among the nine patients with RLND, eight are alive and disease free, one died of progressive disease. Only one is alive and disease free among the four children who received para-aortic lymph node dissection: two died after local and/or metastatic relapse and one with a distant metastases was lost to follow-up. The three patients who had dissection of the renal hilum lymph nodes died, two after metastatic relapse, and one from secondary acute non-lymphoblastic leukemia (ANLL). Three of seven N1 patients and five of nine N2 patients were alive without evidence of disease, at last follow-up.

When compared with those who received limited lymph node resection, the patients who underwent nephrectomy plus RLND had significantly less relapses, including one case of progressive disease, (5/7 vs. 1/9, difference between proportions 60.3%, 95% CI 12.2–82.6; $P = 0.03$), and significantly better survival (DOD 5/7 vs. 1/9, difference between proportions 60.3%, 95% CI 12.2–82.6; $P = 0.03$). Concerning postoperative treatment, all 16 patients received some kind of adjuvant therapy. Six patients received interleukin 2 (IL-2), with the addition of interferon (IFN) in 1 case. Six other patients received IFN, along with chemotherapy (CT) in two cases and radiotherapy (RT) in one of the patients. At last follow-up, eight patients were without evidence of disease, seven of them who underwent RLND as the initial treatment. Four patients died, all of them who underwent non-RLND as primary surgery. Three patients received chemotherapy and along with associated RT in one case. At last follow-up, two patients died and one was lost to follow-up but with active disease. Only one patient received RLND and RT as the initial treatment and was alive and well at last follow-up.

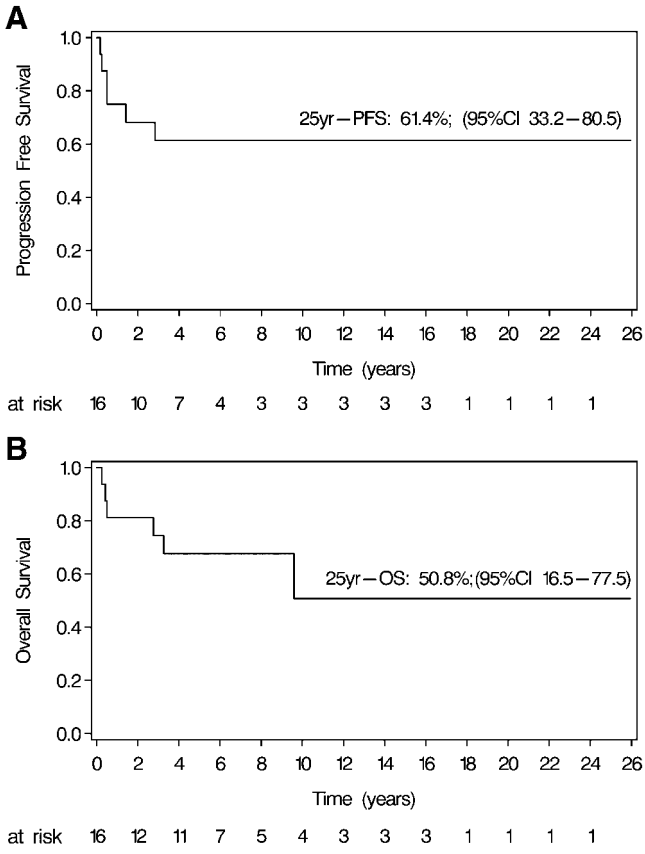

Fig. 1. **A**: Progression free survival (PFS) of patients calculated by Kaplan–Meier method (CI: confidence interval). **B**: Overall survival (OS) of patients calculated by Kaplan–Meier method (CI: confidence interval).

DISCUSSION

As a consequence of the rarity of RCC in children, only limited series of pediatric RCC have been published and treatment options are largely deduced from reports of adults. In most adult series, tumor stage seems to be the most important prognostic indicator [1,2,10–12]. Patients with localized disease (stages 1 and 2) have the best outcome with survival of approximately 80%. When regional lymph nodes are involved by the tumor the survival drops dramatically to 20% [3,4]. This is likely to explain why RLND is considered as standard treatment in adult RCC and adjuvant therapy is attempted in such patients. Previous reports have observed that children with regional lymph node positive RCC may have a better prognosis than their adult counterparts [7,12,13]. In a recent review of published studies, Geller and Dome analyzed 243 pediatric RCC cases; the overall and disease free survival rates of 58 patients with stage 3B were 77.6% and 72.4%, respectively. The authors state that few children with RCC in the review underwent RLND. The conclusion is that second-look lymph node dissection was unnecessary for children who did not receive it as part of their primary surgery [7]. A retrospective analysis of the cases included in the German childhood cancer registry and the Kiel pediatric tumor registry, showed a similar favorable outcome in lymph node positive patients with 5-year EFS and OS rates of 68.8% and 75%, respectively. The authors support the hypothesis that a complete resection of all tumor lesions, including lymph nodes seemed to be the crucial mainstay of successful treatment in these patients [13]. Other studies suggest that lymph node dissection has a positive effect on the survival of children with RCC [12,14].

In our experience, four patients had surgery after preoperative chemotherapy because they were suspected of having Wilms tumor. However, three of them did not undergo lymph node dissection. Of these, two patients died of disease and one with active disease were

lost to follow-up. The patients classified as having stage 3B RCC had a poorer survival (20-year EFS rate, 50%) in our previous study [1]. In the present experience, with an increased number of cases, we confirm that the stage 3B RCC patients had a relatively unfavorable long-term prognosis with an estimated 25-year PFS and OS rates of 61.4% and 50.8%, respectively. Renshaw [15] speculates that children with N + RCC had favorable outcome because of the biology of their tumors, namely many of the pediatric RCC were translocation-associated carcinomas rather than clear cell. For this reason, we are planning to review all samples of our patients to address this important point. Probably the proportion of translocation type pediatric RCC is currently under-estimated, due to the absence of additional TFE3 immunostaining in all RCC tumor specimens as in the study by Bruder et al. [16]. Other biologic features are implicated in clinical differences between adult and pediatric RCC. Only a very small subgroup of adult RCC patients had underlying disorders such as tuberous sclerosis complex [17] or von Hippel-Lindau disease [18,19]. However, a majority of sporadic adult RCC shows VHL gene abnormalities in contrast to childhood RCC.

Several trials in adults have demonstrated a moderate response to immunotherapy (IFNα or IL-2) in patients with advanced stage RCC [20,21]. Given the small number of patients included in our study, little can be said about the value, if any, of adjuvant therapy. Probably, in our cohort of children the quality of surgery, namely complete nephrectomy with RLND, seems to be the main stay of the treatment, but a larger number of patients is needed to support this.

In conclusion, with the limitation of the number of patients in our report, we cannot confirm the Geller and Dome conclusions who propose that RLND is unnecessary. As a consequence, until more data are available to clarify this issue, we recommend performing nephrectomy with RLND in patients with RCC and lymph node involvement at diagnosis.

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