Journal of Pediatric Urology (2009) 5, 308—314

Journal of Pediatric urology

EDUCATIONAL ARTICLE

Pediatric renal cell carcinoma

Justin E. Sausville [a,*], David J. Hernandez [a], Pedram Argani [b], John P. Gearhart [a]

[a] *James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287, USA*
[b] *Department of Pathology, The Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287, USA*

Received 6 February 2009; accepted 2 April 2009
Available online 14 May 2009

KEYWORDS
Pediatric renal cell carcinoma;
Translocation RCC;
Second malignancy;
TFE3;
MiT

Abstract Renal cell carcinoma (RCC) comprises about 5% of pediatric renal neoplasms. It has been recognized as a second malignancy in multiple reports. It is generally symptomatic at diagnosis, and most children with RCC present with more locally advanced disease than do adults. Contemporary investigation of pediatric RCC has demonstrated that a large percentage of these tumors bear cytogenetic translocations involving the MiT family of transcription factors. Surgical therapy for these children resembles operative intervention for adult RCC, though debate continues about the precise role of lymph node dissection. There are no adequately powered studies to support conclusions about adjuvant or neoadjuvant chemotherapy for children with RCC. This may be ameliorated by a multi-institutional protocol which is enrolling patients.

Introduction

Renal cell carcinoma (RCC) is not a common malignancy in children, and attempts at generalization are hampered by the limited amount of published data. Nonetheless, case series are accruing and being reported by multiple centers, and the picture that emerges is one of a frequently advanced neoplasm which differs clinically and biologically from adult RCCs. In this paper, we summarize the current state of knowledge about the clinical presentation and management of pediatric RCC.

* Corresponding author. Tel.: +1 410 328 5570; fax: +1 410 328 1716.
E-mail address: jsausville@smail.umaryland.edu (J.E. Sausville).

Epidemiology

RCC is rare in children and adolescents. Two large studies of tumor registries have recently been reported. In a 25-year survey of the German Childhood Cancer Registry and the Kiel Pediatric Tumor Registry, Selle and colleagues [1] identified 49 children with RCC; the median age at diagnosis was 10.6 years. One third of the patients had underlying medical issues which the authors regarded as potentially predisposing to RCC, including tuberous sclerosis and prior chemotherapy for neoplasia. More recently, Silberstein et al. [2] identified 43 pediatric RCC cases in the California Cancer Registry. Their patients had a median age of 17 years, and represented 4.3% of reported pediatric renal tumors. They noted more cases in girls and African-Americans. Overall RCC incidence

1477-5131/$36
doi:10.1016/j.jpurol.2009.04.007

was estimated at 0.01/100,000 population. No data were analyzed concerning comorbid conditions. Collectively, these studies portray a rare disease which tends to occur in later childhood. The divergent ages of patients in the two studies, as well as their discordance with regard to gender and racial predilections, suggest that even large population-based studies may have difficulty accruing enough cases to be assured of a truly representative sample.

RCC has been recognized as a second malignancy in children diagnosed with other cancers, especially neuroblastoma (NB). Bassal and colleagues [3], in a review of more than 13,000 survivors of childhood malignancy, identified nine RCCs, five of which followed treatment for NB. Fleitz et al. [4] presented 16 cases of RCC following NB; diagnosis of RCC averaged 14.7 years after NB (range 2.4—34 years). Eleven of the patients (68.8%) had stage III or greater NB; the same percentage had received some form of chemotherapy during NB treatment.

Treatment of other primary malignancies has been complicated by late-occurring RCC. These include acute lymphoblastic leukemia, supratentorial primitive neuroectodermal tumors [5], cardiac leiomyosarcoma [6], acute promyelocytic leukemia, and Wilms' tumor [7]. These findings prompt the question of whether RCC in this setting is a manifestation of an underlying tumor diathesis, or if one or more therapeutic modalities promote renal tumorigenesis.

Argani et al. [7] reported on six cases of pediatric RCC following chemotherapy. All of these RCCs displayed translocation histology, the nature of which is discussed further below. Of these patients, three had received chemotherapeutic agents for non-neoplastic conditions. Moreover, five had received cyclophosphamide, an agent with a recognized propensity for promoting bladder neoplasia [8], while others had received topoisomerase II inhibitors. In the previously cited study from Fleitz et al. [4], 10 of 16 RCC patients had received cyclophosphamide for treatment of NB. On the other hand, a specific relationship between neuroblastoma and subsequent RCC has been postulated, and NB survivors appear to be at risk for RCC even if they received no chemotherapy [9]. Post-NB RCC appears to have a distinctive pathologic appearance and has been recognized in the 2004 WHO renal tumor classification as a discrete entity [10]; however, there may be morphologic overlap with translocation RCCs [7].

Diagnosis

Table 1 summarizes the clinical presentations of pediatric RCC in several recently published series. The majority of RCCs were symptomatic at diagnosis, and local findings (abdominal pain, abdominal mass, hematuria) predominated over paraneoplastic phenomena such as weight loss or fever. Notably, only 12% of pediatric RCCs were asymptomatic at diagnosis. Conversely, a recent large series [18] noted that, by 1997, more than 50% of adult RCCs were diagnosed as incidental findings. The same series found that, in 1983, 13% of the adult RCCs were asymptomatic. The similarity between contemporary incidence of asymptomatic pediatric RCC and past incidence of asymptomatic adult RCC may be explained by less abdominal imaging of children or by the long time span covered by many of the pediatric RCC series—institutional and population-based reports may need as long as 20—40 years to accrue patients with this uncommon malignancy. Thus, many patients would have come to attention before the widespread use of sensitive imaging modalities.

As would be expected with the emergence of the incidental RCC as a prominent clinical entity, a remarkable downward stage migration [19] has been seen in adult RCC. Table 2 describes primary tumor staging as reported in recent series as well as the proportion of patients in each series with lymphatic spread and distant metastasis. As might be expected given the high proportion of symptomatic patients, T1 lesions only accounted for 43.7% of the tumors. We suggested above that the large series currently available may not fully reflect the larger number of patients undergoing more sensitive imaging. It may be informative to start accruing more recent (i.e. from the past 10 years) series of RCC patients to try to document a downward stage migration, if one does indeed exist for pediatric RCC. Nodal metastasis is also fairly commonly (29%) seen in pediatric RCC.

Imaging plays a crucial role in distinguishing RCC from more common childhood renal masses, notably Wilms' tumor. Miniati and colleagues [20] analyzed 92 CT studies obtained in children with renal masses. Four of these tumors were subsequently found to be RCC. The authors reported 82% accuracy for radiographic correlation with tumor histology. This relatively low figure underscores the importance of clinical correlation in children with renal masses if inappropriate neoadjuvant chemotherapy is to be avoided. Specifically, hematuria is uncommon in Wilms' tumor, and the patients with RCC tend to be older children [20]. Moreover, calcifications

Table 1 Presenting symptoms at diagnosis of RCC in recently published studies.

Study	Abdominal pain	Hematuria	Abdominal mass	Fever	Weight loss	Asymptomatic
Selle et al. [1]	22/40	12/40	5/40	9/40	2/40	6/40
Indolfi et al. [11]	17/41	12/41	9/41	2/40	2/40	2/40
Cook et al. [12]	4/15	6/15	1/15	2/15	0/15	2/15
Estrada et al. [13]	3/11	4/11	1/11	0/11	0/11	4/11
Labanaris et al. [14]	1/4	2/4	1/4	0/4	0/4	0/4
Bosquet et al. [15]	2/4	2/4	1/4	0/4	0/4	0/4
Tsai et al. [16]	0/4	1/4	1/4	0/4	0/4	2/4
Geller and Dome [17]	8/13	10/13	0/13	4/13	2/13	0/13
Total	**57/132 (43%)**	**49/132 (37%)**	**19/132 (16%)**	**17/132 (13%)**	**6/132 (5%)**	**16/132 (12%)**