Journal of Pediatric Surgery 50 (2015) 1014–1018

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Factors impacting survival in children with renal cell carcinoma

Kristy L. Rialon [a], Brian C. Gulack [a], Brian R. Englum [a], Jonathan C. Routh [b], Henry E. Rice [c,*]

[a] Department of Surgery, Division of General Surgery, Duke University Medical Center, Durham, NC, 27710, USA
[b] Department of Surgery, Division of Urology, Duke University Medical Center, Durham, NC, 27710, USA
[c] Department of Surgery, Division of Pediatric Surgery, Duke University Medical Center, Durham, NC, 27710, USA

ARTICLE INFO

Article history:
Received 27 February 2015
Accepted 10 March 2015

Key words:
renal cell carcinoma
transitional renal cell carcinoma
National Cancer Data Base
partial nephrectomy

ABSTRACT

Purpose: Renal cell carcinoma (RCC) is an uncommon tumor in the pediatric population. We examined a large national cancer database to determine outcomes for children with RCC and to identify variables affecting long-term survival.

Methods: The National Cancer Data Base (NCDB) was queried for patients age 0 to 17 years diagnosed with RCC from 1998–2011. Patient demographics, tumor stage and characteristics, management, and outcomes were evaluated.

Results: A total of 304 children met inclusion criteria. Overall, 39% of children had stage I disease, 16% stage II, 33% stage III, and 12% stage IV. One-year and five-year survival for all children was 87% and 70%, respectively. Eighty-six percent of patients underwent surgical resection. In comparison to children who underwent complete nephrectomy, patients undergoing partial nephrectomy had smaller tumors and were of lower clinical stages. Survival following partial resection was 100% at one and five years. Age and gender had no significant impact on survival. Survival was negatively impacted by increasing tumor size ($P < 0.001$), positive nodal status ($P = 0.001$), and higher pathologic stage ($P < 0.001$).

Conclusion: Children with renal cell carcinoma who undergo surgical resection have excellent one-year and five-year survival. Overall survival is significantly affected by pathologic stage, tumor size, and nodal status.

Renal cell carcinoma (RCC) is an uncommon tumor in children, accounting for 0.1% to 0.3% of all neoplasms and 2% to 6% of all malignant renal tumors [1–3]. The incidence of RCC increases throughout childhood and among children is most commonly seen in the second decade of life [4]. The clinical behavior, genetic abnormalities, and pathologic characteristics of RCC in children are distinct from that in adults [5–7]. Argani et al [8,9] have suggested that pediatric RCC occurs as a result of genetic translocations, mostly commonly involving the *TFE3* gene on locus Xp11.2 and less commonly involving the *TFEB* gene on locus 6p21. Recognition of this genetic basis has led to such pediatric and young adult RCCs being dubbed "translocation carcinomas", a term that is now included in the AJCC (American Joint Committee on Cancer) pathological guides. Furthermore, the triad of gross hematuria, abdominal mass, and flank pain commonly described in adults is a less common presentation in children, occurring in only 9% of patients in one series [7].

In adult RCC, survival for AJCC/TNM stage I and II disease is high, but worsens with increasing stage, with a survival rate of only 15% for stage IV disease [10,11]. Several single center studies in pediatric RCC have identified predictors of poor survival including tumor stage, lymph node status, metastases, and grade [11–15]. However, these reports have wide variation in findings likely because of the small number of patients. For rare diseases, large databases are useful tools to define prognostic characteristics and to determine optimal management. To better understand the care of children with RCC, we examined a large national cancer database to describe characteristics of this tumor and determine prognostic indicators associated with increased survival.

1. Methods

1.1. Data source

The National Cancer Data Base (NCDB) is a voluntary patient registry sponsored by the American College of Surgeons and the American Cancer Society. This dataset contains clinical demographics and outcomes data on cancer treatment for patients in more than 1500 Commission on Cancer-accredited facilities.

1.2. Patient population

The NCDB was queried for all children ages 0 to 17 years who carried a diagnosis of RCC from 1998 to 2011 by International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes 8260, 8310, 8312, 8316, 8317, 8318, 8319, 8320, and 8510. We collected patient demographics, tumor characteristics, treatment, and outcomes. This dataset separates patients by histologic subtype of RCC, including papillary (8260), clear cell (8310), not otherwise specified (NOS, 8312), cyst associated (8316), chromophobe (8317), sarcomatoid (8318), collecting

* Corresponding author at: Duke University Medical Center, Division of Pediatric Surgery, Box 3815, Durham, NC 27710, USA. Tel.: +1 919 681 5077.
E-mail address: henry.rice@dm.duke.edu (H.E. Rice).

http://dx.doi.org/10.1016/j.jpedsurg.2015.03.027
0022-3468/

duct type (8319), and granular cell (8320). Accurate differentiation between adjuvant or neoadjuvant use of chemotherapy and radiation was not available for many patients, and these variables simply represent the use of "any" chemotherapy or radiation.

Resection in the NCDB was categorized as partial, complete, or radical nephrectomy, with clinical and pathologic staging defined using Union for International Cancer Control (UICC)/AJCC criteria [16]. In this staging system, stage I was defined as T1N0M0; II as T2N0M0; III as T1 or T2, N1, M0, or T3, N0 or N1, M0; and IV as T4, any N, M0, or any T, any N, M1. T1 was defined as a tumor ≤7 cm; T2 as >7 cm, but ≤10 cm; T3 as any tumor with extension into major veins or perinephric tissue; and T4 as any tumor invading beyond Gerota's fascia. Any metastases in regional lymph nodes are termed N1. Partial nephrectomy was defined as a segmental or wedge resection; complete as a total or simple nephrectomy; and radical as complete nephrectomy, possibly including removal of portion of vena cava, adrenal gland(s), Gerota's fascia, perinephric fat, or partial/total ureter. Patients categorized as nephrectomy not otherwise specified (NOS) or nephrectomy en bloc were excluded, as it could not be determined if these were subtotal or total nephrectomies.

This study was approved for exempt status by the Duke University Institutional Review Board.

1.3. Statistical analysis

Continuous nonparametric data were compiled as median (interquartile range (IQR)) and categorical data were compiled as frequency (percentage). There were missing data points for some variables; missing data are noted in Table 1. For analysis of resection types, patients with complete or radical nephrectomy were analyzed as one group. Patients with missing variables were not included in the unadjusted or survival analyses. For those with missing positive node data, the TNM pathologic N variable was used. Univariable analysis of resection type was performed using one-way ANOVA for parametric continuous variables, and the Kruskal–Wallis test for nonparametric continuous variables. Categorical variables were compared with Fisher's exact test or the Chi-squared test as appropriate. Survival differences were analyzed using the Kaplan–Meier method, with significance determined by the log-rank test. A P value of less than 0.05 was considered statistically significant for all comparisons. All statistical analysis was performed using R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

2. Results

A total of 304 patients met inclusion criteria and were included in analysis. Of the overall cohort, 159 were male (52%) and 145 (48%) were female (Table 1). The median age at presentation was 13 years (IQR 9–16) and 55% (n = 166) were Caucasian.

The median tumor size was 5.5 cm (IQR 3.0–8.9) and more than 60% were 7 cm or less in size. The most common histologic types were RCC NOS (56%), papillary (16%), and clear cell (12%). Eighty-three patients (39%) had pathologic stage I disease, 35 (16%) had stage II disease, 70 (33%) had stage III disease, and 26 (12%) had stage IV disease. Margins were negative in 91% of cases and positive (6 microscopic and 16 macroscopic) in 9% of cases. Chemotherapy was given to 58 children (20%), and 12 children received radiation therapy (4%). Three children died within 30 days (1%). Eight patients (4%) had unplanned readmissions. The median hospital length of stay was four days (IQR 3.5).

In terms of surgical procedures, 86% of patients underwent some type of resection, with 72% undergoing complete or radical nephrectomy and 14% partial nephrectomy; 39 patients did not undergo formal surgery (Table 2). There was no difference in gender or ethnicity between patients undergoing any type of resection and those who were not resected. Those undergoing partial nephrectomy were more likely to have tumors 4 cm or less in size and be classified as clinical stage I tumors ($P = 0.001$ and <0.001, respectively). Those that did not undergo surgery more often had stage IV disease ($P < 0.001$) and a greater proportion were treated with chemotherapy ($P < 0.001$) and radiation ($P = 0.003$). Seven patients had clinical stage I disease and did not undergo resection; there was no clear indication from the database as to why these patients were excluded from surgery.

Several factors were analyzed for their effect on overall survival (Table 3), including age, gender, nodal status, pathologic stage, resection type, and tumor size (Fig. 1A–F). Overall one-year and five-year survival was 87% (95% CI: 0.82–0.92) and 70% (95% CI: 0.63–0.77), respectively. Age and gender did not significantly affect survival ($P =$ 0.48 and 0.078, respectively). Five-year survival was decreased for children with positive nodes compared to children with negative nodes (55% vs. 83%, $P = 0.001$). Patients who did not undergo resection also had lower five-year survival (20%, 95% CI: 0.08–0.48), compared to partial nephrectomy (100%, 95% CI: 1.00–1.00), and complete nephrectomy (79%, 95% CI: 0.72–0.87) ($P < 0.001$). Survival was also negatively impacted by large tumor size ($P < 0.001$) and higher pathologic stage ($P < 0.001$). Five-year survival for stage I–IV RCC was 100%, 91%, 71%, and 8%, respectively.

Table 1
Demographics, tumor characteristics, and treatment for children with renal cell carcinoma. Other types of pathology include cyst associated, chromophobe, sarcomatoid, collecting duct type, granular cell, and medullary carcinoma. Variables with missing data are noted with adjusted total n. y = years, mi = miles, IQR = interquartile range, NOS = not otherwise specified.

Variable (Total N = 304)	N (%)
Male	159 (52%)
Age, y	
<5	23 (8%)
5–8	40 (13%)
9–13	98 (32%)
>13	143 (47%)
Race/ethnicity	
White	166 (55%)
Black	97 (32%)
Hispanic	25 (8%)
Other	12 (4%)
Missing	4
Insurance	
Private	257 (90%)
Medicare/Medicaid	21 (7%)
Uninsured	8 (3%)
Missing	18
Distance to cancer center (mi) (IQR)	16.1 (7.2, 36)
Tumor size	
≤4 cm	101 (36%)
4.1–7 cm	75 (27%)
7.1–10 cm	55 (20%)
>10 cm	47 (17%)
Missing	26
Median tumor size, cm (IQR)	5.5 (3, 8.9)
Histologic type	
Papillary	48 (16%)
Clear cell	38 (12%)
RCC NOS	170 (56%)
Other	48 (16%)
Pathologic stage	
I	83 (39%)
II	35 (16%)
III	70 (33%)
IV	26 (12%)
Missing	90
Surgical margins	
Negative	232 (91%)
Positive margin	22 (9%)
Missing	50
Positive nodes	76 (30%)
Missing	54
Radiation	12 (4%)
Missing	4
Chemotherapy	58 (20%)
Missing	9