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Image-defined risk factors for nephrectomy in patients undergoing neuroblastoma resection

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ABSTRACT

Background: Although nephrectomy rates are higher in children with neuroblastoma who have image-defined risk factors and/or high-risk disease who undergo resection prior to chemotherapy, no published data outline the key radiographic and clinical characteristics associated with nephrectomy.
Methods: With IRB approval, imaging studies of children undergoing primary resection of intraabdominal neuroblastoma between 2000 and 2014 were retrospectively reviewed. Fisher's exact and Wilcoxon rank-sum tests were used to compare categorical and continuous variables, respectively, with p-values adjusted for multiple testing using the false discovery rate approach.
Results: Twenty-seven of 380 consecutive patients with CT imaging obtained prior to primary neuroblastoma resection underwent partial or total nephrectomy. On preoperative imaging, renal vessel narrowing and encasement and tumor invasion of the renal hilum, pelvis, and/or parenchyma were present significantly more frequently among patients undergoing nephrectomy. Delayed renal excretion of contrast, hydronephrosis, and tumors with *MYCN* amplification were also more prevalent in the nephrectomy group.
Conclusion: Encasement and narrowing of renal vessels, delayed excretion, and tumor invasion into the kidney, particularly pelvis and capsule invasion, are significantly associated with partial or total nephrectomy at initial neuroblastoma resection. These observations provide valuable information for surgical planning as well as presurgical discussions with families prior to neuroblastoma resection.

Neuroblastoma is the most common extracranial cancer in children, with an incidence of 10.5 per million children between 0 and 14 years of age in North America and Europe [1]. Complete surgical resection of the primary tumor and regional nodal metastases is an important component of therapy for many tumors in certain risk groups. In particular, gross total resection (GTR) of the primary tumor may be an important predictor of local control and event-free survival for patients with high-risk disease [2,3]. Tumor involvement of other abdominal organs such as the kidney, however, makes GTR difficult and may necessitate nephrectomy. Up to 45% of patients with localized neuroblastoma are reported to have renal pedicle involvement [4]. There have also been reports of aggressive, high-risk neuroblastoma invading the kidney, causing intrarenal masses mimicking Wilms tumor at initial imaging [5,6]. In such cases, nephrectomy may be required to achieve gross total resection, with rates ranging between 10% and 25% in the literature [2].

Further, many patients with neuroblastoma undergo nephrotoxic chemotherapy regimens, and therefore preservation of renal function is paramount. Image-defined risk factors (IDRFs) have been described as indicators for predicting the overall risk of surgical complications [7] but no studies have outlined the key radiographic and clinical characteristics specifically associated with nephrectomy during surgical treatment of neuroblastoma. In this study, we correlated preoperative radiographic and clinical factors to identify those specifically associated with total or partial nephrectomy during initial neuroblastoma resection.

1. Patients and methods

After obtaining Institutional Review Board approval (#WA0677–13), we retrospectively reviewed pediatric patients who underwent primary resection of intraabdominal neuroblastoma between 2000 and 2014. Patients who had primary resection at an outside hospital were excluded. Only patients with preoperative, contrast enhanced computed tomography (CECT) imaging were analyzed, and divided into nephrectomy or nonnephrectomy groups. Images were

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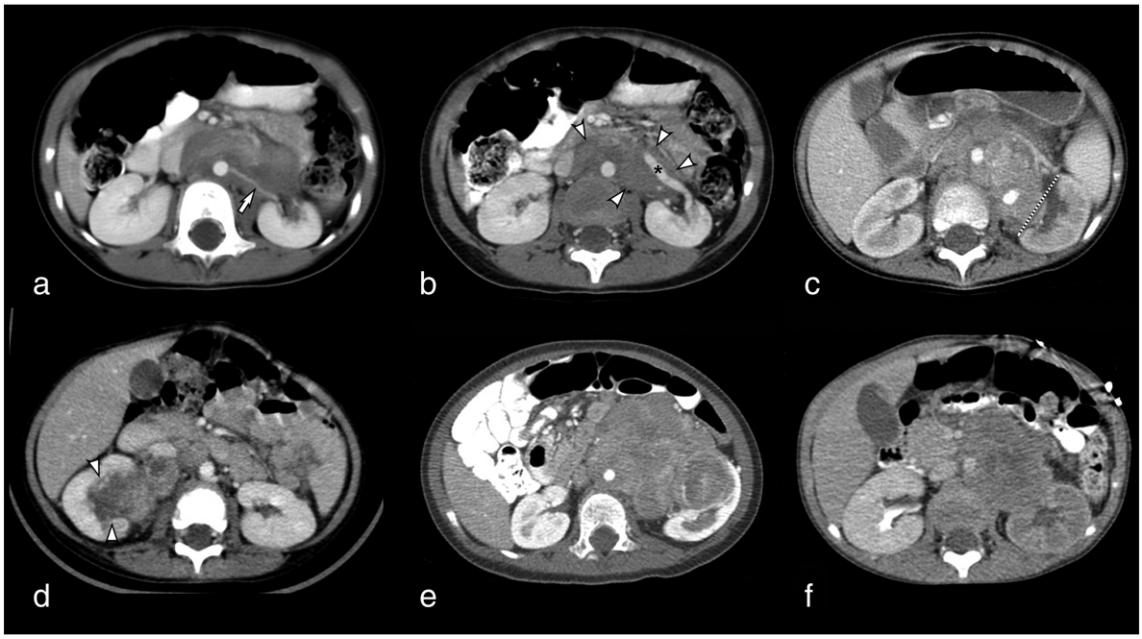

Fig. 1. Axial contrast enhanced CT images illustrate several risk factors for nephrectomy. **(a)***Renal artery or vein narrowing*: The left renal artery (arrow) is both encased by tumor and narrowed in diameter when compared to the right renal artery (not shown). **(b)***Renal artery or vein encasement*: Tumor encasement was defined as contact with the tumor along the entire circumference of the vessel. In this example, the left renal vein (asterisk) is encased by tumor (arrowheads). **(c)***Tumor invasion of renal hilum*: A boundary (dotted) line has been drawn to connect the renal capsule across the entrance of the renal vessels into the kidney. Tumor crossing this line is classified as an invasion into the renal hilum. **(d)***Tumor invasion of renal pelvis*: Tumor (arrowheads) encroaches into the collecting system of the kidney but does not invade the renal parenchyma. **(e)***Tumor invasion of the renal capsule*: Tumor violates the left renal capsule and invades the renal parenchyma. A thin rim of renal capsule is seen at the lateral edge of the tumor. **(f)***Delayed renal excretion of contrast*: Both kidneys should have symmetric enhancement with similar excretion rates. In this example, the left kidney is in the corticomedullary phase in comparison to the right, which is in the excretory phase.

reviewed in consensus by two experienced pediatric radiologists (AP and SA) who were blinded to nephrectomy status. Maximal tumor dimension and presence of calcifications were recorded. Renal vasculature was evaluated for narrowed lumen (Fig. 1a) and tumor encasement (Fig. 1b), or both. Kidneys were assessed for tumor invasion into the renal hilum, pelvis or capsular penetration and extension into the renal parenchyma (Fig. 1c–e). Hydronephrosis and delayed excretion of intravenous contrast (Fig. 1f) were also evaluated.

The primary endpoint of the study was whether partial or total nephrectomy was performed at the time of the first attempted resection. Pathology was reviewed for tumor origin, *MYCN* amplification, Shimada classification, differentiation, and presence of part or all of the kidney in the specimen. Clinical variables included age at diagnosis, stage, hypertension requiring pharmacologic treatment, and neoadjuvant chemotherapy. Associations between imaging, clinical and tumor pathology features with partial or total nephrectomy were tested using Fisher's exact and Wilcoxon rank-sum tests for categorical and continuous variables, respectively, with p-values adjusted for multiple testing using the false discovery rate approach. Differences in the rate of nephrectomy for those that had the feature versus those that did not were measured along with the exact 95% confidence interval. P-values less than 0.05 were considered statistically significant. Because of the small number of events (nephrectomies), multivariate analyses could not be performed. All analyses were performed using SAS 9.4 (The SAS Institute, Cary, NC) and Stata SE 13 (StataCorp, College Station, TX).

2. Results

2.1. Patient characteristics

Of the 580 patients who underwent surgery for neuroblastoma at our institution during the study period, 380 (65.5%) underwent primary resection at our institution for abdominal neuroblastoma and had preoperative CECT imaging available for review. Twenty-seven of these patients (7%) had a partial (n = 9; 2.4%) or total nephrectomy (n = 18; 4.7%). The rate of nephrectomy, partial and total, as well as the proportion of partial nephrectomy, did not follow a discernible pattern over the study period (Fig. 2). Owing to the small number of partial and total nephrectomies, reliable statistical comparisons between the two groups could not be performed, but rather, the two groups were combined into a single nephrectomy group. The nephrectomy and nonnephrectomy groups were similar (Table 1) in terms of median age (26.1 months [range 14.0–245.9] vs 32.8 months [range 0–253.6], p = 0.90), and stage at diagnosis (70.4% vs 78.5% with stage 4 disease, p = 0.46). The majority of patients in both groups had neuroblastoma originating from the adrenal glands (96.3% vs 79.0%, p = 0.41) and were considered high-risk (92.3% vs 80.1%, p = 0.41). The majority of patients (n = 351 of 380; 92.4%) received neoadjuvant chemotherapy. Of the 380 surgical procedures, 348 (91.6%) were gross total resections (GTR). Twenty-seven patients underwent partial or total nephrectomy (4.65% of all neuroblastoma resections in our institution during the study period and 7% in this study population), 25 of which were GTR (25 had high-risk disease, 1 low-risk and 1 intermediate risk). Of the 353 nonnephrectomy procedures, 323 (91.5%) were GTR.

2.2. Clinical presentation

Hypertension at diagnosis (p = 0.0027) and hypertension at preoperative imaging (p = 0.0477) were significantly associated with nephrectomy. There was a 19% difference (95% CI: 2%–36%) in the rate of nephrectomy (26% vs 7%) for those with hypertension at diagnosis, and there was a 13% difference (95% CI: −8% to 35%) in the rate of nephrectomy (18% vs 5%) for those that had hypertension at the time of preoperative imaging.

MYCN amplification was significantly associated with nephrectomy (p = 0.0219), while neither undifferentiated histology (p = 1.00) nor unfavorable Shimada classification (p = 0.08) was found to be associated with nephrectomy (Table 2). The rate of nephrectomy was 12% for those with *MYCN*-amplified tumors while only 5% for those that were not amplified (difference: 7%; 95% CI: −3% to 18%).