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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 intra-abdominal 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

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valuable information for surgical planning as well as presurgical discussions with families prior to neuroblastoma resection.

Keywords

Neuroblastoma; nephrectomy; partial nephrectomy; image defined risk factors

1. Introduction

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, make 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 to 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.

2. Patients and Methods

After obtaining Institutional Review Board approval (#WA0677-13), we retrospectively reviewed pediatric patients who underwent primary resection of intra-abdominal neuroblastoma between 2000 and 2014. Patients who had primary resection at an outside hospital were excluded. Only patients with pre-operative, contrast enhanced computed tomography (CECT) imaging were analyzed, and divided into nephrectomy or non-nephrectomy groups. Images were 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 (Figure 1a) and tumor encasement (Figure 1b), or both. Kidneys were assessed for tumor invasion into the renal hilum, pelvis or capsular penetration and extension into the renal parenchyma (Figure 1c–e). Hydronephrosis and delayed excretion of intravenous contrast (Figure 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).

3. Results

3.1 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 (Figure 2). Due 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 non-nephrectomy 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 non-nephrectomy procedures, 323 (91.5%) were GTR.

3.2 Clinical Presentation

Hypertension at diagnosis ($p=0.0027$) and hypertension at preoperative imaging ($p=0.0477$) were significantly associated with nephrectomy. There was 19% difference (95% CI: 2–36%) in the rate of nephrectomy (26% vs 7%) for those with hypertension at diagnosis, and there was 13% difference (95% CI: –8%–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 ($p=0.08$) were 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% – 18%).

3.3 Imaging Factors in Relation to Nephrectomy

Preoperative Imaging—Nearly all preoperative imaging variables were associated with nephrectomy (Table 3, Preoperative Features). The largest proportional differences between the nephrectomy and non-nephrectomy groups (Figure 3) were seen for renal pelvis (50%; 95% CI: 30–71%) and capsule invasion (57%; 95% CI: 40–73%), and combined vein narrowing and encasement (46%; 95% CI: 26–66%). Tumor size on imaging immediately prior to surgery was not significantly different (4.7 vs 4.6 cm, $p=0.46$).

Imaging at Diagnosis—CECT imaging at diagnosis was reviewed when available, and almost all imaging variables at diagnosis were associated with nephrectomy as well (Table 3, Diagnosis Features). In terms of features at diagnosis, the largest proportional differences in risk of nephrectomy were seen for capsular invasion (38%; 95% CI: 23–53%), and delayed renal excretion of intravenous contrast (37%; 95% CI 21–53%), and invasion into the renal pelvis (32%; 95% CI 17–47%). Patients requiring nephrectomy tended to have significantly larger tumors at diagnosis (median 10.7 vs 8.3 cm, $p=0.0007$).

4. Discussion

Nephrectomy in children is associated with an annual incidence of 2.9 per 100,000 patient years[8], and is performed for benign or malignant conditions. Nephrectomy for malignancy, most commonly Wilms tumor and neuroblastoma, represents between 26% and 41% of pediatric nephrectomy cases reported[8–10]. While long-term effects of nephrectomy in Wilms tumor patients have been well characterized, few studies have followed children with neuroblastoma post-nephrectomy. Most neuroblastoma patients typically require adjuvant chemotherapy, stem-cell treatment and abdominal radiation, all of which can impair function of the remaining kidney[11–12]. Mulder et al reported early and persistent impaired glomerular function in childhood cancer survivors treated with ifosfamide, high doses of cisplatin and nephrectomy[13]. Thus, identifying risk of nephrectomy prior to resection will aid in planning future therapy and management. Recently, work has focused on determining IDRFs in neuroblastoma. These IDRFs have been used for staging and initial treatment decisions, and recently for anticipating surgical outcomes and predicting completeness of resection [14–16]. No studies have focused on identifying imaging risk factors specifically associated with nephrectomy during surgical resection of neuroblastoma.

In this study, we expanded on the previously described IDRFs for neuroblastic tumors in the abdomen and pelvis[17]. For instance, we specified the extent of renal invasion by tumor rather than just limiting to invasion of the renal pedicle, which has been shown to be the most frequently observed IDRF[4]. We subclassified tumor invasion of the kidney based on the extent of renal involvement, i.e. renal hilum, pelvis or parenchyma. Additionally, we evaluated vasculature encasement, which has been shown not to preclude gross total

resection in this patient population[18]. Specifically, we examined tumor encasement of the ipsilateral renal artery or vein in patients with adrenal neuroblastomas and assessed encasement of either renal artery or vein in cases of central abdominal or pelvic tumors. Previous studies have defined vascular encasement as tumor contact of at least 50% of the vessel's circumference[4], but our expectation was that complete encasement of the vessel by tumor tissue would be more informative. Moreover, we differentiated encasement of the renal artery from that of the renal vein as the vessel type could affect difficulty of dissection intraoperatively.

In both the imaging studies performed at diagnosis and immediately prior to surgery, rates of narrowing or encasement of renal vessels were significantly higher among patients who underwent nephrectomy. Combined narrowing and encasement of both renal vessels was also associated with nephrectomy, suggesting that vascular involvement, whether by encasement of tumor, narrowing by tumor or both, can strongly impact the risk of nephrectomy. One of the largest proportional differences in risk of nephrectomy in preoperative imaging was narrowing and encasement of the renal vein, which suggests that both mass effect and circumferential encasement of the renal vein have a significant impact on nephrectomy. Our data also show vasculature involvement does not preclude resection. In fact, over 90% of patients in each group had resections that were considered GTR, despite vascular involvement.

Prior to this study, a partial or total nephrectomy was typically considered, based on the tumor's anatomical location and the potential to remove gross disease. Independent data have suggested that R1 resection is acceptable in neuroblastoma [19] and as such, a negative microscopic tumor margin is not needed. Should a partial or total nephrectomy be necessary to achieve GTR given tumor location, then a nephrectomy is planned. Many times, we have found that tumor can be grossly resected by removing the kidney capsule only, without a formal partial or total nephrectomy. In this study, we confirmed that the extent of tumor invasion into the kidney had significant associations with nephrectomy. Invasion into the hilum, pelvis or capsule prior to surgery was significantly higher in the nephrectomy group, with extension into the pelvis or capsule associated with the two largest proportional differences in risk of nephrectomy. Extension past the hilum, whether in the pelvis or through the renal capsule, should prompt a discussion on the possibility of nephrectomy. Delayed renal excretion of intravenous contrast, when compared to the unaffected kidney, is likely a qualitative marker of the tumor's effect on renal function.

On both diagnosis and preoperative CECT, delayed renal excretion had one of the highest proportional differences in nephrectomy risk. Hydronephrosis was often seen in association with tumor impingement on the ureters, which is likely a marker for extent of disease. Both hydronephrosis and delayed renal excretion of contrast were significantly increased in the nephrectomy group. Preoperative CECT imaging was obtained no more than a month prior to resection. Perhaps radionuclide scans to assess renal function should be performed when these factors are observed on preoperative imaging, so that a quantitative assessment of renal function can be made. Anecdotally, we have utilized radionuclide scans in a handful of patients presenting with preoperative hydronephrosis and delayed renal excretion of contrast. Those who had severely decreased function of one kidney on the radionuclide scan went on

to undergo nephrectomy. Based on our experience, if there is significantly decreased renal function, we recommend en-bloc resection of the tumor and the associated kidney, which may benefit the patient by decreasing operative time while avoiding unnecessarily extensive dissection of renal vessels in an attempt to preserve an otherwise poorly functioning kidney.

There were no differences in clinical presentation between the non-nephrectomy and nephrectomy groups. Notably, almost all patients, and all patients who underwent nephrectomy, received neoadjuvant chemotherapy. Not surprisingly, tumor size was similar between the two groups prior to surgery and after chemotherapy. However, the majority of our patients had stage IV, high risk disease at diagnosis, as our institution is a tertiary referral center. Patients who eventually received nephrectomy had significantly larger tumors at diagnosis, with greater rates of *MYCN* amplification and high risk disease. As a single institution study, these results may not translate to neuroblastoma patients with lower stage and low risk disease. There were also a number of patients in the non-nephrectomy group who had image-defined risk factors seen in the nephrectomy group. While the proportion of these patients in the non-nephrectomy group was significantly smaller than those in the nephrectomy group, the presence of these imaging variables highlights that the majority of patients had high risk disease in our study.

Most patients in our study were diagnosed with neuroblastoma at another institution and presented to our institution for resection only after chemotherapy was completed. This factor limited our analysis in a number of ways. First, we were unable to compare chemotherapy regimens in terms of agents or even the number of cycles used preoperatively as these varied based on where patients initially received care. Consequently, the time difference between initial diagnosis scans and the immediate preoperative scans also varied greatly between the patients. Prospective studies will help address these issues, particularly whether or not neoadjuvant chemotherapy can be altered to increase renal salvage. In addition, fewer patients had imaging available at the time of diagnosis. Thus, the difference in strength of association between features on diagnostic imaging and nephrectomy may reflect the effect of sample size.

Interestingly, hypertension both at diagnosis and prior to first attempted resection were significantly increased in the nephrectomy group. This suggests that perhaps the hypertension seen in neuroblastoma is not solely due to increased catecholamines, as all patients should have similar adrenergic effects, but also an anatomical issue such as encasement or narrowing of renal vessels. Also, the majority of patients who underwent nephrectomy had tumors arising from the adrenal gland. Due to their intimate anatomical relationship, effects on the kidney may be more common with neuroblastomas from the adrenal gland.

Shamberger et al first described the risk of nephrectomy during abdominal neuroblastoma resection but this risk was studied in terms of the surgeon's reason for nephrectomy, not in objective factors like imaging variables[20]. Moreover, there were multiple surgeons and institutions included in this study, all of which can affect rate of nephrectomy. Our study aimed to remove surgeon bias and rather, focused on delineating the objective factors that may be associated with nephrectomy. The total number of nephrectomies in our study,

however, limited the analysis. While our rate of nephrectomy (4.7%) was lower than that reported in the literature, the few nephrectomy cases relative to the total number of resections prohibited a multivariate analysis that would provide further insight. The number of significant variables on univariate analysis, however, highlight the utility of these preoperative factors in operative planning. Future, prospective studies are necessary to determine which combination of imaging factors are predictive of nephrectomy.

5. Conclusion

Key radiologic features, such as renal vasculature narrowing or encasement as well as invasion into the renal hilum, pelvis or parenchyma, are strongly associated with nephrectomy at first resection of neuroblastoma.

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Figure 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.

Figure 2.

Rate of nephrectomy over study period. The proportion of partial and total nephrectomy to the total number of resections in the study (primary resection of abdominal neuroblastoma with preoperative imaging) did not have a discernible pattern over the study period. The proportion of partial nephrectomy compared to the total number of resections in the study also did not increase or decrease over the study period. Note that these numbers do not reflect the overall nephrectomy rates, as they do not include primary resections of abdominal neuroblastoma that did not meet the study's inclusion criteria.

Figure 3.

Risk differences between the nephrectomy and non-nephrectomy groups for all significant imaging variables. The greatest risk differences were seen in patients with tumor invasion of the renal parenchyma and pelvis, as well as in those with narrowed and encased renal veins and delayed renal excretion of contrast.

Table 1

Clinical presentation of non-nephrectomy vs. nephrectomy patients. Variables in terms of clinical presentation were compared between the two groups.

	No Nephrectomy n (%)	Total or Partial Nephrectomy, n (%)	p-value	Risk difference [95% CI]
Age at diagnosis, months (median, range)	32.8 (0.0 – 253.6)	26.1 (14.0 – 245.9)	0.90	
Age <18 months at diagnosis	85 (24.1)	3 (11.1)	0.22	0.08 [–0.12 – 0.27]
Hypertension at diagnosis	29 (13.9)	10 (43.5)	0.0027	0.19 [0.02 – 0.36]
Hypertension prior to surgery	18 (5.2)	4 (19.0)	0.0477	0.13 [–0.08 – 0.35]
Neoadjuvant chemotherapy	324 (92.0)	27 (100)	0.31	0.08 [–0.12 – 0.27]
Stage at diagnosis			0.46	
I	11 (3.1)	0 (0)		
II	11 (3.1)	1 (3.7)		
III	54 (15.3)	7 (25.9)		
IV	277 (78.5)	19 (70.4)		
Risk			0.41	
Low	19 (5.7)	1 (3.8)		
Intermediate	47 (14.2)	1 (3.8)		
High	265 (80.1)	24 (92.3)		
Primary tumor origin			0.31	
Adrenal	279 (79.0)	26 (96.3)		
Abdominal (Central)	36 (10.2)	0 (0)		
Retroperitoneum	30 (8.5)	1 (3.7)		
Pelvis	8 (2.3)	0 (0)		

* Proportions ignore missing data values.

Table 2

Pathology of non-nephrectomy vs. nephrectomy patients. Tumor pathology in terms of differentiation and *MYCN* amplification were compared.

	No Nephrectomy n (%)	Total or Partial Nephrectomy n (%)	p-value	Risk difference [95% CI]
Differentiation			1.00	
Well differentiated	16 (6.2)	1 (4.3)		
Poorly differentiated	182 (70.5)	17 (73.9)		
Undifferentiated	60 (23.3)	5 (21.7)		
<i>MYCN</i> Amplification	117 (34.7)	16 (59.3)	0.0219	0.07 [−0.03 – 0.18]
Shimada Classification			0.08	
Favorable	72 (27.4)	2 (8.7)		
Unfavorable	191 (72.6)	21 (91.3)		

Table 3

Preoperative and diagnosis contrast-enhanced CT imaging features of non-nephrectomy vs. nephrectomy patients.

	No Nephrectomy n (%)	Total or Partial Nephrectomy, n (%)	Adjusted p-value	Risk Difference * [95% CI]	Unadjusted Odds Ratio [95% CI]
PREOPERATIVE FEATURES					
Renal Vasculature Encasement					
Artery	109 (31.7)	21 (77.8)	<0.0001	0.14 [0.03 – 0.24]	7.55 [2.96–19.23]
Bilateral Arteries	6 (1.7)	0 (0)	1.00	–0.07 [–0.52 – 0.37]	NE
Vein	28 (8.2)	14 (51.9)	<0.0001	0.29 [0.13 – 0.45]	24.15 [10.34–56.41]
Renal Vasculature Narrowing					
Artery	69 (20.1)	16 (59.3)	<0.0001	0.15 [0.03 – 0.27]	5.78 [2.56–13.01]
Vein	24 (7.0)	16 (59.3)	<0.0001	0.37 [0.20 – 0.53]	38.54 [16.11–92.24]
Renal Vasculature Narrowing and Encasement					
Artery	54 (15.8)	16 (59.3)	<0.0001	0.19 [0.06 – 0.32]	7.73 [3.40–17.57]
Vein	13 (3.8)	13 (48.1)	<0.0001	0.46 [0.26 – 0.66]	47.00 [18.42–119.90]
Tumor Invasion					
Hilum	21 (6.0)	8 (29.6)	0.0008	0.22 [0.03 – 0.41]	6.64 [2.60–16.93]
Pelvis	11 (3.1)	13 (48.1)	<0.0001	0.50 [0.30 – 0.71]	28.87 [11.0–75.74]
Capsule	14 (4.0)	20 (74.1)	<0.0001	0.57 [0.40 – 0.73]	68.98 [25.04–189.99]
Tumor Calcifications	287 (82.2)	22 (91.7)	0.46	0.04 [–0.09 – 0.17]	2.38 [0.58–10.37]
Hydronephrosis	20 (5.7)	6 (22.2)	0.0115	0.17 [–0.03 – 0.37]	4.74 [1.72–13.07]
Delayed Renal Excretion	8 (2.3)	7 (25.9)	<0.0001	0.41 [0.15 – 0.68]	15.05 [4.96–45.67]
Median Size, cm (range)	4.6 (0.8–15.7)	4.7 (1.6–16.6)	0.43		
DIAGNOSIS FEATURES					
Renal Vasculature Encasement					
Artery	175 (67.0)	23 (100)	0.0006	0.12 [–0.01 – 0.24]	NE
Bilateral Arteries	31 (11.6)	1 (4.3)	0.54	–0.05 [–0.24 – 0.13]	0.35 [0.05–2.67]
Vein	68 (26.5)	16 (69.6)	0.0001	0.15 [0.03 – 0.28]	6.35 [2.51–16.11]
Renal Vasculature Narrowing					
Artery	136 (52.5)	19 (82.6)	0.0130	0.09 [–0.03 – 0.21]	4.30 [1.42–12.98]

	No Nephrectomy n (%)	Total or Partial Nephrectomy n (%)	Adjusted p-value	Risk Difference* [95% CI]	Unadjusted Odds Ratio [95% CI]
Vein	85 (33.2)	19 (82.6)	<0.0001	0.16 [0.04 – 0.28]	9.56 [3.15–28.97]
Renal Vasculature Narrowing and Encasement					
Artery	125 (47.0)	19 (82.6)	0.0020	0.10 [–0.01 – 0.22]	5.36 [1.78–16.17]
Vein	52 (20.3)	15 (65.2)	<0.0001	0.19 [0.05 – 0.32]	7.36 [2.96–18.28]
Tumor Invasion into Kidney					
Hilum	54 (20.4)	5 (21.7)	0.86	0.01 [–0.14 – 0.15]	1.09 [0.39–3.06]
Pelvis	32 (12.0)	17 (73.9)	<0.0001	0.32 [0.17 – 0.47]	20.72 [7.61–56.39]
Capsule	29 (10.9)	19 (82.6)	<0.0001	0.38 [0.23 – 0.53]	38.66 [12.30–121.49]
Tumor Calcifications	188 (70.7)	13 (56.5)	0.24	–0.05 [–0.17 – 0.08]	0.54 [0.23–1.28]
Hydronephrosis	46 (17.3)	11 (47.8)	0.0027	0.14 [0 – 0.28]	4.38 [1.82–10.54]
Delayed Renal Excretion	24 (9.0)	16 (69.6)	<0.0001	0.36 [0.21 – 0.53]	23.05 [8.63–61.55]
Median Size, cm (range)	8.3 (1.1–18.1)	10.7 (5–18.9)	0.0007		

* Boldface values mark the highest proportional risk. NE = not estimable.