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The association between nephroblastoma-specific outcomes and high versus low volume treatment centers☆

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ABSTRACT

Background: Though the volume-outcome relationship has been well-established in adults, low mortality rates and small sample sizes have precluded definitive demonstration in children. This study compares treatment-specific factors for children with nephroblastoma at high (HVC) versus low volume centers (LVC).
Methods: We performed a retrospective cohort study comparing patients ≤18 years with unilateral nephroblastoma treated at HVCs and LVCs using the National Cancer Data Base (1998–2012). Definitions of HVCs included performing above the median, the upper two quartiles, and the highest decile of nephroblastoma resections. Outcomes included nodal sampling, margin status, time to chemotherapy and radiation, and survival. Statistical analyses included χ^2, t-tests, generalized linear, and Cox regression models ($p < 0.05$).
Results: Of 2911 patients from 210 centers, 1443 (49.6%) were treated at HVCs. There was no difference in frequency of preoperative biopsy or days to radiation ($p > 0.05$). High volume centers were more likely to perform nodal sampling (RR 1.04, 95%CI 1.01–1.08) and had fewer days to chemotherapy (RR 0.80, 95%CI 0.69–0.93). Five-year survival was similar (HVC: 0.93, 95%CI 0.92–0.94; LVC: 0.93, 95%CI 0.91–0.94).
Conclusions: HVCs were more likely to perform nodal sampling and had fewer days to chemotherapy. There was no difference in days to radiation or survival between centers.
Level of evidence: Level II (retrospective prognosis study).

The relationship between higher patient volume and improved outcomes has been well established with respect to high risk procedures such as pancreatectomy, esophagectomy, and cardiac surgery [1,2]. The literature for pediatric patients both with cancer and general diagnoses is mixed with some researchers finding a strong volume-outcome association for procedures such as diaphragmatic hernia repair [3] and congenital heart surgery [4,5]. Other researchers have found a weak association or no association [6–10].

Small sample sizes and rarity of typical outcome events such as mortality may partially explain the challenges in demonstrating a clear volume-outcome relationship for pediatric surgery. To address these constraints, we utilized the National Cancer Data Base (NCDB). The NCDB has served as a clinical registry for Commission on Cancer approved hospitals since 1989 and captures a large number of pediatric surgical oncology cases annually. Furthermore, outcomes and treatment factors that go beyond mortality are rigorously collected and reported.

Nephroblastoma represents the second most common abdominal solid tumor in children. It has an annual incidence rate of 8.1 cases per million children and surgical resection remains the main-stay of treatment for these patients [11]. Due to concerted efforts of focused oncology groups, the treatment for nephroblastoma has resulted in dramatic improvements in survival [12]. With more centralized coordination of

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care, treatment nuances and factors associated with prognosis have been well delineated [13,14]. These include the importance of surgical factors such as margin status, tumor spill and lymph node evaluation [15]. Furthermore, the timing and role of adjuvant radiation and chemotherapeutic treatments has evolved over time.

Using the NCDB, our objective was to evaluate treatment factors including margin status and nodal evaluation, timing of adjuvant treatments and mortality to demonstrate the presence of a volume-outcome relationship in patients undergoing surgical resection for nephroblastoma. Our hypothesis was that the sample sizes and outcomes in the NCDB would allow for a clear illustration of a volume-outcome relationship in pediatric surgical oncology.

Methods

Study population

We performed a retrospective cohort study comparing pediatric patients ≤18 years of age undergoing total nephrectomy for unilateral nephroblastoma (International Classification of Disease for Oncology, version 3: 8960/3) with a primary site classification in the kidney (Primary Site Classification: C649) at high volume centers (HVC) to those treated at low volume centers (LVC) using the NCDB from 1998 through 2012. Per the NCDB data collection methodology, there were no duplicate cases. This study was approved by the Seattle Children's Hospital Institutional Review Board (IRB#14,943).

Data source

The NCDB, sponsored by the American College of Surgeons Commission on Cancer and the American Cancer Society, started data collection in 1989 and now contains over 30 million patient records [16]. It captures approximately 70% of all newly diagnosed cases of cancer nationwide from more than 1500 Commission on Cancer-accredited hospitals [16]. The primary use of the NCDB is for the longitudinal examination of cancer care in the United States including quality improvement and quality assurance efforts [17,18]. Data are abstracted from patients' charts using standardized data definitions by trained abstractors [19,20].

Clinical covariates and measures

Demographic characteristics included sex, race, insurance status, household income, educational level and rural versus urban place of residence. Insurance status was defined as private, governmental or uninsured. Race was based on patient report in the medical record. Household income was divided into quartiles based on the patient's home zip code. Education level was based on the percentage of high school graduates in the patient's home zip code and was used as a surrogate measure of socio-economic status. Rural versus urban place of residence was based on the population density and proximity to a metropolitan area of the patient's home zip code. Tumor size was measured in centimeters. Nephroblastoma-specific stage and grade including favorable and unfavorable histology are unavailable in the NCDB.

Treatment factors included whether a biopsy was performed for diagnostic purposes, if the patient had nodal evaluation, the margin status and days to radiation and chemotherapy. Nodal evaluation was categorized as examined or not examined. Margin status was defined as either positive or negative. Positive margin status was defined as any tumor at the inked margins on pathologic examination including microscopic margins and incorporated tumor rupture or intra-operative spill, though microscopic versus macroscopic margins was not delineated. Days to radiation and chemotherapy were analyzed among those patients who received those treatments. Chemotherapy regimens were further assessed based on single agent or multi-agent drug regimens. Of note, specific chemotherapy agents are not reported.

Center volume was defined by the median number of operations performed. For the multivariable analysis high versus low volume was also divided into quartiles (Very high volume: ≥47 patients; High volume: 26–46 patients; Low volume: 15–25 patients; Very low volume: <15 patients over the study period). This translated to very low volume centers averaging less than one nephroblastoma resection annually. Sensitivity analyses were performed using a variety of volume cut-points with consistent results.

Statistical analysis

Patients undergoing total nephrectomy for nephroblastoma at high versus low volume centers were compared using univariate statistics with χ^2 for categorical data and Student's t tests for continuous data ($p < 0.05$). Multivariable adjusted relative risks were estimated using generalized linear models with a log link function and Poisson distribution using robust standard errors. Adjustment factors were determined a priori and included sex, income, education, race, insurance and urban versus rural place of residence. Sensitivity analyses were performed dividing the hospitals into deciles based on the number of patients treated with nephrectomy for unilateral nephroblastoma. The highest decile was then compared to the lowest using the same adjustment factors as the base analysis. Statistical analysis was completed using Stata statistical software version 12. StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.

Results

A total of 2911 patients who underwent a total nephrectomy for unilateral nephroblastoma were captured in the NCDB between 1998 and 2012. There were 1443 (49.6%) patients who underwent resection at 32 (15.3%) HVCs and 1468 (50.4%) at 177 (84.7%) LVCs. When divided into quartiles there were 734 (25.2%) patients treated at 11 (5.3%) very high volume centers, 709 (24.4%) patients treated at 21 (10.0%) high volume centers, 698 (24.0%) patients treated at 37 (17.7%) low volume centers and 770 (26.5%) patients treated at 140 (67.0%) very low volume centers. They were similar in their demographic characteristics in terms of age at diagnosis, sex and urban versus rural place of residence ($p > 0.05$). There were clinically subtle, but statistically significantly different variations in their race, insurance status and median household income. Patients treated at high volume centers were more often White (HVC: 67.1%, LVC 63.3%; $p = 0.047$), with governmental insurance (HVC: 37.2%, LVC 34.6%; $p = 0.031$). Higher volume centers treated more pediatric patients with a higher household income (HVC: 38.9% ≥ $46,000, LVC: 34.6% ≥ $46,000; $p = 0.049$). High volume centers also treated patients from areas of higher educational achievement ($p = 0.042$). (Table 1)

There was no difference in average tumor size ($p = 0.37$) nor frequency of preoperative biopsy ($p = 0.37$) between high and low volume centers. On univariate analysis higher volume centers more frequently examined regional nodes at resection (HVC: 87.4%, LVC: 83.5%; $p = 0.003$) and had more frequent positive surgical margins (HVC: 15.5%, LVC: 12.6%; $p = 0.026$). (Table 2)

Patients treated at HVCs more frequently received chemotherapy ($p < 0.001$) and with no difference in radiation therapy ($p = 0.15$). Additionally, patients treated at HVCs had a shorter unadjusted mean time to chemotherapy (HVC: 10.9 (SD 13.9) days; LVC: 13.5 (SD 24.5) days; $p < 0.001$) with no difference to radiation therapy ($p = 0.4$). (Table 2)

On multivariable analysis, centers were divided into volume quartiles. On adjusted multivariable analysis there were no differences in tumor size, frequency of preoperative biopsy, positive margin status or days to radiation treatment. (Table 3) As seen with the univariate analysis, HVCs were more likely to perform nodal sampling with the highest volume centers more likely to perform nodal sampling than the lowest volume centers (Relative Risk (RR) 1.04 (95% Confidence Interval (CI) 1.01–1.08). Further, highest volume centers had fewer days to