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Patterns of lymph node sampling and the impact of lymph node density in favorable histology Wilms tumor: An analysis of the national cancer database

A.F. Saltzman [a], A. Carrasco Jr [a], A. Amini [b], J.H. Aldrink [c], R. Dasgupta [d], K.W. Gow [e], R.D. Glick [f], P.F. Ehrlich [g], N.G. Cost [a]

[a]Department of Surgery, Division of Urology, University of Colorado School of Medicine, Aurora, CO, USA

[b]Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO, USA

[c]Division of Pediatric Surgery, Department of Surgery, The Ohio State University College of Medicine, Nationwide Children's Hospital, Columbus, OH, USA

[d]Division of Pediatric Surgery, Cincinnati Children's Hospital, Cincinnati, OH, USA

[e]Division of Pediatric Surgery, Seattle Children's Hospital, Seattle, WA, USA

[f]Division of Pediatric Surgery, Steven and Alexandra Cohen Medical Center of New York, New York, NY, USA

[g]Department of Surgery, C.S. Mott Children's Hospital, University of Michigan Medical School, Ann Arbor, MI, USA

Correspondence to: N.G. Cost, 13123 E 16th Ave., Box 463, Aurora, CO, 80045, USA, Tel.: +1 720 777 6167, 214 883 3199, Fax: +1 720 777 7370

nicholas.cost@childrenscolorado.org (N.G. Cost)

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Summary

Introduction
There is controversy about the role of lymph node (LN) sampling or dissection in the management of favorable histology (FH) Wilms tumor (WT), specifically how it performed and how it may impact survival.

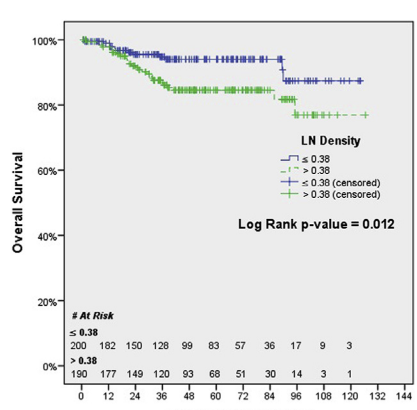
Objective
The objective of this study was to analyze factors affecting LN sampling patterns and the impact of LN yield and density (number of positive LNs/LNs examined) on overall survival (OS) in patients with advanced-stage favorable histology Wilms tumor (FHWT).

Methods
The National Cancer Database (NCDB) was queried for patients with FHWT during 2004–2013. Demographic, clinical and OS data were abstracted for those who underwent surgical resection. Poisson regression was performed to analyze how factors influenced LN yield. Patients with positive LNs had LN density calculated and were further analyzed.

Results
A total of 2340 patients met criteria, with a median age at diagnosis of 3 years (range 0–78 years). The median number of LNs examined was three (range 0–87). Lymph node yield was affected by age, race, insurance, tumor size, laterality, advanced stage, LN positivity, and institutional volume. A total of 390 (16.6%) patients had LN-positive disease. Median LN density for these LN-positive patients was 0.38 (range 0.02–1) (Summary Figure). Estimated 5-year OS was significantly improved for those with LN density $\leq$0.38 vs. $>$0.38 (94% vs. 84.6%, $P = 0.012$). In this population, on multivariate analysis, age and LN density were significant predictors of OS.

Discussion
It is difficult to compile large numbers of cases in rare diseases like WT, and fortunately a large administrative database such as the NCDB can serve as a great resource. However, administrative data come with inherent limitations such as missing data and inability to account for a variety of factors that may influence LN yield and/or OS (specimen designation, pathologist experience, surgeon experience/volume, institutional Children's Oncology Group (COG) association, etc.). In this specific disease, the American Joint Committee on Cancer staging (captured by the NCDB) is different than the COG WT staging system that is used clinically, and the NCDB does not capture oncologic outcomes beyond OS.

Conclusions
In a review of the NCDB, various factors associated with LN yield and observed LN density were identified to be significantly associated with OS in patients with LN-positive FHWT. This reinforces the need for adequate LN sampling at the time of WT surgery, to maximize surgical disease control. It was proposed that LN density as a metric may allow for improved risk-stratification, and possibly allow for therapeutic reduction in a sub-set of patients with low LN density.



Summary Figure Kaplan Meier curve of overall survival in patients with lymph node-positive disease based on lymph node density $\leq$0.38 vs. $>$0.38.

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Introduction

Wilms tumor (WT) represents the most common pediatric renal malignancy, and while remarkable gains have been achieved in survival over the past 50 years, there are still important strides to be made. Current investigational priorities center on risk stratification, with the goal of reducing adjuvant therapies and minimizing potential long-term side effects [1]. The introduction of the very low-risk WT designation in children aged <2 years is an example of such efforts [2]. Another population straddling this divide is favorable histology (FH) stage III WT. Lymph node (LN) positivity is one of several specific stage III criteria that have been found to independently impact event-free and overall survival (OS) [1,3].

Reports from a variety of solid tumors indicate that advanced metrics in assessing LN positivity can serve as useful prognostic markers. However, the absolute number of positive LNs may lose some of its prognostic ability when taken relative to the context of the total number of LNs sampled. To address this issue, the concept of LN density, defined as the proportion of positive LNs relative to the total number of LNs pathologically evaluated, emerged as an advanced metric. Most data on LN density are derived from outcomes in urothelial bladder cancer [4]; multiple series have validated its prognostic ability in this population [5,6]. Lymph node density has subsequently been demonstrated to predict disease recurrence and survival in multiple other malignancies, including: oral [7,8], esophageal [9], prostate [10], and penile cancers [11]. Additionally, and potentially germane to the current proposed investigation, the concept of LN density has been shown to be predictive of survival in adult kidney cancer [12].

Given a desire to more accurately surgically risk stratify this population, the objective of the current study was to identify factors associated with LN sampling patterns and LN yield, and to determine if LN density can aid in further stratification of patients with LN-positive favorable history Wilms tumor (FHWT). It was hypothesized that patients with higher LN density would experience worse OS.

Material and methods

Background

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a hospital-based registry that represents 70% of all cancer cases in the US, drawing data from more than 1500 commission-accredited cancer programs. The data used in the current study were derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the methodologies employed, nor the conclusions drawn from these data. Institutional Review Board exemption was obtained.

Study population

Data on patients with WT diagnosis during 2004–2013 ($n = 3669$) were obtained. Patients without follow-up, with unknown treatment, who did not undergo surgery, with bilateral disease, or with unfavorable histology were then excluded. This resulted in a study population of 2340 patients who underwent surgery and had FHWT. Data on patient demographics, clinical disease information and OS were abstracted. Overall stage was based on the American Joint Committee on Cancer staging guidelines based on corresponding year of diagnosis [13]. A planned sub-analysis was conducted on those with LN-positive disease ($n = 390$) and these patients had a LN density calculated.

Data analysis

Statistical analyses were performed using SPSS V23.0 (SPSS Inc., Chicago, IL, USA). Potentially relevant patient and treatment characteristics were included. Age, facility volume (defined as a continuous variable of the number of cases in the study cohort from each unique institutional code, and also broken categorically into tertiles), LN yield, number of positive LNs, and LN density were analyzed as continuous variables. Tumor laterality was recorded and analyzed. Receipt of chemotherapy or radiation was analyzed as a binary variable (yes/no). Comparisons of continuous variables used the Mann–Whitney *U* test and categorical variables were compared using the Chi-squared or Fisher's exact test. To determine factors influencing LN sampling patterns, a Poisson regression analysis was performed.

For those patients with LN involvement, the study planned to use the median LN density to group patients for comparison in terms of OS. Patients with a LN density above that median threshold were compared to patients with a LN density below this threshold using univariate log-rank testing. Overall survival was graphically compared using the Kaplan–Meier method. For patients with LN-positive disease, univariate survival analysis (UVA) was performed with the log-rank test, with unadjusted Cox proportional hazards regression to estimate hazard ratios (HR). Multivariate Cox regression analysis (MVA) was performed, including variables found to be significant on the UVA ($P \leq 0.05$). All tests were two-sided. A priori, it was decided that the LN density analysis would be performed only on patients with LN-positive disease, as including LN-negative patients (LN density $= 0$) would be a comparison of inherently different populations and skew results in favor of lower LN densities. Lymph node density was treated as a continuous variable for these analyses. In all analyses, $P < 0.05$ or a 95% confidence interval (CI) not crossing 1.0 was considered significant.

Results

A total of 3669 patients were initially identified in the NCDB dataset, 2340 of whom met study criteria. Of this population, 390 (16.6%) patients were reported having at least 1 positive LN, comprising the LN-positive population. Baseline demographics of these populations are summarized in Table 1. Estimated 5-year OS for the entire cohort was 93.4% (95% CI 92.2–94.6), and 89.2% (95% CI 85.9–92.5) for those with LN-positive disease.

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