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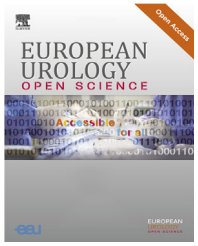

European Association of Urology

Brief Correspondence

The Phenomenon of "Therapeutic" Nodal Yield at Cystectomy for Bladder Cancer: Do Not Discount the Will Rogers Effect

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Abstract

While multiple mechanisms have been hypothesized to explain the therapeutic effect of lymph node (LN) yield in patients with urothelial cell carcinoma (UCC) undergoing radical cystectomy (RC), the effect of stage migration, commonly known as the Will Rogers effect, is often discounted. We reviewed the National Cancer Database for patients with UCC undergoing RC with pathologically node-negative (pN0) disease from 2004 to 2016. We tested for an adjusted association between LN yield and overall survival using multivariable Cox proportional-hazard models. Median survival was estimated using the Kaplan-Meier method. We identified 19 939 patients with pN0 UCC treated with RC. After adjustment, patients in the highest quantile for LN yield (≥26 LNs) had a 34% lower risk of death in comparison to patients in the lowest quantile (≤5 LNs). As we increased the threshold for LN yield for dichotomization from >5 to >15 to >25 LNs, median survival increased from 83 to 95 to 103 mo. The pN0 group with higher LN yield appeared to live longer in this analysis owing to the mathematical artifact of how patients are indexed. Resection of a greater number of negative LNs will lead to higher fidelity for pN0 cohorts being evaluated, as the likelihood of contamination by pN+ cases that were missed will be lower.

Patient summary: A strategy to dissect a high number of lymph nodes in patients undergoing removal of their bladder for bladder cancer can be associated with side effects, and the benefit in terms of cancer control or survival remains uncertain. Urologists and their patients should engage in shared decision-making and consider the risks and benefits of more extensive lymph node dissection during surgery.

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The role of lymphadenectomy and lymph node (LN) yield during radical cystectomy (RC) for patients with urothelial cell carcinoma (UCC) remains a point of ongoing debate. Multiple retrospective studies have demonstrated a survival advantage when more, compared with fewer, LNs are removed [1,2]. Multiple potential mechanisms for the improvement in outcomes with higher LN yield have been proposed: (1) a direct therapeutic benefit of removal of cancerous LNs; (2) modification of treatments and earlier intensification of adjuvant treatments on identification of pN+ disease; and (3) LN yield acting as a surrogate marker for surgeon or institutional factors associated with a higher

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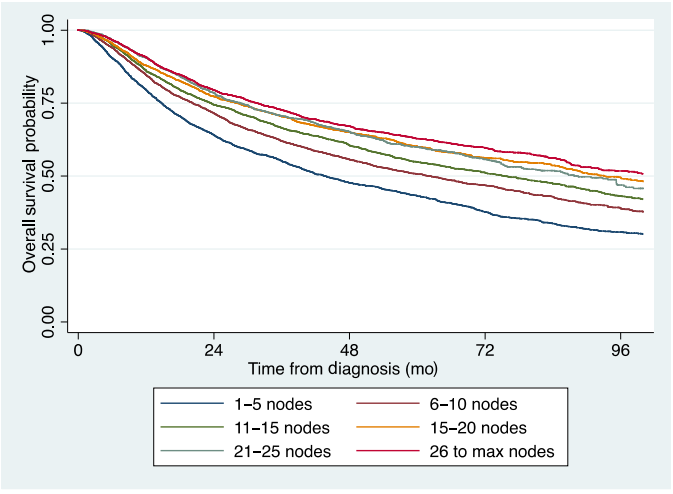
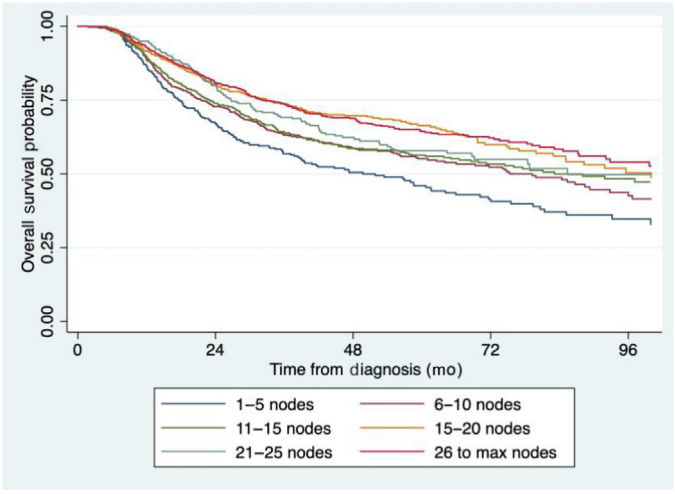
(A)



	HR (95% CI)	*p* value
Model 1 *		
1–5 LNs	Ref.	Ref.
6–10 LNs	0.83 (0.78–0.89)	<0.001
11–15 LNs	0.75 (0.70–0.80)	<0.001
16–20 LNs	0.66 (0.61–0.72)	<0.001
21–25 LNs	0.68 (0.62-0.75)	<0.001
≥26 LNs	0.66 (0.60–0.72)	<0.001
Model 2 *		
Continuous (per 5 LNs)	0.95 (0.94-0.96)	<0.001

(B)



(C)

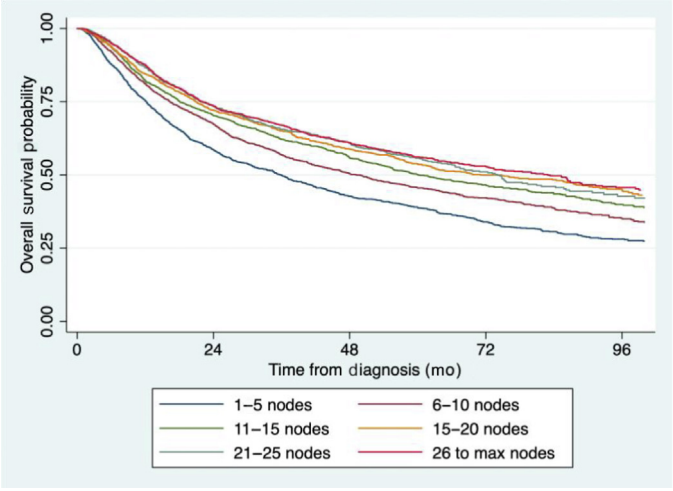


Fig. 1 – (A) Kaplan-Meier overall survival (OS) estimates and multivariable Cox proportional-hazard model for patients with bladder cancer stratified by the number of negative lymph nodes (LNs) removed. LN yield is treated as an unordered categorical variable in model 1, and as a continuous variable in model 2. * Models are adjusted for clinical T stage, hospital cystectomy volume, race, insurance type, receipt of radiotherapy, receipt of neoadjuvant or adjuvant systemic therapy, age, year of diagnosis, income, education status, urban/rural index, comorbidity status, and sex. (B) Kaplan-Meier OS estimate for patients who received neoadjuvant systemic therapy for muscle-invasive bladder cancer (MIBC). (C) Kaplan-Meier OS estimate for patients with MIBC who did not receive neoadjuvant systemic therapy. (D) Kaplan-Meier OS estimates for increasing LN yield thresholds for dichotomization.

(D)

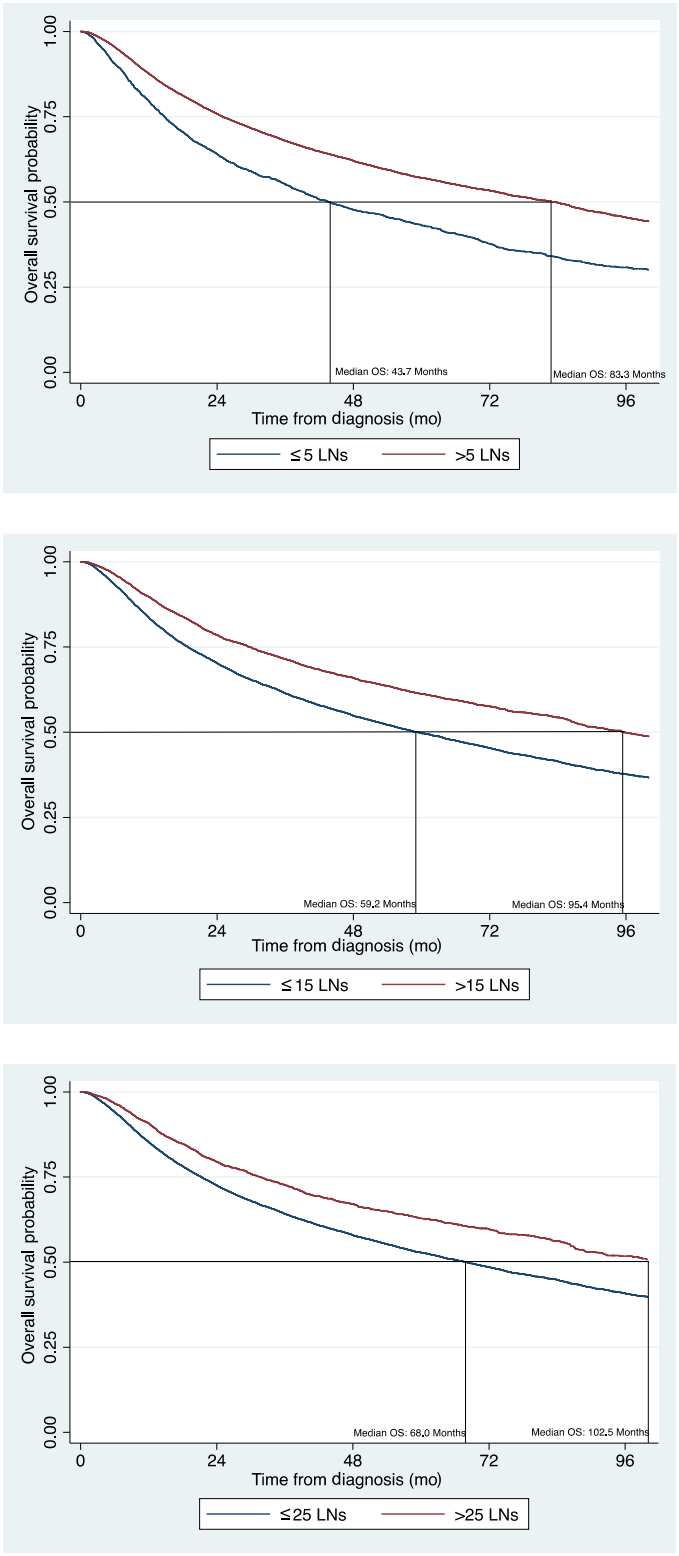


Fig. 1 (*continued*)

quality of care across the disease continuum [3]. While the effect of these factors on patient survival is a matter of debate, the influence of stage migration, also known as the Will Rogers effect, is an often-underappreciated and yet simpler (and arguably more likely) explanation of these findings. The origin of the term in the medical vernacular

has been attributed to Dr. Michael McFarlane referencing the following Will Rogers quote: "When the Oakies left Oklahoma and moved to California, they raised the average intelligence level in both states" [4]. In the context of bladder cancer and increasing LN yield, surgeons are shifting patients with low-volume pN+ disease (Oakies moving to California), which would have been indexed as pN0 (Oklahoma residents), to the pN+ state (California residents). Thus, removal of pN+ contamination from the pN0 cohort leads to an apparent improvement in outcomes for the pN0 group. Furthermore, the pN+ cohort also "benefits" by appearing to have superior outcomes when more nodes are removed, as patients with the lowest volume of pN+ disease, who have a more favorable prognosis than those with high-volume pN+ disease, are now included in the pN+ group. Thus, because of migration of individuals between states (of the USA or of an oncologic condition), both groups appear to benefit from Oakie migration and higher-volume LN dissection, despite the fact no individual has gained intelligence or lived longer and the outcome for the population as a whole did not change.

To illustrate the influence of the Will Rogers effect on outcomes, we provide an analysis of how greater LN yield, even when all resected LNs are negative, is associated with better outcomes. By including only patients with pN0 disease, we aimed to mitigate other hypothesized effects of lymphadenectomy such as a direct therapeutic effect of debulking of cancerous LNs or a change in management or treatment intensification on detection of pN+ disease.

We reviewed the National Cancer Database (NCDB) for patients diagnosed with cTany N0 M0 UCC from 2004 to 2016 who underwent RC and lymphadenectomy. Patients with non-UCC histology and those with pathologically positive disease (pN+) were excluded. The main independent variable was LN yield. The primary dependent variable was overall survival (OS). OS probability was estimated using the Kaplan-Meier method and survival curves were compared using the log-rank test. We fitted multivariable Cox proportional-hazard models with robust standard errors clustered by hospital and adjusted for multiple factors, including use of neoadjuvant or adjuvant systemic therapy, to assess for an adjusted association between LN yield and OS. LN yield was treated as both an unordered categorical variable (1–5, 6–10, 11–15, 16–20, 21–25, and $\geq$26 LNs) and a continuous variable. Kaplan-Meier curves were stratified using three different LN thresholds (greater or less than 5, 15, or 25 LNs). Subgroup analyses included patients with and without neoadjuvant systemic therapy among patients with muscle-invasive bladder cancer (MIBC).

We identified 19 939 patients with pN0 UCC who underwent RC and pelvic LN dissection, of whom 5154 had non–muscle-invasive bladder cancer (NMIBC) and 14 775 had MIBC (Supplementary Table 1). Median follow-up was 34 mo (interquartile range [IQR] 15–64) and the median LN yield was 14 (IQR 8–22). There were 7410 deaths during follow-up. LN yield was associated with better OS in the overall cohort (Fig. 1; $p < 0.001$), in the subgroups of patients with NMIBC ($p < 0.001$) and MIBC ($p < 0.001$) disease, and in the MIBC subgroups treated with (Fig. 1B; $p < 0.001$) and without (Fig. 1C; $p < 0.001$) neoadjuvant systemic therapy. After adjustment for multiple covariates, LN yield remained associated with better OS (Fig. 1A) when treated as both a categorical and a continuous variable. Patients with an LN yield of $\geq$26 had a 34% lower risk of death in comparison to patients with an LN yield of $\leq$5, despite the fact that none of the resected nodes harbored cancer. Furthermore, when we increased the LN threshold from 5 to 15 to 25 LNs for dichotomization, median OS increased from 83 to 95 to 103 mo, respectively (Fig. 1D).

Although we cannot discount the possibility that other potential mechanisms are at play, the marked and orderly "therapeutic effect" of resecting LNs that are negative for cancer very strongly points to the Will Rogers phenomenon as the explanation for the effect observed. Resection of a greater number of nodes means that the pN0 cohort evaluated is simply of higher fidelity and is less likely to be contaminated by patients with oligometastatic pN+ disease. Despite the fact that no patient's therapeutic destiny may have been altered when more LNs were resected, the pN0 group with higher LN yield appears to live longer in this analysis because of the artifact of how patients are indexed.

Despite numerous retrospective series demonstrating an improvement in oncological outcomes with larger and more extensive LN dissections, level 1 evidence is absent. The one published randomized trial assessing standard versus extended lymphadenectomy failed to demonstrate statistically significant differences in recurrence-free survival, cancer-specific survival, or OS between the standard and extended lymphadenectomy groups [5]. However, the trial results do not fit the classic narrative and thus its findings have been criticized. Results from SWOG 1011, which randomized more than 650 patients to extended or standard lymphadenectomy, are yet to be reported and are likely to shed more light on the debate.

In addition to the nonrandomized nature of our analysis, which may introduce selection bias, this analysis is limited by the lack of centralized pathology review, which is not feasible in the NCDB.

These data provide a plausible explanation for the therapeutic yield phenomenon seen in the management of not only bladder cancer but also urothelial cancer of the upper urinary tract, prostate cancer, and kidney cancer. The persisting narrative that a greater number of resected LNs results in better outcomes is likely to find itself down for the count as the often-discounted Will Rogers effect may prevail with the maturation of definitive prospective trials.

Author contributions: Kevin B. Ginsburg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ginsburg, Kutikov, Magee, Schober, Bukavina.
Acquisition of data: Ginsburg, Kutikov.
Analysis and interpretation of data: Ginsburg, Kutikov.
Drafting of the manuscript: Ginsburg, Bell, Kutikov.
Critical revision of the manuscript for important intellectual content: Ginsburg, Bell, Kutikov, Bukavina, Schober, Magee.
Statistical analysis: Ginsburg.
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Supervision: Kutikov.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.11.004.

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