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Lymph node yield in pediatric, adolescent and young adult Renal Cell Carcinoma – How many are enough?☆,☆☆,★,★★

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ABSTRACT

Purpose: Pediatric, adolescent and young adult (PAYA) patients with renal cell carcinoma (RCC) have a high rate of LN involvement, yet data to guide surgical lymph node (LN) management in this group is limited. The objective is to describe a LN yield threshold to quantify the chance of missing occult LN involvement at ≤10% in PAYAs with RCC.

Materials & methods: The National Cancer Database was queried for patients aged ≤30 y with unilateral, non-metastaticRCC from 2004 to 2013. The probability of a false negative LN sampling was determined on the cohort of patients who had at least one positive LNand ≥ 2 LNs examined. For a given LN yield, the probability that a positive LN exists but none were found was estimated using a beta-binomial model.

Results: We identified 112 patients meeting study criteria. Median age was 24 y and median tumor size was 9.5 cm (IQR 5.8–14). The median number of LNs sampled was 7 (IQR 4–12) and the median number of LNs positive was 4 (IQR 2–7). To achieve ≤10% probability of a false-negativeLN sampling, the beta-binomial model estimated that 5 LNs (95% CI4–7) must be sampled.

Conclusions: The desired LN yield to reduce the risk of a false-negativeLN sampling in PAYAs with RCC to ≤10% is 5. This is in keeping with prior studies identifying a LN yield of 6–10 to achieve the same. These data may be used to standardize surgical guidelines when treating PAYAs with renal tumors.

Level of Evidence: II.

For pediatric, adolescent and young adult (PAYA) patients with a renal tumor, surgical resection is typically the first step in management. At the time of resection, a pathologic diagnosis is not definitively known, thus Children's Oncology Group (COG) surgical protocols are not diagnosis-specific, and mandate lymph node (LN) sampling for accurate tumor staging since a variety of diagnoses may be encountered [1]. In favorable histology Wilms tumor (FHWT) for example, the importance of LN sampling for staging and risk stratification cannot be overstated, as it guides adjuvant therapy. LN involvement is one criterion for stage III designation, which mandates local radiation therapy as well as chemotherapeutic intensification with doxorubicin, and associated toxicities. While formal LN dissection has not been found to influence OS, in LN positive FHWT patients, there are data to suggest that decreased LN density is associated with an improved 5 yr. overall survival (OS) [2].

However, for renal cell carcinoma (RCC) in PAYA patients, data to guide surgical LN management are limited. There is a relatively high rate of LN involvement in PAYAs with RCC, regardless of pre-operative clinical suspicion or renal tumor size [3], and some argue for performing LN dissection as a second procedure if it was omitted with extirpation [4]. Yet across all hospitals, regardless of COG association, LN sampling is performed in <15% of PAYAs undergoing surgery for RCC and is thus potentially underutilized [5]. In adults, LN involvement is highly correlated with pre-operative clinical suspicion and it is unclear if LN dissection or sampling provides clinical benefit [6–10]. Regardless of therapeutic utility, it appears that adult treatment guidelines are being applied to PAYAs with RCC (i.e.,no role for LN dissection), despite COG surgical protocol guidelines mandating it [1,5].

Based on prior work that has identified a LN yield threshold for FHWT to minimize the chance of missing occult metastatic disease to

Abbreviations: PAYA, pediatric, adolescent and young adult; LN, lymph node; RCC, renal cell carcinoma; FH, favorable histology; WT, Wilms tumor; tRCC, translocation renal cell carcinoma.

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≤10% [11], the objective of this study is to apply this same methodology to PAYAs with RCC. Statistical models are presented to quantify how many LNs must be sampled to reduce the chance that a positive LN is missed ≤10% of the time. This threshold was then compared to the previously described FHWT threshold [11] (6–10 LNs) to determine how these diseases align.

1. Methods and materials

The National Cancer Database (NCDB) was reviewed to identify the study population. All data obtained from the NCDB are de-identified and IRB exemption was obtained. This study was modeled after that of Robinson etal. [12] and Saltzman etal. [11], which used NCDB data to assess the adequacy of LN sampling in patients with both thyroid cancer and unilateral, non-syndromicFHWT [11,12].

1.1. Study population

The NCDB was queried for patients aged ≤30 y with unilateral, non-metastatic (non-M1) RCC managed with resection (radical or partial nephrectomy) from 2004 to 2013. This date range was selected to reflect more modern practice patterns. The selected age cutoff was used due to prior work on cancer patients considered to be PAYAs and were included in current COG protocols, specifically the most recent COG study which included RCC patients (AREN 0321) [13–16].

3262 patient records were identified that met initial criteria. Patients who did not undergo LN sampling (n = 2741), were missing LN yield (n = 47) and those missing both LN yield and LN positivity information (n = 28) were excluded. 446 patients remained. Further, patients without involved LNs (n = 197), those with <2 LNs sampled (n = 24), or both (n = 111) were excluded. This resulted in a population of 112 patients surgically managed for unilateral, non-metastaticRCC who had ≥2 LNs sampled, had ≥1 LN involved and had detailed count information available about LN sampling. 2 patients had missing stage information and 1 patient missing tumor size information and were excluded from subgroup analyses. LN yield was defined as the number of LNs surgically obtained and evaluated by pathology.

1.2. Data analysis

Statistical analyses were performed using R (v.3.4.1) statistical software package. For a given LN yield, the probability that a positive LN exists but none were found (false negative LN sampling) was estimated and then stratified by American Joint Committee on Cancer (AJCC) group stage (III vs. IV), patient age (0–15 y, 16–20 y and 21–30 y)and tumor size (<7 cm, 7–10 cm and >10 cm) [17]. Specifically, to determine the probability that a positive LN was missed during LN sampling, the analysis was limited to patients with LN involvement. For patients without LN involvement, it was not possible to determine whether there was truly no nodal involvement or whether occult disease may have existed but was missed due to limited LN sampling. This is the key reasoning behind restricting the analysis to those with positive LNs.

For the purposes of this study, it was decided a priori that a probability of missing a positive LN of ≤10%, or a false-negativeLN sampling rate of ≤10%, was acceptable [11,12]. Importantly, the false negative rate was determined by identifying the rate at which 90% of patients would be correctly identified (true positive), with the remaining 10% being the false negative patients.

1.3. Statistical models

The false-negative probability was estimated using two models. The first assumed the number of positive LNs followed a beta-binomial distribution given the LN yield (Vector Generalized Linear and Additive Models package in R). The beta-binomial model was chosen both due to its use in similar studies [12,18] and because it allows the LN positivity rate to vary across patients. Given intrinsic heterogeneity of the patient population this is a more realistic assumption compared to the fixed rate that would be assumed if a binomial distribution were used to model LN positivity.

Internal validation was conducted on the beta-binomial model where subjects were randomly resampled with replacement using bootstrap resampling 1000 times to assess the variability in the LN yield needed to maintain a false negative rate of ≤10%. The mean and estimated 95% CI were obtained from the bootstrap samples.

As a sensitivity analysis for the beta-binomial model, an empirical approach based on the binomial model was included. Here, the rate of LN positivity was averaged based on the entire cohort and the binomial model was then used to determine the false-negative rate for a given LN yield. Since the empirical approach relies on a fixed LN positivity rate applied to the entire population, the variance will be underestimated and biases the results towards underestimating the LN yield needed for a given false-negative probability.

2. Results

Only 16% (521/3262) of the study population underwent LN sampling, of which 112 patients met study criteria described in the methods (Table1). Median age was 24 y and median tumor size was 9.5 cm (IQR 5.8–14). The median number of LNs sampled was 7 (IQR 4–12) and the median number of LNs positive was 4 (IQR 2–7).

Table1
Demographics for patients who had LN yield ≥2 and at least 1 positive LN.

Characteristic	n (%)
Age	
0–15	21 (18.8)
16–20	15 (13.4)
21–30	76 (67.9)
Sex	
Male	51 (45.5)
Female	61 (54.5)
Race	
White	76 (67.9)
Black	28 (25.0)
Other	6 (5.4)
Unknown	2 (1.8)
Laterality	
Right	41 (36.6)
Left	71 (63.4)
Surgical approach	
Radical nephrectomy	109 (97.3)
Partial nephrectomy	3 (2.7)
LN yield (median [IQR])	7 [4–12]
Number positive LNs (median [IQR])	4 [2–7]
Histology	
Papillary	24 (21.4)
Clear cell	22 (19.6)
NOS	58 (51.8)
Sarcomatoid	8 (7.1)
Fuhrman grade	
2	11 (9.8)
3	54 (48.2)
4	24 (21.4)
Unknown	23 (20.5)
Tumor size (cm)	
<7	39 (35.1)
7–10	21 (18.9)
>10	51 (45.9)
Stage	
III	49 (43.8)
IV	63 (56.2)

The beta-binomial model had an estimated mean of 0.59. Thus, for each patient, on average, a positive LN was found 59% of the time, while in the empirical calculation it was 50%. LN yield thresholds to achieve ≤10% probability of a false-negativeLN sampling are summarized in Tables2 and 3. Overall, the beta-binomial model estimated that 5 LNs (95% CI4–7) must be sampled and this was slightly higher in stage III patients (8 LNs, 95% CI5–12) than in stage IV patients (4 LNs, 95% CI3–5). The empirical calculations were similar to the beta-binomial model. When stratifying by tumor size or patient age, there was no apparent trend in their relationship with the probability of false negative LN sampling.

Additionally, the observed and corrected prevalence of nodal disease in the patient population among those that had one or more LN examined was calculated, which was examined in the overall population and separately in stage III and IV patients [12]. In the overall population the corrected prevalence of nodal disease was found to be 5% higher (35% vs. 29%) when accounting for individuals where nodal disease was missed in the population. The stage III population saw the largest increase in nodal disease after correcting the prevalence while the increase seen in stage IV was similar to the overall population, with increases of 19% (65% vs. 46%) for stage III and 6% (83% vs. 77%) for stage IV. The beta-binomial results stratified by tumor stage are presented in Fig.1.

Internal validation (bootstrapping) of the beta-binomial model demonstrated little variation in the LN yield needed to maintain a false negative rate ≤ 10%, with an inter quartile range (IQR) of 4–7 LNs (Table2).

3. Discussion

Despite conflicting data on the therapeutic impact of LN sampling/dissection, this is mandated by COG surgical protocols for all PAYAs with a renal tumor undergoing resection, regardless of approach or surgical modality. These data suggest that at least 5 LNs should be sampled to reduce the risk of missing occult LN involvement to ≤10% in PAYAs with RCC, assuming an involved LN exists. This aligns well with prior work that has established a LN threshold of 6 to 10 LNs for patients with FHWT [11]. Using the findings from these two studies, a LN yield threshold could be used to standardize LN sampling for the two most common renal malignancies affecting the PAYA population. These data can be used by surgeons and study committees to further establish a LN threshold goals and templates for any renal mass, regardless of pathology, to reduce the chance of missing an involved LN to ≤10%. The important nuance here is that if the surgeon assumes the worst case scenario, i.e. there are involved LNs, then they know that if the LN yield is at least 10, regardless of pathology, they are 90% certain there were no involved LNs that were missed.

A recent study from the NCDB suggests a 5-year overall survival (OS) of 70% for all histologic types of pediatric RCCs [19]. Patients without nodal involvement have an estimated OS between 91 and 100%, patients with LN involvement 71%, and patients with distant metastases 8%. Tumor size, LN involvement and lack of surgical resection are factors predictive of worse OS, emphasizing the important role surgical resection plays in management [19,20]. These outcomes suggest that the prognosis is similarly good in children and adults with localized disease, however the outcome in the setting of nodal involvement in pediatric patients is better than a similar scenario in adults (5 y OS 72.7% vs. 20% respectively [21,22]). A hypothesis for this difference is perhaps due to the histologic type of RCC in this population (i.e. translocation RCC (tRCC)) and pediatric renal tumor protocols mandating LN sampling and thus more children than adults have surgical management of their LNs.

There is a high prevalence of nodal involvement in PAYA tRCC, regardless of preoperative imaging and tumor size [3]. A 2004 Italian study compared pediatric patients with RCC treated with formal retroperitoneal LN dissection (n = 9) vs. those who received a more limited LN dissection (LN sampling, n = 7), with the LN dissection group having fewer relapses (1/9 vs. 5/7) and a significant survival advantage (1/9 vs. 5/7 death due to disease) over the more limited group [4]. The Italian study authors feel that the importance of LN sampling is so great that it is reasonable to pursue a second look retroperitoneal LN dissection for patients with tRCC treated with nephrectomy alone, although the timing at which patients underwent nephrectomy (i.e. at diagnosis vs. delayed after neoadjuvant chemotherapy) was not accounted for and ay play a role in the Italian study's results [4,23]. While there are no published data yet on improved outcomes of LN sampling/dissection in PAYAs specifically, through extrapolation of available studies, the authors of the present study believe that these findings identify a potential missed opportunity for improving outcomes for PAYAs with RCC. This may be a unique opportunity for surgeons and urologists to improve the care of young adult patients and extrapolate from the pediatric population: perform adequate LN sampling on all PAYA patients with a renal mass suspicious for malignancy, especially those over age 12 yrs., due to the significant chance of harboring tRCC. This study, along with prior work, attempts to quantify what “adequate” LN sampling is, i.e. 5 LNs for RCC and 6 to 10 LNs for FHWT [11].

This difference in rates of LN involvement based on patient age may be due to the different histologies of RCC typically encountered in adults vs PAYAs: in PAYAs, the rate of translocation RCC (tRCC) is 47% [3], which decreases to 15% in patients <45 y [24], and even further to just 2.4% in those >50 y [25]. In the authors' opinion, LN sampling at the time of extirpation in accordance with COG guidelines (which includes patients up to age 30 y)is reasonable and associated with few risks [26].

Lack of LN sampling represents the most frequent surgical protocol deviation in FHWT [27] and for PAYA patients with RCC treated anywhere, not just COG centers, <15% of patients receive LN sampling, despite COG surgical guidelines [5]. But unlike FHWT,LN involvement itself does not change current treatment protocols in RCC despite its association with a poor prognosis compared to patients with RCC without LN involvement. Given the higher rate of tRCC pathology in younger patients, with higher prevalence of nodal involvement (especially with

Table2
LN yield to achieve ≤10% probability of false negative LN sampling, overall and stratified by stage, age and tumor size using the beta-binomial model. Note the 95% CIs were determined from bootstrap resampling.

		Number of patients	LN yield (95% CI)
All patients		112	5 (4–7)
Stage	III	49	8 (5–12)
	IV	63	4 (3–5)
Age (y)	0–15	21	6 (3–9)
	16–20	15	3 (2–5)
	21–30	76	5 (4–8)
Size (cm)	<7	40	6 (4–9)
	7–10	22	4 (2–8)
	>10	52	5 (3–7)

Table3
The beta-binomial and empirical probability of a false-negative LN sampling as a function of LN yield (overall and then stratified by tumor stage).

	False negative probability (%)					
	Beta-binomial model			Empirical estimation		
LN yield	All patients (n = 112)	Stage III (n = 49)	Stage IV (n = 63)	All Patients (n = 112)	Stage III (n = 49)	Stage IV (n = 63)
2	24	34	17	25	39	18
3	17	25	10	13	24	8
4	12	20	7	6	15	3
5	10	16	5	3	9	1
6	8	13	4	2	6	1
7	7	11	3	1	4	0
8	6	10	3	0	2	0
9	5	9	2	0	1	0
10	4	8	2	0	1	0

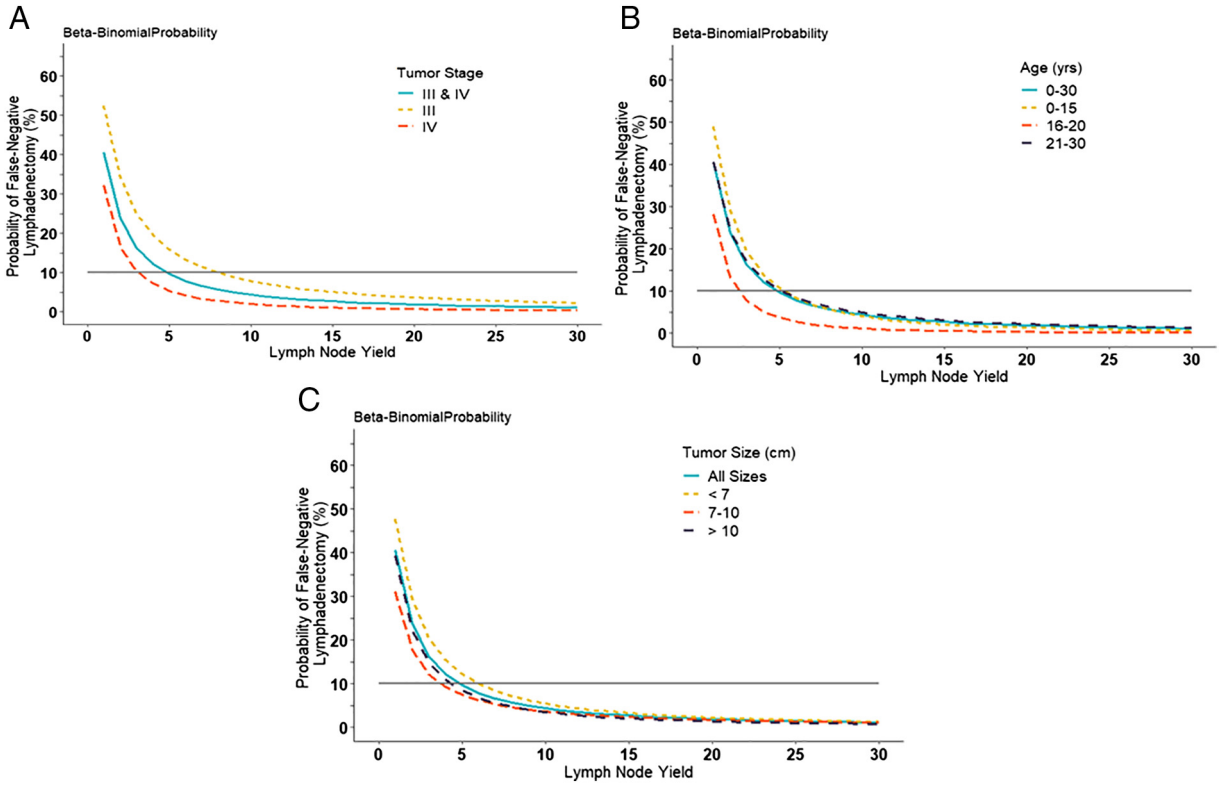

Fig. 1. The beta-binomial model probability of a false-negative LN sampling as a function of LN yield stratified by stage (A), patient age (B)and tumor size (C). Blue line is the entire study population in all panels, gray line is the 10% false negative threshold.

small masses), and the subsequent need for aggressive surgical control of disease, adequate LN sampling is potentially underutilized in this population. The present study provides some goal for those surgically treating these patients, which aligns with COG guidelines.

While systemic treatment regimens (immune checkpoint inhibitors and targeted therapies) for adult RCC may be useful, for adolescents and young adults with advanced disease, there is evidence that these therapies rarely provide durable remissions [20]; a true cure can likely only be achieved with complete surgical control [19]. Importantly, there is not a limited opportunity for surgical control; should there be a recurrence in the surgical bed or local LNs, there may still be a role for resection of this recurrence. Perhaps in the future there will be a trial of the newer immune-modulating checkpoint inhibitors (PD-1 and PD-L1 inhibitors) in this age cohort like those that have shown efficacy in adults with clear cell RCC.

The extent of LN sampling, as well as the location of LN sampling, must be better defined to further study and understand how this specific part of renal tumor treatment impacts outcomes. This is a major limitation of any study on LN management as the extent or location of LNs sampled is not recorded and cannot be determined. The National Wilms Tumor Study (NWTS), COG and the International Society of Pediatric Oncology (SIOP) would perhaps be better databases to use to study this aspect of renal tumor surgical care, but, given the restrictions of funding and general unavailability of data from these groups, the NCDB is the next best (and largest) available dataset with patients to study. And despite these funding and availability issues, even these databases do not record extent or location of LN sampling. Studies such as this may serve as a call to prospectively study this issue, likely through surgical templates and/or protocols, to validate the findings of this study.

When considering the implication of utilizing such a LN threshold, it is important to balance potential benefit versus harm in applying this threshold. For those with occult LN disease, it potentially reduces the chance of missing the involved LN and thus allows for a more complete surgical resection given the poor adjuvant therapeutic options in RCC. The addition of LN dissection during nephrectomy has not been demonstrated to add significant morbidity to the procedure [26,28,29], and in adults, the chance of finding unsuspected LN metastasis is low (3.3%) [8]. Given the combination of the higher likelihood of PAYA patients having tRCC and LN involvement, and the importance of the protocol-mandated surgical LN investigation for these patients, it is important to direct educational efforts towards more consistent application of surgical LN management for these patients. More extensive LN sampling however, does not come without potential risk, mainly chylous ascites, vascular injury or damage to surrounding organs. Two separate publications have investigated the rate of chylous ascites in both large and small series of FHWT resections, both reporting a rate of <4%, which was lower than the reported rates of splenic, diaphragmatic or pancreatic injury [28,29]. So while more extensive LN sampling may carry an increased risk of complications, the authors feel that the low complication rate is likely worth the benefit of increasing the goal LN yield to ensure an adequate resection and allow for future study of the therapeutic implications of LN sampling for PAYAs with RCC. For the adult urologist who may see a PAYA patient in practice with a renal mass, it is important to remember that adequate LN sampling is indicated, regardless of preoperative imaging characteristics [3] and operative approach (radical vs. partial nephrectomy, open vs. minimally invasive [MIS]).

The present study comes with several limitations. An important consideration for tRCC is that it only became a recognized renal tumor classification in 2004 [30] and studies including patients prior to 2004 do not address this specific patient population. Additionally, databases that allow for compilation of large numbers of patients with rare diseases, such as PAYAs with RCC, including the NCDB and Surveillance, Epidemiology and End Results (SEER) do not capture this diagnosis and patients may be misclassified. Thus, the data presented does not have a tRCC classification and it is reasonable to assume that a significant

portion of these patients, while not classified as tRCC in administrative databases, do indeed harbor tRCC [3]. The NCDB was selected for the current study because it captured the most number of applicable patients and the most data granularity, despite it still having limitations which have been discussed.

Data from an administrative dataset come with inherent limitations, such as missing values and reporting and selection bias. It was not designed for this study and allows only secondary analysis. For this study specifically, most patients were >18 years old and few underwent LN sampling, an important distinction from prior studies [3] that included only COG centers and patients <21 years old. There are several factors that could contribute to this trend that cannot be further examined using the NCDB because of the data recorded. The current study design cannot account for surgeon experience, annual volume or surgeon specialty (pediatric urologist, adult urologist, pediatric surgeon, etc.). Additionally, operative approach (MIS vs. open) and was not captured and may be linked to LN sampling, as this is performed less often with MIS approaches to renal tumors [31]. Surgeon bias, where surgeons may perform a more extensive LN dissection when concerned about positive LNs, could not be accounted for, even though preoperative clinical nodal staging was included in the dataset. The location of sampled LNs was not detailed in the NCDB either. Pathologist scrutiny of specimens also cannot be accounted for. The NCDB also does not comment on how many or which institutions are NCCN or COG institutions, which very likely affects protocol awareness, adherence and clinical outcomes.

4. Conclusion

The desired LN yield to reduce the risk of a false-negativeLN sampling in PAYAs with RCC to ≤10% is 5, regardless of tumor size or patient age. This aligns nicely with similar prior study which has identified a LN yield of 6 to10 to achieve the same goals in FHWT. This is an objective attempt to determine the desired LN yield to accurately stage PAYAs with RCC and these data may be used to further standardize surgical guidelines when treating all PAYAs with renal tumors.

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