The role of lymph node dissection in non-metastatic renal cell carcinoma with tumor thrombosis: a retrospective analysis

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Abstract

Background

To assess therapeutic value of lymph node dissection (LND) in non-metastatic renal cell carcinoma (RCC) with tumor thrombosis (TT) and identify the prognostic factor in these population.

Methods

We retrospectively reviewed 128 patients with RCC and TT in our institution from February 2015 to January 2019. The baseline characteristics of LND and no LND group were compared. Kaplan–Meier analysis, univariable and multivariable Cox regression models were used to analyze these population.

Results

Of 128 patients, 58(45%) underwent LND and 70(55%) without LND. Patients who received LND had significantly higher cN1 rate (64% vs 37%; P = 0.004), longer operation time (357 min vs 307 min; p = 0.002) and longer hospital stay (12.6d vs 9.5d; p = 0.094) than that in no LND group. There were 102 patients (79.7%) received followed up with the median 12 months (IQR:8 ~ 19). Estimated three-year overall survival was worse in LND group (75% vs 90%; p = 0.048) but were not significantly different in subgroup of cN0 and cN1. The overall survival were not significantly different between two groups after adjustment for age, tumor size, surgical approach, tumor thrombosis level and histologic type. Non-CCRCC (HR:4.97; 95%CL:1.56 ~ 15.78; P = 0.006) and occurrence of major complication (HR:3.33; 95%CL:1.05 ~ 10.58; P = 0.041) were the predictors of worse OS while positive lymph node is the only independent predictor of worse OS (HR:5.26; 95%CL:1.28 ~ 21.66; P = 0.021) in these populations after receiving LND.

Conclusion

In this study, we confirm that LND in non-metastatic RCC with TT was not associated with a survival benefit, even we adjusted for clinic node status. Category like age, tumor size, surgical approach, tumor thrombosis level and histologic type were not a indication for LND. Lymph node positive was identified as an independent poor prognostic factor. Therefore, LND in RCC with TT should be considered as a staging procedure rather than therapeutic one.

Background

Lymph node dissection (LND) plays an integrity part of surgical management in many genitourinary malignancies. However, the value of lymph node dissection at the time of radical nephrectomy for patients with renal cell carcinoma (RCC) is controversial. The only prospective research of LND at time of
nephrectomy was conducted by European Organization for Research and Treatment of Cancer (EORTC) in 1988 and failed to show a statistically significant difference between patients treated with nephrectomy and LND to those treated with nephrectomy alone\(^1\). However, most of these patients in the study were classified to the localized or low grade RCC. With regard to the high risk RCC, the role of LND is unclear and no prospective study are found. Some retrospective researches were found that LND might be beneficial in patients with high-risk RCC or in cases with unfavourable conditions\(^2\)\textsuperscript{–}\textsuperscript{6}. According to the EAU guideline\(^7\), LND in localized RCC can add staging information but the survival benefits are unclear, thus we need further investigations.

RCC with tumor thrombosis are classified to localized RCC according to the guideline. In these unique populations, surgical resection is widely accepted as the management option for patients with venous tumor thrombosis. However, due to the rarity of the RCC with tumor thrombosis, the data of LND in these patients are rare. LND can spend a long time owing to the complexity of the surgical procedure in these population, so the meaning of LND are worth investigating.

Therefore, we retrospectively analyzed the 128 RCC with TT patients in our institution treating by the radical nephrectomy and thrombectomy with or without LND from February 2015 to January 2019, aiming to find out the survival benefits of LND in these population.

**Methods**

**Patients selection and data collection**

After obtaining approval from our institutional review board, we retrospectively reviewed medical records of 208 patients from Peking University Third Hospital between February 2015 to January 2019 who were diagnosed with renal neoplasms with tumor thrombosis. The clinical data, surgical data and pathological data were collected. Additional exclusions criteria consisted of patients with distant metastasis (n=52), refused operation (n=3), not renal cell carcinoma (n=25). The final population consisted of 128 patients treated with radical nephrectomy and thrombectomy with or without LND were analyzed retrospectively.

**Variable definition**

All patients included in this study underwent CT scan, MRI, chest X-ray or PET-CT when suspected distant metastasis before surgery. We classified RCC stage according to the 2009 American Joint Committee on Cancer classification\(^\text{AJCC}\)\(^8\)\(\text{–}\)\(^9\) and defined tumor thrombosis level according to the Mayo classification by imaging result\(^8\)\(\text{–}\)\(^9\). Level 0: TT is at the renal vein not entry the inferior vena cava (IVC). Level I: TT entry the IVC <2 cm from the confluence of the renal vein and the IVC. Level II: Thrombus extends within the IVC >2 cm above the confluence of the renal vein and IVC but still remains below the hepatic veins. Level III: Thrombus involves the above the hepatic IVC but under the diaphragm. Level IV: Thrombus extends above the diaphragm.
After surgery we classified complication according to Clavien-Dindo classification\textsuperscript{10}. Grade 1: Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions. This grade also includes wound infections opened at the bedside. Grade 2: Requiring pharmacologic treatment with drugs. Blood transfusions and total parenteral nutrition are also included. Grade 3: Requiring surgical, endoscopic, or radiologic intervention. (3a: Intervention not under general anesthesia; 3b: Intervention under general anesthesia). Grade 4: Life-threatening complication (including CNS complications) requiring ICU management (4a: Single organ dysfunction; 4b: Multiple organ dysfunction). Grade 5: Death as a result of complications. We classified Grade 1\textsuperscript{-}2 as minor complication and 3\textendash{}5 as major complication.

**Surgical procedure and follow up**

All patients were underwent operation randomly assigned by 11 surgeons in our institution. Open or laparoscopic method was performed based on the clinical judgment of each surgeon. LND was performed by surgeon's preference and templates were not standardized. All specimen were fixed in 10\% buffered formalin and examined by the pathologist. After surgery we followed up patients mainly rely on the telephone call or outpatient clinic, and the data were collected by our research secretary. Our primary outcome was overall survival (OS) in patients with RCC and TT who underwent surgery with or without LND.

**Statistical analysis**

We used SPSS 22.0 software to perform statistical analysis. The t-test were performed to analyze the significant difference of means and the chi-square tested were performed to analyze the significant difference of proportions. The Kaplan-Meier method was performed to calculate overall survival between LND and no LND group, and differences were assessed with the log-rank tests. We also calculated OS divided by clinic node status and other risk factors like age, tumor size, surgical approach, tumor thrombosis level, and histologic type between two groups. Univariable and multivariable survival analyses were performed using the Cox proportional hazard regression model associated with the increased risk of OS in LND group. All reported P values are two-sided, and statistical significance was set at P<0.05.

**Result**

The entire cohort of study include 128 patients diagnosed with RCC and TT. All of these patients underwent radical nephrectomy and thrombectomy. The clinicopathologic features of these patients are summarized in Table 1. Of these patients, 58(45\%) underwent LND and 70(55\%) without LND. The proportion of gender, symptom, ASA score, tumor side and tumor thrombosis level were not statistically difference between the LND and no LND group. The diameter of the tumor of LND group seems to be much bigger than the no LND group but are not statistically difference (9.1 cm vs 8.1 cm; p = 0.070).
There was no significant difference in age, BMI, Hgb level, Alb level, SCr level between two group. Patients who received LND had significantly higher cN1 rate than that in no LND group (64% vs 37%; P = 0.004).

The approach of the surgery, transfusion rate and perioperative complication between two groups were not significantly different but the operation time (357 min vs 307 min; p = 0.002) and hospital stay (12.6d vs 9.5d; p = 0.094) were much longer in the LND group. The pathologic characteristics include histologic type and grade were not significantly difference. In the LND group, 14 (11%) of these patients had pathologically confirmed lymph node metastases.

Of these study cohort, 102 patients (79.7%) received followed up. The median follow-up after surgery was 12 months (IQR: 8 ~ 19). During the study period, 16 patients (11.7%) died after surgery. A Kaplan-Meier curve for overall survival stratified by LND or without LND were shown in Fig. 1. Estimated three-year overall survival was worse for patients who received LND than those who did not (75% vs 90%; p = 0.048). Overall survival were not significantly different between LND and without LND in subgroup cN0 and cN1 (show in the Fig. 2). Then overall survival were not significantly different between two groups after adjustment for age, tumor size, surgical approach, tumor thrombosis level and histologic type (show in the supplement Fig. 1).

Next, we examined the associations of some clinicopathologic features with OS in LND groups to identify prognostic factors. Univariable survival analysis between two groups are summarized in Table 2. Non-CCRCC (HR: 4.970; 95%CL: 1.566 ~ 15.766; P = 0.006) and occurrence of major complication (HR: 3.33; 95%CL: 1.049 ~ 10.586; P = 0.041) were the predictors of worse OS. After that, we put some suspected factors(p < 0.15) into multivariable survival analysis, positive lymph node is the only independent predictor of worse OS. (HR: 5.260; 95%CL: 1.279 ~ 21.662; P = 0.021).

**Discussion**

LND is an indispensable part of many urological tumors, such as bladder cancer, prostate cancer and urothelial cancer. The role of LND in patients with renal cell carcinoma has been controversial in recent years. Patients with RCC and TT represents a unique population of patients, which were classified as T3 according to the TNM classification. As we all know that according to the EUA guideline, all patients with non-metastatic renal cell carcinoma and tumor thrombosis should be considered for surgery if patient status acceptable. However, LND could spend a long time especially in the patients with RCC and TT, but the benefits were unclear. Our research provides an opportunity to learn more about the role of LND on such unique patients.

From the baseline of our cohort we found between LND and no LND group, the clinic characteristics were relatively similar except the proportion of cN+. LND was more likely underwent in patients with cN+ disease than in those with cN0. It reflects that the surgeon’s preference of LND using in the population with potential lymph node metastasis, which was consistent with published guideline. The operation time (357 min vs 307 min; p = 0.002) and hospital stay (12.6d vs 9.5d; p = 0.094) are much longer in the LND.
group, which means the LND can increased the difficulty of surgery and add the hospitalization expense. The complications were not increased in LND group, which were consistent with EORTC 30881 study that increased LND were not associated with more complications\textsuperscript{1}. Besides, the recent ASSURE trial showed there were no differences in preoperative complications between the LND and no LND groups in non-metastatic RCC of high risk group\textsuperscript{11}. Combined with our study, it appears that the safety of LND, even in the operation of patients with RCC and TT, may be acceptable.

Although EORTC 30881 did not show any improvement in progression-free survival in patients receiving LND, most patients in the study were classified as the localized or low grade RCC\textsuperscript{1}. In the high-risk group, the survival benefit of LND were on the debate. Some retrospective analyses suggested that patients with high risk factors may benefit from LND\textsuperscript{2–6}. Blute et al.\textsuperscript{2} and Crispen et al.\textsuperscript{5} found that patients with large tumor size (> 10 cm), high furhman grade, pT3-pT4, coagulative necrosis and sarcomatoid differentiation may benefit from LND. Capitanio et al.\textsuperscript{3,4,6} showed LND in the high-risk population like bulky tumor (> 10 cm), locally advanced or metastatic RCC could improve CSS. However, Feuerstein et al.\textsuperscript{12} and Gershman et al.\textsuperscript{13} observed that LND did not improve either CSM or OS across all stages, as well as in patients with increased risk of LN metastasis.

Patients with RCC and TT may represent a special type of high risk feature, but our Kaplan-Meier curve shows that LND had worse OS compared to no LND groups. We suspected the result may attribute to the high proportion of cN1 in LND group, which may potential affect OS. So we analyzed OS in subgroup of cN0 and cN1 but failed to find any survival benefit of LND either for cN0 or cN1. After that, We analyze the OS adjusting for some risk factors like age, tumor size, surgical approach, tumor thrombosis level and histologic type, trying to find the certain part of population whom can potential benefit from LND but failed. Some of the existing studies are similar to our results. Michele Marchioni et al.\textsuperscript{14} carried out a research in SEER database and found that LND have an adverse protective effect on CSM either in the pT2 or pT3 patients. In the pT3 patients, the 5-year CSM-free survival were worse in LND compared with no LND group (65.1% vs 80.9%, P < 0.001). Michael A. Feuerstein et al.\textsuperscript{15} reviewed data on 258 patients who underwent LND during cytoreductive nephrectomy and found LND had worse OS compared those who did not received LND. Benjamin T. Ristau et al.\textsuperscript{11} analyzed the high-risk patients without metastasis in the ASSURE trial and showed LND was associated with worse DFS (HR 1.27, p = 0.001). Besides, LND were not associated with OS after in subgroup analysis of treatment arm, grade, stage, gender, age, performance status, symptoms at diagnosis, lactate dehydrogenase level, anemia, histology and surgery type (HR 1.14, p = 0.20). Some of researchers were attribute to the selective bias that patients with high-risk features are more likely to choose LND. Others suspected because lymph node metastasis is rare in renal cell carcinoma, LND can be regard as unnecessary aggressive surgical resection. Patients who underwent unnecessary aggressive surgical resection could increase potential morbidity. Similar findings were also found in other malignancies\textsuperscript{16}. Thus due to the controversial result of current study, we need a high-quality randomize trial to further demonstrated the survival benefit of LND in high risk population.
Finally, to identify prognostic factors of RCC with TT whom underwent LND, we examined the associations of some clinicopathologic features. Non-CCRCC and occurrence of major complication were the predictors of worse OS while positive lymph nodes was the only independent prognostic factor presenting worse OS. Derya Tilki et al.\textsuperscript{17} reviewed 1978 patients with RCC and TT and found the number of positive nodes harvested during LND and LN density was strong prognostic indicators of CSS. The similar results were showed by Juan Chipollini et al.\textsuperscript{18}. They conducted a research on patients with metastatic RCC treated by cytoreductive nephrectomy and LND, and found the number of nodes positive was predictive of survival. Boris Gershman et al.\textsuperscript{13} followed up 138 patients with isolated pN1M0 RCC underwent partial or radical nephrectomy and LND at the median of 8.5 year. The 5-yr and 10-yr MFS, CSS, and OS rates were 16% and 15%, 26% and 21%, and 25% and 15%, respectively. So patients with lymph node positive may potentially benefit from LND. However, owing to rarity of lymph node metastasis in RCC even in cN1 patients, it is essential for us to develop a tool that can distinguish the lymph node metastasis before surgery.

This retrospective study has several limitations. Firstly, our research is single-institutional retrospective review, which Inevitably include missing data and confounding variable and selection bias that we could not control. Secondly, LND template was not standardized and was based on surgeon discretion, which might inherently influence the study results. Thirdly, because of short follow-up time and high loss of follow up rate, we can only estimate three-year overall survival in these population. Despite these limitations, our study is significant because we are the only single-institution study to assess the role of LND among patients with RCC and TT.

**Conclusion**

In this study, we confirm that LND in non-metastatic RCC with TT was not associated with a survival benefit, even we adjusted for clinic node status. Category like age, tumor size, surgical approach, tumor thrombosis level and histologic type were not a indication for LND. Lymph node positive was identified as an independent poor prognostic factor. Therefore, LND in RCC with TT should be considered as a staging procedure rather than therapeutic one.

**Abbreviations**

RCC: renal cell carcinoma; TT: tumor thrombosis; LND: lymph node dissection; OS: overall survival; SCr: serum creatinine; Alb: albumin; Hgb: hemoglobin; CCRCC: clear cell renal cell carcinoma; EUA: The European Urology Association; EORTC: European Organization for Research and Treatment of Cancer;

**Declarations**

Ethics approval and consent to participate
The study was approved by the Peking University Third Hospital Medical Science Research Ethics Committee. All of the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China. Because of the retrospective nature of the study, patient consent for inclusion was waived.

**Consent to publish**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

Not applicable.

**Authors’ Contributions**

RX and CX collected and analyzed the data and wrote the manuscript. GW, SZ, HY, XH, XT and LZ made substantial contributions to the design of this work. LM and CL substantially revised the work and manuscript. All authors have read and approved the manuscript.

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**Tables**

*Table 1:* The clinicopathologic features of the entire cohort patients divided by LND and No LND.
| Variable                  | Total (N=128) | LND (N=58;45%) | No LND (N=70;55%) | P value |
|--------------------------|--------------|----------------|-------------------|---------|
| **Gender**               |              |                |                   |         |
| Male                     | 93(72%)      | 45(77%)        | 48(68%)           | 0.320   |
| female                   | 35(28%)      | 13(23%)        | 22(32%)           |         |
| **Age(yr)**              | 58(53~65)    | 56(50~62)      | 60(53~68)         | 0.520   |
| **Symptoms**             |              |                |                   |         |
| Incidental               | 35(27%)      | 16(28%)        | 19(27%)           | 0.906   |
| Local                    | 62(48%)      | 27(46%)        | 35(50%)           |         |
| General                  | 31(25%)      | 15(26%)        | 16(23%)           | 0.391   |
| BMI(kg/m²)               | 24.1(21.6~26.4) | 23.8(20.9~25.9) | 24.4(21.9~26.7) | 0.070   |
| **ASA score**            |              |                |                   |         |
| I                        | 11(8%)       | 5(8%)          | 6(8%)             | 0.718   |
| II                       | 98(77%)      | 46(79%)        | 52(75%)           |         |
| III                      | 19(15%)      | 7(13%)         | 12(17%)           |         |
| Hgb(g/L)                 | 123(107~139) | 121(107~138)   | 125(111~142)      | 0.445   |
| Alb(g/L)                 | 38.8(35.8~43.0) | 39.1(36.7~43.0) | 38.7(34.5~43.0)   | 0.725   |
| SCr(umol/L)              | 94.1(79.0~108.0) | 93.7(78.5~106.5) | 94.4(78.7~110.0) | 0.892   |
| **Tumor size(cm)**       | 8.5(6.2~10.3) | 9.1(6.3~11.9)  | 8.1(5.5~10.0)     |         |
| **Tumor site**           |              |                |                   |         |
| left                     | 42(33%)      | 20(34%)        | 22(31%)           | 0.718   |
| Right                    | 86(67%)      | 38(66%)        | 48(69%)           |         |
| **cN0**                  | 65(50%)      | 21(36%)        | 44(63%)           | 0.004   |
| **cN1**                  | 63(49%)      | 37(64%)        | 26(37%)           |         |
| **TT level**             |              |                |                   |         |
| 0                        | 29(23%)      | 11(19%)        | 18(26%)           | 0.730   |
| I                        | 28(22%)      | 14(24%)        | 14(20%)           |         |
| II                       | 43(33%)      | 22(38%)        | 21(30%)           |         |
| III                      | 19(15%)      | 7(12%)         | 12(17%)           |         |
| IV                       | 9(7%)        | 4(7%)          | 5(7%)             |         |
| **Opened**               | 57(44%)      | 31(53%)        | 26(37%)           | 0.065   |
| laparoscopic             | 71(56%)      | 27(47%)        | 44(63%)           |         |
| Operating time(min)      | 330(238~403) | 357(270~449)   | 307(204~381)      | 0.002   |
| Blood loss(ml)           | 1220(200~1950) | 1382(300~2525) | 1102(200~1500)    | 0.313   |
| **Transfusion**          |              |                |                   |         |
| Yes                      | 61(47%)      | 30(52%)        | 31(44%)           | 0.402   |
| No                       | 67(53%)      | 28(48%)        | 39(56%)           |         |
| **Histologic type**      |              |                |                   |         |
| CCRCC                    | 108(84%)     | 48(83%)        | 60(86%)           | 0.647   |
| No CCRCC                 | 20(16%)      | 10(17%)        | 10(14%)           |         |
| **Grade**                |              |                |                   |         |
| I-II                     | 64(50%)      | 28(48%)        | 36(51%)           | 0.662   |
| III-IV                   | 63(49%)      | 30(52%)        | 33(47%)           |         |
| **pNx**                  | 70(55%)      | -              | 70(55%)           |         |
| **pN0**                  | 44(34%)      | 44(34%)        | -                 |         |
| **pN1**                  | 14(11%)      | 14(11%)        | -                 |         |
| **Perioperative complication** |          |                |                   |         |
|                  | minor | major | Hospital stay(d) |
|------------------|-------|-------|------------------|
|                  | 21(16%) | 13(22%) | 8(11%) | 0.064 |
|                  | 12(9%) | 3(5%) | 9(13%) |
|                  | 10.9(6.0~13.0) | 12.6(7.0~13.3) | 9.5(6.0~12.0) | 0.049 |

* missing one data

Data are reported as median or mean (interquartile range) for continuous variables and as n (%) for categorical variables.

Table 2. Univariable and multivariable Cox regression models predicting OS after patients underwent LND

| variable                        | univariable HR | 95%CL      | P        | multivariable HR | 95%CL      | P        |
|---------------------------------|----------------|------------|----------|------------------|------------|----------|
| Age > 65 yr                     | 0.915          | 0.200~4.190 | 0.909    |                  |            |          |
| BMI> 27kg/m²                    | 0.780          | 0.170~3.590 | 0.749    |                  |            |          |
| Symptom at presentation         | 1.092          | 0.630~1.880 | 0.751    |                  |            |          |
| Hgb<120 g/L                     | 0.280          | 0.075~1.051 | 0.059    | 0.424            | 0.095~1.894 | 0.261    |
| diameter> 8cm                   | 1.848          | 0.542~6.298 | 0.326    |                  |            |          |
| TT level >3                     | 2.630          | 0.803~8.612 | 0.110    | 1.733            | 0.323~9.281 | 0.521    |
| cN1                             | 1.162          | 0.349~3.875 | 0.806    |                  |            |          |
| Open surgery                    | 1.261          | 0.404~3.940 | 0.689    |                  |            |          |
| Non-CCRCC                       | 4.970          | 1.566~15.766 | 0.006   | 0.293            | 0.049~1.748 | 0.178    |
| pN+                             | 2.650          | 0.786~8.935 | 0.116    | 5.260            | 1.279~21.662 | 0.021    |
| Nuclear grade>2                 | 0.329          | 0.760~2.271 | 0.329    |                  |            |          |
| Major complication              | 3.333          | 1.049~10.586 | **0.041** | 1.237            | 0.267~5.736 | 0.786    |

**Supplemental Legends**

**Supplement Fig. 1.** Kaplan-meier curves of overall survival adjusting for age, tumor size, surgical approach, tumor thrombosis level and histologic type between two groups.

**Figures**
Figure 1

Kaplan-meier curves of overall survival between LND and without LND groups.

Figure 2

Kaplan-meier curves of overall survival between LND and without LND groups in subgroup cN0 and cN1.

Supplementary Files

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