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# The critical role of lymph node dissection in selecting high-risk nonmetastatic renal cancer candidates for adjuvant therapy after nephrectomy

Paolo Capogrosso, M.D.,[a,b,*], Alessandro Larcher, M.D.,[a,b], Alessandro Nini, M.D.,[a,b], Fabio Muttin, M.D.,[a,b], Francesco Cianflone, M.D.,[a,b], Francesco Ripa, M.D.,[a,b], Alberto Briganti, M.D., PhD[a,b], Andrea Necchi[c], Francesco Montorsi, M.D.,[a,b], Andrea Salonia, M.D., PhD[a,b], Roberto Bertini, M.D.,[a,b], Umberto Capitanio, M.D.,[a,b]

[a] *Department of Urology, IRCCS San Raffaele Hospital, Milan, Italy*
[b] *Division of Experimental Oncology/Unit of Urology; URI; IRCCS San Raffaele Hospital, Milan, Italy*
[c] *Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

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**Abstract**

**Background:** The role of lymph node dissection (LND) during nephrectomy for renal cell carcinoma (RCC) is controversial. We looked at the clinical usefulness of performing LND to stratify the risk of patients with RCC and select candidates for systemic treatment after nephrectomy.

**Materials and Methods:** We identified 730 patients with nonmetastatic RCC treated with nephrectomy and LND at a single center. We compared the accuracy and clinical usefulness of a base model including factors defining high-risk patients according to the S-TRAC trial [(pT3 and Grade≥2 and performance status score ≥1) or pT4] relative to the base model plus pN stage for the prediction of early progression after surgery.

**Results:** LN invasion resulted the most informative predictor of early progression (odds ratio: 6.39; 95% confidence interval [CI]: 3.26, 12.54; $P < 0.0001$). The accuracy was higher ($P = 0.008$) for the model implemented with pN (area under the curve: 0.76; 95% CI: 0.71, 0.80) as compared to the base model (area under the curve: 0.72; 95% CI: 0.68, 0.76). Performing LND to select patients for postoperative systemic treatment, resulted in a slightly higher net benefit as compared to a strategy defining risk on the base of factors other than pN. Patients with high-risk disease showed a large difference in the risk of progression according to pN-status (1-year risk: 58% [95% CI: 45, 72] for pN1; 31% [95% CI: 25, 38] for pN0; $P < 0.001$).

**Conclusions:** Performing LND at the time of nephrectomy improves risk stratification, resulting into a small but nonnegligible clinical advantage for selecting high-risk patients for further treatment after surgery. Further trials should investigate whether high-risk pN1 patients would benefit from a different postoperative management. 

*Keywords:* Renal cancer; Lymph node dissection; Lymph node metastasis; Adjuvant therapy; Staging

## 1. Introduction

The role of lymph node dissection (LND) in the management of renal cell carcinoma (RCC) has been largely investigated and is still controversial [1,2].

Currently available evidence does not support a survival advantage for RCC patients treated with nephrectomy and LND. Indeed, a randomized trial and several retrospective studies have failed to prove higher disease-free and overall survival rates associated with LND [1,3–11]. However, the prognostic value of positive LNs is undeniable, with a number of previous studies demonstrating an increased cancer-specific and overall mortality for patients found with pN1 disease at the time of nephrectomy [12–16]. As such, the staging role of LND may be crucial for the management of patients with RCC: patients with nodal disease could be selected for a more intensive surveillance protocol; more

*Corresponding author. Tel.: +39 02 26435506; fax: +39 02 26432969.
*E-mail address:* paolo.capogrosso@gmail.com (P. Capogrosso).

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importantly, they may be the optimal candidates for adjuvant systemic treatments after surgery.

The US Food and Drug Administration has recently approved sunitinib for the adjuvant treatment of patients at high risk of recurrent RCC following nephrectomy. The approval was based on the results of the S-TRAC trial testing the effect of adjuvant sunitinib in patients with high-risk nonmetastatic clear cell cancer [17]. Patients treated with sunitinib had a significantly longer median disease-free survival as compared to placebo. When stratifying the cohort according to disease characteristics, patients at higher risk for recurrence, defined on the base of disease stage, Fuhrman grade and on the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), harbored a 26% lower risk of disease progression associated with adjuvant treatment after surgery. Translating these results into clinical practice, we could argue that those patients are the ones who may greatly benefit from systemic therapy after nephrectomy, although other randomized trials did not confirm a survival advantage with adjuvant treatment [18,19]. Interestingly, patients with pN1 disease were classified as high risk regardless of all other risk factors [17]; as such, performing LND at the time of surgery could allow to detect patients with LN metastases who may otherwise not be selected for adjuvant treatments on the solely base of T stage, disease grade and PS. In this case LN staging would greatly influence clinical practice; however, in the S-TRAC trial a LND was not routinely performed and not standardized, thus leaving the question unanswered.

To evaluate the clinical advantage of performing LND to identify nonmetastatic high-risk patients who may benefit from systemic treatment after surgery, we tested if the addition of nodal staging in a model accounting for factors that were used to define high-risk disease in the S-TRAC trial would result in a higher accuracy for predicting early disease progression after surgery, in a cohort of patients treated with nephrectomy and LND at a single academic center.

## 2. Methods

After institution review board approval, we collected data from a cohort of 861 patients with nonmetastatic RCC who were treated with nephrectomy and LND from 1987 to 2016 at a single academic center.

All patients had histology-proven clear cell disease and were free of metastases at preoperative staging. Clinical and pathologic data, including the ECOG-PS score, pathologic stage (TNM classification) and Fuhrman grade were collected for each patient. Histological tumor necrosis was defined as the presence of any microscopic coagulative tumor necrosis. A sarcomatoid component was defined as a spindle cell malignancy with histological appearance of a sarcoma. No patient received either neoadjuvant or adjuvant therapy.

The LND procedure was performed based on the clinical judgment of each treating physician, according to preoperative patient and cancer characteristics and intraoperative assessment by direct palpation. The procedure consisted of excising the fibro-fatty tissue along anatomically defined areas (hilar, interaortocaval, paraaortic, pre-, and retrocaval) as previously described [20].

The follow-up was based on clinical evaluation and chest-abdomen CT scans performed at 3 to 6 months and at 12 months after surgery over the first year, and annually thereafter. Additional imaging assessments were performed if the patient's symptoms raised clinical suspicion of relapse.

Disease progression after surgery was defined as the evidence of retroperitoneal or distant recurrence demonstrable on imaging at least 1 month after treatment; patients who did not experience relapse were censored at the date at the last follow-up.

Patients missing clinical or pathologic data (131 [15.8%]) relevant to the study outcome were excluded from the analysis.

### 2.1. Statistical analysis

The aim of the study was to test whether adding pN stage to a model including factors identifying patients at high risk of progression according to the criteria defined within the S-TRAC randomized clinical trial ([T3 disease and Fuhrman grade ≥2 and performance status score ≥1] or T4 disease) [17] would improve disease-risk stratification. Therefore, we compared a model including pT stage, disease grade and ECOG-PS with a same model implemented with pN stage, in terms of the accuracy for predicting early disease progression after surgery, defined as relapse within 12 (±3) months post-treatment. We selected this outcome as a clinically reasonable indicator of patients who may deserve adjuvant treatment after surgery. Moreover, given that performing a LND in all cases would not represent the everyday clinical practice, we tested the accuracy of a third model mirroring a risk-based strategy to select patients for LND: we used a reliable and externally validated risk score [21,22] identifying patients with 2 or more risk factors for LN invasion (e.g., tumor size ≥10 cm; Fuhrman grade ≥3; pT ≥3; tumor necrosis; sarcomatoid component) as deserving LND. Those patients were included in the model considering the actual pN stage (e.g., N0 or N1), while those with less than 2 risk factors for positive LNs were considered as pNx/pN0 regardless of their pN status. Logistic regression analysis was used considering early disease progression as a binary outcome: patients were considered to have progressed if disease was evident at follow-up assessments within 12 months after surgery; likewise, patients were considered free from early progression if they had a last negative assessment at 12 months or at further follow-up, or if they relapsed after 12 months from surgery. Patients with a last negative follow-up before 9 months postsurgery ($n = 20$) and those with a recurrence after 15 months but without a previous negative assessment within the 12 (±3) months window ($n = 6$) were excluded from the early progression outcome analysis. As a sensitivity analysis, we included all patients with follow-up data, using

the assessment closest to 1 year; moreover, we checked for the potential influence of year of surgery and of the number of LN removed by including these factors in the multivariable model.

The accuracy of the predictive models was assessed by area under the curve (AUC). We used decision curve analysis to evaluate the clinical consequences of model predictions by comparing net benefit, based on true positives and false positives, at various threshold probabilities of progression [23]. Because it is unlikely that a physician would submit a patient to adjuvant treatment if the probability of early progression was <5% or would avoid additional treatment for patients with a probability higher than 40%, we examined the range of threshold probabilities between 5% and 40%. The accuracy of the models and decision curves was corrected for overfitting using 10-fold cross-validation.

Finally, we used Kaplan-Meier analysis to estimate the risk of disease progression and overall mortality of high-risk patients with either pN0 or pN1 disease. Statistical analyses were conducted using Stata 15.0 (StataCorp, College Station, TX), with a 2-sided significance level set at $P < 0.05$.

## 3. Results

Table 1 reports the clinical and pathological characteristics of the entire cohort ($n = 730$). The majority of patients was treated with radical nephrectomy (95%). Lymph node metastases were found in 7% of cases; according to the S-TRAC trial definition, 257 (35%) patients would be categorized as high-risk; of them, 21% had pN1 disease. A total of 341 (47%) patients would deserve a LND according to a risk-based approach [21,22]. In our cohort, this approach showed a good accuracy (AUC: 0.70; 95% confidence interval [CI]: 0.64−0.75) with a sensitivity of 83.3% a specificity of 56.2% and a positive and negative predictive value of 13.2% and 97.7%, respectively.

At logistic regression analysis, pN stage was significantly associated with early disease progression when included in a model accounting for the other factors defining patients at high-risk (Table 2) both when considering pN stage as all patients would receive a LND (e.g., N0 vs. N1; odds ratio: 6.39; 95% CI: 3.26, 12.54; $P < 0.0001$) and when considering the pN status only for patients who would undergo a LND according to a risk-based approach (e.g., NX/0 vs. N1; odds ratio: 5.63; 95% CI: 2.72, 11.68); $P < 0.0001$). The predictive models implemented with pN stage showed a significantly higher accuracy ($P = 0.008$), with an AUC of 0.76 (95% CI: 0.71, 0.80) and 0.75 (95% CI: 0.71, 0.79) for model 2 and 3, respectively, as compared to 0.72 (95% CI: 0.68, 0.76) for the base model, after cross-validation.

Decision curve analysis shows the clinical benefit of using each model to select patients at high-risk of early progression who may benefit from systemic treatment postsurgery (Fig. 1). The models including pN stage showed a slightly higher net benefit, which looks prominent for threshold probabilities higher than 30%: if we accept a threshold risk of progression ranging from 10% to 35%, a strategy accounting for pN status would allow to detect from 0.3% to 1.6% more patients at high risk eventually deserving adjuvant treatment, without any unnecessary treatment. Comparable results were observed when considering a strategy submitting to LND only patients at higher risk of LN invasion (Fig. 1).

Table 1
Clinical and pathological characteristics of the entire cohort ($n = 730$) of nonmetastatic RCC patients.

| | |
|---|---|
| Age [yrs] Median(IQR) | 60 (51, 69) |
| Number of LN removed Median(IQR) | 6 (3,10) |
| ECOG-PS score | |
| 0 | 228 (31%) |
| 1 | 395 (54%) |
| 2 | 101 (14%) |
| 3 | 6 (1%) |
| Clinical node stage | |
| 0 | 588 (81%) |
| 1 | 142 (19%) |
| Fuhrman grade | |
| G1 | 86 (12%) |
| G2 | 354 (48%) |
| G3 | 225 (31%) |
| G4 | 65 (9%) |
| pN stage | |
| N0 | 676 (93%) |
| N1 | 54 (7%) |
| pT stage | |
| T1 | 290 (40%) |
| T2 | 118 (16%) |
| T3 | 305 (42%) |
| T4 | 17 (2%) |
| Histological tumor necrosis | 358 (49%) |
| Histological sarcomatoid component | 29 (4.0%) |
| Number of risk factors for LN invasion[a] | |
| 0 | 228 (31%) |
| 1 | 161 (22%) |
| 2 | 130 (18%) |
| 3 | 121 (17%) |
| 4 | 81 (11%) |
| 5 | 9 (1.2%) |
| Type of treatment | |
| RN | 690 (95%) |
| PN | 40 (5%) |
| Perioperative complications | 156 (21%) |
| Clavien-Dindo | |
| 1 | 19 (2.6%) |
| 2 | 109 (15%) |
| 3 | 23 (3.2%) |
| 4 | 3 (0.4%) |
| 5 | 2 (0.3%) |
| High-risk patients[b] | 257 (35%) |
| pN0 | 203 (79%) |
| pN1 | 54 (21%) |
| Follow-up [mos] Median(IQR) | 49 (13, 125) |

ECOG-PS = Eastern Cooperative Oncology Group-Performance Status; LN = lymph nodes.

[a] Including: tumor size ≥10 cm; Fuhrman grade ≥3; pT ≥3; tumor necrosis; sarcomatoid component [21,22].

[b] Defined as pT3 and Fuhrman grade ≥2 and ECOG-PS≥1 or pT4 or pN1, as described in the S-TRAC [17].

Table 2
Logistic regression model predicting disease progression within 12 months; model 1 accounting for factors defining high-risk nonmetastatic patients regardless of pN stage; model 2 accounting for factors defining high risk patients including pN stage and assuming that all patients would receive lymph node dissection; model 3 including pN stage only for patients at high risk of positive nodes who would undergo lymph node dissection.

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | 95% CI | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| pT stage pT1-2 vs. pT ≥3 | 5.56 | 3.61, 8.56 | <0.0001 | 4.95 | 3.18, 7.71 | <0.0001 | 4.70 | 3.02, 7.31 | <0.0001 |
| ECOG-PS score 0 vs. ≥1 | 1.34 | 0.87, 2.08 | 0.2 | 1.28 | 0.81, 2.02 | 0.3 | 1.29 | 0.82, 2.02 | 0.3 |
| Fuhrman grade G1 vs. G ≥2 | 5.55 | 1.31, 23.47 | 0.02 | 5.09 | 1.20, 21.59 | 0.02 | 5.13 | 1.21, 21.71 | 0.02 |
| pN stage 0/x vs. 1 | – | – | – | 6.39 | 3.26, 12.54 | <0.0001 | 5.63 | 2.72, 11.68 | <0.0001 |

ECOG-PS = Eastern Cooperative Oncology Group-Performance Status.

Moreover, high-risk nonmetastatic patients with pN1 disease showed significantly worse outcomes (Fig. 2), with a risk of disease progression at 1 year post-treatment of 58% (95% CI: 45, 72) as compared to 31% (95% CI: 25, 38) for high-risk patients with negative LNs ($P = 0.0001$; Table 3). Likewise, the estimated 1-year overall mortality risk was 33% (95% CI: 22, 48) and 13% (95% CI: 9, 18) for node-positive and node-negative nonmetastatic high-risk patients ($P < 0.0001$).

Same results were found at sensitivity analyses including all patients with at least 1 follow-up assessment but who were not evaluated within the eligible time frame; moreover, the number of LNs removed and the year of surgery were not independently associated with early progression when included in the multivariable logistic model (all $P > 0.4$; Supplementary Table 1).

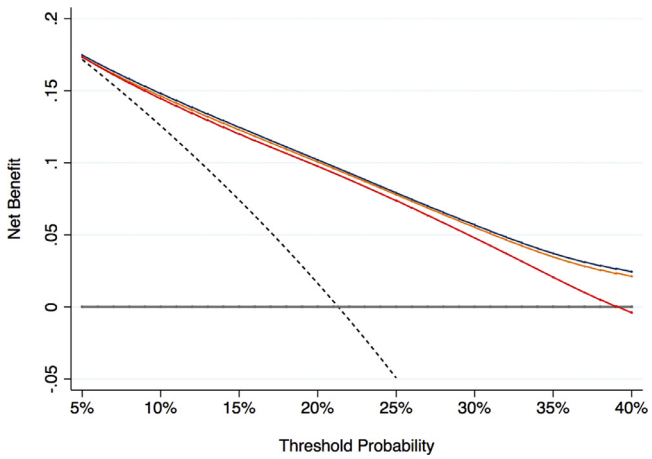


Fig. 1. Decision curve analysis assessing net benefit for prediction of disease progression within 12 months after surgery in high-risk nonmetastatic patients. The red line represents the net benefit of using a risk stratification model without lymph node status. The blue line represents the net benefit of using a risk stratification considering lymph node status and assuming that all patients would receive a lymph node dissection. The orange line represents the net benefit of using a risk stratification considering lymph node status only for patients who would receive a lymph node dissection according to the risk of lymph node invasion. The dashed line represents the "treat-all" strategy. The gray line represents the "treat–none" strategy. (Color version of figure is available online.)

## 4. Discussion

We looked at the clinical advantage of performing LND to better stratify the risk of postoperative progression of RCC and to identify patients at high-risk who may deserve additional treatments after surgery. Our interest was fueled by the recent findings of the S-TRAC trial suggesting that patients considered at high-risk of progression may benefit more from adjuvant systemic treatment [17]. Those patients were defined by local T-stage, disease grade and PS or by pN stage if LND was performed. Our results showed that the information on LN status allows for higher accuracy in the prediction of early progression after surgery. However, performing LND in each case to include pN stage in risk-stratification would allow to detect less than 2% more patients potentially deserving additional treatment, as compared to a strategy assessing patients-risk according to risk factors other than LN status. Similar results would be obtained when performing LND only in patients at higher risk of positive LNs according to a risk-stratification tool [21,22]. In light of these findings, the clinical advantage of performing a time-consuming and challenging procedure like retroperitoneal LND might be considered questionable. On the other hand, LND has shown low perioperative morbidity [5,24,25]: in a recently matched-cohort analysis, nephrectomy along with LND was associated with a comparable risk of Clavien grade ≥3 complications as compared to nephrectomy alone [24]. As such, even a slightly higher clinical benefit for detecting high-risk patients could justify performing LND for staging purpose, at least in those at higher risk for LN invasion.

Previous studies confirmed the independent prognostic significance of LN status in RCC patients [1,7,12–16]: in a large multicenter cohort of 3,507 patients, Capitanio et al. showed that pN1 disease was associated with a 3.2 times higher risk of cancer-specific mortality after adjusting for T

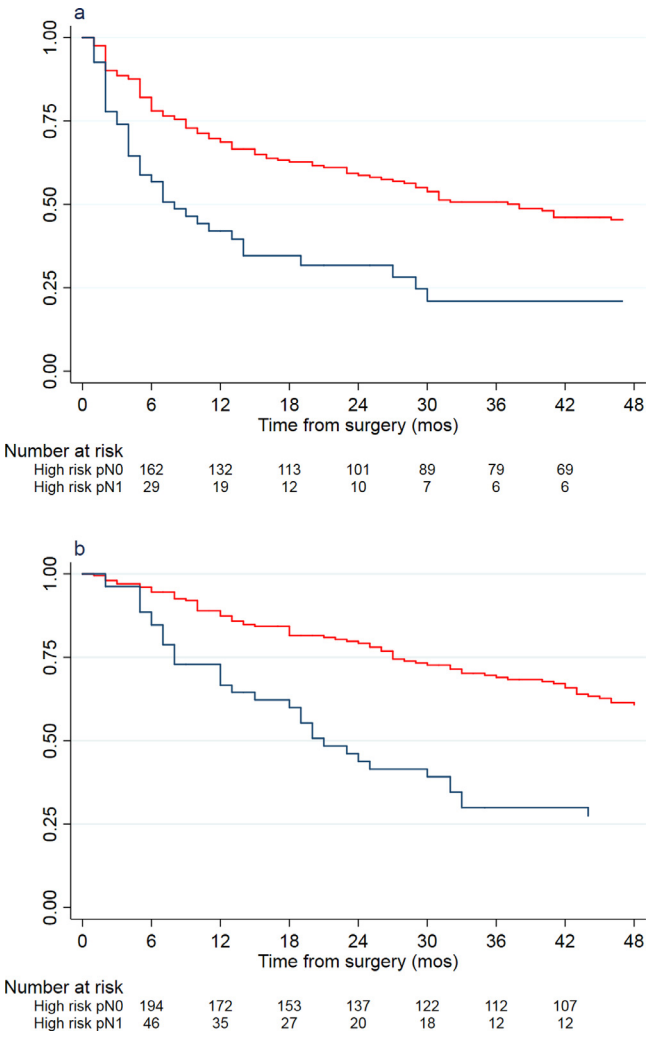


Fig. 2. Estimated probability of disease free survival (a) and overall survival (b); the red line represents high-risk nonmetastatic patients with pN0 disease; the blue line represents high-risk nonmetastatic patients with pN1 disease. The log-rank test indicate significant difference between groups ($P < 0.0001$). (Color version of figure is available online.)

stage and Fuhrman grade [12]; similarly, in a population-based cohort study, the percentage of positive nodes emerged as an independent predictor of post-treatment mortality when included in a model accounting for several clinical and pathological factors [13].

Patients with positive LNs have shown worse oncological outcomes in several series [1,7,26,27]. Gershman et al. recently analyzed the long-term survival of 138 patients with isolated LN involvement after nephrectomy [26]: the 5-year CSS and OS rate were only 26% and 25%, with a median time to development of metastases of 4.2 months. Similar data were reported in other series, with a postoperative 5-year CSS rate ranging from 22% to 39% for pN1 patients [1]. In line with these findings, we observed that even among patients with high-risk disease, those with LNs metastases showed about 2-fold higher probability of progression and overall mortality as compared with same risk node negative patients. These results, suggest that LND may be of particular value for high-risk nonmetastatic patients, by further stratifying disease risk and inform postoperative management. Indeed, we could argue that postoperative adjuvant treatment may lead to a greater survival advantage in high-risk patients with pN1 disease relative to pN0; at the same time, given the large difference observed in the risk of progression, patients with LN metastases may benefit from different therapeutic protocols as compared to high risk node negative patients. These findings call for further clinical trials, including large cohorts of patients properly staged for LN disease at the time of nephrectomy, aimed to better define the best candidates for additional treatments after surgery.

Our study has some limitations. As a retrospective analysis there is a risk of selection bias, which might have influenced the results. Indeed, by including only patients treated with LND, we could have selected those at higher risk of LN metastasis and therefore submitted to nephrectomy along with LND; indeed, the majority of patients received a radical nephrectomy, even for low stage disease. However, about 40% of patients included were staged as T1, thus suggesting that even lower risk patients received a LND. Moreover, we applied a validated risk score used to define patients at high risk of positive LNs who would deserve a LND: according to this score 53% of patients would not be submitted to LND. As such, our cohort could be considered as representative of the majority of patients commonly submitted to surgical treatment for RCC in clinical practice.

The number of LNs removed was not equal for every patient. Some of them could have received a suboptimal staging thus potentially altering the results. However, the number

Table 3
Estimated oncological outcomes of high risk nonmetastatic RCC patients treated with surgery, according to Kaplan-Meier analysis.

| Risk of disease progression (95% CI) | High risk pN0 | High risk pN1 | *P* value |
|---|---|---|---|
| 6 mos | 22% (17, 28) | 43% (31, 58) | 0.0001 |
| 12 mos | 31% (25, 38) | 58% (45, 72) | |
| 24 mos | 41% (35, 49) | 68% (55, 81) | |
| 60 mos | 59% (52, 67) | 79% (64,90) | |
| Risk of overall mortality (95% CI) | | | |
| 6 mos | 5% (3, 10) | 15% (8, 28) | <0.0001 |
| 12 mos | 13% (9, 18) | 33% (22, 48) | |
| 24 mos | 21% (16, 27) | 56% (43, 71) | |
| 60 mos | 44% (37, 52) | 80%(67, 90) | |

of LNs removed was not significantly associated with the risk of early progression when included in the multivariable model.

Finally, considering the large time interval covered by our study, patients could have been treated differently in more recent years, eventually resulting in better outcomes. To control for this bias we checked for the influence of the year of surgery on the risk of disease progression without observing a significant correlation.

## 5. Conclusions

Our results suggest that performing LND at the time of nephrectomy for RCC would result in a small clinical advantage for selecting candidates to further treatment after surgery. However, LND allows to better define the risk of progression even among high-risk cases. Whether patients with high-risk nonmetastatic RCC may benefit from a different postoperative management according to LN status needs to be investigated in further clinical trials.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.01.009.

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