Current Problems in Cancer 45 (2021) 100619

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

# Is lymph node dissection necessary for staging while undergoing nephrectomy in patients with renal cell carcinoma?

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A B S T R A C T

*Objective:* The essential treatment for patients with renal cell carcinoma is nephrectomy. As no lymph node dissection (LND) could be performed in the majority of these patients, healthy staging could not be carried out. In this study, we investigated the impact of LND during nephrectomy on patient survival. *Methods:* A total of 181 patients—58 (32%) were female and 123 (68%) were male—were included in the study. Median follow-up period was 48 months. The patients were separated into 4 groups according to their stage during diagnosis; group 1 (T1–3N0M0), group 2 (T1–3NXM0), group 3 (T1–3N1M0), and group 4 (T1–4N0/XM1). The disease-free survival of nonmetastatic patients and the overall survival of all groups were calculated. *Results:* Mean age was 58.4 ± 12.0 years. Median survival for Group 1 could not be reached. Median survival was 89 months in Group 2, 50 months in Group 3, and 39 months in Group 4 ($P < 0.001$). There was no statistically significant difference between the N1 and M1 groups ($P = 0.297$). For the NX patient group without LND, median survival was 89 months, which is worse than the N0 group and better than the N1 group ($P = 0.002$). *Conclusions:* Our study presumes that the patients without LND are not staged sufficiently, NX patients have worse survival rates when compared with N0 patients, node-

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https://doi.org/10.1016/j.currproblcancer.2020.100619

positive patients have poor survival rates as do the metastatic patients, and it should be defined as TNM stage4.



ARTICLE INFO

*Keywords:* AJCC staging system; Lymph node dissection; Lymph node metastasis, Nephrectomy; Renal cell carcinoma

## Introduction

Although lymph node dissection is the most accurate and most reliable therapeutic approach in various operable urological cancers when added to primary tumor surgery,[1,2] the majority of urologists do not believe it benefits cancer control in renal cell carcinoma (RCC) cases.[3,4] In current practice, lymph node dissection (LND) is applied if there is suspected clinical LN metastasis. Therefore, the proportion of patients undergoing LND represents <5% of all RCC patients.[5] On the other hand, it is essential to implement a staging system that accurately reflects RCC progression or death risk.[6]

Some data in a few studies showed that LND might contribute to the survival of certain select patient groups.[7,8] For example, patients with local advanced (T3/T4) or unfavorable clinical and pathological features (high Fuhrman grade, large tumors, the presence of sarcomatoid features, coagulative tumor necrosis, and oligometastatic disease) would benefit from LND.[9,10] Because of these suspicious situations, the guidelines suggest that LND should be performed if there are some risk factors (cNod positivity or palpable/visible adenopathy at the time of surgery) in patients with RCC.[11] In other words, the subjective evaluation of the surgeon during the operation based on the imaging technique decide whether there is a LND. Unfortunately, the available technology is incapable of accurately identifying small LN metastases. It is not possible to view a normal-sized LN with micro metastases that will benefit from LND with current technology.[12,13] Therefore, the absence of suspicion of LN metastasis from current imaging techniques should not convince the surgeon not to perform LND.[13]

Additionally, a recently published large retrospective study shows that the prognosis of node-positive patients is almost as bad as metastatic patients,[14] and the surgeon's awareness of the patient's LN status is important for their treatments and follow-up. Because of limited data in this area, this is not clearly understood.

In the present study, we sought to define the effect of LN status on survival in operable RCC cases.

## Materials and methods

In this cross-sectional, retrospective study, archive records between January 2011 and July 2018 of all RCC patients who were treated in 4 different centers in Turkey were used. Patients who were not in follow-up, whose pathology report could not be obtained, who could not undergo a nephrectomy, and who with pathological (p) T4 (nonmetastatic patient) were not included. Patients with intial nephrectomy, whose pathology reports could be accessed, who had pT1/2/3 or pN0/X/1 with or without metastasis were included.

We used the 2017 AJCC staging system (8th Edition) for pathological TNM staging (13). We separated the patients into four groups according to their stages during diagnosis: Group 1 (T1–3N0M0), Group 2 (T1–3NXM0), Group 3 (T1–3N1M0), and Group 4 (T1–4N0/XM1). In addition to these, pathological nodal parameters included nodal involvement and extranodal extension. The Fuhrman nuclear grading system was used for grading in pathological staging. The char-

acteristics affecting the prognosis—such as the presence of a sarcomatoid component and the presence of fat invasion—were recorded. Hematuria and flank pain symptoms were classified as local; respiratory, gastrointestinal, fatigue, night sweats, fever, and weight loss were classified as systemic symptoms. Recurrence type (local or distant) was recorded. New mass development at the postoperative nephrectomy bed or retroperitoneum was described as local recurrence.

Data from 453 patients were examined. One hundred sixty-seven patients were lost to follow-up. In total, 286 patients with RCC met the conditions for inclusion and were evaluated. We excluded 105 patients who did not undergo nephrectomy and patients with pT4/Nany/M0 disease. A total of 181 patients were included in the study for statistical analysis.

### *Statistical analysis*

All statistical analyses were performed using IBM SPSS ver. 24 (SPSS Inc., Chicago, IL). Normality tests were carried out using the Kolmogorov–Smirnov test. The Kruskal-Wallis test was used to compare the permanent variables between groups, and a Chi-square test was applied for categorical variables. The Kaplan-Meier method was used to calculate overall survival (OS) and disease-free survival (DFS) data, and differences between groups were assessed by the log-rank test. In order to determine the factors' effect on mortality, the Cox proportional hazard analysis method was used, and univariant and multivariant Cox regression analyses were performed. Statistical significance was defined as $P < 0.05$.

## Results

### *Patient characteristics*

Demographic data from 4 subgroups are shown in Table 1. The mean age of Group 1 was 56.5 ± 13.2 years, and the highest mean age was in Group 4 as 60.5 ± 12.1 years. Ages were statistically similar in all groups ($P = 0.739$). The size of the tumor detected after nephrectomy was significantly lower in the T1–3NX group with no LN dissection when compared with the other subgroups ($P < 0.001$). This indicates that in patients with small primary tumor sizes, not getting a LN dissection may have been good clinical practice. One hundred twenty-two patients in all groups had no local symptoms; 59 patients presented with local symptoms ($P = 0.878$). The rate of detecting systemic symptoms at diagnosis was similar in all groups ($P = 0.214$). One of the patients included in the study had a performance status of 2, and all other patients were found as 0-1. There was no significant difference between the subgroups ($P = 0.078$). T1–3N1M0, T1–4N0/XM1, and T1–3N0M0 had partial nephrectomy at rates of 95%, 95%, and 84.6%, respectively.

### *OS*

Fig. 1 shows the Kaplan-Meier estimates for OS for all patient groups. Median follow-up was 48 months. No median survival was reached in the T1–3N0M0 group. In patients with T1–3NXM0, T1–3N1M0, and T1–4N0/XM1, median survival values were 89 months (67- 111 months, 95% confidence interval [CI]), 50 months (25.3- 74.7 months, 95% CI), and 39 months (2.3-75.7 months, 95 % CI) ($P < 0.001$), respectively. The 3-year OS rates were 86.5%, 81.5%, 61.1%, and 44.4% in the T1–3N0, T1–3NX, T1–3N1, and T1–4N0/XM1 patients, respectively.

Metastatic patients had the shortest survival period of 39 months, and median survival in the node-positive patient group was determined to be 50 months. There was no statistically significant difference between the 2 groups ($P = 0.297$). Median survival in the (NX) patient group without LN dissection was 89 months, which is worse than the N0 group and better than the

**Table 1**
Demographic features and tumor characteristics of the patients stratified by subgroups.

| | T1-3N0M0 (Group1) | T1-3NXM0 (Group2) | T1-3N1M0 (Group3) | T1-4N0-XM1 (Group4) | *P* value |
|---|---|---|---|---|---|
| Gender | | | | | |
| Female | 4/26 (%15.4) | 45/115 (%39.1) | 6/20 (%30) | 3/20 (%15) | 0.034 |
| Male | 22/26 (%84.6) | 70/115 (%60.9) | 14/20 (%70) | 17/20 (%85) | |
| Age (mean ± sd) | 56.5 ± 13.2 | 58.5 ± 11.9 | 58.1 ± 12.1 | 60.5 ± 12.1 | 0.739 |
| Tumor size (mean ± sd) | 8.9 ± 3.9 | 6.1 ± 3.2 | 9.5 ± 4.1 | 10.4 ± 3.8 | *P*<0.001 |
| Local symptom | | | | | |
| Present | 8/26 (%30.8) | 36/115 (%31.3) | 7/20 (%35) | 8/20 (%40) | *P*= 0.878 |
| Absent | 18/26 (%69.2) | 79/115 (%68.7) | 13/20 (%65) | 12/20 (%60) | |
| Systemic symptom | | | | | |
| Present | 18/26 (%69.2) | 62/115 (%53.9) | 15/20 (%75) | 12/20 (%60) | *P*= 0.214 |
| Absent | 8/26 (%30.8) | 53/115 (%46.1) | 5/20 (%25) | 8/20 (%40) | |
| ECOG-PS | | | | | |
| 0 | 13/26 (%50) | 51/115 (%44.3) | 8/20 (%40) | 5/20 (%25) | *P*=0.078 |
| 1 | 13/26 (%50) | 64/115 (%55.7) | 11/20 (%55) | 15/20 (%75) | |
| 2 | 0/26 (%0) | 0/115 (%0) | 1/20 (%5) | 0/20 (%0) | |
| FUHRMAN Grade | | | | | |
| 1 | 1/26 (%3.8) | 5/115 (%4.3) | 0/20 (%0) | 0/20 (%0) | *P*=0.372 |
| 2 | 11/26 (%42.3) | 49/115 (%42.6) | 5/20 (%25) | 4/20 (%20) | |
| 3 | 9/26 (%34.6) | 46/115 (%40) | 12/20 (%60) | 13/20 (%65) | |
| 4 | 5/26 (%19.2) | 15/115 (%13) | 3/20 (%15) | 3/20 (%15) | |
| Type of surgery | | | | | |
| radical | 4/26 (%15.4) | 62/115 (%53.9) | **19/20( %95)** | **19/20 (%95)** | *P*<0.001 |
| partial | 22/26 (%84.6) | 53/115 (%46.1) | **1/20 (%5)** | **1/20 (%95)** | |
| Tumor localization | | | | | |
| Right | 14/26 (%53.8) | 59/115 (%51.3) | 10/20 (%50) | 10/20 (%50) | *P*= 0.993 |
| Left | 12/26 (%46.2) | 56/115 (%48.7) | 10/20 (%50) | 10/20 (%50) | |
| Histology | | | | | |
| Clear cell | 23/26 (%88.5) | 106/115 (%92.2) | 11/20 (%55) | 16/20 (%80) | *P*< 0.001 |
| Non-clear cell | 3/26 (%11.5) | 9/115 (%7.8) | 9/20 (%45) | 4/20 (%20) | |
| Sarcomatoid component | | | | | |
| Present | 0/26 (%0) | 10/115 (%8.7) | 5/20 (%25) | 7/20 (%35) | *P*<0.001 |
| Absent | 26/26 (%100) | 105/115 (%91.3) | 15/20 (%75) | 13/20 (%65) | |

ECOG-PS, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS).

N1 group ($P=0.002$). In light of these data, it is revealed that an NX patient group is a heterogeneous group of patients that includes N0 and N1 patients and the LND can be used to make a more accurate risk classification of these patients.

*DFS*

Fig. 2 shows the Kaplan-Meier estimates for DFS by the nonmetastatic patient group. The non-DFS of 161 patients in the T1–3N0M0, T1–3NXM0, and T1–3N1M0 patient groups—who were not metastatic during diagnosis—was evaluated. Disease-free median survival times were 73 months (64-82 months, 95% CI), 78 months (67.2-88.8 months, 95% CI) and 28 months (11.3-44.8 months, 95% CI) in the T1–3N0M0, T1–3NXM0, and T1–3N1M0 patient groups, respectively ($P=0.017$). The 3-year DFS scores were 63.9%, 66.4%, and 31.3% in the T1–3N0M0, T1–3NXM0, and T1–3N1M0 patient groups, respectively. The DFS in the N1 patient group was significantly low ($P=0.017$), and no difference was determined between the N0 and NX groups ($P=0.955$).

*Cox regression analysis for OS*

Univariate Cox regression analysis for the evaluation of factors affecting OS is shown in Table 2. According to this, the presence of systemic symptoms at the time of diagnosis was

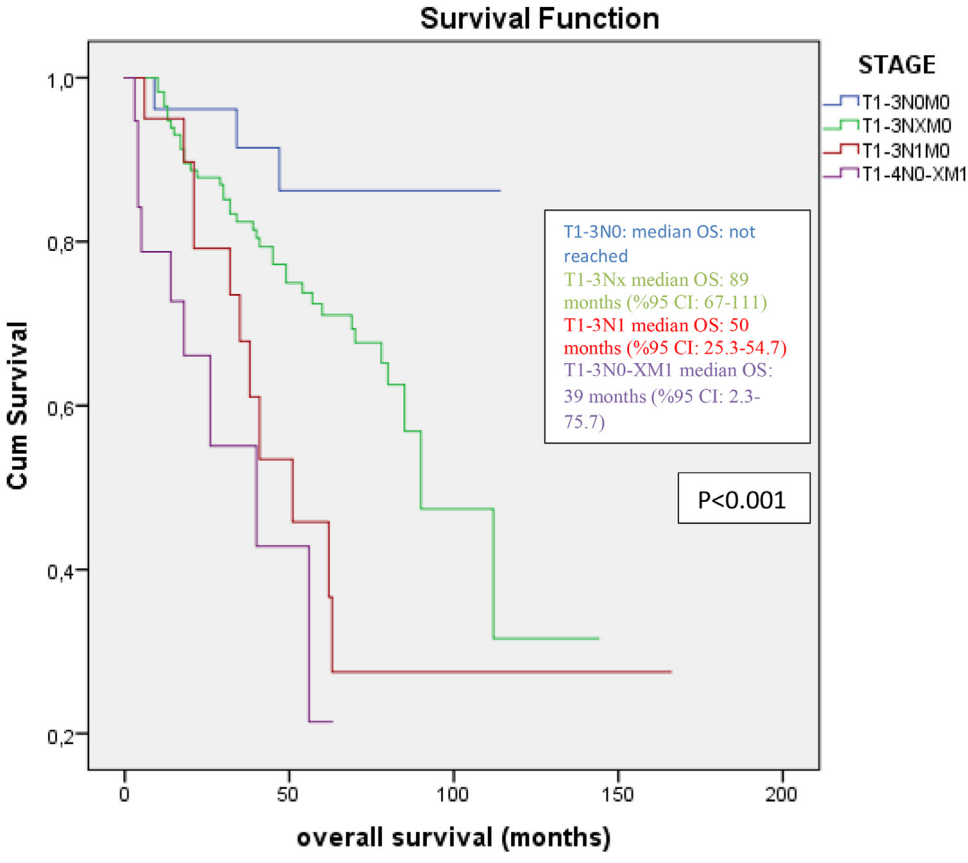


**Fig. 1.** Overall survival analysis for subgroups (OS: overall survival).

related to a significant increase in death risk (hazard ratio [HR]: 6.14) ($P$ <0.001). The risk of death in patients who underwent radical nephrectomy was significantly lower than those who underwent partial nephrectomy (HR: 0.15) ($P$ <0.001). The risk of death in patients with non–clear cell histology was found to be approximately 5 times higher than those with clear cell histology (HR: 4.95) ($P$ <0.001). The presence of perinephric fatty tissue invasion was found to be associated with significant death risk when compared with patients without invasion (HR: 3.32) ($P$ <0.001). Stage during diagnosis was also found to have an effect on survival: when we used the T1–3N0M0 group as the reference, there was no significant increase in risk of death in the T1–3NXM0 group (HR: 2.87, $P$ = 0.079); theT–3N1M0 (HR: 6.18, $P$ = 0.005) and T1–4N0/XM1 (HR: 11.21, $P$ <0.001) groups were found to be at a higher risk of death. Pathologic evaluations determined that patients with sarcomatoid components had a higher risk of death than patients without those (HR: 6.01, $P$ <0.001).

Gender, right-left tumor localization, ECOG performance status, and Fuhrman grade were not considered to have an impact on survival.

Presence of a sarcomatiod component in multivariant cox regression analysis (HR:2.1, $P$ = 0.032) was found to be related with the presence of systemic symptoms during diagnosis (HR: 3.57, $P$ = 0.003), performing a partial nephrectomy instead of a radical nephrectomy (HR: 3.67, $P$ = 0.007), non–clear cell histology (HR: 2.36, $P$ = 0.014), presence of metastatic disease at the time of diagnosis (HR: 9.57, $P$ = 0.001) with an increased risk of death.

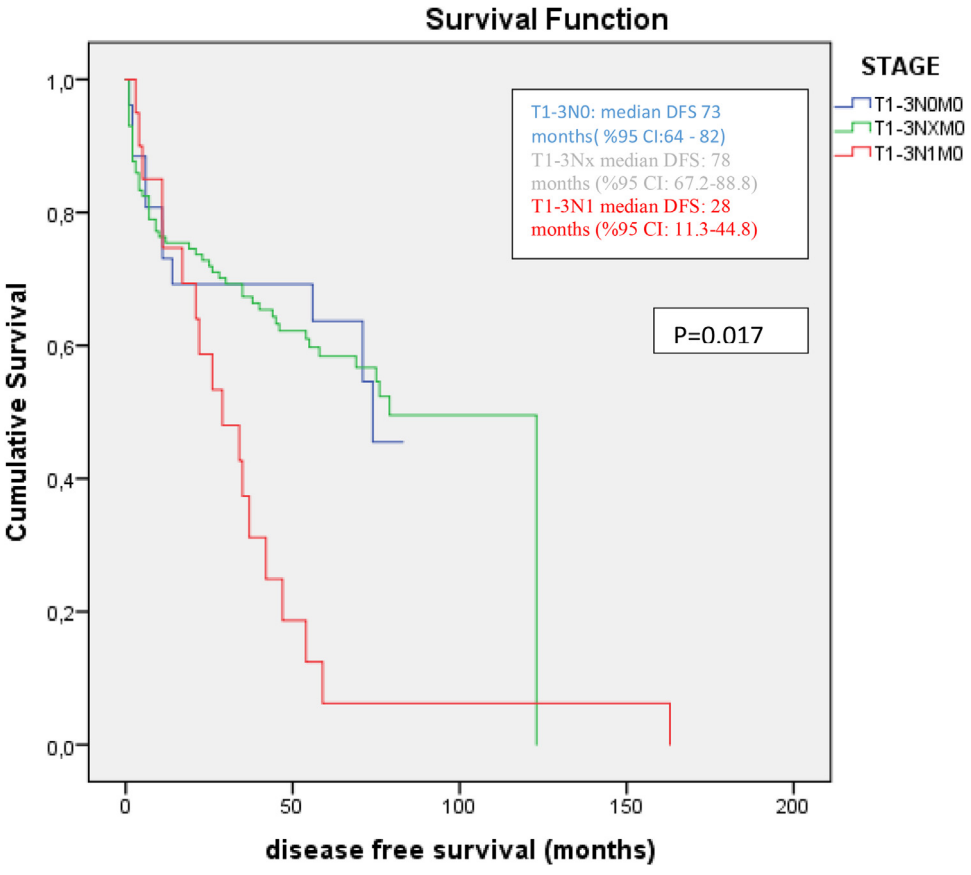


**Fig. 2.** Disease-free survival analysis for subgroups (DFS: Disease free survival).

## Discussion

In our study, the survival rates of node-positive stage-3 patients were better than those of metastatic (stage-4) patients, but this difference was not statistically significant. Although the median survival in the NX patient group is 89 months and worse than the N0 group, it was better than the N1 group, and this difference was statistically significant.

LN involvement in RCC is known to portend a poor prognosis, even in the absence of distant metastases. The 5-year OS rate was 38.4% for pTany/pN1 patients and 83.8% for pTany/pN0 patients. A worse OS was seen for pN1 patients across all pathologic T stages.[16] These results are consistent with our finding that LN involvement is associated with worse survival outcomes. In our study, 3-year OS and DFS rates of N1 patients were61.1% and 31.3%, respectively; 3-year OS and DFS rates of N0 patients were86.5% and 63.9%, respectively. However, in current practice, LNs are not routinely dissected by urologists in all RCC cases, as a benefit for cancer control has not been entirely proven. EORTC study results are the most important reason that many urologists do not perform LN dissection.[17]

Although some studies have shown that LND may contribute to survival in specific patient groups,[7,8] many studies have shown that LND does not contribute to OS or DFS.[4,13,14,17] As they have indicated in the discussion of the EORTC study, selection of patients with low node-positive development risk, inadequacy in pathological assessment, and frequent scanning methods may

**Table 2**
Prognostic factors of overall mortality.

| | | Univariate analysis HR (%95 CI) | *P* value | Multivariate analysis HR (%95 CI) | *P* value |
|---|---|---|---|---|---|
| Gender | Female | Reference | *P*= 0.424 | | |
| | Male | 1.25 (0.72-2.16) | | | |
| systemic symptom | Absent | Reference | *P*<0.001 | Reference | *P*= 0.003 |
| | Present | 6.14 (2.79-13.52) | | 3.57 (1.56-8.15) | |
| ECOG-PS | 0 | Reference | *P*= 0.595 | | |
| | 1 | 1.15 (0.68-1.94) | | | |
| Type of surgery | Radical | Reference | *P*<0.001 | Reference | |
| | Nephrectomy | 6.91(2.97-16.12) | | 3.67 (1.44-9.38) | *P*= 0.007 |
| | Partial nephrectomy | | | | |
| Tumor localization | Left | Reference | *P*= 0.388 | | |
| | Right | 1.25 (0.75-2.08) | | | |
| Histology | Clear cell | Reference | *P*<0.001 | Reference | |
| | Non-clear cell | 4.95 (2.80-8.77) | | 2.36 (1.19-4.68) | *P*= 0.014 |
| FUHRMAN Grade | 1 | Reference | | | |
| | 2 | 1.30 (0.17-9.98) | *P*=0.802 | | |
| | 3 | 3.73 (0.51-27.42) | *P*= 0.196 | | |
| | 4 | 4.84 (0.63-37.39) | *P*= 0.131 | | |
| Perinephritic fattyt issue invasion | Absent | Reference | *P*<0.001 | Reference | *P*= 0.345 |
| | Present | 3.32 (1.99-5.52) | | 1.31 (0.75-2.29) | |
| Stage | T1-3N0 | Reference | | Reference | |
| | T1-3NX | 2.87 (0.88-9.31) | *P*= 0.079 | 3.99 (1.20-13.29) | *P*= 0.024 |
| | T1-3N1 | 6.18 (1.72-22.21) | *P*= 0.005 | 2.41 (0.61-9.54) | *P*= 0.212 |
| | T1-4N0-XM1 | 11.21 (2.99-41.97) | *P*<0.001 | 9.57 (2.47-37.09) | *P*= 0.001 |
| Sarcomatoid component | Absent | Reference | *P*<0.001 | Reference | *P*= 0.032 |
| | Present | 6.01 (3.27-11.04) | | 2.10 (1.06-4.15) | |

ECOG-PS, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS).

have caused the obvious discarding of node-positive patients and rare node-positive patients. In a surveillance, epidemiology, and end results-based analysis of patients with nonmetastatic RCC, the rate of pathologic LN involvement was 11% overall.[16] In the EORTC study, LN retention was witnessed only in 4% of patients. However, it should be kept in mind that this study is the first randomized prospective study on LN dissection.[17]

In spite of all these data, we believe that the reason for the intense focus of research on LN dissection is the adjuvant studies that have been carried out. This interest was further increased by the S-TRAC study, which specifically allowed sunitinib to be approved by the FDA for adjuvant therapy in RCC patients.[18] Since we know that this will be followed by adjuvant immunotherapy treatments, we think that it is necessary to know which group of patients benefits more, especially when using such costly medications with side effects for an adjuvant therapy. At this point, the importance of complete and reliable staging is increasing.

Are the current RCC patients subjected to safe staging with the recommendation of guides? Today, according to guides, it is recommended that the surgeon perform a LN dissection in 2 cases: in cases where there is clinical suspicion and in cases where there is radiological suspicion. The detection of LN metastasis radiologically should be discussed. While imaging modalities such as magnetic resonance imaging, computed tomography, and ultrasonography are sufficiently successful in diagnosing RCC, they are not successful enough for LN retention. The LN size should be at least 5 mm to show LN retention with these methods.[13,19,20] However, with current imaging methods, false- negative rates are around 10% and suggests that these micrometastasis ratios may be even higher. Also, imaging of a LN that is larger than 2 cm in the abdomen or the retroperitoneal area with computed tomography often indicates malignancy, but this should

be confirmed by pathology.[21] However, most of the time, reactive LNs can increase false-positive rates. In a study on this subject, only 42% of patients were diagnosed correctly.[22] In light of these data, we think that the decision for LND should not be given to the patient with current imaging methods. Guides, who know that the most important factor is the surgeon because of the inadequacy of imaging methods, suggest the surgeon make the decision for LND independent of radiological suspicion.[11] Can every patient have the chance to be operated on by an experienced surgeon? In our opinion, this is impossible. In fact, in our study, the survival of NX patients was significantly worse when compared to N0 patients, indicating that the node-positive status of these patients was omitted during radiology or surgery.

Another issue with LN-positive patients is that it is classified as stage 3 in the eighth edition of AJCC (2017). Previously, Pentuck et al (2003) published a study stating that there is no difference in the survival of node-positive patients and metastatic patients; we do not consider this study to be a homogeneous study that contributes to our theory because T4 patients are not differentiated.[7] The study published by Kai-Jie Yu et al (2018) was a more homogeneous study and did not include any T4 cases. Furthermore, this study showed that node-positive patients' survival rates were almost as bad as metastatic patients'.[14] Although we do not know the treatments received by metastatic patient groups in this study, considering the developments in stage 4 RCC patients' survival rates, changes such as staging will be inevitable in the future. Similar to these studies, the survival of stage 3 node-positive patients in our patient group was numerically longer than that of the metastatic patients, but the difference between the 2 groups was statistically insignificant; this finding supports both studies.

According to the AJCC eighth edition (2017), which is used for staging today, pT3a–cN0 and pT1–3N1 patients are defined as stage 3.[15] Our data indicate that T1–3N0M0 and T1–3N1M0 patients have obvious DFS and OS differences, and they should not be defined with the same staging degree. Considering that these patients are those who could not yet access immunotherapies used recently in Turkey, it would be more appropriate to define node-positive patients as stage 4 in a staging system where pT3N0 patients are defined as stage3.

Limitations of this study are that it is retrospective and the number of patients is relatively low. Also, the fact that many patients were included in the study from various centers makes it impossible to standardize the surgical technique, pathology, and imaging methods.

Consequently, nodal involvement is independently associated with adverse prognosis in both M0 and M1 settings. There is a significant increase in survival time in patients with M1 RCC because of developing therapies. Therefore, we recommend performing LND on all patients for proper staging of RCC and including node-positive patients into the stage 4 patient group.

## Ethical approval

This study was approved by the institutional review board of the hospital and was performed in compliance with all principles of the Helsinki Declaration. As the data were retrospective in nature and analyzed anonymously, informed consent was not obtained from the patients.

## Conflict of interest

All authors declare no conflicts of interest, real or perceived, financial or nonfinancial.

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