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Reassessing the Current TNM Lymph Node Staging for Renal Cell Carcinoma

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Abstract

Objective: The most commonly used staging system for renal cell carcinoma (RCC) is the tumor-node-metastasis (TNM) system. In the most recent TNM edition, lymph node (LN) involvement is defined as pN0, pN1, or pN2, depending on the number of metastatic LNs (none, 1, or >1). This study evaluated the prognostic value of this classification and tried to improve its clinical impact by considering an additional parameter, that is, LN density (ratio between number of positive LNs and total number of LNs retrieved).

Methods: All pathologic reports of radical nephrectomies performed for RCC in two urologic centers between November 1983 and December 1999 were reviewed. For each patient, complete clinical and pathologic data, number of LNs removed, location and number of positive LNs, and LN density were recorded. The Kaplan-Meyer method and the log-rank test were used to calculate cause-specific survival rates and to compare survival curves, respectively.

Results: A total of 735 patients underwent radical nephrectomy. Lymphadenectomy was performed in 618 cases, and the rate of positive LNs was 14.2%. The 5-yr cause-specific survival rate of pN+ patients was 18%, with no statistically significant difference between pN1 and pN2. The average number of LNs removed was 13 (range, 1–35). The median number of LNs involved was 3 (range, 1–18). LN density ranged between 3.7% and 100% (median, 22.9%). The number of LNs removed had no impact on

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survival in pN+ patients. The only significant unfavorable prognostic factors were >4 LNs involved ($p = 0.02$) and LN density >60% ($p = 0.01$).

Conclusion: The results show that in RCC the current TNM stratification of positive LNs is not significantly correlated with prognosis. From our data it appears that classification as ≤4 or >4 LNs involved, supported by LN density, better reflects the impact of the disease on survival.

1. Introduction

Renal cell carcinoma (RCC) is the third most common genitourinary tumor, accounting for about 2% of all cancers. Lately, the incidence of RCC in Europe is steadily increasing, with concomitant decreasing mortality rates [1]. The mean annual increase in RCC incidence in Italy is 5.4% among men and 2.7% among women [2]. Despite early detection, both locally advanced and metastatic RCCs still account for about 20% of newly diagnosed kidney cancers [3,4].

One of the most important prognostic factors in RCC is lymph node (LN) involvement. Life expectancy decreases considerably when nodal metastases are present, with the overall 5-yr survival rate ranging from 11% to 35% [5–14].

Currently, the most commonly used staging system for RCC is the tumor-node-metastasis (TNM) system [15]. This enables patients throughout the world to be stratified into comparable groups, improving treatment decisions and prediction of clinical outcomes. Of course, this staging system requires continual and dynamic revisions as demonstrated by many recent controversies (T1a/T1b substratification, tumor size breakdown between T1 and T2 tumors, importance of urinary collecting system involvement) [16–21]. Indeed, classification of the N parameter (initially based on number and side, subsequently on number and size) has undergone several changes over the years [15–18]. The latest two editions of the TNM system simply consider the absolute number of metastatic LNs (pN0 = none, pN1 = 1, pN2 = ≥2), assuming that regional lymphadenectomy includes at least eight lymph nodes [15,18].

Few reports in the literature deal with the pN1/pN2 classification [12,13], but none consider its clinical impact, so it remains to be established whether such subdivision reflects real differences in terms of prognosis and survival. Moreover, almost no data are available regarding the prognostic significance in RCC of LN density (ratio between number of positive LNs and total number of LNs retrieved) [11], already evaluated in other genitourinary cancers [22–24].

This present study reconsidered the current TNM nodal classification for patients with RCC, in terms of prognostic value and contribution of additional parameters such as LN density.

2. Patients and methods

2.1. *Patient selection and therapeutic approaches*

All radical nephrectomies performed for RCC in two urologic centers between November 1983 and October 1999, and between October 1988 and December 1999, respectively, were reviewed with the approval of the local Institutional Review Boards. Familial genetic cases were not included in this series. Ten fully qualified surgeons, all from the same surgical school, performed the operations. Regional lymph node involvement or distant metastases, or both, at diagnosis were not considered a contraindication for surgery. Lymph node dissection extended from the crus of the diaphragm to the aortic or caval bifurcation, including the primary lymph centers of the corresponding kidney (hilar, precaval, retrocaval, laterocaval, and interaortocaval nodes for the right kidney and hilar, preaortic, retroaortic, and lateroaortic nodes for the left kidney). In patients of advanced age or with significant comorbidity affecting life expectancy, lymphadenectomy was not performed or was limited to the renal hilum. Patients with LN involvement in the absence of distant metastases received no adjuvant treatment. Metastatic disease was treated with continuous circadian infusion of floxuridine with an implantable and programmable pump, or with subcutaneous recombinant interleukin 2 (from 1993), or with both [25].

2.2. *Histopathologic evaluation*

All palpable and macroscopically detectable nodes were prepared for paraffin embedding. Their anatomic location was routinely recorded (hilar, precaval, retrocaval, laterocaval, interaortocaval, preaortic, retroaortic, lateroaortic). LN metastases were identified on 2-mm thick sections after hematoxylin and eosin staining. Fat-clearing techniques and immunohistochemical staining for cytokeratins were not routinely applied. Nodes were considered metastatic only after microscopic assessment. The original analysis was undertaken by five different pathologists, finally reviewed by a single experienced uropathologist (E.B.), and classified by the sixth edition of the TNM and Fuhrman systems [15,26]. The histologic subtypes were reevaluated according to the new World Health Organization classification [27]. For each patient, complete clinical and pathologic data, number of LNs removed, location and number of positive LNs, and LN density were recorded.

2.3. Clinical follow-up

Follow-up consisted of physical examination, determination of serum creatinine and alkaline phosphatase levels, urinalysis, abdominal computed tomography (CT) scan, and chest radiography at 3 mo, then every 6 mo for 3 yr, and yearly thereafter. After 60 mo, abdominal ultrasonography replaced CT scan. Bone scans and head CT scans were performed only in the presence of related symptoms or elevated alkaline phosphatase levels. Cause-specific survival data were obtained from medical records and cancer registries.

2.4. Data analysis and statistical methods

The χ^2 test was used to determine the difference between frequencies. The Mann-Whitney *U* test with Spearman rank were used to compare and correlate continuous variables with nonparametric distribution. Cause-specific survival rates were calculated by the Kaplan-Meyer method; the log-rank test was used to compare survival curves. The survival distribution was evaluated for the following variables: number of positive LNs, number of LNs removed, site of positive LNs, and LN density. To establish a threshold for number of LNs removed and LN density as categoric variables, in the absence of any prognostically established cut-off value, we took the median levels. A receiver operating characteristic (ROC) curve, plotting sensitivity versus one minus specificity, was adopted to further examine the optimum decision threshold, discriminating uncensored cases from those censored at 5 yr for the two above variables. To avoid subjectivity in selecting a cut-off point, we also evaluated continuous variables by the Wald test using the proportional hazards model. The significant prognostic factors identified by the univariate analysis were then fitted into the Cox proportional hazards regression model. Two-tailed tests were used for all comparisons; $p < 0.05$ was considered statistically significant. Statistical analysis was performed using a commercially available software, STATISTICA for Windows 6.0 (Statsoft srl, Italy).

3. Results

A total of 735 patients underwent radical nephrectomy. There were 609 cases (82.8%) of clear cell RCC, 81 (11%) of papillary RCC, 36 (4.8%) of chromophobe RCC, and 9 (1.2%) of unclassified-type RCC. Lymphadenectomy was performed in 618 cases (84.0%), and the rate of positive LNs (pN+) was 14.2% (88 of 618). The 117 cases of nephrectomies without lymphadenectomy included 10 cases of hilar dissections declared by the surgeons in which the pathologist could find no LNs. Overall, 522 patients of 618 (84.4%) had a complete LN dissection. Therefore, limited lymphadenectomy was performed in 96 cases (15.6%). Only 17 pN+ cases had limited lymphadenectomy. There were 29 pN1 (32.9%) and 59 pN2 cases (67.1%). The characteristics of the 618 patients undergoing lym-

Table 1 – Characteristics of the patients submitted to lymphadenectomy

	pN+	pN0
No. pts.	88	530
No. gender (%)		
male	62 (70.4)	356 (67.1)
female	26 (29.6)	174 (32.9)
Median (range) age	60.0 (21–82)	60.0 (42–88)
No. incidental tumour detection (%)	15 (17.0)	221 (41.6)
No. side of tumours (%)		
left	44 (50.0)	264 (49.9)
right	44 (50.0)	266 (50.1)
No. pT1a (%)	0 (0.0)	85 (16.0)
No. pT1b (%)	7 (7.9)	141 (26.6)
No. pT2 (%)	13 (14.7)	91 (17.1)
No. pT3a (%)	21 (23.8)	104 (19.6)
No. pT3b (%)	27 (30.6)	97 (18.3)
No. pT3c (%)	0 (0.0)	4 (0.7)
No. pT4 (%)	20 (22.7)	8 (1.5)
Median (range) number of lymph nodes removed	13 (1–35)	9 (1–43)
Median (range) number of lymph nodes involved	3 (1–18)	0
No. M1 (%)	43 (48.8)	80 (15.0)
No. GI (%)	3 (3.4)	41 (7.7)
No. GII (%)	31 (35.2)	311 (58.6)
No. GIII (%)	47 (53.4)	165 (31.1)
No. GIV (%)	7 (7.9)	13 (2.4)
Median (range) tumour size, cm	10.0 (3.5–30)	7.0 (1.0–22.0)

phadenectomy are reported in Table 1. In the pN1 group there were more locally advanced tumors (pT3–pT4), but fewer metastatic and poorly differentiated cases than in the pN2 group (without statistically significant differences).

Excluding the pN+ patients who had limited lymphadenectomy, the hilar LNs were involved in 46 cases overall (64.7%) and in 25 cases as the sole anatomic location (35.2%). The hilar LNs were bypassed in 25 cases (35.2%). Most of the patients undergoing extended lymphadenectomy had LN metastases at a single anatomic site (39 of 71; 54.9%).

The median number of LNs removed was 13 (range, 1–35); in pN1 cases there were significantly fewer removed than in pN2 cases (8.0 versus 14.0; $p = 0.003$). In the patients who had extended lymphadenectomy, similar numbers of LNs were removed in the two groups (13.0 versus 15.0; $p > 0.05$).

The number of metastatic LNs was significantly correlated with the number of LNs removed ($r = 0.30$; $p = 0.006$). LN density ranged from 3.7% to 100% (median, 22.9%). Median LN density was 12.6% and 31.6%, respectively, in pN1 and pN2 tumors ($p < 0.001$).

Patients with LN involvement were followed for a median time of 14 mo (range, 0–169 mo). Their median cause-specific survival time was 14.4 mo. Only two patients (both pN2) died of unrelated causes, free of RCC relapse (one had a heart attack after 97 mo, the other died of colon cancer after 14 mo); 74 patients died of RCC. Eighteen patients lived longer than 5 yr, but only 9 of them were free of

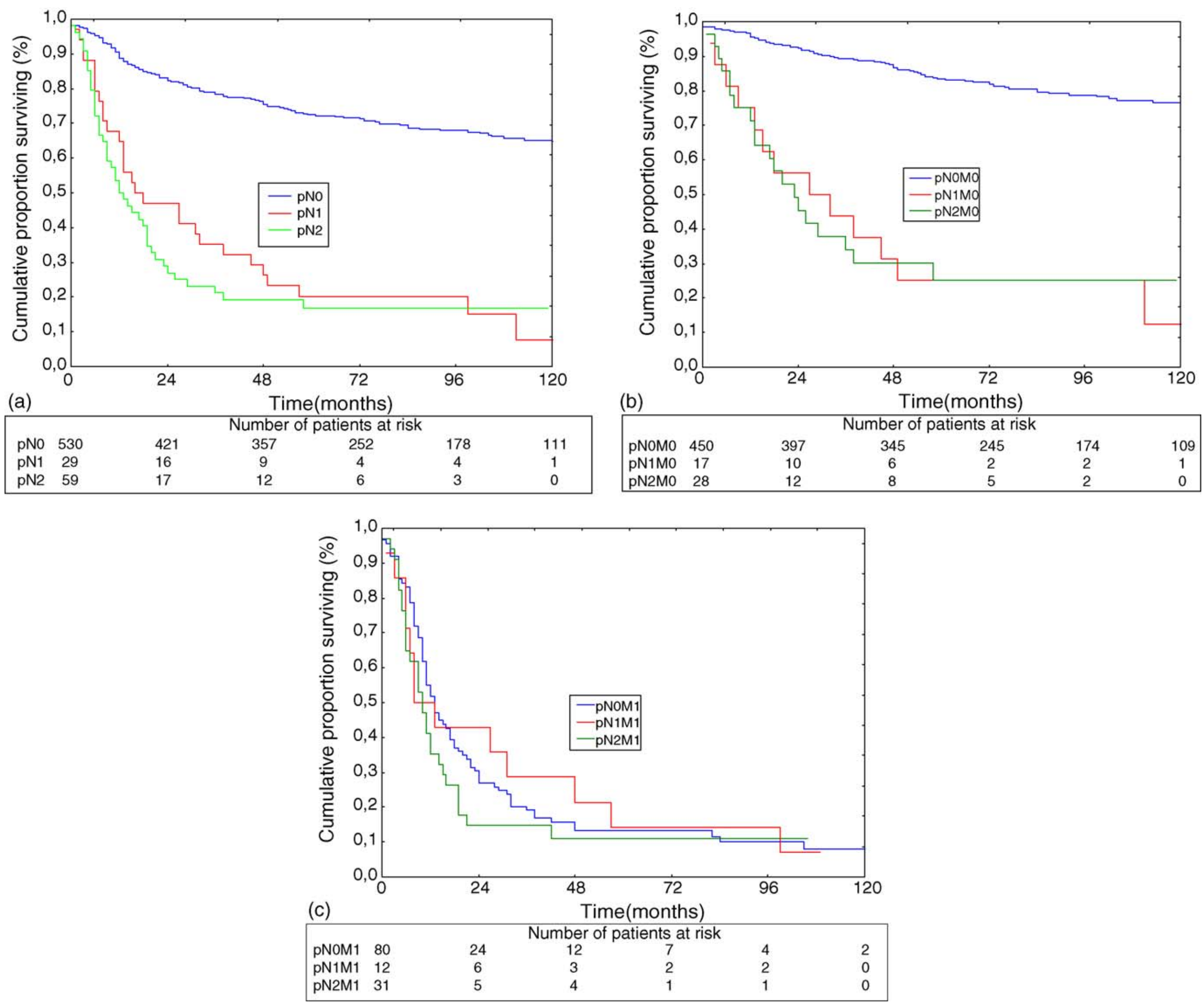

Fig. 1 – Kaplan-Meyer estimates of cause-specific survival. The pN1 and pN2 cases had a similar worse outcome ($p > 0.05$) irrespective of their M status. The pN0 patients have better survival only when M0 ($p < 0.00001$). (a, all patients; b, M0 patients; c, M1 patients).

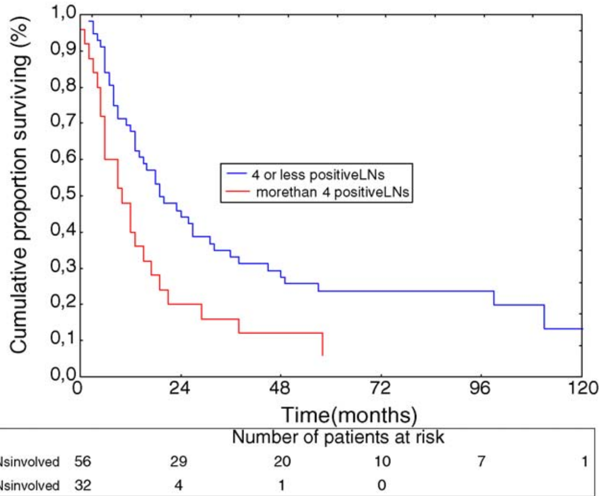

Fig. 2 – Cause-specific survival of LN positive patients by more or less than 4 LN involved ($p = 0.02$).

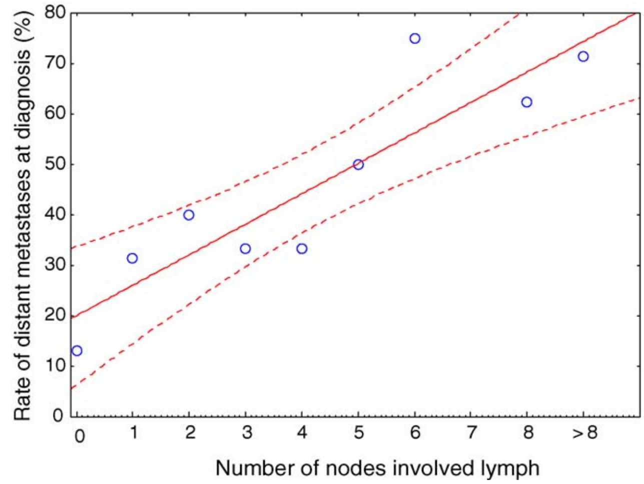

Fig. 4 – Relationship between the number of positive LNs and the rate of distant metastases ($r = 0.89$; $p = 0.001$). The linear regression line and the 95% interval of confidence are indicated.

disease at the most recent follow-up. At the time of nephrectomy, 8 of these 9 patients had pN2 disease, 6 had an organ-confined tumor, and 2 had synchronous metastatic disease (adrenal gland and mesentery, both treated surgically).

The 5-yr cause-specific survival rate of the pN0 patients was significantly higher than that of the pN+ patients (74.4% versus 18.0%; $p < 0.00001$). There was no statistically significant difference in 5-yr cause-specific survival rates between pN1 and pN2 cases (20.0% versus 17.2%), even considering pN1M0/pN2M0 (25.0% both) and pN1M1/pN2M1 cases separately (14.0% versus 11.2%; Fig. 1). This result did not change if only pN1 patients submitted to extended lymphadenectomy were considered (19 patients). Patients with nodal metastases at a single anatomic location and at different regional sites had a similar outcome. The number of LNs retrieved did not affect the cause-specific survival rate, either considering a threshold of 13 (the median value) or taking the number of LNs harvested as a continuous variable. The only prognostic factors with a statistically significant impact on survival were found to be >4 LNs involved ($p = 0.02$) and LN density > 60% ($p = 0.01$; Figs. 2 and 3). The risk of cause-specific death increased by 1.92 times for patients with >4 LNs involved (95%CI, 1.48–2.50) and by 2.1 times for patients with a LN density >60% (95%CI, 1.65–2.87). The number of positive LNs was correlated with the rate of distant metastases at diagnosis ($r = 0.89$; $p = 0.001$; Fig. 4). Patients with >4 LNs involved had a significantly higher rate of distant metastases than patients with fewer positive nodes (62.9% versus

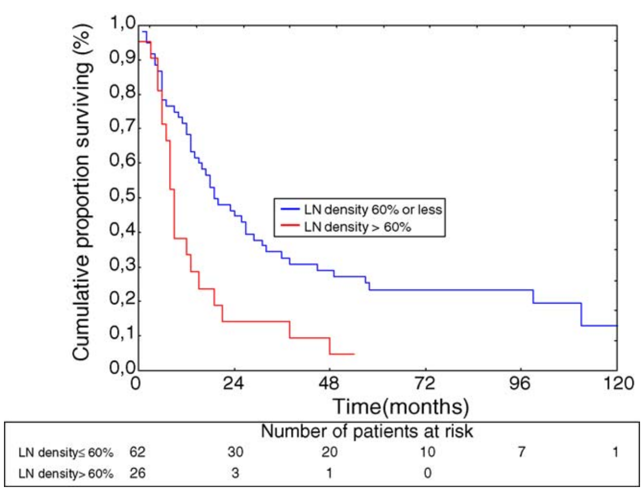

Fig. 3 – Cause-specific survival of LN positive patients stratified by LN density less or greater than 60% ($p = 0.01$).

Table 2 – Multivariate analysis of cause specific survival in patients with LN positive RCC

Variable	HR (95% IC)	p value
pT pT1-T2 vs. pT3-T4	2.24 (1.59–3.16)	0.01
LN density ≤60% vs. >60%	1.80 (1.33–2.45)	0.05
No. positive LNs 1–4 vs. >4	1.54 (1.15–2.06)	n.s.
Metastases M0 vs. M1	1.43 (1.10–1.84)	n.s.
Tumour grade	1.41 (1.07–1.87)	n.s.

n.s.: not significant.

37.2%; $p = 0.02$). In the multivariate analysis, LN density >60% had independent prognostic significance, whereas metastases and tumor grade did not enter the model (Table 2).

4. Discussion

In RCC, the LN involvement is often associated with a poor prognosis [5–14]. We report a median cause-specific survival time of 14.4 mo, with 18 of 88 pN+ patients living longer than 5 yr and only 9 free of disease. This poor outcome is correlated with the distant spread of the disease, often occurring synchronously. In fact, 48.8% of our pN+ patients had distant metastases at the time of surgery. This rate is even higher in others series [9,12,13].

Both the overall percentage of pN+ cases (about 14%) and the rate of pN1 and pN2 (32.9% and 67.1%) in our study are comparable to what are published in the most studies with similar series of patients [9–13]. The rate of patients with positive LNs is influenced by several factors, particularly disease stage and extension of lymphadenectomy [7–13,28]. Greater than 12 LNs retrieved during radical nephrectomy is associated with more accurate nodal staging with a significantly higher incidence of nodal metastases, because some pN0 cases may be understaged if lymphadenectomy is inadequate [28]. According to the sixth edition of the TNM classification, a regional lymphadenectomy specimen in RCC should ordinarily include at least eight nodes [15], but, in fact, this suggestion is not always adopted [11]. Of course, the therapeutic role of lymphadenectomy in RCC still remains controversial, but its importance in the correct RCC staging is not doubted [29]. Furthermore, lymphadenectomy could improve survival in patients with regional lymph node involvement or with clinical lymphadenopathy, without adding morbidity [9,12,13,30]. From the clinical standpoint, lymphadenectomy, when indicated, should not be limited, because many patients may have LN metastases skipping the hilum and at a single anatomic site. In any case, in the present study, neither the number of LNs retrieved nor the location of positive LNs (single or multiple) significantly affected the cause-specific survival rate of pN+ patients.

Furthermore, we demonstrate that the number of positive LNs is correlated to the number of LNs removed. In our series, the pN1 cases had a significantly lower median number of LNs removed than the pN2 cases. If nodal dissection is not complete, pN1 disease could be understaged. But is the current distinction between pN1 and pN2 cases really relevant from the prognostic standpoint? Little has been reported about this aspect. We found no difference in cause-specific survival between pN1 and pN2 patients, and most long-term surviving patients had pN2 disease. These results could be influenced by the different extensions of lymphadenectomy in the two groups of patients; however, even when only patients subjected to extended lymphadenectomy with no difference in the number of LNs removed are considered, we obtained similar results. According to our findings, a threshold of four positive LNs stratifies patients into two categories with different clinical outcomes.

The simple number of positive LNs does not in any case indicate the extension of lymphadenectomy, itself fundamental in determining this number, and we thus sought a parameter that could deal with it. The concept of LN density was first introduced in bladder cancer [22,23], where the ratio of the number of positive LNs to the total number of LNs removed better defined the surgical outcome than conventional LN staging. Recently, the prognostic role of the LN density was also applied to the nonseminomatous germ cell tumor [24], but failed to predict relapse. To our knowledge only one study deals with the prognostic usefulness of LN density in 2831 RCC patients undergoing radical nephrectomy and lymphadenectomy [11]. An increase in number of positive nodes and in LN density was associated with a decrease in cause-specific survival. The greatest difference in survival rates was in the groups with >4 LNs involved and with LN density >75%. However, this study has several limitations (many surgeons and many pathologists involved, no precise median number of LNs removed, no clarification of the type of lymphadenectomy performed, lymphadenectomy data only from 60% of patients, many patients with no LNs removed, lack of information about adjuvant immunotherapy or chemotherapy or combination of both).

In our series, LN density was a significant risk factor for cause-specific survival and maintained a relationship with the outcome in the multivariate analysis after adjusting for the number of positive LNs (≤4 versus >4), metastases, and tumor stage and grade. In the group of 56 patients with ≤4 LNs involved, there were eight patients (14.2%) with LN density >60%, meaning that in these cases the number of LNs removed ranged from a minimum of one (one positive LN; LN density 100%) to a maximum of six (four involved LNs; LN density 66%). When so few regional LNs are dissected we believe these pN1 cases are very likely to be understaged, and thus LN density is a useful tool to identify cases in which lymphadenectomy was too restricted. Limiting the analysis to patients receiving extended LN dissection, there were no cases with LN density >60% in the group with ≤4 LNs involved. This means that LN density does indeed help to unmask possible false pN1 staging due to limited LN dissection.

5. Conclusion

The study clearly shows that the current TNM stratification of LN+ RCC patients is not correlated with clinical outcome. Rather, a threshold of four positive LNs instead of one correlates with clinical outcome. Furthermore, by encapsulating two crucial data, that is, number of LNs removed and number of metastatic LNs, LN density provides better discrimination between pN1 and pN2 categories. However, our results could be conditioned by the retrospective nature of the study and by the relatively small percentage of patients stratified in the various groups. Many variables were omitted, such as the correlation between the pN status, preoperative imaging, and macroscopic nodal features including size, histologic features of capsular penetration, or microvascular invasion. These data therefore need to be confirmed in larger prospective and standardized studies, based on uniform surgical techniques and pathologic evaluation.

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