Abstract:

Objective: To assess the effect of lymph node dissection (LND), number of removed nodes (NRN) and number of positive nodes (NPN) on cancer specific mortality (CSM), in contemporary vs. historical patients, with $pT_{2-3}N_{any}M_0$ renal cell carcinoma (RCC) treated with radical nephrectomy (RN).

Methods: Within the SEER database (2001-2013), we identified patients with non-metastatic pT_{2-3} N_{any} RCC who underwent RN with or without LND. Kaplan–Meier analyses and multivariable Cox regression models with propensity score weighting for inverse probability of treatment were used.

Results: Of 25,357 patients, 24.8% underwent lymph node dissection (2001-2007: 3,167 patients vs. 2008-2013: 3,133 patients). M~~The m~~edian NRN was 3 (IQR 1-7). Positive nodes were identified in 17.1%: 9.3% of pT_2 and 21.6% of pT_3 patients, who underwent LND. M~~The m~~edian NPN was 2 (IQR 1-2). In multivariable models, LND did not decrease CSM (HR 1.29, p<0.001). ~~Also~~ LND extent, defined as NRN, did not decrease CSM (HR: 0.94, p=0.3). Finally, multivariable models testing the effect of NPN showed increased CSM, in pT_3 but not in pT_2 patients (HR:1.29 and 1.58, p=0.02 and 0.1, respectively). ~~Interestingly,~~ NRN exerted a protective effect on CSM in patients with positive nodes (HR:0.98; p=0.007).

Conclusion: In contemporary and historical patients LND or its extent, do not protect from CSM. However, the NPN increases the rate of CSM in pT_3 patients. In consequence, LND and its extent appear to have little or any therapeutic value in $pT_{2-3}N_{any}M_0$ patients, besides its prognostic impact. High risk non-metastatic patients may represent a target population for a multi-institutional prospective trial.

Keywords: Lymph node dissection; radical nephrectomy; renal cell carcinoma; SEER database

Introduction

The evidence regarding the benefit of lymph node dissection (LND) at radical nephrectomy (RN) is controversial. The randomized clinical trial of Blom et al., that recruited between 1988 and 1991, showed no survival benefit of LND.[1] However, it was underpowered and included respectively, 389 and 383 patients in the no LND and LND arms respectively. Moreover, it predominantly included T_{1-2} patients, 72 vs. 69% respectively, underwent RN without or with LND. Finally, only 28 vs. 31% of total patients were staged pT_3, in whom lymph node invasion risk is highest.[1]

Other series focused on even more historical patients (1987-2011). These reports showed benefit of LND, but also relied on small single-institution databases.[2,3] The most contemporary single-institution analysis (N= 1,797) showed no benefit of LND in pT_{1-4} patients operated between 1990-2010.[4] Furthermore, no benefit of LND was shown in a large population-based analysis (1983-1998), that included patients with localized, regional and distant disease.[5]

Based on the historical nature limitations, or sample size limitations, or stage inclusion limitations of most reports, we performed a comprehensive analysis, examining the effect of LND, of its extent, and the effect of number of positive nodes (NPN) at LND on cancer specific mortality (CSM) at RN. We focused on patients diagnosed between 2001 and 2013 and stratified the cohort between historical and contemporary patients, in all the analyses.

Patients and Methods

Data source

The study cohort consisted of individuals diagnosed with RCC (International Classification of Disease for Oncology C64.9) within Surveillance, Epidemiology, and End Results (SEER) database. The SEER collects patient demographics and publishes cancer incidence and survival data from several cancer registries. The SEER database covers approximatively 26% of the United States population.[6]

Study Population

Only patients affected by kidney parenchymal tumors aged ≥ 18 years and treated with RN between 2001 and 2013 were included. We focused on patients with histologically confirmed RCC, stage $pT_{2\text{-}3}$ N_{any} M_0. Included histological subtypes were: clear cell RCC (ccRCC), papillary, chromophobe, sarcomatoid, cyst-associated RCC, collecting duct carcinoma and any RCC. Death certificate only, autopsy cases and bilateral tumors were not included. Finally, we excluded patients without information about tumor size.

Description of Covariates

Adjustment variables consisted of age, gender, race (white, black, other), marital status (married, single, previously married, unknown) and year of diagnosis (historical: 2001-2007, contemporary: 2008-2013). Tumor size was coded as a continuous variable. Fuhrman grade was categorized as G1/G2, G3/G4 and GX for unknown. Pathological tumor stage was defined as pT_2 and pT_3. Nodal stage was classified as N_0, N_1 and Nx. In all analyses, histological subtypes were stratified as ccRCC and non-ccRCC.

Statistical analysis.

Descriptive statistics including frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The Chi-square tested the

statistical significance in proportions differences. The t-test examined the statistically significance in means differences.

To reduce the effect of selection bias, we used a propensity score adjustment that relied on weighting based on inverse probability of treatment (IPTW).[7] In the first step of the analyses, we evaluated changes in LND rates over the time. Temporal trends were quantified using the annual percentage change (APC) with the least squares linear regression. Then, we evaluated the effect of LND on CSM. In the second step, we examined the effect of number of removed nodes (NRN) on CSM in patients who underwent LND. The population was stratified according to NRN median. In the third step, we tested the effect of NPN on CSM in patients with documented lymph node invasion. The population was stratified according to the NPN median. In all ~~the~~ analyses, Kaplan-Meier (KM) plots graphically depicted the CSM-free survival rates. Univariable and multivariable Cox regression models (CRMs) tested for differences in CSM. All analyses were repeated according to T-stage (pT_2 and pT_3), in the subgroup of patients with ccRCC. All the analyses were adjusted according to historical and contemporary year of diagnosis intervals.

All tests are two-sided, and a level of significance was set at $p<0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.3.0; http://www.r-project.org/).

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Results

The entire study cohort consisted of 25,357 patients. The median age was 62 (IQR 54-71) years. Of all, 50.5% were diagnosed between 2001 and 2007, while 49.5% were diagnosed between 2008 and 2013. Stage pT_2 and pT_3 were recorded in 41.6 and 58.4% of patients. The median tumor size was 82 (IQR: 68-103) mm. Fuhrman grade G1/G2 was recorded in 43.0%, G3/G4 in 41.3% and GX in 15.7% of all patients. Of all, 59.4% harbored ccRCC. Most were male (66.6%), married (64.3%) and Caucasian (84.3%) **(Table 1)**.

Temporal trends revealed that the proportion of LND in pT_2 patients decreased from 22.9 in 2001 to 20.4% in 2013 (p=0.04). Conversely, the proportion of LND in pT_3 patients remained stable during the study period (p=0.5) **(Figure S1)**. Among patients who underwent LND, the median NRN was 3 (1-7). Positive nodes were identified in 17.1% of patients: 9.3 of pT_2 and 21.6% of pT_3 patients, who underwent LND. Of patients with nodal metastases, the median NPN was 2 (IQR 1-3). Patients who underwent an LND were younger (60 vs 63 years), more frequently harbored pT_3 stage (63.9% vs 56.6%), had larger tumors (92 vs 80 mm) and more frequently had Fuhrman grade G3/G4 (51.9% vs 37.8%) than patients without LND.

Stratification according NRN revealed that patients with NRN above median were younger (60 vs 61 years), more frequently harbored pT_3 stage (66.7% vs 60.7%) and Fuhrman grade G3/G4 (54.2% vs 49.3%), had larger tumors (95 vs 90 mm) than patients with lower NRN. Finally, stratification according NPN revealed that patients with NPN above median were also younger (60 vs 61 years), had higher proportion of Fuhrman grade G3/G4 (73.7% vs 66.5%), and harbored higher proportion of non-ccRCC (61.4% vs 54.4%). The median follow-up respectively was: 46 (IQR19-83), 39 (IQR 16-77) and 19 (IQR 8-42) months in the entire cohort, in LND patients and in patients with positive nodes.

In the first step of our analyses, we tested the effect of LND on CSM according to pathological T-stage: pT_2 and pT_3. In KM analyses LND did not have a protective effect on CSM, both in pT_2 and pT_3 patients. Specifically, in pT_2 patients the 5-year CSM-free survival according to absence or presence of LND was, respectively, 89.1 vs. 83.8%. In pT_3 patients, the 5-year CSM-free survival according to absence or presence of LND was, respectively, 80.9% vs. 65.1%. ($p<0.001$) **(Figure 1)**. In the entire cohort of pT_2 and pT_3 patients, multivariable propensity score adjusted CRMs showed that LND did not exhibit a protective effect on CSM (HR:1.29, CI: 1.21-1.36; $p<0.001$). Instead, LND showed an increased risk of CSM, in both pT_2 (HR:1.13, CI: 1.01-1.25; $p=0.03$) and pT_3 (HR: 1.31, CI: 1.22-1.40; $p<0.001$) patients. **(Table 2)**. All the analyses were repeated in patients with ccRCC and yielded virtually the same results. Moreover, contemporary patients, exhibited lower risk of CSM (HR: 0.77, CI:0.72-0.83; $p<0.001$).

In the second step of our analyses, we tested the effect of median NRN on CSM according to pathological T-stage: pT_2 and pT_3. In KM analyses NRN had no effect on CSM. Specifically, in pT_2 patients the 5-year CSM-free survival was 83.7 vs. 83.8% ($p=0.3$) in respectively, patients with NRN below vs. above the median NRN. In pT_3 patients, the 5-year CSM-free survival was 65.7 vs. 64.6% ($p=0.4$) in respectively, patients with NRN below vs above the median **(Figure 2)**. In the entire cohort of pT_2 and pT_3 patients, multivariable propensity score adjusted CRMs showed that NRN did not exhibit an effect on CSM (HR: 0.94, CI: 0.85-1.04; $p=0.3$). The NRN was not associated with lower risk of CSM, in both pT_2 (HR:0.82, CI:0.66-1.01; $p=0.06$) and pT_3 (HR:0.98, CI:0.87-1.09; $p=0.7$) patients. **(Table 3)**. All the analyses were repeated in patients with ccRCC and yielded virtually the same results. Moreover, contemporary patients, exhibited lower risk of CSM (HR: 0.78, CI:0.70-0.88; $p<0.001$).

In the third step of our analyses, we tested the effect of median NPN on CSM according to pathological T-stage: pT_2 and pT_3. KM analyses showed no CSM differences according to NPN in pT_2 patients (5-years CSM-free survival 46.8% vs. 46.2%, in respectively, patients with NPN below vs. above the median, p=0.87). Otherwise, in pT_3 patients the 5-years CSM-free survival was 37.7% vs. 28.7% in respectively, patients with NPN below vs. above the median (p=0.02) **(Figure 3).** In the entire cohort of pT_2 and pT_3 patients, multivariable CRMs showed that NPN increases CSM (HR:1.32, CI:1.08-1.61, p=0.007). Contemporary patients exhibited the same rate of CSM (HR:0.91, CI:0.75-1.09; p=0.3). The NPN effect on CSM in pT_2 subgroup analyses was not confirmed (HR:1.58, CI:0.91-2.74; p=0.1). However, worse survival with higher NPN was confirmed in pT_3 patients (HR:1.29, CI:1.03-1.60; p=0.02) **(Table 4).** All the analyses were repeated in patients with ccRCC and yielded virtually the same results.

Interestingly, NRN exerted a protective effect on CSM in the entire cohort of pT_{2-3} patients with positive nodes (HR:0.98, CI:0.96-0.99; p=0.007) as well as, in separate subgroup analyses of pT_2 (HR:0.94, CI:0.89-0.99; p=0.02) and pT_3 (HR:0.98, CI:0.96-0.99; p=0.04). However, NRN failed to achieve statistical significance in patients with clear cell histology in the entire cohort (HR:0.99, CI:0.96-1.02; p=0.5) as well as, in pT_2 (HR:0.94, CI:0.87-1.01; p=0.1) and in pT_3 (HR:0.99, CI:0.97-1.02; p=0.9) subgroup analyses.

Discussion

The one and only randomized clinical trial examining the effect of LND on cancer survival outcomes at RN failed to show any benefit of such procedure.[1] However, that trial was underpowered, relied on very small patient numbers per participating institution, enrolled historical patients between (1988 ~~and~~ 1991), and included pT_1 patients in whom lymph node invasion rates are so low that the benefit of LND is difficult to conceptualize. It is also noteworthy, that the proportions of patients with pT_3 disease in whom LND may be more beneficial were only 28 and 31% respectively in no LND vs. LND arms (101 and 112 patients).[1]

Other non-randomized studies relied on equally historical or even more historical patients. Some reported a survival benefit [2,3,8], other did not.[4,5,9–11] Of contemporary studies, the Mayo Clinic reported on a large RN cohort: 1797 patients of whom 606 underwent a LND. Here, no survival benefit was associated with LND at RN.[4] Conversely, Whitson et al. showed a CSM benefit, when more extensive LND was performed in patients with positive lymph nodes at RN or partial nephrectomy.[8] However, this report was challenged by Sun et al., who questioned the methodological flaws, that might have been introduced with missing data imputation.[9] Also the recent secondary analysis of the Adjuvant Sorafenib and Sunitinib for Unfavorable Renal Carcinoma (ASSURE) trial (2006-2010, N=1942), despite their prospective data source, failed to report a survival benefit of LND (in press) [12]. It could be hypothesized that there is a role of LND in high risk, non-metastatic RCC patients that are candidates for adjuvant systemic therapy based on the presence of lymph nodes metastases, in addition to other risk factors.

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In consequence, it may be postulated that large-scale contemporary analyses of the effect of LND on CSM are warranted to corroborate or refute the benefit of LND on CSM. Ideally, such analyses should focus on the potential benefit of LND vs. no LND, on the effect of the NRN and on the

relationship between NPN and NRN in patients with positive lymph nodes, using the most methodologically comprehensive analyses. Our study, fulfilled those criteria and showed important findings that are not going to be ~~pointed out~~addressed by ongoing or even planned randomized trials, since no such trial is ongoing or planned. Based on this consideration, we hypothesized that LND, NRN and NPN may have an effect on CSM. To test our hypotheses, we performed three analytic steps.

First, we tested temporal trends of LND rates at RN and examined if LND improves CSM-free survival. Here, we found a significant decrease in LND rates in pT_2 patients, but no differences over time were found in pT_3 patients. Our results corroborate ~~that~~ those of Kates et al. that relied on ~~the~~ more historic SEER database version (1988 to 2005), where authors found a significant decrease in LND rates for localized RCC.[13]~~[12]~~ We also found that LND does not improve CSM-free survival. These observations applied to all pT_2 and pT_3 patients. Moreover, they applied to all histological subtypes, as well as to patients with exclusive ccRCC.

Our results corroborate the findings of Joslyn et al. that were based on an historical version of the SEER database (1983 to 1998). The authors observed an inverse relation between cancer specific survival and NRN. However, their study did not only include non-metastatic RCC patients, but allowed inclusion of patients with distant metastases.[5] In a more recent analysis, by Feuerstein et al., that focused on 524 non-metastatic patients with RCC, 7 cm or greater, the authors observed that LND and its extension were unrelated to recurrence-free or overall survival.[11] Finally, in the most recent analysis that relied on an institutional database, Gershman et al. also observed that LND does not improve CSM- and all-cause mortality-free survival across all stages, as well as in patients with increased risk of nodal metastases.[4] Conversely, Capitanio et al. showed improved cancer specific survival after LND in patients with localized, locally advanced or metastatic RCC. [2,3,14]~~[2,3,13]~~

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Second, we tested if the NRN, as indicator of LND extent, may have a protective effect on CSM. Our results showed that NRN has no effect on CSM. Our findings corroborate those of several other authors. For example, Sun et al, relied on the historic version of the SEER database (1988-2008), and observed no survival benefit according LND extent at nephrectomy.[9] Taken together our findings, as well as those of several other investigators, show no benefit of LND at RN on CSM or other related cancer control outcomes in patients with non-metastatic RCC. Nonetheless, our data also indicate that as many as 20 and 30% of respectively, pT_2 and pT_3 patients undergo LND at RN. Such practice might still be justified for prognostic purpose and its extent might improve its diagnostic ability.[15]~~[14]~~ In fact, the prognostic value associated with the presence of lymph nodes metastases is well recognized in literature.[16–19]~~[15–18]~~

Third, we tested the role of NPN on CSM. We found an increase in CSM that was proportional to NPN. These findings applied to all patients and to patients with ccRCC cohort. In stratified analyses, statistical significance was only confirmed in the pT_3 but not in pT_2 subgroup. It is of interest that the extent of LND exerted a protective effect on CSM in all patients, but not in those with clear cell histology. Our findings regarding NPN corroborate those of Capitanio et al. [3]. They relied on an institutional database and found a correlation between NPN and CSM. Our findings regarding the effect of NRN in node positive patients partially agree with Whitson et al., who also showed a protective effect in pT_{1-4} patients, regardless of histological subtype, using missing data imputation.[8] This approach to missing data was challenged by Sun et al., who failed to demonstrate the protective effect of LND extent in their analysis.[9] We did not use imputation, but performed subgroup analyses in clear cell histology patients. Moreover, our analyses focus on more contemporary patients namely 2001-2013 vs. 1988-2006 in Whitson et al. analyses, as well as on clear cell histology only subgroup, where the benefit of LND extent is lost. Finally, Trinh et al., also in a more historic version of the

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SEER database (1988-2006), focused on node-positive patients without metastases. The authors reported no association between NRN and CSM.[10]

The present study is not devoid of limitations. Most importantly, as in previously reported analyses that relied on prospective and retrospective databases and examined the effect of LND on RCC mortality, the extent and LND technique ~~of LND was~~ were not standardized. In consequence, no standardized template could be used to define the LND boundaries. Therefore, in the current study important ~~great~~ variability exists in NRN, across pathological stages and according to the presence or absence of lymph nodes metastases. Additionally, the specific indication for LND is not known. We have no data that could explain why a large proportion of patients underwent LND and why an even larger proportion did not. As in previous prospective and retrospective analyses, the decision to perform LND was delegated to the discretion of the operating surgeon. Moreover, we have no data about clinical N-stage in patients with available pathological N-stage. Similarly, pathological N-stage is unavailable in patients with clinical N-stage in whom LND was not performed. In consequence, the ability of clinical N-stage to predict pathological N-stage could not be examined. Similarly, we have no data on intraoperative nodal appearance. However, available analyses that compared imaging clinical staging to pathological staging indicate limited ability to predict that outcome.[20] Nonetheless, several multivariable models are capable of predicting the presence of lymph node metastases.[2,21–23] ~~Moreover~~Furthermore, the population-based nature of the current cohort precludes a standardized pathological assessment and tissue processing. In consequence, not all removed nodes might have been examined or analyzed with the same detail, according to strict institutional protocols or preferences. Actually, to date only one group of investigators examined the rate of pathological N_1 stage in clinical N_0, high risk patients, within a prospective dataset with central pathology review (ASSURE trial). In a secondary analysis of that trial, the rate of occult metastases was 1.98%. However, as in all previous analyses there was no predefined LND template.[12] Last but not least, limitations related to the

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retrospective nature of the SEER database and lack of potentially important variables ~~represents additional limitations.~~also need to be acknowledged.

In conclusion~~s~~, in contemporary and historical patients LND or its extent do not protect from CSM. However, NPN increases the rate of CSM in pT_3 patients. In consequence, LND and its extent appear to have little or any therapeutic value in $pT_{2\text{-}3}N_{any}M_0$ patients, besides its prognostic impact. Finally, the uncertainty about LND benefit remains, even in high risk M0 patients. This uncertainty represents potential grounds for a randomized prospective clinical trial of no LND vs. standardized template LND with overall survival as primary outcome and CSM as secondary outcome.

Conflict of interest

There was no external financial support for this study. The authors declare that they have no conflict of interest.

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Figures

Figure 1 – Kaplan-Meier plots depicting cancer specific mortality-free survival in pT_2 (a) and pT_3 (b) patients according to lymph node dissection status.

Figure 2 – Kaplan-Meier plots depicting cancer specific mortality-free survival in pT_2 (a) and pT_3 (b) patients according to number of removed nodes.

Figure 3 - Kaplan-Meier plots depicting cancer specific mortality-free survival in pT_2 (a) and pT_3 (b) patients according to number of positive nodes.

Supplementary materials

Figure S1 - Graphical presentation of temporal trends for lymph node dissection rates at radical nephrectomy in pT_2 and pT_3 patients.

Tables

Table 1 – Descriptive characteristics of patients with renal cell carcinoma who underwent radical nephrectomy with or without lymph node dissection, stratified according lymph node dissection status, number of removed nodes and number of positive nodes.

Table 2 – Multivariable Cox regression models predicting cancer specific mortality according to presence or absence of lymph node dissection after adjustment with inverse probability of treatment weighting.

Table 3 - Multivariable Cox regression models predicting cancer specific mortality according to number of lymph nodes removed in patients who underwent lymph node dissection after adjustment with inverse probability of treatment weighting. (Ref. <3 nodes removed).

Table 4 - Multivariable Cox regression models predicting cancer specific mortality according to number of positive nodes in patients with positive nodes metastases. (Ref. ≤ 2 positive nodes).