Inflammatory lymphadenopathy in renal cell carcinoma: prognostic tool?

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Significant lymphadenopathy in renal cell carcinoma (RCC) is often considered an important poor prognostic factor (1). A recent study by Muttin *et al.* (2) published in the *World Journal of Urology* attempts to refute this notion. As a pathologist, I am mighty pleased when he concludes that "a radiological suspicion of nodal metastases should not be considered as a poor prognostic factor, at least not until confirmation of nodal involvement at final pathology".

In the current study the authors retrospectively analyze a cohort of 719 patients with "inflammatory lymphadenopathy" i.e., pathologic node negative (pN0) renal cell carcinoma who have undergone lymph node dissection over a period of 28 years. These were categorized as clinically node positive (16% cN1) or clinically node negative (84% cN0) and were followed up for a median period of 77 months. At univariable analysis, inflammatory lymphadenopathy was associated with worse Cancer Specific Mortality (CSM) (HR 2.45; P<0.0001). However, at multivariable analysis, this was not an independent predictor of CSM (HR 0.81; P=0.4).

Surprisingly, there is limited literature on this aspect of inflammatory lymphadenopathy and radiologically enlarged lymph nodes in cancer patients are conventionally considered synonymous with metastatic disease. Such patients may be subjected to unwarranted lymph-node dissection often resulting in pathologic node negative pN0 disease on histopathologic examination, as in this series.

An interesting experimental study assessed contrast-enhanced ultrasonography to differentiate tumor-induced and inflammation-induced lymph node enlargement using animal models. Filling defect was noted in the region of metastatic deposit whereas uniform dense staining was noted in the inflammation model (3). However, no such radiologic tool is currently available in clinical practice.

Various authors have developed predictive normograms for nodal metastasis in RCC. Babian *et al.* (4) used a combination of local symptoms, ECOG PS, cN status and LDH levels to reach a C index of 0.89. Whereas, Gershman *et al.* (5) used a two-parameter combination of maximum LN short-axis diameter and presence of radiographic perinephric/sinus fat invasion (AUC 0.85). Histopathologic examination remains the gold standard.

Determination of lymph node (LN) involvement is critical to determining TNM classification, as it influences long-term survival. Accurate determination of LN stage is critical to patient treatment course, pre-surgical counseling, and surgical planning.

Inflammatory lymphadenopathy in cancer is an obvious outcome of activation of innate and adaptive immune responses to control tumor progression. The adaptive immune response to tumors is directed against tumor-associated/tumor-specific antigens expressed specifically by the tumor. Tumor immune surveillance determines the formation of metastatic deposits based on a balance between anti-tumor response by the host immune system and immune suppression by tumor cells (6). Enlarged lymph

nodes in cancer may also be a result of secondary infections and inflammatory reaction to tumor necrosis.

The concept of inflammatory lymphadenopathy in RCC was first addressed by Studer *et al*. (7). 43 patients with enlarged lymph nodes were diagnosed on the preoperative scan and this was confirmed at nephrectomy and pathologically. In 18 of these 43 patients (42%) histological study showed metastases of the renal cell carcinoma in the enlarged lymph nodes. In the other 25 patients (58%) the enlarged nodes showed only inflammatory changes and/or follicular hyperplasia. The authors concluded that significant lymph node enlargement frequently may be caused by inflammatory changes and this radiological finding should not be misinterpreted as metastatic disease.

In a study employing frozen section analysis of radiologically enlarged retroperitoneal lymph nodes (>1 cm), Ming *et al*. (8) reported that 69.4% patients had inflammatory lymphadenopathy, with no evidence of metastatic deposits even at final pathologic examination (100% positive predictive value and 95% negative predictive value).

Cases have been reported from developing countries where markedly enlarged retroperitoneal lymph nodes in patients of RCC turned out to be tubercular on histopathologic examination (9). The radiologic findings of tubercular and metastatic lymph nodes show considerable overlap. These patients were subjected to unwarranted extended lymph node dissection based on radiologic suspicion. The high incidence of tuberculosis in these countries combined with the immunosuppressive effects of malignancy per se and accentuated by chemotherapy, can explain this association. Falagas *et al*. (10) elaborate that the malignancy can mimic, follow or co-exist with tuberculosis in a wide range of clinical scenarios. They note that palpable lymph nodes due to tuberculous lymphadenitis may lead to overstaging in the TNM system.

The role of lymph node dissection (LND) in the management of RCC has been well reviewed by Zareba *et al*. (11). A plethora of studies have been published analyzing the role of LND in RCC. The methodologies and the results have both been conflicting and contrasting. The only prospective trial of these was the European Organization for Research and Treatment of Cancer (EORTC) randomized trial 30881 in patients with clinically localized RCC that revealed unsuspected lymph node metastasis in only 4% patients and reported no difference in progression-free survival (PFS) or overall survival (OS) between patients undergoing Radical nephrectomy (RN) and LND and those treated with RN alone (12).

So, when the present study proves that inflammatory lymphadenopathies have no impact on CSM, we seem to be flowing with the tide. However, the existing studies (7-10) merely document the existence of inflammatory lymphadenopathy in the setting of RCC. A major strength of the present study is that it is the first of its kind to attempt systematic analysis of the prognostic impact of inflammatory lymphadenopathy (pN0) in renal cell carcinoma. The rationale for the study and hypothesis are structured and well written.

However, a closer look at the analysis does raise a few questions with respect to methodology and analysis. The two groups of cN1 and cN0 patients do not seem comparable with a wide variation in the percentage of patients in the two categories (16% *vs*. 84%). Also, the cN1 group has three times greater proportion of high stage and metastatic disease. It is well established that the incidence of lymph node involvement varies with stage and grade of tumor (13). This is likely to bias results especially on univariable analysis.

Some of the statistical aspects need to be seen in the right perspective and demand attention. In view of significant differences in the two groups, propensity score matching would have made the groups comparable. In the multivariable analysis, 'Hazard Modeling' was performed under the paradigm of competing risk model. In such modelling procedures, the proportionality hazard assumption is an important aspect that needs to be seen before reporting the results. Under the methodological aspects this should also have been part of illustration. Furthermore, under the multivariable analysis for CSM, adjustment in P value for multiple comparisons would have enhanced the reliability of data analysis.

The authors acknowledge the use of primitive radiologic technology and lack of radiologic re-review which may have a significant impact on the results. Detection of metastatic nodes was based on dimensional thresholds, with LNs greater than 1 cm in diameter considered positive. Pre-operative computerized tomogram (CT) used alone has low specificity of 71% and poor positive predictive value of 56% to detect lymph node involvement at radical nephrectomy (14). Using only a maximum dimension 1 cm cut off has only 42% predictive probability and AUC of 0.72 (5). Micro-metastases are frequently overlooked. Hence the reliability of the cN0 status in the current study is questionable.

The authors have interpreted association of adverse

tumor characteristics with inflammatory lymphadenopathy on univariable analysis as an indicator of the poor prognosis. However, the skewed distribution of cases between the two groups with respect to tumor size/grade/stage/metastatic disease makes this interpretation questionable. The co-morbid status of the patients or association with markers of systemic inflammation is not discussed with respect to presence of associated systemic disease.

As in most other retrospective studies on lymph node dissection (LND) in RCC, the lymph node dissection template was not standardized. There is no data to explain why such a large proportion of cN0 patients underwent LND. The extent of the dissection in the cN0 category is not specified and is likely to be limited to hilar nodes. Although the hilar LNs are the most commonly excised LNs at the time of RN, up to 46% of patients with paraaortic or paracaval LN involvement will have negative hilar LNs (15). The incidence of nodal metastasis is influenced by the extent of lymphadenectomy as well as the number of nodes examined (13). As acknowledged by the authors, cN1 patients were more likely to have extended LND than cN0 (P=0.001). Therefore, the possibility of underreporting of the pN1 status cannot be ruled out.

It is not clear from the data presented that how many pathologically positive lymph nodes (pN1) were found during the study period of 28 years. This data is crucial to assess whether adequate pathologic assessment was performed before assigning a patient to the pN0 category.

Visual examination of 3 mm haematoxylin and eosin (H&E)-stained slices was the methodology used for pathologic involvement of lymph nodes by metastatic disease in this study. However, a fair proportion of micrometastasis (MIC) may be missed by this technique. The International Union Against Cancer defines tumor deposits between 0.2 and 2 mm as MICs and clusters and single cell infiltrations below this cutoff as isolated tumor cells (ITCs). This is equivalent to 0.032% to 1.6% of the total cells in the lymph node and can be easily missed by even serial sectioning or immunohistochemistry (16).

Three to five mm thick sections of the whole lymph node which are routinely examined, represent less than 0.1% of the node volume. It has been demonstrated that 19.4% of nodes that were MIC free under H&E examination were shown to be positive for MICs by immunohistochemistry (IHC) (17). There is no mention of use of IHC to detect MIC in the present study.

Hartana *et al*. (16) used flow cytometry to detect MICs in RCC patients using a combination of intracellular marker cytokeratin 18 (CK18) with the surface markers carbonic anhydrase IX (CA9) and Cadherin 6. In this study four out of five patients were diagnosed with positive MICs in lymph nodes by flow cytometry, whereas all of them were negative by H&E examination. These patients were restaged from pN0 to pN1. The focus of the current study being separation of pN0 from pN1 disease, more input on pathologic examination was essential for the same.

The authors compare their results to an old publication by Vasseli *et al*. (18) which assesses the impact of IL2 therapy with and without cytoreductive nephrectomy/metastatectomy/retroperitoneal lymphadenectomy, exclusively in cases of metastatic renal cell carcinoma (MRCC). Therefore, this data is not comparable to the present study. Also, there is no mention of pathologic examination of lymph nodes in Vasseli's paper and therefore cannot be equated with "inflammatory lymphadenopathy" in the present study. Similarly, the cN1 of Gershman's study (19) does not equate with the inflammatory lymphadenopathies in the current study which focuses on pN0 cases and includes metastatic disease. Gershman analyzed non-metastatic (M0) cases and included pN1 disease in their analysis. Additionally, he did propensity score matching to ensure the various groups being analyzed were comparable.

The authors findings contrast with those of Lee *et al*. and Babaian *et al*. (4,20) who have reported significantly worse cancer specific survival (CSS) in cN1pN0 compared to cN0pN0 disease. Both authors have studied non-metastatic disease, which is justified in view of their divergent management guidelines. In stark contrast to the present study, Lee *et al*. (20) report 5-year CSS of 70.1% in cN1pN0 *vs*. 91.3% in cN0pN0 disease (P<0.001). In Babian's study median OS was 123 months for cN0pN0 compared to 80.7 months in the cN1pN0 category (P<0.001).

Contemporary literature has provided ample evidence in favour of the prognostic impact of lymphadenopathy in RCC (1,13). Zareba *et al*. (11) state that pathologic LN status is one of the strongest predictors of prognosis in patients with clinically localized RCC undergoing nephrectomy. Karakiewicz *et al*. (21) demonstrate that the presence of LN metastases portends a poor prognosis that is similar to that of patients with visceral or bone metastases. An analysis of the SEER registry reported 5-year CSS probabilities of 84% and 38% among pN0 and pN1 patients, respectively (1). Importantly, the detrimental impact of LN metastases was found to be greatest among

patients with localized and low-grade tumors (13). The EORTC trial (12) negating the prognostic impact of LND was widely criticized for being underpowered, relying on very small patient numbers per participating institution, enrolling historical patients [1988–1991], and including mainly pT1 patients in whom LN invasion rates are so low that the benefit of LND is difficult to conceptualise (22).

A study carried out by Marchioni *et al.* (22) showed that in pT3 patients, the 5-year CSM-free survival according to absence or presence of LND was, 80.9% *vs.* 65.1%, respectively (P<0.001). Capitanio *et al.* (23) demonstrated that the number of positive nodes impacted CSM in pT4 patients. Lymph node metastases have been found to be associated with worse overall survival even in metastatic disease treated with targeted therapy (24). At 3 years after cytoreductive nephrectomy, the cancer-specific mortality-free rates of lymph node-negative and lymph node-positive MRCC patients differ by as much as 20% (25).

Unlike most other studies, Muttin *et al.* have included metastatic cases to the analysis of pN0 disease with the justification that this would reduce false positives. The percentage of these metastatic cases is minor and varies significantly between the two groups being analyzed (3% & 11% for cN0 and cN1respectively). Going by the above discussion on how micrometastases can be easily missed on routine 3 mm H&E sections, we are not sure as to how many truly represented pN0 disease. When the purpose was to analyze purely inflammatory lymphadenopathy (pN0), it was safe to exclude metastatic disease, especially when no special techniques were applied to exclude MICs and ITCs. In fact, in Babian's study the CSS of cN1pN0 and cN0pN1 patients was similar. They attributed this to the possible presence of systemic disease or micrometastasis in the latter group. Inclusion of metastatic as well as non-metastatic disease in the present study has made the data incomparable to majority of existing literature as well as irrelevant from the perspective of disease management.

The authors conclude by acknowledging a large number of limitations to the study including lack of radiologic re-review, utilization of primitive radiologic technology, retrospective nature of the study and lack of a standardized lymph node template.

The study started on a good note but detracted from the chosen path at some stage in the analysis. The authors present controversial results without convincing analytic backup. A more logical outcome of the present study would be that a significant proportion of lymphadenopathy in RCC is likely to be inflammatory and such lymphadenopathy has no impact on CSM of these patients. However, the rider here would be that these nodes must be adequately assessed radiologically and pathologically to confirm the absence of micro-metastatic (MIC) disease; which is a difficult and labor-intensive task in the current scenario. However much we may like to believe the statement that inflammatory lymphadenopathy in RCC does not impact CSM, the limitations in the present study demand a reassessment of the same.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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