Inflammatory lymphadenopathies predicting renal cell carcinoma prognosis: association not so convincing yet

Rizwan Ishtiaq[1], Zubair Khan[2]

[1]Department of Internal Medicine, Mercy St. Vincent Medical Center, Toledo, OH, USA; [2]Department of Internal Medicine, University of Toledo Medical Center, Toledo, OH, USA

Correspondence to: Zubair Khan, MBBS, MD, CMQ. Chief Resident (PGY-IV), Internal Medicine Residency, Department of Internal Medicine, University of Toledo Medical Center, 3000 Arlington Ave, Toledo, OH 43614, USA. Email: zubair.khan@utoledo.edu.

Provenance: This is an invited article commissioned by Section Editor Xiao Li (Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Muttin F, Pecoraro A, Larcher A, *et al.* Predictive and prognostic effect of inflammatory lymphadenopathies in renal cell carcinoma. World J Urol 2019;37:701-8.

Submitted Feb 25, 2019. Accepted for publication Mar 10, 2019.
doi: 10.21037/atm.2019.03.32
View this article at: http://dx.doi.org/10.21037/atm.2019.03.32

Renal cell carcinoma (RCC) is the most common cancer originating from the kidneys and is the most lethal genitourinary cancer (1). It is the ninth most common cancer worldwide (2). Almost 65,000 cases of RCCs are diagnosed in the United States annually (3). RCC is further classified into four independent entities based on histology i.e., clear cell carcinoma, papillary and chromophobe RCC and collecting duct RCC (4,5). Tumor node metastasis (TNM) system by American Joint Committee on Cancer (AJCC) is the most commonly used cancer staging system for RCC. This system was revised in 2010 for the last time and contains three components. T donates the size and extent of the invasion of the primary tumor, N shows extent of spread to local lymph nodes and M donates if there is metastasis (6). Based on information from the TNM system, RCCs are assigned from stage I to stage IV anatomically. Overall prognosis of the patients with RCC depends on the stage of the disease. 5 years disease specific survival rates in patients with stage I RCC is around 80–95% where as in patients with stage II RCC is approximately 80% (7). Five-year survival in stage III RCC is 60% (7). Several other factors also play a significant role in prognosis. Invasion of urinary collecting system in stage I–II RCC is associated with a worse prognosis decreasing the five-year survival to about 60% compared to 90% in patients without invasion of urinary system (8).

The first step in the diagnosis of RCC is the imaging of the abdomen in the form of CT scan or ultrasonography. Ultrasonography is usually helpful in differentiating benign cyst from a complex cyst or malignancy. If ultrasonography is inconclusive, CT scan of the abdomen with contrast is the imaging of choice. CT scan also helps in establishing the staging of malignancy. There are several other benign entities and premalignant conditions that mimic RCC on imaging. Such conditions include angiomyolipoma and oncocytomas (9). The definite diagnosis is made by histological examination of the tissue specimen obtained by complete or partial nephrectomy. Tissue diagnosis is necessary to obtain the tissue classification, and analysis of molecular and genomic markers which can help establish disease specific individualized approach for management. Tissue sampling is also necessary in differentiating RCC from metastasis of any distant malignancy into the kidneys, abscess, lymphoma or any other benign cyst (10). A study was conducted in Norway which revealed that the number of people diagnosed with RCC have increased from 21% in 1978–1987 to a 57% in 2005–2010 (11,12). Most obvious reason explained for this trend is the more frequent use of imaging for other comorbid conditions which leads to incidental diagnosis of RCCs. It was also shown that the chances of mortality in such patients was higher due to their comorbid conditions and other malignancies rather than directly from RCC (12).

Recently, an article published by Muttin *et al.* investigated the role of inflammatory lymphadenopathies in the

predictiveness and prognosis of RCC (13). They studied 719 patients who underwent radical or partial nephrectomy and lymph node dissection between 1987 and 2015. The aim of their study was cancer specific mortality and other cause mortality. They compared the patients with and without lymphadenopathy seen on CT or MRI preoperatively. All patients had pathologically no lymph node involvement. Their results revealed that patients who had lymphadenopathy seen on imaging (cN1) had larger tumors, higher tumor stage, more necrosis and distant metastasis compared to patients who had no lymphadenopathy seen preoperatively (cN0). At univariate analysis, inflammatory lymphadenopathy was seen to increase cancer specific mortality. However, in case of multivariate analysis, the inflammatory lymphadenopathy failed to reach the independent predictor status.

Although this study had a very long follow up of almost 29 years, it is a proven fact that the prognosis of RCC itself has improved a lot over the years which was not adjusted in this study. 1980s to 2005 was labelled as the cytokine era. Patients with stage IV RCC had a five-year disease specific survival rate of almost 10% with a median survival of 10–15 months (14,15). With the advancement in target organ therapy and more effective arsenal to tackle RCC, the medial overall survival in patients with stage IV RCC has been extended beyond two years (16). Secondly, this study itself did not include inflammatory indices into consideration. There are several causes of inflammatory lymphadenopathy which include infectious mononucleosis, anthrax, mesenteric lymphadenitis, AIDS, cat scratch disease, sarcoidosis, systemic lupus erythematosus (SLE) and rheumatoid arthritis (17). Several medicines like allopurinol, cephalosporins, sulfonamides, phenytoin, carbamazepine and several other drugs are also responsible for causing inflammatory lymphadenopathy (17). There is hardly any study in the literature that discussed the mortality rates associated with inflammatory lymphadenopathy in chronic medical conditions like sarcoidosis, SLE, rheumatoid arthritis, and other systemic infections. It is a known fact that mortality rates in patients with co-morbid conditions depend on their health status, aggressiveness of the disease and extent of complications from the comorbid conditions. This information is vital in order to access predictiveness and prognosis of RCC with the help of inflammatory lymphadenopathy. This information was missing from the study. Inflammatory lymphadenopathies include both infections and non-infectious granulomatous disorders (18). Non-infections cause like sarcoid have a relatively better prognosis compared to infectious causes which include a wide range of disorders like suppurative and non-suppurative lymphadenitis. Considering this fact, it is true that inflammatory lymphadenopathies may have a greater risk of morbidity but the effect of predictiveness and prognosis in patients with RCC cannot be established (18). One major limitation to this study in our point of view included that lack of information regarding types of RCC. As we discussed above, prognosis and predictiveness of RCC varies depending on the histological subtype of cancer. This information is necessary to accurately access the role of inflammatory lymphadenopathies in RCC patients. Lastly, an important point to take into consideration is that most of the patients in the study had pathologically pT1–T2 stage compared to advanced stage like pT3–T4. The fact that mortality was not found associated with the inflammatory lymphadenopathy can be related to the earlier stage of the disease itself.

Conclusively, in order to truly access the role of inflammatory lymphadenopathies in predictiveness and prognosis of RCC, a large-scale study is required with a limited time span with the use of recent technology which can consider the different type of lymphadenopathies and its associated morbidity and mortality. It should specifically focus equally or more in patients who have advanced stage of lymphadenopathy. Clinicians must always consider the nodal status based on pathology rather than on imaging in order to make the treatment directed decision for treatment of patients with RCC. It is true that with underlying inflammatory lymphadenopathy, the morbidity in patients with RCC will increase depending on the type of RCC. With the advancement in technology, the overall prognosis of conditions like RCC and inflammatory lymphadenopathies have both increased. So, a prospective study should be designed which should cover large number of patients over a limited number of years in order to truly depict the predictiveness and prognosis of inflammatory lymphadenopathies in RCC patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. International Agency for Research on Cancer. GLOBOCAN. Kidney—estimated incidence, all ages: both sexes. 2012
3. Shingarev R, Jaimes EA. Renal cell carcinoma: new insights and challenges for a clinician scientist. Am J Physiol Renal Physiol 2017;313:F145-54.
4. Eble JN, Sauter G, Epstein J, et al. Pathology and genetics of tumours of the urinary system and male genital organs. Lyon: World Health Organization, 2004.
5. Patard JJ, Leray E, Rioux-Leclercq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005;23:2763-71.
6. Edge SB, Byrd DR, Compton CC, et al. American joint committee on cancer staging manual. 7th Edition. NY: Springer, 2010.
7. Elmore JM, Kadesky KT, Koeneman KS, et al. Reassessment of the 1997 TNM classification system for renal cell carcinoma: A 5-cm T1/T2 cutoff is a better predictor of clinical outcome. Cancer 2003;98:2329-34.
8. Verhoest G, Avakian R, Bensalah K, et al. Urinary collecting system invasion is an independent prognostic factor of organ confined renal cell carcinoma. J Urol 2009;182:854-9.
9. Jonasch E, Gao J, Rathmell WK. Renal cell carcinoma. BMJ 2014;349:g4797.
10. Lardas M, Stewart F, Scrimgeour D, et al. Systematic review of surgical management of nonmetastatic renal cell carcinoma with vena caval thrombus. Eur Urol 2016;70:265-80.
11. Beisland C, Medby PC, Beisland HO. Renal cell carcinoma: gender difference in incidental detection and cancer-specific survival. Scand J Urol Nephrol 2002;36:414-8.
12. Sand KE, Hjelle KM, Rogde ÅJ, et al. Incidentally detected renal cell carcinomas are highly associated with comorbidity and mortality unrelated to renal cell carcinoma. Scand J Urol 2013;47:462-71.
13. Muttin F, Pecoraro A, Larcher A, et al. Predictive and prognostic effect of inflammatory lymphadenopathies in renal cell carcinoma. World J Urol 2019;37:701-8.
14. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530-40.
15. Mekhail TM, Abou-Jawde RM, BouMerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 2005;23:832-41.
16. Gore ME, Larkin JM. Challenges and opportunities for converting renal cell carcinoma into a chronic disease with targeted therapies. Br J Cancer 2011;104:399-406.
17. Ferrer R. Lymphadenopathy: differential diagnosis and evaluation. Am Fam Physician 1998;58:1313-20.
18. Asano S. Granulomatous lymphadenitis. J Clin Exp Hematop 2012;52:1-6.

Cite this article as: Ishtiaq R, Khan K. Inflammatory lymphadenopathies predicting renal cell carcinoma prognosis: association not so convincing yet. Ann Transl Med 2019;7(8):164. doi: 10.21037/atm.2019.03.32

