Editorial Commentary

Strengthening the foundation of kidney cancer treatment and research: revising the AJCC staging system

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Introduction

For decades, the tumor-node-metastasis (TNM) classification system has served as a standard for cancer staging. Developed by the American Joint Commission on Cancer (AJCC) and the Union for International Cancer Control (UICC), the TNM staging system has been essential for cancer classification, prognostication, management, data registration, and clinical research. TNM subgroups have been clustered to create a prognostic staging classification system, which portends overall survival (OS) and disease severity. In 2016, the AJCC published the 8th edition of the AJCC Cancer Staging Manual (8E AJCC) in order to: (I) update staging definitions based on contemporary pathology terminology; (II) clarify tumor histology classifications; (III) present predictive factors in a methodical fashion.

While genomic and biochemical research have resulted in a rapid expansion of novel kidney cancer therapies within the last decade (1-4), the kidney cancer prognostication system saw minimal changes despite more contemporary data. In particular, the updates for kidney cancer in the 8E AJCC include the adoption of the four-tiered WHO/ISUP nucleolar histological grading system and clarification of T3a disease. Since the incorporation of renal sinus invasion as pT3a in the AJCC staging system in 2002, subsequent studies had confirmed the importance of this finding as it is believed to be the principal route of extrarenal extension (5). While the 7E AJCC relied on gross inspection for pT3a staging purposes, the 8E AJCC removed the word "grossly" to describe renal vein invasion, which can be commonly missed on gross examination, especially on partial nephrectomy specimens. Additionally, "muscle containing" was replaced with involvement of "segmental veins" to describe tumor extension, and invasion of the pelvicalyceal system was added (6). These changes have rather large implications as they change the definition of locally advanced disease.

Evidence in support of modifying the AJCC for renal cell carcinoma

Given the implications of these changes, the prognostic accuracy of the 8E AJCC has been evaluated for many different types of cancers. Similarly, Shao *et al.* examined the prognostic accuracy of different TNM subgroups based on 8E AJCC for kidney cancers in the Fudan University Shanghai Cancer Center (FUSCC) cohort, which included 2,120 patients (7). Using this data, TNM subgroups were regrouped based on the OS to create a modified AJCC stage grouping (*Table 1*), which better predicted patient outcomes. This modified AJCC stage grouping was then validated using 74,506 patients from the Surveillance, Epidemiological and End Results (SEER) database. Shao *et al.* demonstrated that the modified AJCC stage grouping can better predict the OS in stage II–IV renal cell carcinoma (RCC). In their modified staging scheme, T1-3N1M0 was grouped with T4N0M0 disease, which had a similar OS. Importantly, these results highlight that the 8E AJCC staging system does not adequately stratify OS

Table 1 Comparison of 8E AJCC prognostic groups to other proposed classification schemes

Stage	8E AJCC (8)	Shao *et al.* proposed staging (7)	Yu *et al.* proposed staging (9)	Integrated proposed staging
I	T1N0M0	Ia: T1N0M0	T1N0M0	T1N0M0
		Ib: T2N0M0		
II	T2N0M0	T3N0M0	T2N0M0	T2N0M0
III	T1-2N1M0, T3NanyM0	T1-3N1M0, T4N0M0	T3N0M0	T3N0M0
IV	T4NanyM0, TanyNanyM1	T4N1M0, TanyNanyM1	T1-3N1M0, T4NanyM0, TanyNanyM1	IVa: T3N1M0, T3N0M1, T4N0M0
				IVb: T4N1M0, T4N0M1, T4N1M1

for stage III and IV disease as patients with T4N0M0 were grouped with stage IV disease, yet had significantly higher OS compared to patients with T4N1M0 and TanyNanyM1 disease.

While survival data from the FUSCC cohort was used to modify the 8E AJCC, the reclassified system was validated using the SEER database. However, approximately 82% of the patients in the FUSCC cohort had clear cell RCC compared to 59% of patients in the SEER cohort. While unspecified data in the SEER database may account for this disparity, genetic variations in the predominantly Asian patient population may also explain this disparity. Largely associated with Asian population, the vascular endothelial growth factor (VEGF) rs699947 polymorphism was associated with increased risk of RCC (10). A larger proportion of the FUSCC cohort was <65 years of age compared to the SEER cohort further supporting that inherent differences likely exist between the two cohorts. Despite these differences, the modifications made to the 8E AJCC better prognosticate OS for both cohorts.

In a similar study, Yu *et al.* from MD Anderson Cancer Center performed a retrospective analysis comparing the OS in patients Stage III RCC with and without nodal disease. Specifically, patients with pT1-3N1M0 RCC had a significant survival disadvantage compared to those with pT3N0M0 RCC (OS: 10.2 *vs.* 2.4 years, P<0.0001) and, importantly, overall and cancer-specific survival for pT1-3N1M0 was most similar to patients with pT1-3NanyM1 RCC (OS: 2.4 *vs.* 2.4 years, P=0.62; CSS: 2.8 *vs.* 2.4 years, P=0.10) (9). In fact, Yu *et al.* suggested that pT1-3N1M0 disease should be considered stage IV disease and further highlights the significant survival differences between TNM staging subgroups. In an arena where therapies are constantly being tested, it is imperative that the prognostic staging provide the most accurate information for both patients and clinicians. While the 8E AJCC recognizes nuances of T3 disease, further modifications may allow more accurate coupling of stage and prognosis. Considering this, this may warrant that clinical trial data should be re-analyzed based on TNM staging to see how therapies distinct subgroups rather than prognostic groups, which under the current 8E AJCC system inaccurately congregates TNM subgroups.

Implications for surgical management

Reclassification may also explain why surgical interventions such as lymphadenectomy (LND) for locally advanced RCC have little clinical benefit. Recent work by Farber *et al.* demonstrated that LND provided no significant survival benefit even among patients with clinical node positive disease (11). One possible explanation for these results might be these patients have a higher staging than once believed. Another possibility is the subjective nature of some histological assessments contributing to pT3 (12). Our proposed prognostic staging system (*Table 1*) considers T3N0M0 as Stage III and breaks Stage IV into two subgroups. Stage IVa includes T3N1M0, T3N0M1, and T4N0M0 while Stage IVb includes T4N1M0, T4N0M1, and T4N1M1. This is consistent with the observation made by Shao *et al.* that T3N0M0 should not be considered as a high-risk stage group. Moreover, our classification scheme subdivides stage IV into distinct populations. Therefore, patients with nodal disease under our proposed classification system would have stage IVa disease. Patients with stage IVb disease, based on the extent of their disease and performance status, may benefit more from immediate systemic therapy compared to cytoreductive nephrectomy (13,14).

For some patients with metastatic foci, surgical resection of distant metastatic lesions, or metastatectomy, can be a feasible and curative option. While staging stratification does very little to identify these patients, it is important to note that complete resection of solitary metastases is associated with a survival benefit (15). However, histological features are also important for prognosis as different features of RCC behave differently. For example, while sarcomatoid differentiation can be seen in 1–8% of renal tumors, it has consistently been associated with a poor prognosis (16). While modifying staging classification may provide accurate OS, it does not provide the nuances of which individuals will benefit from different therapies, such as systemic therapy or metastatectomy. Furthermore, prognostic staging serves to provide an overall impression whereas the individual patient may have other important comorbidities that will influence survival.

Implications for systemic therapy

A revised AJCC staging system that reclassifies N+ disease as stage IV and recognizes both a stage IVa and IVb will improve our use of systemic therapies for metastatic RCC. Since we believe that these two prognostic subgroups represent distinct survival profiles, they would likely benefit from different therapies. The CARMENA trial demonstrated that systemic therapy with sunitinib was noninferior to cytoreductive nephrectomy in patients with intermediate and poor-risk disease (13). Similarly, the SURTIME trial showed that patients' progression-free survival at 28 weeks was not improved by when patients were started on neoadjuvant sunitinib prior to cytoreductive nephrectomy compared to immediate cytoreductive nephrectomy (17). It is abundantly clear that patients with intermediate and poor-risk disease should be further stratified based on their risk score to provide the best treatment option (i.e., systemic therapy versus surgical intervention). For example, patients with poor risk score would likely benefit from systemic therapy rather than surgical intervention, as this would likely delay further treatment and subject patients to unnecessary surgical complications (14,18). It should be noted that poor-risk disease is not synonymous with stage IV disease. Therefore, care still needs to be taken when deciding which patients will benefit from systemic therapy or surgical intervention. This warrant further investigation given that approximately one-third of patients present initially with advanced disease (19).

Within the last decade, there has been an explosion of trial data that has evaluated the use of systemic therapy to treat metastatic disease. Various novel systemic therapies have been approved based on these trials as well. In hindsight, recent trial warrants closer examination to identify which TNM staging groups maximally benefited from systemic therapies. Patients often get grouped based on the prognostic staging when clinical trial data is presented and therefore, stratification may allow for better resolution of the benefit a therapy may offer. Perhaps, trial data should be evaluated using TNM staging until reclassification is standardized to better prognosticate survival for patients with different disease pathology.

Implications for research

Regardless of the classification scheme used, Shao *et al.* have highlighted a major shortcoming of the 8E AJCC staging system—it fails to provide adequate prognostic accuracy for stage III and IV RCC. These are the patients who may require multimodal or multi-agent therapy. Patients with stage I and II RCC most often can be treated with surgery alone; however, some patients will recur and approximately 20–30% of patients present with distant disease at the time of diagnosis (19,20). Modifying the 8E AJCC not only alters how we think about treating these patients but also changes who is eligible for clinical trials. While this changes clinical practice, the burden of incorrect classification is much larger as the propagation of an insufficient staging system results in misjudging the risks associated with treatments and their outcomes, undermining the scientific validity of the research being conducted (21,22).

TNM staging provides researchers an important way to screen patients who are most suitable for any given clinical trial. However, this assumes that the filtering method correctly categorizes each patient such that the treatment arms offered are sound (understanding that equipoise is present and that risks are minimized while potential benefits are maximized for all research participants). The work from Shao *et al.* strongly suggests that reclassifying prognostic staging groups would affect which patients are included and excluded in clinical trials. This raises serious ethical concerns as it is difficult to ensure fair subject selection, adequate informed consent, and appropriate regulatory review/oversight when a suboptimal staging system is used to design clinical trials (23). Patients who might benefit from a novel clinical therapy may be excluded or the suboptimal patient population might be exposed

to increased risk of harm. Since prospective clinical trials provide the foundation upon which we base our clinical decision practice, the effect of a misclassified staging system can be magnified and perpetuated.

Conclusions

Creating a prognostic system that fits an entire population is a dynamic process and requires an interdisciplinary approach given that specific pathological factors has implication for survival. The onus of accurately characterizing the prognosis of these patients with RCC lies, not in the AJCC, but in the multiple specialties that care for these patients. The multiple proposed classification systems (*Table 1*), which must be validated, suggest that our understanding of Stage III and IV RCC is still evolving and as new information is synthesized this classification should be revisited and re-evaluated. The next decade will see a continued increase in the therapies offered for RCC, and especially for the management of high-volume disease. Therefore, providing accurate information both to patients and physician is of the utmost importance.

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Footnote

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References

1. Ball MW, Singer EA, Srinivasan R. Renal cell carcinoma: molecular characterization and evolving treatment paradigms. Curr Opin Oncol 2017. [Epub ahead of print].
2. Farber NJ, Kim CJ, Modi PK, et al. Renal cell carcinoma: the search for a reliable biomarker. Transl Cancer Res 2017;6:620-32.
3. Modi PK, Farber NJ, Singer EA. Precision Oncology: Identifying Predictive Biomarkers for the Treatment of Metastatic Renal Cell Carcinoma. Transl Cancer Res 2016;5:S76-S80.
4. Modi PK, Singer EA. Improving our understanding of papillary renal cell carcinoma with integrative genomic analysis. Ann Transl Med 2016;4:143.
5. Bonsib SM. The renal sinus is the principal invasive pathway: a prospective study of 100 renal cell carcinomas. Am J Surg Pathol 2004;28:1594-600.
6. Paner GP, Stadler WM, Hansel DE, et al. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. Eur Urol 2018;73:560-9.
7. Shao N, Wang HK, Zhu Y, et al. Modification of American Joint Committee on cancer prognostic groups for renal cell carcinoma. Cancer Med 2018;7:5431-8.
8. Edge SB, Fritz AG, Byrd DR, et al. editors. American Joint Committee on Cancer. AJCC cancer staging handbook: from the AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
9. Yu KJ, Keskin SK, Meissner MA, et al. Renal cell carcinoma and pathologic nodal disease: Implications for American Joint Committee on Cancer staging. Cancer 2018;124:4023-31.
10. Song Y, Hu J, Chen Q, et al. Association between vascular endothelial growth factor rs699947 polymorphism and the risk of three major urologic neoplasms (bladder cancer, prostate cancer, and renal cell carcinoma): A meta-analysis involving 11,204 subjects. Gene 2018;679:241-52.
11. Farber NJ, Rivera-Núñez Z, Kim S, et al. Trends and outcomes of lymphadenectomy for nonmetastatic renal cell carcinoma: A propensity score-weighted analysis of the National Cancer Database. Urol Oncol 2019;37:26-32.
12. Williamson SR, Rao P, Hes O, et al. Challenges in Pathologic Staging of Renal Cell Carcinoma: A Study of Interobserver Variability Among Urologic Pathologists. Am J Surg Pathol 2018;42:1253-61.
13. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med 2018;379:417-27.
14. Motzer RJ, Russo P. Cytoreductive Nephrectomy - Patient Selection Is Key. N Engl J Med 2018;379:481-2.
15. Shinder BM, Rhee K, Farrell D, et al. Surgical Management of Advanced and Metastatic Renal Cell Carcinoma: A Multidisciplinary Approach. Front Oncol 2017;7:107.
16. Psutka SP, Master VA. Role of metastasis-directed treatment in kidney cancer. Cancer 2018;124:3641-55.
17. Bex A, Mulders P, Jewett M, et al. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncol 2018. [Epub ahead of print].

18. Bhindi B, Habermann EB, Mason RJ, et al. Comparative Survival following Initial Cytoreductive Nephrectomy versus Initial Targeted Therapy for Metastatic Renal Cell Carcinoma. J Urol 2018;200:528-34.
19. Lam JS, Leppert JT, Belldegrun AS, et al. Novel approaches in the therapy of metastatic renal cell carcinoma. World J Urol 2005;23:202-12.
20. Janzen NK, Kim HL, Figlin RA, et al. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003;30:843-52.
21. Rid A, Emanuel EJ, Wendler D. Evaluating the risks of clinical research. JAMA 2010;304:1472-9.
22. Modi PK, Singer EA. Ethical Issues in the Management of Renal Cell Carcinoma. Kidney Cancer J 2015;13:10-7.
23. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000;283:2701-11.

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