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To Be or "Node" to Be: Nodal Disease and the Role of Lymphadenectomy in the Treatment of Renal Cell Carcinoma

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Abstract

Lymph node involvement in renal cell carcinoma (RCC) correlates with poor oncologic outcomes. However, current RCC staging guidelines may not fully reflect the survival impact of lymph node positive disease. Recent data demonstrates that nodal disease has significant impact on survival and modifications to current staging guidelines have been proposed. Lymph node dissection (LND) at the time of surgical intervention for RCC remains controversial. While clinical trial data have demonstrated conflicting evidence for LND, some institutional studies suggests that carefully selected patients at high-risk for recurrence may benefit from LND. Prospectively, clinical trials are examining treating nodal disease and disease at high-risk of recurrence in the neoadjuvant and/or adjuvant setting at the time of nephrectomy. These promising trials are poised, if successful, to influence the treatment paradigm for localized RCC.

Keywords

renal cell carcinoma; lymph node dissection; immunotherapy

Introduction:

In 2020, an estimated 73,750 incident cases and 14,830 deaths due to renal cell carcinoma (RCC) are expected in the United States alone.[1] Lymph node involvement in RCC is associated with a poor prognosis in both locally advanced and metastatic disease.[2, 3] Several studies have demonstrated that pathologic lymphadenopathy predicts worse survival.[4–7]

The gold standard for RCC is surgical extirpation with either partial nephrectomy (PN) or radical nephrectomy (RN). For many urologic malignancies, lymph node dissection (LND) has been shown to be an important surgical intervention for disease staging and improving oncologic outcomes. Nevertheless, LND during PN or RN remains controversial. More recent data suggests that lymph node disease has significant impact on staging and survival. In fact, the American Urological Association advocates for LND at the time of nephrectomy for clinically concerning regional lymphadenopathy.[8] This review will examine the role of

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lymph node disease in RCC and its impact on disease staging and survival. Finally, we will review current clinical trials that are examining nodal disease in localized RCC.

1. The Role of Lymph Node Dissection in Renal Cell Carcinoma

Despite worse outcomes with lymph node metastases, the role of LND in RCC remains controversial. LND can provide diagnostic information; however, the lack of a consistent template for LND, lack of strong evidence supporting a survival advantage, and low incidence of LN metastases in the absence of clinical suspicion has led to poor adoption of LND in clinical practice.[9–11]

Lymphatic drainage for the kidneys remains unpredictable. Elegant injection studies by Parker et al. in cadavers demonstrated that the right kidney drains into the paracaval, precaval, retrocaval, and interaortocaval nodes and left kidney drain into the para-aortic, preaortic nodes, and retroaortic nodes.[12] However, inter-connections between the retroperitoneal lymphatic system make lymphatic drainage unpredictable.[13, 14] Furthermore, posterior efferent lymphatic vessels in some cases drain directly into the thoracic duct, which may contribute to distant metastasis without any nodal disease in the retroperitoneum.[12] To this end, in up to 29% of cases with distant disease there is a lack of ipsilateral hilar involvement.[11] The complex lymphatic drainage of both kidneys makes it difficult to reliably predict the pattern of nodal involvement during surgical intervention.

Originally, the use of LND was first described in 1969 by Robson and colleagues and was suggested to be associated with higher overall survival (OS) when used in conjunction with radical nephrectomy for RCC.[15] Several studies have weighed in on the role and efficacy of LND in treatment of RCC since.[5, 16–19] The only prospective phase 3 clinical trial, EORTC 30881, to assess the efficacy of LND during nephrectomy for RCC demonstrated that there were no significant differences in OS and progression-free survival between the nephrectomy/LND group and nephrectomy only group.[9] Importantly, in this study the rate for unsuspected LN metastases was 4%, suggesting that there was no additional survival advantage of performing an LND at time of nephrectomy. However, patients selected for this trial, representing a lower risk subset of those undergoing nephrectomy, had a resectable renal mass with cN_0M_0; such a patient population that would likely not benefit from LND in any case. Subsequent retrospective trials have suggested that patients with “high risk” features would benefit from LND and that increased LN yields can improve disease-specific survival in these patients.[5, 10, 16, 19] However, work by Farber et al. evaluating 11,867 patients that underwent LND for RCC demonstrated that there was no overall survival advantage with LND among the general population, patients with clinical node positive disease, or in any subgroup of patients undergoing LND[20] Moreover, this study also highlighted the overutilization of LND among patients with pT1 and pT2 RCC, which Capitanio et al. have shown that only 1.1% and 2.3% of patients, respectively, have nodal disease.[7, 20]

The diagnostic accuracy of staging LN disease has also been assessed. Radadia et al. demonstrated that among patients that received a lymph node dissection, preoperative clinical LN staging had a 95% specificity to detect positive pathological LN compared to the 67% sensitivity to detect positive pathological LN.[21] Furthermore, this study demonstrated

patients with clinical node negative LN disease were likely to have pathologically negative LN disease with a negative predictive value of 94%, compared to the positive predictive value of 74%. However, the most recent American Urological Association guideline based on expert opinion supports the surgical excision of clinically positive LN disease, despite poor sensitivity and PPV. Clinical risk factors such as >10cm primary tumor, cT3/T4, high tumor grade, sarcomatoid features, and histologic tumor necrosis are associated with increased incidence of positive nodal disease, as patients with 2 or more of these risk factors have a >40% increased risk of nodal disease.[22] This suggests that a comprehensive preoperative evaluation is needed prior to the surgical resection, especially in patients with risk factors.

2. Nodal disease in Renal Cell Carcinoma

Pathologic staging for RCC is a critical aspect in the management and treatment of RCC as surveillance and adjuvant treatment selection vary based on staging. This is especially true when a staging system is used to determine the risk of RCC progression or mortality from the disease. The tumor-node-metastasis (TNM) classification has been critical for classifying, prognosticating, treating cancers, as well as enrolling patients into clinical trials. Nevertheless, a system that has remained rather important for all the aforementioned reasons has seen minimal changes despite contemporary evidence. In 2016, the American Joint Commission on Cancer updated the TNM staging guidelines for RCC to update staging definitions based on contemporary pathology terminology, clarify histological classifications, present predictive factors in a methodical fashion.

In fact, nodal involvement in RCC has been shown to be associated with a poor prognosis, despite the absence of metastatic disease.[23, 24] Several studies have shown that the 5-year cancer-specific survival (CSS) ranges between 25% and 40% in this subgroup of patients.[5, 25, 26] Sun et al. examined the 5-year CSS after nephrectomy in patients with nodal disease relative to patients without nodal disease in non-metastatic RCC using the Surveillance, Epidemiological and End Results (SEER) database.[27] Furthermore, they stratified the cohort based on pathological tumor stage. Multivariable analysis demonstrated that there was 6-, 3.6-, 3.2-, and 2-fold increased risk of death after nephrectomy in patients with nodal disease among pT_1, pT_2, pT_3, and pT_4 RCC, respectively. Taken together, the prognostic impact that nodal disease has on accurate staging is critical.

Recently, several studies have questioned the prognostic accuracy of the TNM staging system. Shao et al. examined used a single institution database of 2120 patients to determine the overall survival (OS) each TNM group.[28] TNM groups with similar survival curves were grouped together to create a modified TNM stage grouping. They validated this modified grouping of 74,506 patients with RCC from the SEER database. Using a modified AJCC staging system, they were able to better predict OS in stage II-IV RCC compared to the current TNM staging method. Importantly, patients with $T_{1–3}N_1M_0$ had similar OS to patients with $T_4N_0M_0$ disease, suggesting that nodal disease has significant impact on OS and prognostication.

A recent single-institution retrospective study from MD Anderson Cancer Center compared the overall survival in patients with Stage III RCC with and without disease.[3] Patients with

$pT_{1–3}N_1M_0$ RCC had a significant survival disadvantage compared to those with $pT_3N_0M_0$ RCC (OS: 10.2 vs 2.4 years, p<0.0001). Furthermore, $T_{1–3}N_1M_0$ patients had an OS and cancer-specific survival (CSS) that was similar to $T_{1–3}N_{any}M_1$ RCC (OS: 2.4 vs 2.4 years, p=0.62; CSS: 2.8 vs 2.4 years, p=0.10). This underscores the prognostic implication of nodal disease and in line with this, Yu et al. recommended that $pT_{1–3}N_1M_0$ RCC should be considered Stage IV disease rather than current AJCC recommendations for Stage III disease.

Work from our group, utilizing the National Cancer Database (NCDB), has further corroborated these findings using a nationally representative cohort of patients.[29] The outcomes were compared for patients with Stage III node-positive ($pT_{1–3}N_1M_0$), Stage III node-negative ($pT_3N_0M_0$) disease or Stage IV metastatic disease ($pT_{1–3}N_0M_1$). Patients with Stage III node-negative disease had increased survival compared to Stage III node-positive and Stage IV metastatic disease. Like Yu et al., our data shows that Stage III node-positive disease (22.7%; 95% CI: 20.6%–24.9%) and Stage IV RCC patients and (15.6%; 95% CI: 11.1%–23.8%) have similar 5-year survival rates. Recently, Han et al. used the Surveillance, Epidemiology, and End Results (SEER) database performed a similar analysis to compare survival outcomes for patients with $pT_{1–3}N_1M_0$ to $pT_3N_0M_0$ and $pT_{1–3}N_0M_1$ RCC.[30] Using propensity score matching to adjust for baseline confounders, patients with Stage III nodal-positive had similar OS and cancer-specific survival (CSS) to patients with Stage IV disease (median OS 41.0 vs. 38.0 months, p=0.77; CSS 45.0 vs. 39.0 months, p=0.59). This study then created modified AJCC staging where Stage IIIa ($pT_3N_0M_0$), IIIb ($pT_{1–3}N_1M_0$, $pT_4N_{any}M_0$), and IV ($pT_{any}N_{any}M_1$) showed higher predictive accuracy than AJCC stage system. These studies strongly suggest that lymph node positive disease should be considered as Stage IV disease, which has significant implications for survival as well as prognostication and treatments that may be offered to this cohort of patients. We have proposed an integrated staging system to aid in better classifying these patients. We suggest creating a subdivision of Stage IV disease, where Stage IVa would include patients with $T_{1–3}N_1M_0$ and $T_4N_0M_0$ disease and Stage IVb would encompass $T_4N_1M_0$, $T_4N_1M_1$, $T_4N_0M_1$ RCC (Table 1).[31]

3. Future

Upward of 40% of patients who undergo surgical resection have recurrence due to micrometastatic disease at the time of surgery.[32] Nodal disease is one of the high-risk features that portends a high likelihood for recurrence and may explain decreased overall survival in patients with nodal disease. Other factors besides nodal status such as histological grade, ≥T3 staging, performance status may also contribute to overall survival. Contemporary studies have therefore been interested in augmenting overall survival and recurrence-free survival in patients undergoing nephrectomy for RCC.

The discovery of oxygen-sensing pathways, essential for the growth of RCC, was recently recognized by the 2019 Nobel Prize in Physiology and Medicine.[33] This discovery has led to targeted therapies against vascular endothelial growth factor (VEGF), its receptor (VEGFR), and the mammalian target of rapamycin (mTOR) that have been successful in treating metastatic RCC. Application of these agents earlier in the disease process was thought to be

a rational choice for patients with increased likelihood of recurrence. To date over 13 randomized trials have evaluated systemic adjuvant therapies for RCC; however, only one study has yielded positive results.[34]

Of the reported trials, only the S-TRAC trial has demonstrated improved disease-free survival (DFS; HR 0.74, 95% CI 0.55–0.99, p=0.04) in patients with high risk for RCC recurrence (T3, unknown or no nodal involvement, T4±nodal disease, Fuhrman grade ≥2), but no difference in OS at median follow up of 5.4 years.[35] Furthermore, no subgroup analysis has specifically evaluated nodal disease. Importantly, only 56% of patients were able to complete the full 1-year treatment, with 28% of patients having to discontinue sunitinib due to adverse events. Hand-foot skin reactions were prevalent in 15% of patients receiving sunitinib. Furthermore, a large proportion of patients required dose reduction in order to continue taking sunitinib. Data from this study supported the approval by the US FDA in November 2017 for sunitinib in the adjuvant setting for high-risk clear cell RCC after nephrectomy, although its use seems muted. Nevertheless, the other trials using targeted therapies have demonstrated no significant differences and does provide conflicting evidence on the efficacy of adjuvant TKI therapy for patients with high-risk nonmetastatic RCC (Table 2).

The advent of novel immunotherapies has revolutionized how RCC is managed and treated.[36] Immune checkpoint proteins, such as CTLA-4, PD-1, LAG-3, and TIM-3, are key regulators of the immune system that when stimulated can inhibit the anti-tumor response.[37] The expansion of new immunotherapies has exploited this evasion strategy to develop therapies that target these immune checkpoints, which was awarded the 2018 Nobel Prize in Physiology and Medicine.[38] These therapies have largely been evaluated for patients with metastatic RCC, where surgical intervention may not be feasible. In fact, the efficacy of ipilimumab/nivolumab has brought much fervor into the field, as the combination has improved OS, progression-free survival, and objective responsive rates with manageable toxicities in patients in metastatic RCC.[39] Since this combination was approved, several additional combination therapies have been shown to also have similar efficacy and are FDA-approved for management of metastatic RCC.[40, 41] Given the success of this combination in metastatic RCC, the efficacy of immunotherapies in treating micrometastatic disease after nephrectomy remains to be understood. Several ongoing trials are currently investigating the use of adjuvant immunotherapy and one trial is investigating the use of perioperative immunotherapy in patients with high-risk of recurrence post-nephrectomy for RCC (Table 3).

Enhancing the immune response in metastatic RCC has been an important aspect of immunotherapies. Current trials examining the use of neoadjuvant, perioperative, and adjuvant immunotherapies have sought to use this response to curtail disease progression in patients with high-risk of recurrence after nephrectomy (Table 3). However, the immune response in these three different settings may also be different.

In the adjuvant setting, the nephrectomy is thought to decrease the PD-1 expression on all peripheral mononuclear cell types and subsequent administration of anti-PD-1 therapy elicits antitumor T cells within the tumor microenvironment, lymph node, and any additional

distant site. On the contrary, neoadjuvant dose of anti-PD-1 therapy can elicit the antitumor response prior to nephrectomy and lead to the treatment of possible areas of micrometastases. Perioperative therapy combines neoadjuvant and adjuvant dosing in order to maintain the antitumor response post-nephrectomy.[42]

As the results from these trials are still pending, it remains to be seen what strategy is sufficient to generate a durable recurrence-free survival. Particularly, patients with nodal disease represent a subpopulation of patients that are at high-risk for recurrence and likely to benefit from adjuvant or neoadjuvant immunotherapy. However, neoadjuvant therapy may help curtail disease progression and increase oncologic favorability prior to tumor resection. While the use of a single dose of neoadjuvant nivolumab in the PROSPER RCC trial may not be enough to eliminate all micrometastatic disease, it may help elicit a strong antitumor response prior to nephrectomy, since the tumor antigens are still present, which can further downregulate PD-1 expression.[42]

4. Conclusion

Accurately detecting nodal disease in RCC is of paramount importance for clinical staging, as prognostic and survival outcomes are drastically reduced in the presence of nodal disease. Even though LND during nephrectomy for RCC remains controversial, a select group of patients at high-risk for recurrence may benefit from LND. Therefore, developing detection methods to identify patients with nodal disease will help determine who will benefit most from LND and potential systemic therapy. Furthermore, LND provides important staging, prognostic, and counseling value, which based on recent studies has drastic survival outcomes.[3, 29, 30] The onus of creating a more accurate TNM staging system will need to be a multidisciplinary effort in order to provide physicians with reliable information for counseling patients and accurately stratifying patients within clinical trials and standard of care practice.

Clinical trials targeting nodal disease in the neoadjuvant and adjuvant setting are currently underway (Table 3) and if successful, they will change the paradigm for managing and treating high risk RCC. As recent clinical trials for metastatic RCC have shown that combination therapies have improved overall survival and progression-free survival, the role of these combination therapies in localized RCC remains to be understood.[43, 44] Urologists and medical oncologists should encourage all potential research participants to consider enrolling in a clinical trial so we may answer these critical questions about the role of lymphadenectomy and perioperative therapy in the management of renal cell carcinoma.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30. [PubMed: 31912902]

2. Kroeger N, Pantuck AJ, Wells JC, Lawrence N, Broom R, Kim JJ, et al. Characterizing the impact of lymph node metastases on the survival outcome for metastatic renal cell carcinoma patients treated with targeted therapies. Eur Urol. 2015;68(3):506–15. [PubMed: 25524810]

3. Yu KJ, Keskin SK, Meissner MA, Petros FG, Wang X, Borregales LD, et al. Renal cell carcinoma and pathologic nodal disease: implications for american joint committee on cancer staging. cancer. 2018;124(20):4023–31. [PubMed: 30276798]

4. Rodriguez-Covarrubias F, Castillejos-Molina R, Sotomayor M, Mendez-Probst CE, Gomez-Alvarado MO, Uribe-Uribe N, et al. Impact of lymph node invasion and sarcomatoid differentiation on the survival of patients with locally advanced renal cell carcinoma. Urol Int. 2010;85(1):23–9. [PubMed: 20693824]

5. Whitson JM, Harris CR, Reese AC, Meng MV. Lymphadenectomy improves survival of patients with renal cell carcinoma and nodal metastases. J Urol. 2011;185(5):1615–20. [PubMed: 21419453]

6. Blute ML, Leibovich BC, Cheville JC, Lohse CM, Zincke H. A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. J Urol. 2004;172(2):465–9. [PubMed: 15247704]

7. Capitanio U, Jeldres C, Patard JJ, Perrotte P, Zini L, de La Taille A, et al. Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma. BJU Int. 2009;103(1):33–7.

8. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA Guideline2017 Available from: https://www.auanet.org/guidelines/renal-cancer-renal-mass-and-localized-renal-cancer-guideline.

9. Blom JH, van Poppel H, Marechal JM, Jacqmin D, Schroder FH, de Prijck L, et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol. 2009;55(1):28–34. [PubMed: 18848382]

10. Crispen PL, Breau RH, Allmer C, Lohse CM, Cheville JC, Leibovich BC, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. Eur Urol. 2011;59(1):18–23. [PubMed: 20933322]

11. Hadley DA, Stephenson RA, Samlowski WE, Dechet CB. Patterns of enlarged lymph nodes in patients with metastatic renal cell carcinoma. Urol Oncol. 2011;29(6):751–5. [PubMed: 20056460]

12. Parker AE. Studies on the main posterior lymph channels of the abdomen and their connections with the lymphatics of the genito-urinary system. American Journal of Anatomy. 1935;56(3):409–43.

13. Brouwer OR, Noe A, Olmos RA, Bex A. Lymphatic drainage from renal cell carcinoma along the thoracic duct visualized with SPECT/CT. Lymphat Res Biol. 2013;11(4):233–8. [PubMed: 24364847]

14. Karmali RJ, Suami H, Wood CG, Karam JA. Lymphatic drainage in renal cell carcinoma: back to the basics. BJU Int. 2014;114(6):806–17. [PubMed: 24841690]

15. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. J Urol. 1969;101(3):297–301. [PubMed: 5765875]

16. Capitanio U, Suardi N, Matloob R, Roscigno M, Abdollah F, Di Trapani E, et al. Extent of lymph node dissection at nephrectomy affects cancer-specific survival and metastatic progression in specific sub-categories of patients with renal cell carcinoma (RCC). BJU Int. 2014;114(2):210–5. [PubMed: 24854206]

17. Delacroix SE Jr., Chapin BF, Chen JJ, Nogueras-Gonzalez GM, Tamboli P, Matin SF, et al. Can a durable disease-free survival be achieved with surgical resection in patients with pathological node positive renal cell carcinoma? J Urol. 2011;186(4):1236–41. [PubMed: 21849197]

18. Kwon T, Song C, Hong JH, Kim CS, Ahn H. Reassessment of renal cell carcinoma lymph node staging: analysis of patterns of progression. Urology. 2011;77(2):373–8. [PubMed: 20817274]

19. Pantuck AJ, Zisman A, Dorey F, Chao DH, Han KR, Said J, et al. Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. J Urol. 2003;169(6):2076–83. [PubMed: 12771723]

20. Farber NJ, Rivera-Nunez Z, Kim S, Shinder B, Radadia K, Sterling J, 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(1):26–32. [PubMed: 30446458]
21. Radadia KD, Rivera-Nunez Z, Kim S, Farber NJ, Sterling J, Falkiewicz M, et al. Accuracy of clinical nodal staging and factors associated with receipt of lymph node dissection at the time of surgery for nonmetastatic renal cell carcinoma. Urol Oncol. 2019;37(9):577 e17–e25.
22. Capitanio U, Becker F, Blute ML, Mulders P, Patard JJ, Russo P, et al. Lymph node dissection in renal cell carcinoma. Eur Urol. 2011;60(6):1212–20. [PubMed: 21940096]
23. Bazzi WM, Sjoberg DD, Feuerstein MA, Maschino A, Verma S, Bernstein M, et al. Long-term survival rates after resection for locally advanced kidney cancer: Memorial Sloan Kettering Cancer Center 1989 to 2012 experience. J Urol. 2015;193(6):1911–6. [PubMed: 25524244]
24. Canfield SE, Kamat AM, Sanchez-Ortiz RF, Detry M, Swanson DA, Wood CG. Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease (clinical stage TxN1–2M0): the impact of aggressive surgical resection on patient outcome. J Urol. 2006;175(3 Pt 1):864–9. [PubMed: 16469567]
25. Gershman B, Moreira DM, Thompson RH, Boorjian SA, Lohse CM, Costello BA, et al. Renal cell carcinoma with isolated lymph node involvement: long-term natural history and predictors of oncologic outcomes following surgical resection. Eur Urol. 2017;72(2):300–6. [PubMed: 28094055]
26. Trinh QD, Schmitges J, Bianchi M, Sun M, Shariat SF, Sammon J, et al. Node-positive renal cell carcinoma in the absence of distant metastases: predictors of cancer-specific mortality in a population-based cohort. BJU Int. 2012;110(2 Pt 2):E21–7. [PubMed: 22044638]
27. Sun M, Bianchi M, Hansen J, Abdollah F, Trinh QD, Lughezzani G, et al. Nodal involvement at nephrectomy is associated with worse survival: a stage-for-stage and grade-for-grade analysis. Int J Urol. 2013;20(4):372–80. [PubMed: 23039208]
28. Shao N, Wang HK, Zhu Y, Ye DW. Modification of American Joint Committee on cancer prognostic groups for renal cell carcinoma. Cancer Med. 2018;7(11):5431–8. [PubMed: 30306741]
29. Srivastava A, Rivera-Nunez Z, Kim S, Sterling J, Farber NJ, Radadia KD, et al. Impact of pathologic node positive renal cell carcinoma on survival in patients without metastasis: Evidence in support of expanding the definition of Stage IV kidney cancer. Cancer. 2020:In Press.
30. Han J, Li Q, Li P, Wang S, Zhang R, Qiao Y, et al. Reassessment of american joint committee on cancer staging for stage iii renal cell carcinoma with nodal involvement: propensity score matched analyses of a large population-based study. Frontiers in Oncology. 2020;10.
31. Patel HV, Srivastava A, Shinder B, Sadimin E, Singer EA. Strengthening the foundation of kidney cancer treatment and research: revising the AJCC staging system. Ann Transl Med. 2019;7(Suppl 1):S33. [PubMed: 31032312]
32. Chin AI, Lam JS, Figlin RA, Belldegrun AS. Surveillance strategies for renal cell carcinoma patients following nephrectomy. Rev Urol. 2006;8(1):1–7. [PubMed: 16985554]
33. The Nobel Prize in Physiology or Medicine 2019 [press release]. Nobel Media AB 20202020.
34. Harshman LC, Xie W, Moreira RB, Bosse D, Ruiz Ares GJ, Sweeney CJ, et al. Evaluation of disease-free survival as an intermediate metric of overall survival in patients with localized renal cell carcinoma: A trial-level meta-analysis. Cancer. 2018;124(5):925–33. [PubMed: 29266178]
35. Motzer RJ, Ravaud A, Patard JJ, Pandha HS, George DJ, Patel A, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results. Eur Urol. 2018;73(1):62–8. [PubMed: 28967554]
36. Patel HV, Shinder B, Srinivasan R, Singer EA. Challenges and opportunities in the management of metastatic renal cell carcinoma: combination therapy and the role of cytoreductive surgery. Curr Opin Oncol. 2020;32(3):240–9. [PubMed: 32195679]
37. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017;3:17009. [PubMed: 28276433]
38. The Nobel Prize in Physiology or Medicine 2018 [press release]. Nobel Media AB 20202020.

39. Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378(14):1277–90. [PubMed: 29562145]
40. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1103–15. [PubMed: 30779531]
41. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New England Journal of Medicine. 2019.
42. Patel HD, Puligandla M, Shuch BM, Leibovich BC, Kapoor A, Master VA, et al. The future of perioperative therapy in advanced renal cell carcinoma: how can we PROSPER? Future Oncol. 2019;15(15):1683–95. [PubMed: 30968729]
43. Motzer RJ, editor JAVELIN Renal 101: a randomized, phase 3 study of avelumab + axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma (aRCC) European Society for Medical Oncology (ESMO) 2018 Congress; 2018 10/21/2018; Munich, Germany: ESMO.
44. Rini BI, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet. 2019;393(10189):2404–15. [PubMed: 31079938]
45. Edge SB, American Joint Committee on Cancer., American Cancer Society. AJCC cancer staging handbook : from the AJCC cancer staging manual. 7th ed. New York: Springer; 2010 xix, 718 p. p.
46. Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOGACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2016;387(10032):2008–16. [PubMed: 26969090]
47. Motzer RJ, Haas NB, Donskov F, Gross-Goupil M, Varlamov S, Kopyltsov E, et al. Randomized phase iii trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol. 2017;35(35):3916–23. [PubMed: 28902533]
48. Gross-Goupil M, Kwon TG, Eto M, Ye D, Miyake H, Seo SI, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. Ann Oncol. 2018;29(12):2371–8. [PubMed: 30346481]

Table 1:

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

Stage	8E AJCC[45]	Shao et al.[28]	Yu et al.[3]	Han et al.[30]	Proposed Integrated Staging
I	T1N0M0	**Ia:** T1N0M0 **Ib:** T2N0M0	T1N0M0	T1N0M0	T1N0M0
II	T2N0M0	T3N0M0	T2N0M0	T2N0M0	T2N0M0
III	T1–2N1M0, T3NanyM0	T1–3N1M0, T4N0M0	T3N0M0	**IIIa:** T3N0M0 **IIIb:** T1–3N1M0, T4NanyM0	T3N0M0
IV	T4NanyM0, TanyNanyM1	T4N1M0, TanyNanyM1	T1–3N1M0 T4NanyM0 TanyNanyM1	TanyNanyM1	**IVa:** T3N1M0, T3N0M1, T4N0M0 **IVb:** T4N1M0, T4N0M1, T4N1M1

Adapted from Patel, H.V. et al.[31]

Table 2:

Clinical trials evaluating adjuvant tyrosine kinase and mTOR inhibition for renal cell carcinoma.

Trial	Treatments	Stage for Inclusion	Histology	Primary Endpoint (*Outcome*)
ASSURE[46]	Sunitinib, sorafenib, or placebo for 54 weeks	pT1b (G3–4) pT2–4 TanyN1	Clear cell Nonclear cell	DFS *No difference*
S-TRAC[35]	Sunitinib or placebo for 1 year	pT3–4 TanyN1	Clear cell	DFS *Improved for sunitinib*
PROTECT[47]	Pazopanib or placebo for 1 year	pT2 (G3–4) pT3–4 TanyN1	Clear cell Predominantly clear cell	DFS *No difference*
ATLAS[48]	Axitinib or placebo for 1–3 years	pT2 TanyN1	Clear cell Predominantly clear cell	DFS *No difference*
SORCE NCT00492258	Sorafenib (3 years), Sorefenib (1 year) or placebo	Leibovich score 3–11	Clear cell Nonclear cell	DFS *Ongoing*
EVEREST NCT01120249	Everolimus or placebo for 54 weeks	pT1b (G3–4) pT2–4 TanyN1	Clear cell Nonclear cell	RFS *Ongoing*

Adapted from Patel, H.D. et al.[42] DFS: disease-free survival; RFS: recurrence-free survival

Table 3:

Clinical trials evaluating neoadjuvant, perioperative, & adjuvant immunotherapies for renal cell carcinoma.

Trial	Treatments	Setting (doses)	Stage for Inclusion	Histology	Primary Endpoint
Checkmate 914 NCT03138512	Ipilimumab + Nivolumab	Adjuvant (24 weeks)	pT2a (G3/4), ≥pT2b TanyN1M0	Primarily clear cell	DFS
RAMPART NCT03288532	Durvalumab ± Tremelimumab	Adjuvant D only (13 cycles) D+T (13+2 cycles)	Leibovich score 3–11	Any RCC histology	DFS, OS
KEYNOTE-564 NCT03142334	Pembrolizumab	Adjuvant (17 cycles)	pT2 (G3, sarcomatoid) ≥pT3, pTanyN+M0 (any G) M1 NED	Clear cell RCC (including sarcomatoid)	DFS
IMmotion010 NCT03024996	Atezolizumab	Adjuvant (16 cycles)	pT2 (G4), pT3 (G3/4), ≥pT3b, pTxN+, M1 NED	Clear cell RCC (including sarcomatoid)	DFS
NEOAVAX NCT03341845	Axitinib + Avelumab	Neoadjuvant (12 weeks)	High-risk nonmetastatic RCC	Clear cell RCC	Partial response
PROSPER NCT03055013	Nivolumab	Neoadjuvant (1 dose) Adjuvant (9 doses)	≥T2Nx or TanyN+ or M1 *	Any RCC histology	RFS

G: Grade; DFS: disease-free survival; OS: overall survival; RFS: recurrence-free survival

* M1 disease has be resected/definitively treat at the same time or within 12-week window of surgical intervention such as that patient is considered “No Evidence of Disease”