Review Article

Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for renal cell carcinoma 2017

Abdullah Alsharm, Shouki Bazarbashi[1], Abdullah Alghamdi[2], Sultan Alkhateeb[3], Ali Aljubran[1], Ashraf Abusamra[4], Hulayel Alharbi[5], Mohammed Alotaibi[6], Mubarak Almansour[7], Hussein Alkushi[8], Imran Ahmed[9], Esam Murshid[10], Amin Eltijani[11], Danny Rabah[12]

Department of Medical Oncology, Comprehensive Cancer Center, King Fahad Medical City, [1]Oncology Center, Section of Medical Oncology, King Faisal Specialist Hospital and Research Center, [2]Department of Urology, Prince Sultan Military Medical City, [3]Department of Surgery, Division of Urology, King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, [6]Department of Urology, King Faisal Specialist Hospital and Research Center, [10]Department of Oncology, Oncology Center, Prince Sultan Military Medical City, [11]Department of Oncology, Division of Medical Oncology, King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, Riyadh, [12]Department of Surgery, College of Medicine and Uro-Oncology Research Chair, King Saud University, Riyadh, [5]Department of Medical Oncology, King Fahed Specialist Hospital, Dammam, [4]Department of Surgery, Urology Section, King Khalid Hospital, King Abdulaziz Medical City, Departments of [7]Oncology and [8]Pathology, King Abdulaziz Medical City and King Saud bin Abdulaziz University for Health Sciences, [9]Department of Oncology, Section of Medical Oncology, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

Abstract

In this report, we update the previously published Saudi guidelines for the evaluation and medical and surgical management of renal cell carcinoma. It is categorized according to the stage of the disease using the tumor node metastasis staging system 7th edition. The recommendations are presented with supporting evidence level.

Keywords: Guidelines, management, renal cell carcinoma, Saudi Oncology Society, Saudi Urological Association

Address for correspondence: Dr. Shouki Bazarbashi, Section of Medical Oncology, Oncology Center, King Faisal Specialist Hospital and Research Center, P.O Box 3354, Riyadh - 11211, Saudi Arabia.
E-mail: bazarbashi@gmail.com
Received: 18.11.2017, **Accepted:** 18.12.2017

INTRODUCTION

Renal cancer represents the 10th most common cancer type in males (13th most common cancer type in females) in the Saudi Arabian population. There were 313 cases of renal cancer in 2013, accounting for 2.7% of all newly diagnosed cancer cases. In 2013, the male-to-female ratio for this cancer was 1.6:1, and the age-standardized rate was 2.9/100,000 for males and 1.7/100,000 for females. The median age at diagnosis was 56 years among males and 49 years among females.[1]

All cases of renal cell carcinoma (RCC) should preferably be seen or discussed in a multidisciplinary forum.

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/UA.UA_175_17

How to cite this article: Alsharm A, Bazarbashi S, Alghamdi A, Alkhateeb S, Aljubran A, Abusamra A, *et al*. Saudi oncology society and Saudi urology association combined clinical management guidelines for renal cell carcinoma 2017. Urol Ann 2018;10:123-32.

PRETREATMENT EVALUATION

Evaluation of suspicious renal mass

1. History and physical examination
2. Blood count, renal, and hepatic profiles
3. Computed tomography scan of the chest, abdomen, and pelvis
4. Urine analysis
5. Urine cytology should be done if urothelial cancer is suspected
6. Indications of renal mass biopsy include as follows: suspicion of renal abscess, suspicion of metastases, suspicion of renal lymphoma, and before systemic therapy. Furthermore, biopsy is strongly advocated before nonsurgical options (i.e., active surveillance, cryo [cryoablation], and radiofrequency ablation)
7. Brain imaging and bone scan should be done only if clinically indicated.

STAGING

The American Joint Committee on Cancer staging definitions for RCC should be adopted[2] [Tables 1 and 2].

PATHOLOGY

The recommended pathology report adopts the College of the American Pathologists 2016 Guidelines [Appendix 1].

TREATMENT

Localized disease (T1a)

1. The recommended treatment is surgical excision, preferably by partial nephrectomy (PN) (open, laparoscopic, or robotic), in all cases, especially in patients with solitary kidney, bilateral tumors, familial renal cell cancer, or renal insufficiency (EL-1) [Figure 1][3-9]
2. Radical nephrectomy (RN) (preferably laparoscopic) should be reserved for cases where PN is not technically feasible after consultation with an experienced surgeon (EL-1)[3-16]
3. Nonsurgical options (i.e., active surveillance,

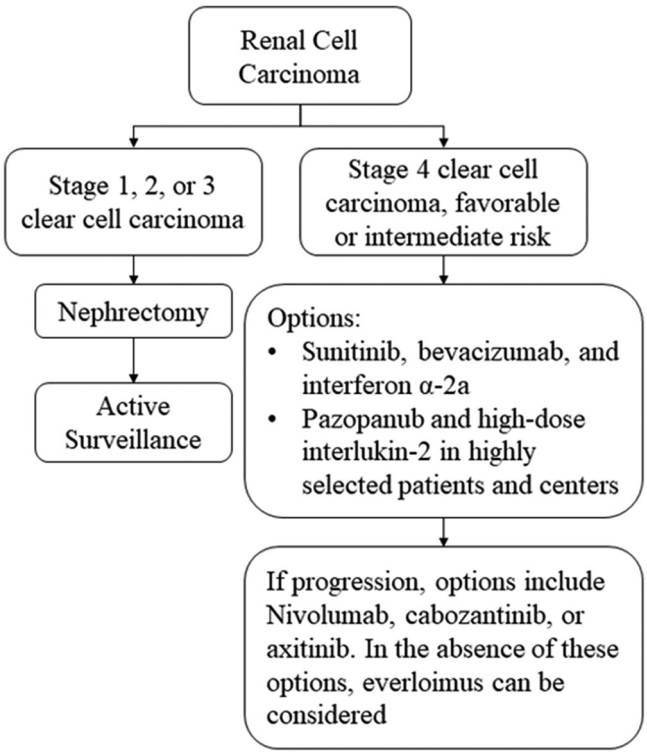

Figure 1: Renal cell carcinoma management diagram

Table 1: Tumor, node, and metastasis staging for renal cell carcinoma

Primary tumor (T)	Regional lymph nodes (N)	Distant metastasis (M)
TX: Primary tumor cannot be assessed	NX: Regional lymph node(s) cannot be assessed	M0: No distant metastasis
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M1: Distant metastasiscytology
T1: Tumor <7 cm, limited to the kidney	N1: Metastasis in a single regional lymph node	
T1a: Tumor <4 cm, limited to the kidney	N2: Metastasis in more than one regional lymph node	
T1b: Tumor >4 cm, but <7 cm in greatest dimension		
T2: Tumor >7 cm in greatest dimension, limited to the kidney		
T2a: Tumor >7 cm but<10 cm in greatest dimension		
T2b: Tumor >10 cm, limited to the kidney		
T3: Tumor extends into major veins or directly invades adrenal gland or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia		
T3a: Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches or tumor invades perirenal and/or renal sinus (peripelvic) fat but not beyond Gerota's fascia		
T3b: Tumor grossly extends into the vena cava below the diaphragm		
T3c: Tumor grossly extends into vena cava above the diaphragm or invades the wall of the vena Cava		
T4a: Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		

cryoablation, and radiofrequency ablation) are all inferior to surgical excision in terms of oncological outcome and are not recommended, except in patients with significant comorbidities that interdict surgical intervention (EL-2).[17-21]

Localized disease (T1b)

1. The recommended treatment is RN (preferably laparoscopic) (EL-1)[10-16,22-27]
2. PN may be an option, especially in patients with a solitary kidney, bilateral tumors, familial renal cell cancer, or renal insufficiency. However, this should only be performed by an experienced surgeon in a high-volume center (EL-1)[22-29]
3. Nonsurgical options (i.e., active surveillance, cryoablation, and radiofrequency ablation) are not recommended.

Localized disease (T2)

1. The recommended treatment is RN (EL-1)[10-16,22-27]
2. PN and nonsurgical options (i.e., active surveillance, cryoablation, and radiofrequency ablation) are not recommended.

Localized disease (T3)

1. The recommended treatment is RN with complete excision of all venous thrombus in the renal vein, inferior vena cava, and right atrium (EL-2)[28,29]
2. These surgeries should only be performed in a tertiary care centers with the availability of a cardiac, vascular, or hepatic surgeon, depending on the case (EL-2).[28,29]

Excision of the ipsilateral adrenal gland

1. Ipsilateral excision of the adrenal gland during RN is indicated in upper pole kidney tumors or the presence of a concurrent radiologically detectable adrenal gland lesion(s) (EL-2).[30-33]

Lymph node dissection

1. Resection of the regional lymph nodes (within Gerota's fascia) is an integral part of RN
2. Resection of the nonregional lymph nodes provides no therapeutic advantages but is used for staging purposes (EL-1).[34]

When doing PN, the surgeon should aim to obtain adequate surgical margin and avoid tumor inoculation, except in patients with von Hippel–Lindau syndrome.[35-37]

For postoperative follow-up after treatment, use the European Association of Urology Guidelines [Table 3].

Metastatic advanced, unresectable disease

1. For risk stratification of metastatic RCC, there are two valid options [Appendix 2]
   i. The Memorial Sloan Kettering cancer center (MSKCC/Motzer) risk classification for metastatic disease[38]
   ii. Heng Score for Metastatic RCC Prognosis.[39]
2. Potentially resectable primary tumors with solitary metastasis or multiple resectable lung metastases: these patients should undergo primary nephrectomy and resection of the metastatic lesion/s (EL-2). Following complete resection, no further therapy or "adjuvant therapy" is indicated (EL-3)
3. Potentially resectable primary and multiple nonresectable metastasis: those patients should undergo resection of the primary tumor if in good performance status (EL-1),[40,41] then start systemic therapy according to the following guidelines:
   i. Clear cell histology with good or intermediate risk: options of therapy include systemic therapy with either sunitinib (EL-1),[42] bevacizumab and interferon α-2a, or pazopanib (EL-1).[4,43-45] High-dose interleukin -2 may be used in highly selected patients and centers[46]
   ii. Clear cell histology with poor risk: temsirolimus is the preferred treatment (EL-1).[18,47] An alternative option is sunitinib (EL-2)
   iii. Nonclear cell histology: options of therapy include

Table 2: Renal cell carcinoma anatomical stages and prognostic groups

Stage grouping	T stage	N stage	M stage
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1–T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	N2	M0
	Any T	Any N	M1

Table 3: Surveillance guidelines following surgery for renal cell cancer, adapted from the European Association of Urology

Risk profile	Treatment	Surveillance						
		6 months	1 year	2 years	3 years	4 years	5 years	After 5 years
Low	RN/PN	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/cryo/RFA	CT	US	CT	US	CT	CT	CT, alternate 2 years
High	RN/PN/cryo/RFA	CT	CT	CT	CT	CT	CT	CT, alternate 2 years

CT: Computed tomography, cryo: Cryoablation, PN: Partial nephrectomy, RFA: Radio frequency ablation, RN: Radical nephrectomy, US: Ultrasound

temsirolimus (EL-2),[47] sunitinib (EL-2),[48] or sorafenib (EL-2).[49] Medullary and collecting duct carcinomas should be treated with platinum-based chemotherapy (EL-3)[50]

iv. Unresectable primary tumor with or without metastatic disease: These patients with good performance status should be offered systemic therapy according to their histological results and MSKCC risk group as in Item 4.9.3

v. Recurrent disease postprimary nephrectomy: treatment will depend if resectable or not:

i. If resectable solitary metastasis: surgical resection should be attempted (EL-2).[51-53] No systemic therapy is of benefit following complete resection (EL-3)

ii. If nonresectable recurrence: patient should be treated as metastatic disease according to their histological results, using MSKCC Risk Score and/or Heng Score as in Item 4.9.3.

4. Second-line therapy posttyrosine tyrosine kinase inhibitor (TKI) failure: patients who fail with first-line TKIs should receive second-line therapy if in reasonable performance status. Options of second-line agents include: nivolumab (EL-1),[54] cabozantinib (EL-1),[55] or axitinib (EL-1).[56] In the absence of these options, everolimus can be considered[57,58]
5. Third-line therapy: consider everolimus (Level 3), sorafenib (Level 3), or clinical trials [Figure 1].

Financial support and sponsorship

Funding was provided by the Saudi Oncology Society for this work.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Saudi Cancer Registry. Annual Report; 2013. Available from: http://www.shc.gov.sa/Ar/HealthCenters/NCC/CancerRegistry/Pages/CancerRegistryRecords.aspx. [Last accessed on 2017 Jul 11].
2. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
3. Gill IS, Kavoussi LR, Lane BR, Blute ML, Babineau D, Colombo JR Jr., *et al*. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol 2007;178:41-6.
4. Gong EM, Orvieto MA, Zorn KC, Lucioni A, Steinberg GD, Shalhav AL, *et al*. Comparison of laparoscopic and open partial nephrectomy in clinical T1a renal tumors. J Endourol 2008;22:953-7.
5. Kim SP, Murad MH, Thompson RH, Boorjian SA, Weight CJ, Han LC, *et al*. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: A systematic review and meta-analysis. J Urol 2012. pii: S0022-5347(12)05254-8.
6. Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs. nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. Mayo Clin Proc 2000;75:1236-42.
7. Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P, *et al*. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. J Urol 2000;163:730-6.
8. Tan HJ, Norton EC, Ye Z, Hafez KS, Gore JL, Miller DC, *et al*. Long-term survival following partial vs. radical nephrectomy among older patients with early-stage kidney cancer. JAMA 2012;307:1629-35.
9. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, *et al*. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011;59:543-52.
10. Berger A, Brandina R, Atalla MA, Herati AS, Kamoi K, Aron M, *et al*. Laparoscopic radical nephrectomy for renal cell carcinoma: Oncological outcomes at 10 years or more. J Urol 2009;182:2172-6.
11. Burgess NA, Koo BC, Calvert RC, Hindmarsh A, Donaldson PJ, Rhodes M, *et al*. Randomized trial of laparoscopic v open nephrectomy. J Endourol 2007;21:610-3.
12. Gabr AH, Gdor Y, Strope SA, Roberts WW, Wolf JS Jr. Patient and pathologic correlates with perioperative and long-term outcomes of laparoscopic radical nephrectomy. Urology 2009;74:635-40.
13. Hemal AK, Kumar A. A prospective comparison of laparoscopic and robotic radical nephrectomy for T1-2N0M0 renal cell carcinoma. World J Urol 2009;27:89-94.
14. Hemal AK, Kumar A, Kumar R, Wadhwa P, Seth A, Gupta NP, *et al*. Laparoscopic versus open radical nephrectomy for large renal tumors: A long-term prospective comparison. J Urol 2007;177:862-6.
15. Luo JH, Zhou FJ, Xie D, Zhang ZL, Liao B, Zhao HW, *et al*. Analysis of long-term survival in patients with localized renal cell carcinoma: Laparoscopic versus open radical nephrectomy. World J Urol 2010;28:289-93.
16. Weight CJ, Lieser G, Larson BT, Gao T, Lane BR, Campbell SC, *et al*. Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. Eur Urol 2010;58:293-8.
17. Abouassaly R, Lane BR, Novick AC. Active surveillance of renal masses in elderly patients. J Urol 2008;180:505-8.
18. Chen DY, Uzzo RG. Optimal management of localized renal cell carcinoma: Surgery, ablation, or active surveillance. J Natl Compr Canc Netw 2009;7:635-42.
19. Kunkle DA, Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass: A meta-analysis. Cancer 2008;113:2671-80.
20. O'Malley RL, Berger AD, Kanofsky JA, Phillips CK, Stifelman M, Taneja SS, *et al*. A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. BJU Int 2007;99:395-8.
21. Rais-Bahrami S, Guzzo TJ, Jarrett TW, Kavoussi LR, Allaf ME. Incidentally discovered renal masses: Oncological and perioperative outcomes in patients with delayed surgical intervention. BJU Int 2009;103:1355-8.
22. Dash A, Vickers AJ, Schachter LR, Bach AM, Snyder ME, Russo P, *et al*. Comparison of outcomes in elective partial vs. radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. BJU Int 2006;97:939-45.
23. Leibovich BC, Blute M, Cheville JC, Lohse CM, Weaver AL, Zincke H, *et al*. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. J Urol 2004;171:1066-70.
24. Peycelon M, Hupertan V, Comperat E, Renard-Penna R, Vaessen C, Conort P, *et al*. Long-term outcomes after nephron sparing surgery for renal cell carcinoma larger than 4 cm. J Urol 2009;181:35-41.
25. Simmons MN, Weight CJ, Gill IS. Laparoscopic radical versus partial nephrectomy for tumors >4 cm: Intermediate-term oncologic and functional outcomes. Urology 2009;73:1077-82.
26. Thompson RH, Siddiqui S, Lohse CM, Leibovich BC, Russo P, Blute ML, *et al*. Partial versus radical nephrectomy for 4 to 7 cm renal cortical tumors. J Urol 2009;182:2601-6.

27. Weight CJ, Larson BT, Gao T, Campbell SC, Lane BR, Kaouk JH, *et al.* Elective partial nephrectomy in patients with clinical T1b renal tumors is associated with improved overall survival. Urology 2010;76:631-7.
28. Eastham JA. Do high-volume hospitals and surgeons provide better care in urologic oncology? Urol Oncol 2009;27:417-21.
29. Joudi FN, Konety BR. The impact of provider volume on outcomes from urological cancer therapy. J Urol 2005;174:432-8.
30. Kuczyk M, Münch T, Machtens S, Bokemeyer C, Wefer A, Hartmann J, *et al.* The need for routine adrenalectomy during surgical treatment for renal cell cancer: The hannover experience. BJU Int 2002;89:517-22.
31. Kuczyk M, Wegener G, Jonas U. The therapeutic value of adrenalectomy in case of solitary metastatic spread originating from primary renal cell cancer. Eur Urol 2005;48:252-7.
32. Lane BR, Tiong HY, Campbell SC, Fergany AF, Weight CJ, Larson BT, *et al.* Management of the adrenal gland during partial nephrectomy. J Urol 2009;181:2430-6.
33. O'Malley RL, Godoy G, Kanofsky JA, Taneja SS. The necessity of adrenalectomy at the time of radical nephrectomy: A systematic review. J Urol 2009;181:2009-17.
34. Blom JH, van Poppel H, Maréchal JM, Jacqmin D, Schröder 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;55:28-34.
35. Blackley SK, Ladaga L, Woolfitt RA, Schellhammer PF. *Ex situ* study of the effectiveness of enucleation in patients with renal cell carcinoma. J Urol 1988;140:6-10.
36. Marshall FF, Taxy JB, Fishman EK, Chang R. The feasibility of surgical enucleation for renal cell carcinoma. J Urol 1986;135:231-4.
37. Rosenthal CL, Kraft R, Zingg EJ. Organ-preserving surgery in renal cell carcinoma: Tumor enucleation versus partial kidney resection. Eur Urol 1984;10:222-8.
38. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J, *et al.* Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530-40.
39. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, *et al.* Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol 2009;27:5794-9.
40. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, *et al.* Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655-9.
41. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R; European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial. Lancet 2001;358:966-70.
42. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.
43. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, *et al.* Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial. Lancet 2007;370:2103-11.
44. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, *et al.* Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26:5422-8.
45. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. J Clin Oncol 2010;28:1061-8.
46. Alva A, Daniels GA, Wong MK, Kaufman HL, Morse MA, McDermott DF, *et al.* Contemporary experience with high-dose interleukin-2 therapy and impact on survival in patients with metastatic melanoma and metastatic renal cell carcinoma. Cancer Immunol Immunother 2016;65:1533-44.
47. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-81.
48. Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, *et al.* Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): A multicentre, open-label, randomised phase 2 trial. Lancet Oncol 2016;17:378-88.
49. Stadler W, Figlin R, Ernstoff M, Curti B, Pendergrass K, Srinivas S, *et al.* The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial: Safety and efficacy in patients (pts) with non-clear cell (NCC) renal cell carcinoma (RCC). J Clin Oncol 2007;25 18 Suppl: 5036.
50. Oudard S, Banu E, Vieillefond A, Fournier L, Priou F, Medioni J, *et al.* Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: Results of a GETUG (Groupe d'etudes des tumeurs uro-génitales) study. J Urol 2007;177:1698-702.
51. Adam R, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M, *et al.* Hepatic resection for noncolorectal nonendocrine liver metastases: Analysis of 1,452 patients and development of a prognostic model. Ann Surg 2006;244:524-35.
52. Kavolius JP, Mastorakos DP, Pavlovich C, Russo P, Burt ME, Brady MS, *et al.* Resection of metastatic renal cell carcinoma. J Clin Oncol 1998;16:2261-6.
53. Piltz S, Meimarakis G, Wichmann MW, Hatz R, Schildberg FW, Fuerst H, *et al.* Long-term results after pulmonary resection of renal cell carcinoma metastases. Ann Thorac Surg 2002;73:1082-7.
54. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803-13.
55. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, *et al.* Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814-23.
56. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, *et al.* Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: Overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552-62.
57. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, *et al.* Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer 2010;116:4256-65.
58. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, *et al.* Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.

APPENDIX

Appendix 1: Sample pathology report

PROCEDURE

___ Partial nephrectomy

___ Radical nephrectomy

___ Other (specify): _____

___ Not specified

SPECIMEN LATERALITY

___ Right

___ Left

___ Not specified

+ TUMOR SITE (SELECT ALL THAT APPLY)

+ ___ Upper pole

+ ___ Middle

+ ___ Lower pole

+ ___ Other (specify): _____

+ ___ Not specified

TUMOR SIZE (LARGEST TUMOR IF MULTIPLE)

Greatest dimension: ___ cm

+ Additional dimensions: ___ x ___ cm

___ Cannot be determined (see "Comment")

TUMOR FOCALITY

___ Unifocal

___ Multifocal

MACROSCOPIC EXTENT OF TUMOR

___ Primary tumor cannot be assessed

___ No evidence of primary tumor

___ Tumor limited to kidney

___ Tumor extension into perinephric tissues

___ Tumor extension into renal sinus

___ Tumor extension beyond Gerota's fascia

___ Tumor extension into major veins (renal vein or its segmental (muscle containing) branches, inferior vena cava)

___ Tumor extension into pelvicaliceal system

+ ___ Major calyx

+ ___ Minor calyx

___ Tumor extension into adrenal gland

___ Direct invasion (T4)

___ Noncontiguous (M1)

___ Tumor extension into other organ(s)/structure(s) (specify): _____

Histologic Type

___ Clear cell renal cell carcinoma

___ Multilocular clear cell renal cell carcinoma

___ Papillary renal cell carcinoma

___ Chromophobe renal cell carcinoma

___ Carcinoma of the collecting ducts of Bellini

___ Renal medullary carcinoma

___ Translocation carcinoma (Xp11 or others)
___ Carcinoma associated with neuroblastoma

___ Mucinous tubular and spindle cell carcinoma

___ Tubulocystic renal cell carcinoma

___ Renal cell carcinoma, unclassified

___ Other (specify): _____

SARCOMATOID FEATURES

___ Not identified

___ Present

Specify percentage of sarcomatoid element: _____%

+ TUMOR NECROSIS (ANY AMOUNT)

+ ___ Not identified

+ ___ Present

HISTOLOGIC GRADE (FUHRMAN NUCLEAR GRADE)

___ Not applicable

___ GX: Cannot be assessed

___ G1: Nuclei round, uniform, approximately 10 μm; nucleoli inconspicuous or absent

___ G2: Nuclei slightly irregular, approximately 15 μm; nucleoli evident

___ G3: Nuclei very irregular, approximately 20 μm; nucleoli large and prominent

___ G4: Nuclei bizarre and multilobated, 20 μm or greater, nucleoli prominent, chromatin clumped

___ Other (specify): _____

MICROSCOPIC TUMOR EXTENSION (SELECT ALL THAT APPLY)

___ Primary tumor cannot be assessed

___ No evidence of primary tumor

___ TUMOR LIMITED TO KIDNEY

___ Tumor extension into perinephric tissue (beyond renal capsule)

___ Tumor extension into renal sinus

___ Tumor extension beyond Gerota's fascia

___ Tumor extension into major vein (renal vein or its segmental (muscle containing) branches, inferior vena cava)

___ Tumor extension into pelvicalyceal system

___ Tumor extension into adrenal gland

- ___ Direct invasion (T4)
- ___ Noncontiguous (M1)

___ Tumor extension into other organ(s)/structure(s) (specify): _____

MARGINS (SELECT ALL THAT APPLY)

___ Cannot be assessed

___ Margins uninvolved by invasive carcinoma

___ Margin(s) involved by invasive carcinoma

- ___ Renal parenchymal margin (partial nephrectomy only)
- ___ Renal capsular margin (partial nephrectomy only)
- ___ Perinephric fat margin (partial nephrectomy only)
- ___ Gerota's fascial margin
- ___ Renal vein margin
- ___ Ureteral margin
- ___ Other (specify): _____

+ LYMPH-VASCULAR INVASION

(excluding renal vein and its muscle containing segmental branches and inferior vena cava)

+ ___ Not identified

+ ___ Present

+ ___ Indeterminate

PATHOLOGIC STAGING (PTNM)

TNM Descriptors (required only if applicable) (select all that apply)

___ m (multiple primary tumors)

___ r (recurrent)

___ y (posttreatment)

PRIMARY TUMOR (PT)

___ pTX: Primary tumor cannot be assessed

___ pT0: No evidence of primary tumor

pT1: Tumor 7 cm or less in greatest dimension, limited to the kidney

___ pT1a: Tumor 4 cm or less in greatest dimension, limited to the kidney

___ pT1b: Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney

pT2: Tumor more than 7 cm in greatest dimension, limited to the kidney

___ pT2a: Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney

___ pT2b: Tumor more than 10 cm, limited to the kidney

pT3: Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia

___ pT3a: Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia

___ pT3b: Tumor grossly extends into the vena cava below the diaphragm

___ pT3c: Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava

___ pT4: Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

REGIONAL LYMPH NODES (PN)

___ pNX: Regional lymph nodes cannot be assessed

___ pN0: No regional lymph node metastasis

___ pN1: Metastasis in regional lymph node(s)

___ No nodes submitted or found

Number of Lymph Nodes Examined

Specify: ____

___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved

Specify: ____

___ Number cannot be determined (explain): _____

DISTANT METASTASIS (PM)

___ Not applicable

___ pM1: Distant metastasis

Appendix 2: Metastatic renal cell carcinoma prognostic models

MSKCC risk classification

Prognostic criteria
Time from diagnosis to treatment <1 year
Hemoglobin < lower limit of normal
Calcium >10 mg/dl (more than 2.5 mmol/L)
Lactate dehydrogenase >1.5 x upper limit of normal
Karnofsky performance status <80%
Risk stratification
favorable-risk group: No prognostic factors
Intermediate risk: 1 or 2 prognostic factors
Poor risk :3 prognostic factors

MSKCC: Memorial Sloan Kettering Cancer Center

Heng risk classification

Prognostic criteria
Time from diagnosis to systemic treatment <1 year
Hemoglobin < lower limit of normal
Calcium >10 mg/dl (more than 2.5 mmol/L)
Karnofsky performance <than 80%
Neutrophil count > upper limit of normal
Platelets count > upper limit of normal
Risk stratification
favorable-risk group : no prognostic factors
Intermediate risk : 1 or 2 prognostic factors
Poor risk: 3 or more prognostic factors