ANTICANCER RESEARCH *38*: 3013-3018 (2018)
doi:10.21873/anticanres.12555

Cytoreductive Nephrectomy in Elderly Patients with Metastatic Renal Cell Carcinoma in the Targeted Therapy Era

DIPESH UPRETY[1], AMIR BISTA[1], ANGELA L. SMITH[2], YAZHINI VALLATHARASU[1] and DAVID E. MARINIER[1]

[1]*Department of Medical Oncology, Gundersen Health System, La Crosse, WI, U.S.A.;*
[2]*Division of Medical Research, Gundersen Lutheran Medical Foundation, La Crosse, WI, U.S.A.*

Abstract. *Background/Aim: The role of cytoreductive nephrectomy (CN) for metastatic renal cell cancer (mRCC) is not clearly understood after the approval of targeted therapies, particularly in the elderly population. The aim of this study was to compare survivals between patients who did and did not receive CN. Patients and Methods: The SEER-18 database was utilized in order to identify elderly patients with mRCC to compare overall survival (OS) and cancer-specific survival (CSS) between patients who did or did not receive CN between February 2006 and 2012. Kaplan–Meier curve and log rank test were used to compare OS and CSS between these two arms. Cox proportional hazard model was used for multivariate analysis and statistical significance was defined as p≤0.05. Results: There was a significant survival benefit for those who received CN compared to those who did not receive CN (median OS: 18 months vs. 4 months, p<0.001; median CSS: 21 months vs. 5 months, p<0.001). Conclusion: CN offered significant survival benefit, even in elderly patients with metastatic renal cell cancer.*

People older than 65 years are the fastest growing segment of the population in the United States of America. This segment is projected to reach 21 percent by 2050 (1). Renal cell carcinoma (RCC) is a disease of elderly and is most frequently diagnosed among patients between 65-74 years of age (2, 3). In the interferon era, cytoreductive nephrectomy (CN) was associated with a significant survival benefit when used in combination with interferon immunotherapy in patients with metastatic renal cell carcinoma (mRCC). This benefit was demonstrated in two randomized controlled trials (4, 5). A combined analysis of these two major prospective trials (4, 5) performed by Flanigan *et al.* demonstrated a median survival of 13.6 months for the nephrectomy plus interferon group *vs.* 7.8 months for the interferon group alone (1).

However, the role of CN in mRCC patients is not clearly understood following the approval of targeted small-molecule tyrosine kinase inhibitors in the early 2000s. In this targeted era, rates of CN have steadily declined and older age has been identified as an independent factor associated with decreased receipt of CN (6, 7). To our knowledge, the role of cytoreductive nephrectomy in elderly patients has never been investigated at a population level. Considering renal cell carcinoma (RCC) occurs predominantly in the elderly population (2), survival outcomes (CN *vs.* no CN) among elderly patients with mRCC at a population level in the targeted era were evaluated.

Patients and Methods

The National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) database is a population-based database and embodies approximately 28% of the United States population (8). The SEER-18 registry includes Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey Tumor Registries. Since the registry contains de-identified dataset, local institutional Review Board approval was waived.

The SEER-18 database was utilized to identify elderly (≥65 years of age) patients with mRCC as the first primary malignancy. "Renal carcinoma" was selected from the ICCC site recode extended ICD-3-/WHO 2008 and ICD-3-0 histological code 8050/3, 8260/3, 8310/3, 8312/3, 8317/3, 8318/3 and 8319/3 to identify patients with papillary, clear cell, chromophobe, sarcomatoid and collecting duct carcinoma types of RCC. Inclusion criteria were: patients whose disease was histologically confirmed, were actively followed, had a known age and were included in the research database. Patients whose diagnosis was made from a death certificate or at autopsy along with those still living but with no survival data were excluded. See Figure 1 for CONSORT diagram.

To limit the heterogeneity with targeted agent use, the targeted era was defined as February 2006 to December 2011 as sunitinib

Correspondence to: Dipesh Uprety, MD, Mail Stop EB2-001, 1900 South Avenue, La Crosse, WI 54601, U.S.A. Tel: +1 6087750726, e-mail: upretydipesh@gmail.com

Key Words: Cytoreductive nephrectomy, renal cell carcinoma, targeted era, elderly.

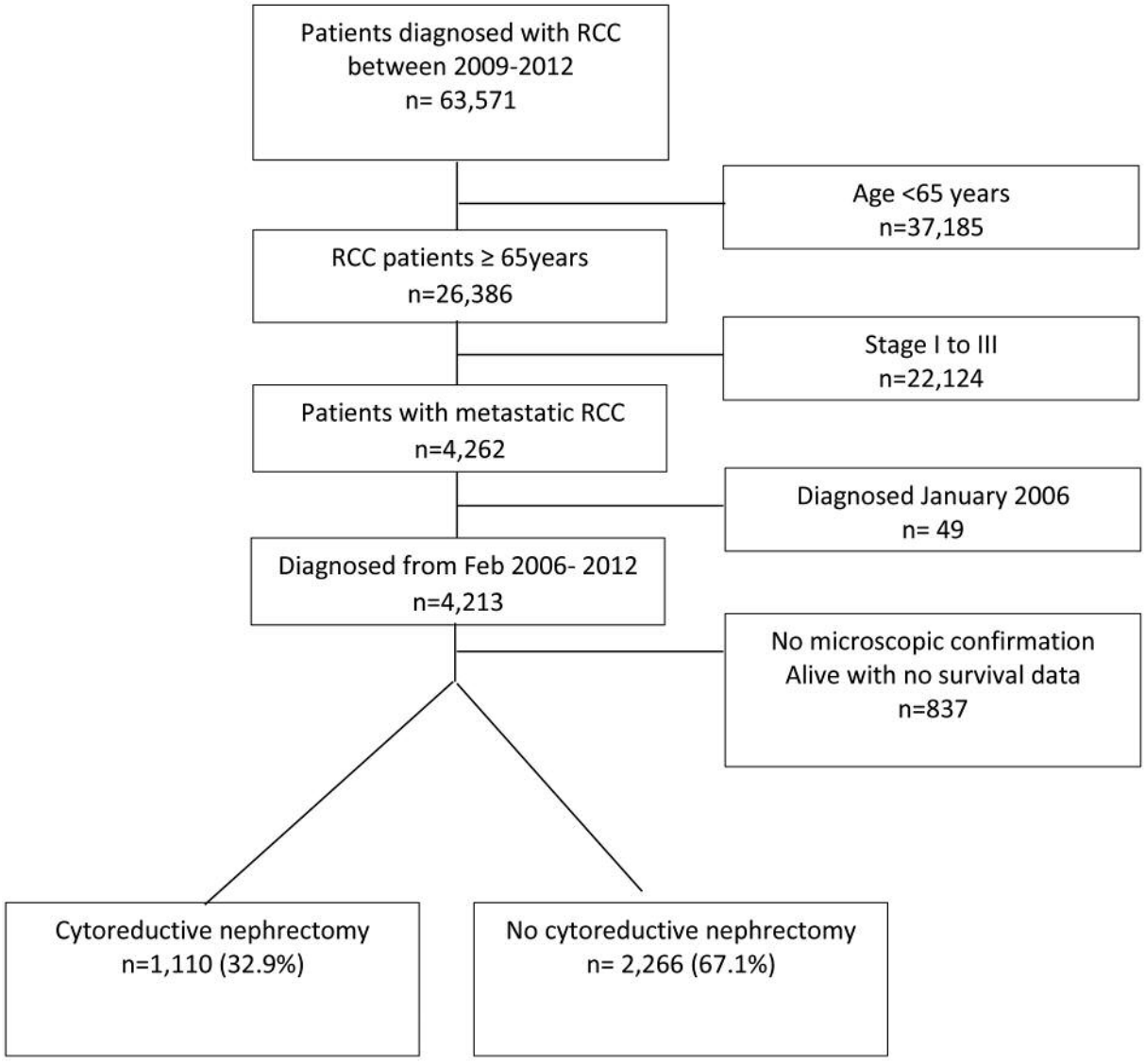

Figure 1. *Flowchart of patients included in the study. N: Sample size; RCC: renal cell carcinoma.*

was approved for use in mRCC by the Food and Drug Administration in January 2006.

The design of the study was a retrospective, population-based, case-control study. The treatment arm included patients receiving CN, while the control arm included patients not receiving CN (no CN). Patients were considered to have received CN if they had partial, subtotal, total, radical nephrectomies or nephrectomy NOS. Patients with segmental resection or wedge resection were coded with the same code for site specific surgery as local tissue destruction in the SEER database so this subset were not included in cytoreductive nephrectomy group. Kaplan-Meier curve (3-year) and log rank test were used to compare overall survival (OS) and cancer-specific survival (CSS) between these two arms. Cox proportional hazard model was used for multivariate analysis and statistical significance was defined as $p \leq 0.05$.

Results

In total, 3,376 elderly patients with mRCC who met the inclusion criteria were identified in the SEER database between 2006 and 2012 and analyzed. Of them, only 32.8 % (n=1,110) received CN. The demographics of the study are summarized in Table I.

There was a significant survival benefit for those who received CN as compared to those who did not receive CN (Median OS: 18 months *vs.* 4 months, $p<0.001$; Median CSS: 21 months *vs.* 5 months, $p<0.001$) (Figure 2). After adjusting for age, sex, race, T-stage, N-stage, histology subtype and year of diagnosis, patients receiving CN had

Table I. *Baseline characteristics of patients*.

Parameters	Total (%) N=3376	No CRN (%) N=2266	CRN (%) 1110	*p*-Value
Age				<0.001
65-69	1119 (33.1%)	642 (57.4%)	477 (42.6%)	
70-74	847 (25.1%)	526 (62.1)	321 (37.9%)	
75-79	678 (20.1%)	486 (71.7%)	192 (28.3%)	
80-84	472 (14.0%)	370 (78.4%)	102 (21.6%)	
85+	260 (7.7%)	242 (93.1%)	18 (6.9%)	
Gender				0.238
Male (%)	2112 (62.2%)	1402 (66.4%)	710 (33.6%)	
Female (%)	1264 (37.4%)	864 (68.4%)	400 (31.6%)	
Race				0.009
Caucasians (%)	2874 (85.1)	1909 (66.4%)	965 (33.6%)	
African American (%)	260 (7.7%)	199 (76.5%)	61 (23.5%)	
Others (%)	234 (6.9%)	153 (65.4%)	81 (34.6%)	
Unknown	8 (0.2%)	5 (62.5%)	3 (37.5%)	
Histology				<0.001
Clear cell (%)	1483 (43.9%)	771 (52.0%)	712 (48.0%)	
Others (%)	1893 (56.1%)	1495 (79.0%)	398 (21.0%)	
Tumor size (T)				<0.001
T0 (%)	28 (0.8%)	28 (100.0%)	0 (0%)	
T1 (%)	625 (18.5%)	462 (73.9%)	163 (26.1%)	
T2 (%)	445 (13.2%)	294 (66.1%)	151 (33.9%)	
T3 (%)	1135 (33.6%)	443 (39.0%)	692 (61.0%)	
T4 (%)	352 (10.4%)	266 (75.6%)	86 (24.4%)	
TX (%)	791 (23.4%)	773 (97.7%)	18 (1.6%)	
Nodal involvement (N)				<0.001
N0 (%)	1849 (54.8%)	1073 (58.0%)	776 (42.0%)	
N1 (%)	517 (15.3%)	371 (71.8%)	146 (28.2%)	
N2 (%)	326 (9.7%)	215 (66.0%)	111 (34.0%)	
NX (%)	684 (20.3%)	607 (88.7%)	77 (11.3%)	
Year of diagnosis				0.583
2006	395 (11.7%)	273 (69.1%)	122 (30.9%)	
2007	496 (14.7%)	320 (64.5%)	176 (35.5%)	
2008	513 (15.2%)	341 (66.5%)	172 (33.5%)	
2009	487 (14.4%)	317 (65.1%)	170 (34.9%)	
2010	455 (13.5%)	307 (67.5%)	148 (32.5%)	
2011	520 (15.4%)	354 (68.1%)	166 (31.9%)	
2012	510 (15.1%)	354 (69.4%)	156 (30.6%)	

significantly better 3-year OS and 3-year CSS compared to patients not receiving CN with a Hazard Ratio (HR) of 0.43, 95%CI=0.39-0.47, $p<0.001$ and HR of 0.44, 95%CI=0.39-0.49, $p<0.001$ respectively. Among patients who received CN, younger age at diagnosis, race other than Caucasians and African Americans and zero nodal (N0) stage were found to be independent factors predicting better OS (Table II).

Discussion

Our study demonstrates a substantial survival benefit with CN in elderly patients with mRCC in the targeted era, after adjusting for other factors. To our knowledge, this is the largest population-based study to date showing survival benefit with CN specifically in the elderly population. Two retrospective studies utilizing the National Cancer Data Base (NCDB) and the SEER database also showed a significant survival benefit with cytoreductive nephrectomy in targeted therapy era (10, 11). However, these studies did not look at survival benefit specifically for the elderly population.

Despite lack of sound evidence, elderly patients are perceived to be less able to tolerate standard treatment by their providers. Overall CN is generally a safe procedure with excellent reported perioperative outcomes (12). A study utilizing US-based Nationwide Inpatient Sample registry showed that patients with advanced age (≥75 years) were more likely to acquire operative mortality (13). However, this study had a significant limitation of lack of adjustment for case complexity and performance status. Matin *et al*. suggested that for patients undergoing laparoscopic urological

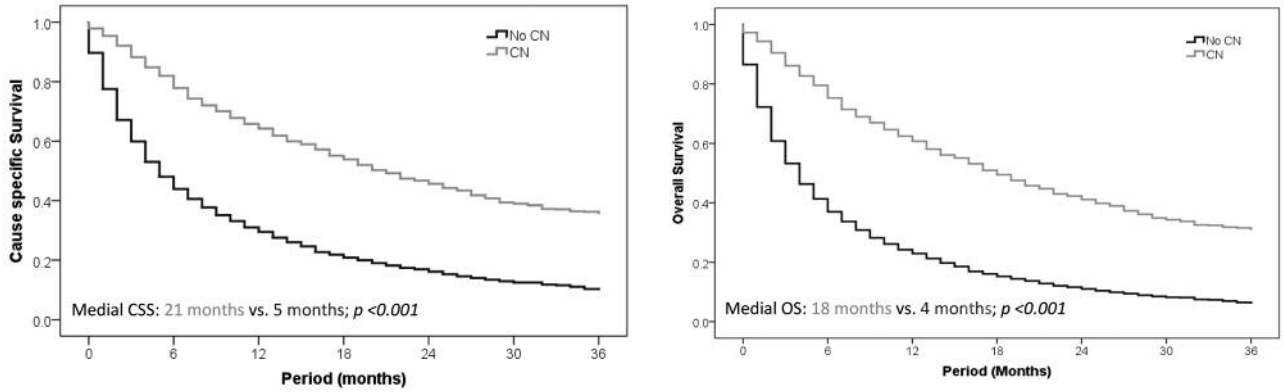

Figure 2. *Kaplan–Meier curves for comparison of survival.*

Table II. *Factors associated with survival in patients with and without CN.*

Parameters	No CRN		CRN	
	Adjusted HR	*p*-Value	Adjusted HR	*p*-Value
Age				
65-69	Reference		Reference	
70-74	1.04 (0.92-1.18)	0.5	1.12 (0.94-1.34)	0.2
75-79	1.15 (1.02-1.30)	0.03	1.16 (0.94-1.43)	0.18
80-84	1.22 (1.06-1.40)	0.004	1.4 (1.08-1.82)	0.012
85+	1.38 (1.18-1.61)	<0.001	1.66 (0.98-2.81)	0.06
Gender				
Male (%)	Reference			
Female (%)	1.08 (0.99-1.18)	0.11	1.06 (0.91-1.24)	0.46
Race				
Caucasians (%)	Reference		Reference	
African American (%)	0.86 (0.74-1.01)	0.058	0.87 (0.62-1.21)	0.41
Others (%)	0.96 (0.81-1.15)	0.68	0.74 (0.54-0.996)	0.047
Unknown	1.04 (0.43-2.51)	0.94		
Histology				
Clear cell (%)	Reference		Reference	
Others (%)	1.33 (1.21-1.46)	<0.001	1.51 (1.29-1.76)	<0.001
Tumor size (T)				
T0 (%)	Reference			
T1 (%)	0.66 (0.44-0.99)	0.042	Reference	
T2 (%)	0.74 (0.49-1.11)	0.14	0.85 (0.45-1.59)	0.6
T3 (%)	0.84 (0.56-1.25)	0.39	0.95 (0.50-1.79)	0.87
T4 (%)	0.85 (0.57-1.28)	0.44	1.2 (0.66-2.17)	0.56
TX (%)	0.79 (0.54-1.18)	0.25	1.65 (0.88-3.10)	0.12
Nodal involvement (N)				
N0 (%)	Reference		Reference	
N1 (%)	1.27 (1.12-1.44)	<0.001	1.76 (1.43-2.17)	<0.001
N2 (%)	1.24 (1.06-1.44)	0.006	2.17 (1.71-2.75)	<0.001
NX (%)	1.0 (0.89-1.12)	0.94	1.20 (0.89-1.63)	0.23
Year of diagnosis				
2006	Reference		Reference	
2007	0.98 (0.83-1.15)	0.78	1.02 (0.77-1.35)	0.9
2008	0.97 (0.82-1.14)	0.68	1.04 (0.78-1.39)	0.78
2009	0.94 (0.79-1.11)	0.45	1.1 (0.83-1.46)	0.52
2010	0.96 (0.81-1.14)	0.66	1.1 (0.82-1.48)	0.53
2011	0.96 (0.81-1.13)	0.63	1.12 (0.83-1.48)	0.5
2012	0.94 (0.79-1.12)	0.48	1.01 (0.73-1.39)	0.96

surgery, age ≥65 years does not increase the risk of intraoperative, postoperative or late operative complications (14). Furthermore, Burdjis *et al*. demonstrated that advanced age (≥75 years) alone was not associated with significant mortality and morbidity as compared to younger patients (15).

There are other studies suggesting older age as an independent factor for perioperative complications (16, 17). Elderly patients with low physiological reserve, multiple comorbidities and poor performance status are more likely to have worse operative outcomes. Physiological age, underlying comorbidities and performance status should therefore be the guiding factors for selecting patients for CN and not just the chronological age.

CARMENA (Clinical Trial to Assess the Importance of Nephrectomy) and SURTIME (Immediate surgery or surgery after sunitinib malate in treating patients with metastatic kidney cancer) are two large randomized phase III trials that are investigating the role of CN in the targeted era. Elderly patients with ECOG performance status of 0-1 and life expectancy of at least 3 months are included in these trials (22, 23). The final results of these trials will potentially give us definitive guidance about the role of CN in the elderly population. Interestingly though, results of the Checkmate-214 study comparing the combination immunotherapy nivolumab and ipilumumab to sunitib in the front line setting of mRCC are available now and may change the treatment paradigm of mRCC in the near future (24). The study showed superiority of immunotherapy over sunitinib in terms of ORR and PFS and OS in the intermediate and poor risk groups. Future studies analyzing the benefits of CN with the use of immunotherapy are likely to be needed.

The SEER database is large and comprehensive. It includes approximately 28% of the United States population and is comparable to the general United States population with regard to measures of poverty and education (18). Because of its generalizability, we were able to evaluate the impact of treatment at a population level outside of randomized clinical trials. These are the major strengths of our study.

Our study is limited by lack of prospective randomization, a product of its retrospective study design. It is important to note that allocation of patients to CN is not randomized, potentially leading to selection bias and hence overestimating the benefit of CN. Moreover, patients with mRCC are more likely to have one or more adverse prognostic factors including poor performance status, elevated LDH, anemia, hypercalcemia, bone metastasis and more than one sites of metastasis (19-21) and the SEER database lacks individual patient information on these parameters.

In summary, our data support that CN remains an independent predictor of OS in the targeted era even in the elderly population over the age of 65. It should be a serious consideration in elderly patients, particularly with excellent performance status.

Conflicts of Interest

No Authors have relevant disclosures to report.

References

1 65 + in the United States: 2010, U.S. Government Printing Office, Washington, DC, 2014. Assessed May 10, 2017 at https://www.census.gov/content/dam/Census/library/publications/2014/demo/p23-212.pdf

2 Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H and Crawford ED: Cytoreductive nephrectomy in patients with metastatic renal cancer: A combined analysis. J Urol *171*: 1071-1076, 2004.

3 Tsao CK, Small AC, Kates M, Moshier EL, Wisnivesky JP, Gartrell BA, Sonpavde G, Godbold JH, Palese MA, Hall SJ, Oh WK and Galsky MD: Cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy in the United States: a SEER analysis. World J Urol *31(6)*: 1535-1539, 2013.

4 Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR Jr, Munshi N and Crawford ED: Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med *345(23)*: 1655-1659, 2001.

5 Mickisch GH, Garin A, van Poppel H, de Prijck L and Sylvester R: Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial. Lancet *358(9286)*: 966-970, 2001.

6 Psutka SP, Kim SP, Gross CP, Van Houten H, Thompson RH, Abouassaly R, Weight C, Boorjian SA, Leibovich BC and Shah ND: The impact of targeted therapy on management of metastatic renal cell carcinoma: trends in systemic therapy and cytoreductive nephrectomy utilization. Urology *85(2)*: 442-450, 2015.

7 Tsao CK, Small AC, Kates M, Moshier EL, Wisnivesky JP, Gartrell BA, Sonpavde G, Godbold JH, Palese MA, Hall SJ, Oh WK and Galsky MD: Cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy in the United States: a SEER analysis. World J Urol *31(6)*: 1535-1539, 2013.

8 NIH National Cancer Institute Surveillance, Epidemiology, and End Results Program. Overview of the SEER Program. Assessed May 7, 2017 at https://seer.cancer.gov/about/overview.html

9 Conti SL, Thomas IC, Hagedorn JC, Chung BI, Chertow GM, Wagner TH, Brooks JD, Srinivas S and Leppert JT: Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. Int Cancer *134(9)*: 2245-2252, 2014.

10 Hanna N, Sun M, Meyer CP, Nguyen PL, Pal SK, Chang SL, de Velasco G, Trinh QD and Choueiri TK: Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: A National Cancer Data Base study. J Clin Oncol *34(27)*: 3267-3275, 2016.

11 Abern MR, Scosyrev E, Tsivian M, Messing EM, Polascik TJ and Dudek AZ: Survival of patients undergoing cytoreductive surgery for metastatic renal cell carcinoma in the targeted-therapy era. Anticancer Res *34(5)*: 2405-2411, 2014.

12 Jackson BL, Fowler S and Williams ST; British Association of Urological Surgeons (BAUS) – Section of Oncology: Perioperative outcomes of cytoreductive nephrectomy in the UK in 2012. BJU Int *116(6)*: 905-910, 2015.

13 Trinh QD, Bianchi M, Hansen J, Tian Z, Abdollah F, Shariat SF, Montorsi F, Perrotte P, Karakiewicz PI and Sun M: In-hospital mortality and failure to rescue after cytoreductive nephrectomy. Eur Urol *63(6)*: 1107-1114, 2013.

14 Matin SF, Abreu S, Ramani A, Steinberg AP, Desai M, Strzempkowski B, Yang Y, Shen Y and Gill IS: Evaluation of age and comorbidity as risk factors after laparoscopic urological surgery. J Urol *170(4 Pt 1)*: 1115-1120, 2003.

15 Berdjis N, Hakenberg OW, Novotny V, Froehner M and Wirth MP: Treating renal cell cancer in the elderly. BJU Int *97(4)*: 703-705, 2006.

16 Thoroddsen A, Gudbjartsson T, Jonsson E, Gislason T and Einarsson GV: Operative mortality after nephrectomy for renal cell carcinoma. Scand J Urol Nephrol *37(6)*: 507-511, 2003.

17 Kader AK, Tamboli P, Luongo T, Matin SF, Bell K, Jonasch E, Swanson DA and Wood CG: Cytoreductive nephrectomy in the elderly patient: the M. D. Anderson Cancer Center experience. J Urol *177(3)*: 855-860, 2007.

18 Surveillance, Epidemiology, and End Results (SEER) Program Assessed May 7, 2017 at https://www.epa.gov/sites/production/files/2015-06/documents/aceappendixb_surveillance epidemiologyandendresults.pdf

19 Motzer RJ, Bacik J and Mazumdar M: Prognostic factors for survival of patients with stage IV renal cell carcinoma: Memorial Sloan-Kettering cancer center experience. Clin Cancer Res *10(18 Pt 2)*: 6302S-6303S, 2004.

20 Beuselinck B, Oudard S, Rixe O, Wolter P, Blesius A, Ayllon J, Elaidi R, Schöffski P, Barrascout E, Morel A, Escudier B, Lang H, Zucman-Rossi J and Medioni J: Negative impact of bone metastasis on outcome in clear-cell renal cell carcinoma treated with sunitinib. Ann Oncol *22(4)*: 794-800, 2011.

21 Mekhail TM, Abou-Jawde RM, Boumerhi G, Malhi S, Wood L, Elson P and Bukowski R: 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 *23(4)*: 832-841, 2005.

22 ClinicalTrials.gov: Clinical trial to assess the importance of nephrectomy (CARMENA). Assessed July 18, 2017 at https://clinicaltrials.gov/show/NCT00930033

23 ClinicalTrials.gov: Immediate surgery or surgery after sunitinib malate in treating patients with metastatic kidney cancer (SURTIME). Assessed July 18, 2017 at https://clinicaltrials.gov/show/NCT01099423

24 Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B and CheckMate 214 Investigators: Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med *378(14)*: 1277-1290, 2018.

Received March 15, 2018
Revised March 27, 2018
Accepted March 28, 2018