Asian Journal of Surgery 46 (2023) 328–336

Contents lists available at ScienceDirect

Asian Journal of Surgery

journal homepage: www.e-asianjournalsurgery.com

Original Article

Shifting role of cytoreductive nephrectomy according to type of systemic therapy: A nationwide cohort study

Se Young Choi [a, b, 1, *], Moon Soo Ha [c, 1], Jeong Woo Lee [d], Jae Hwan Kim [d], Jung Hoon Kim [e], Byung Hoon Chi [a], Jin Wook Kim [e], In Ho Chang [a], Tae-Hyoung Kim [a], Soon Chul Myung [a]

[a] Department of Urology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, South Korea
[b] Biomedical Research Institute, Chung-Ang University Hospital, South Korea
[c] Department of Urology, Hyundae General Hospital, Chung-Ang University College of Medicine, Gyeonggi-do, South Korea
[d] Data Science Team, Hanmi Pharm. Co.,Ltd, Seoul, South Korea
[e] Department of Urology, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gyeonggi-do, South Korea

ARTICLE INFO

Article history:
Received 18 October 2021
Received in revised form
31 January 2022
Accepted 7 April 2022
Available online 18 April 2022

Keywords:
Cytoreductive nephrectomy
Metastatic renal cell carcinoma
Overall survival
Cytokine therapy
Target therapy

SUMMARY

Purpose: The best protocol of cytoreductive nephrectomy (CN) and systemic therapy (ST) in the treatment of metastatic renal cell carcinoma (mRCC) remains unclear. We sought to evaluate overall survival (OS) in patients with mRCC treated with ST with or without CN.

Methods: We collected data from the National Health Insurance Service database. We excluded 2 years of washout period, 2 years of follow-up period, other cancer diagnoses within 2 years, and ≥4 months interval between ST and CN. The patients were divided into two groups according to whether CN was performed. Kaplan–Meier, propensity score matching, Cox regression model, and incremental survival analyses were conducted. Additionally, we performed subgroup analysis according to whether cytokine therapy or targeted therapy was used as first-line ST.

Results: Of 6478 patients, 1707 (26.4%) underwent CN. The CN group showed significantly better OS than the no CN group ($p < 0.001$). In the cytokine therapy subgroup, patients who underwent CN had significantly higher OS than those who did not ($p < 0.001$). In the targeted therapy subgroup, no significant difference was found ($p = 0.867$). In multivariate analysis, CN was associated with better OS in the total cohort (hazard ratio 0.819, $p < 0.001$). The incremental OS benefit of CN ranged from +0.98 in patients who survived for <24 months to +2.13 in those who survived during all periods.

Conclusion: About a quarter patients with mRCC from a nationwide database were treated with CN and ST. CN was beneficial in specific patients with mRCC. Patient selection is crucial for obtaining the benefits of CN.

1. Introduction

Renal cell carcinoma (RCC) was newly diagnosed in >400,000 patients and was responsible for >170,000 deaths worldwide in 2018.[1] Although advances in screening have helped diagnose RCC in the early stage, a study in the United States reported detecting regional disease in 17% and distant disease in 16% of patients at the time of diagnosis.[2] Despite the improved survival rates in recent years, the 5-year survival rate of patients with distant disease was reported to be only 12%.[2] In the cytokine therapy era, two randomized clinical trials have proven that cytoreductive nephrectomy (CN) with interferon-α therapy provides an about 6 months longer overall survival (OS) than interferon-α therapy alone.[3] In the mid-2000s, targeted therapy became the new standard of care, providing superior benefit over cytokine therapy.[4] In the targeted therapy era, the role of CN became ambiguous in metastatic RCC

* Corresponding author. Department of Urology, Chung-Ang University Hospital, Chung-Ang University College of Medicine 102, Heukseok-ro, Dongjak-gu, Seoul, 06973, Republic of Korea.
E-mail addresses: urosyc@cau.ac.kr (S.Y. Choi), karlzavi@daum.net (M.S. Ha), jeongwoo.lee@hanmi.co.kr (J.W. Lee), jaehwan.kim@hanmi.co.kr (J.H. Kim), simbauro80@hanmail.net (J.H. Kim), jeebang@naver.com (B.H. Chi), jinwook@cau.ac.kr (J.W. Kim), caucih@cau.ac.kr (I.H. Chang), kthlmk@nate.com (T.-H. Kim), uromyung@cau.ac.kr (S.C. Myung).
[1] Both authors contributed equally to this work, **Co-first authors:** Se Young Choi, Moon Soo Ha.

https://doi.org/10.1016/j.asjsur.2022.04.008

(mRCC) because of the lack of randomized trials during the first decade of its use.

Recently, two randomized trials reported their results. One is the CARMENA trial, which confirmed the noninferiority of sunitinib alone to CN with sunitinib in intermediate- and high-risk clear cell mRCC.[5] This trial suggested that CN may not be needed in all patients with mRCC and can even be harmful to some patients. The other trial is the SURTIME trial, which investigated the timing of CN in patients with mRCC. Unfortunately, the trial was underpowered because the target enrollment number was not met. However, it showed that deferment of CN until after the first three cycles of sunitinib resulted in more favorable OS than upfront CN.[6] This trial also suggested that immediate systemic therapy (ST) may be important to control mRCC. Despite these trials, the best protocol for CN and ST in the treatment of mRCC remains unclear.

In this study, we sought to evaluate OS in patients with mRCC treated with ST with or without CN, by using nationwide population-based data.

2. Materials and methods

2.1. Database

We collected data from the National Health Insurance Service (NHIS) database. The NHIS is a universal health coverage system in South Korea. More than 97% of Koreans (>50 million individuals) are enrolled in the NHIS.

2.2. Study design

All patients were diagnosed with primary RCC (diagnostic code: C64), and were treated with ST between 2002 and 2018. The diagnostic codes defined by the International Classification of Diseases were used in this study. The STs were classified as cytokine therapy, tyrosine kinase inhibitor (TKI), mammalian target of rapamycin (mTOR) inhibitor, and others. We excluded 2 years of washout period (2002–2003) and 2 years of follow-up period (2017–2018). Cases with other cancer diagnoses within 2 years and

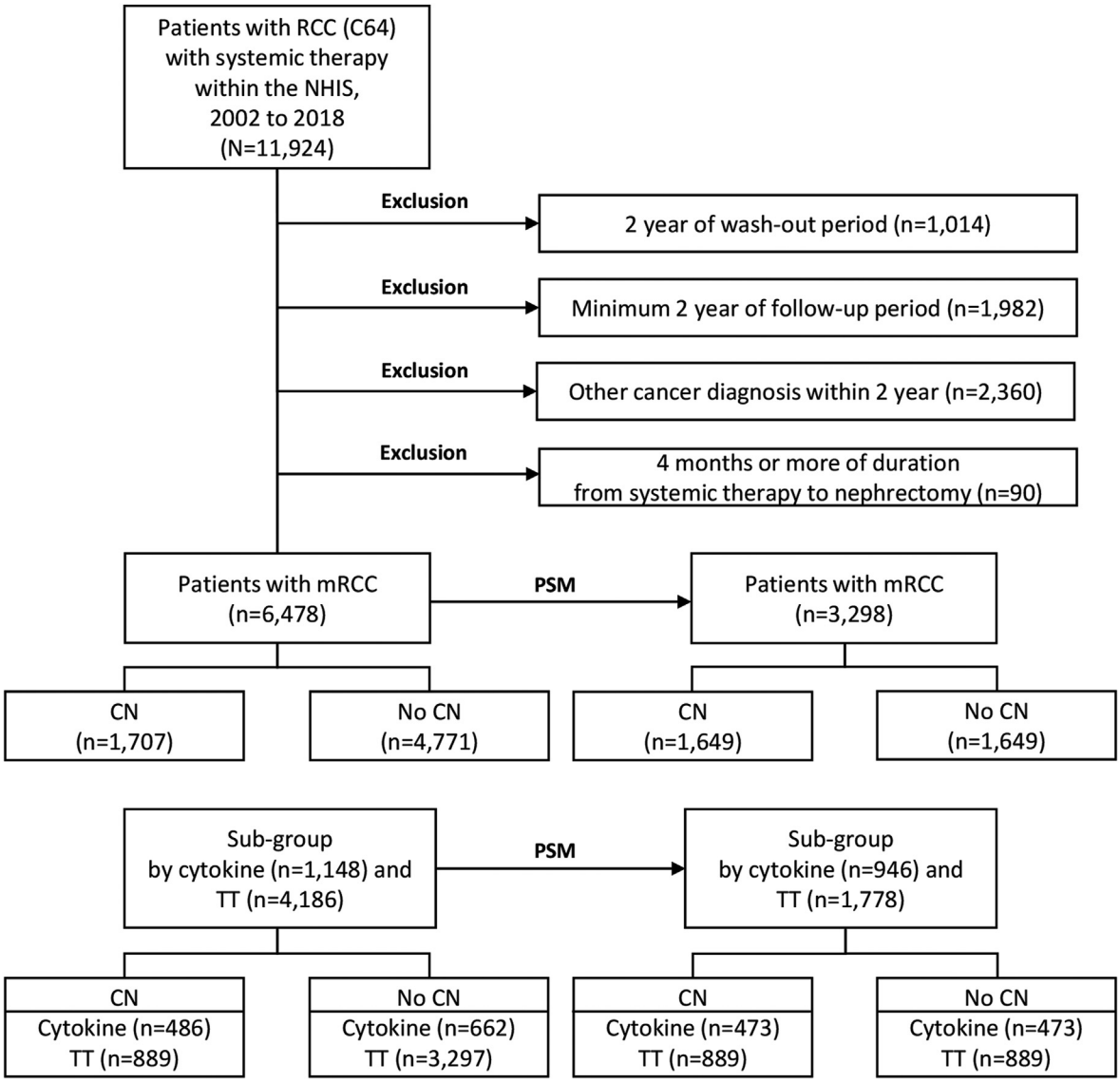

Fig. 1. Flowchart of the study design
RCC, renal cell carcinoma; NHIS, National Health Insurance Service; mRCC, metastatic renal cell carcinoma; CN, cytoreductive nephrectomy, PSM, propensity score matching; TT, targeted therapy.

those with ≥4 months interval between ST and nephrectomy were also excluded. CN was identified using surgery codes (R3271, R3273, and R3274). Our total cohort consisted of 6478 patients, of whom 1707 patients underwent CN (CN group) and 4771 patients did not undergo CN (no CN group) (Fig. 1).

2.3. Variables

The patient variables included age, diagnosis year, sex, and diagnostic history. The comorbidity status was assessed using the Charlson comorbidity index (CCI).[7] We also collected data on the duration from CN to ST, type of ST, granulocyte colony-stimulating factor (G-CSF) use and rate of use, hospitalization duration at CN, transfusion at CN and transfusion volume, admission without ST or CN and number of such admissions, and mortality within 3 months after CN.

2.4. Statistical analyses

Patient characteristics were compared based on whether CN was performed or not (CN group vs. no CN group). The clinical trends are expressed as means ± standard deviations or numbers with percentages. The groups were compared using Student's t-test for continuous variables and the chi-square test for categorical variables. We classified the patients into the following two subgroups: patients treated with cytokine therapy as the first-line ST and those who received targeted therapy as the first-line ST; targeted therapy included both TKI and mTOR inhibitor therapies, including sunitinib, pazopanib, sorafenib, axitinib, cabozantinib, bevacizumab, everolimus, and temsirolimus. OS was estimated using the Kaplan–Meier method with a log-rank test, and compared between the groups. Survival was assessed starting from the period of ST and was censored at the date of the last follow-up or death. Propensity score matching (PSM) was performed according to age, sex, and CCI. We performed 1:1 nearest matching with a caliper set of 0.1. A Cox proportional hazard model was used for multivariate analysis. The incremental OS benefits were compared between the groups of patients with who survived for <12, <24, <36, and <48 months, and during all periods.

All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). A p-value of <0.05 was considered statistically significant.

3. Results

Our final cohort comprised 6478 patients, with 4771 patients (73.6%) in the no CN group and 1707 patients (26.4%) in the CN group, between 2004 and 2016 (Table 1). The CN group was younger and had a lower CCI (all $p < 0.001$). The rates of CN were 37.2% in 2004–2006, 28.2% in 2007–2010, and 21.9% in 2011–2016 ($p < 0.001$). The proportion of each sex was similar between the groups. The survival rates of all medical histories, except for acquired immune deficiency syndrome, were lower in the no CN group than in the CN group (all $p < 0.05$). After PSM, the CN and no CN groups showed a well-matched distribution in the total cohort, subgroup of cytokine therapy, and target therapy (all standardized mean difference <0.1, Table 2).

Clinical trends after treatment are summarized in Table 3. The

Table 1
Patient characteristics.

	No CN (n = 4771)	CN (n = 1707)	p value
Age (years)			<0.001
<55	1192 (25.0%)	715 (41.9%)	
55-64	1300 (27.2%)	481 (28.2%)	
65-74	1486 (31.1%)	399 (23.4%)	
≥75	793 (16.6%)	112 (6.6%)	
Diagnosis year			<0.001
2004–2006	611 (12.8%)	362 (21.2%)	
2007–2010	1360 (28.5%)	558 (32.7%)	
2011–2016	2800 (58.7%)	787 (46.1%)	
Sex			1.000
Male	3512 (73.6%)	1256 (73.6%)	
Female	1259 (26.4%)	451 (26.4%)	
Medical history			
Hypertension	3301 (69.2%)	977 (57.2%)	<0.001
Cerebrovascular disease	1206 (25.3%)	279 (16.3%)	<0.001
Chronic pulmonary disease	3412 (71.5%)	1060 (62.1%)	<0.001
Congestive heart failure	755 (15.8%)	173 (10.1%)	<0.001
Dementia	245 (5.1%)	33 (1.9%)	<0.001
Diabetes without chronic complication	1381 (28.9%)	434 (25.4%)	0.006
Mild liver disease	2852 (59.8%)	851 (49.9%)	<0.001
Myocardial infection	322 (6.7%)	88 (5.2%)	0.024
Peptic ulcer disease	3008 (63.0%)	872 (51.1%)	<0.001
Peripheral vascular disease	1339 (28.1%)	306 (17.9%)	<0.001
Rheumatologic disease	829 (17.4%)	169 (9.9%)	<0.001
Diabetes with chronic complication	1097 (23.0%)	253 (14.8%)	<0.001
Hemiplegia or paraplegia	205 (4.3%)	38 (2.2%)	<0.001
Renal disease	683 (14.3%)	128 (7.5%)	<0.001
Moderate or severe liver disease	216 (4.5%)	50 (2.9%)	0.005
AIDS	6 (0.1%)	2 (0.1%)	1.000
Charlson comorbidity index			<0.001
0	225 (4.7%)	171 (10.0%)	
1, 2	1185 (24.8%)	637 (37.3%)	
3-6	2461 (51.6%)	744 (43.6%)	
7-10	798 (16.7%)	145 (8.5%)	
>10	102 (2.1%)	10 (0.6%)	

CN, cytoreductive nephrectomy; AIDS, Acquired Immune Deficiency Syndrome.

Table 2
Balanced patient characteristics after propensity score matching.

	Total cohort			Subgroup of cytokine therapy			Subgroup of target therapy		
	No CN (n = 1649)	CN (n = 1649)	p value (SMD)	No CN (n = 473)	CN (n = 473)	p value (SMD)	No CN (n = 889)	CN (n = 889)	p value (SMD)
Age (years)			0.781 (−0.016)			0.815 (−0.023)			0.806 (−0.014)
<55	641 (38.9%)	657 (39.8%)		168 (35.5%)	175 (37.0%)		294 (33.1%)	298 (33.5%)	
55-64	474 (28.7%)	481 (29.2%)		148 (31.3%)	145 (30.7%)		289 (32.5%)	288 (32.4%)	
65–74	409 (24.8%)	399 (24.2%)		120 (25.4%)	123 (26.0%)		226 (25.4%)	234 (26.3%)	
≥75	125 (7.6%)	112 (6.8%)		37 (7.8%)	30 (6.3%)		80 (9.0%)	69 (7.8%)	
Sex			0.658 (0.017)			0.219 (0.082)			0.293 (0.051)
Male	1245 (75.5%)	1233 (74.8%)		371 (78.4%)	354 (74.8%)		714 (80.3%)	695 (78.2%)	
Female	404 (24.5%)	416 (25.2%)		102 (21.6%)	119 (25.2%)		175 (19.7%)	194 (21.8%)	
Charlson comorbidity index			0.731 (0.013)			0.685 (−0.038)			0.923 (0.005)
0	147 (8.9%)	163 (9.9%)		34 (7.2%)	43 (9.1%)		51 (5.7%)	58 (6.5%)	
1, 2	601 (36.5%)	588 (35.7%)		195 (41.2%)	202 (42.7%)		264 (29.7%)	267 (30.0%)	
3-6	759 (46.0%)	743 (45.1%)		221 (46.7%)	204 (43.1%)		457 (51.4%)	444 (49.9%)	
7-10	135 (8.2%)	145 (8.8%)		21 (4.4%)	23 (4.9%)		110 (12.4%)	111 (12.5%)	
>10	7 (0.4%)	10 (0.6%)		2 (0.4%)	1 (0.2%)		7 (0.8%)	9 (1.0%)	

CN, cytoreductive nephrectomy; SMD, standardized mean difference.

Table 3
Clinical trends after the treatments.

	Before match			After match		
	No CN (n = 4771)	CN (n = 1707)	p value	No CN (n = 1649)	CN (n = 1649)	p value
Period from CN to ST (days)	NA	30.5 ± 38.3 [28.0, 14.0–49.0]	NA	NA	31.9 ± 37.1 [29.0, 15.0–49.0]	NA
Type of ST			<0.001			<0.001
- Cytokine therapy	662 (14.2%)	486 (29.6%)		263(15.9%)	485(29.41%)	
- TKI	2951 (63.3%)	797 (48.5%)		942(57.1%)	797(48.33%)	
- mTOR inhibitor	346 (7.4%)	92 (5.6%)		119(7.2%)	92(5.58%)	
- Other	812 (17.0%)	332 (19.4%)		325(19.7%)	275(16.68%)	
G-CSF usage	409 (8.6%)	279 (16.3%)	<0.001	200(12.1%)	231(14.01%)	0.1212
G-CSF usage number per person	3.8 ± 2.6 [1.0, 1.0–3.0]	6.6 ± 5.5 [2.0, 1.0–7.0]	<0.001	5.5 ± 11 [2.0,1.0–5.0]	5.2 ± 9 [1.0,1.0–5.0]	0.7404
G-CSF usage after the first ST within 3 months	261 (5.5%)	192 (11.2%)	<0.001	142(8.61%)	150(9.10%)	0.6679
Hospitalization duration at CN (days)	NA	16.3 ± 11.1 [13.0, 10.0–19.0]	NA	NA	16.3 ± 11.1 [13,10.0–19.0]	NA
Transfusion at CN	NA	913 (53.5%)	NA	NA	892(54.09%)	NA
Transfusion volume per person (pack)	NA	1.4 ± 1.1 [1.0, 1.0–1.0]	NA	NA	1.4 ± 1.1 [1.0,1.0–1.0]	NA
Admission without ST or CN	3820 (80.1%)	1369 (80.2%)	0.935	1351(81.93%)	1315(79.75%)	0.1215
Admission number without ST or CN per person	5.7 ± 8.4 [3.0, 2.0–7.0]	6.3 ± 9.5 [4.0, 2.0–7.0]	0.075	6 ± 9.1 [4.0,2.0–7.0]	6.1 ± 9.5 [4.0,2.0–7.0]	0.8848
Admission without ST or CN within 3 months	NA	615 (36.0%)	NA	NA	574(34.81%)	NA
Mortality after CN within 3 months	NA	61 (3.6%)	NA	NA	60(3.64%)	NA

CN, cytoreductive nephrectomy; ST, systemic therapy; TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; G-CSF, granulocyte colony-stimulating factor; NA, not analyzed. Mean ± standard deviation [median, interquartile range].

period from CN to ST was 30.5 ± 38.3 days. TKIs were the most commonly used agents in both groups. G-CSF was used more frequently in the CN group than in the no CN group (16.3% vs. 8.6%, $p < 0.001$). The number of G-CSF uses per person was higher in the CN group than in the no CN group (6.6 ± 5.5 vs. 3.8 ± 2.6, $p < 0.001$). The rate of G-CSF use within 3 months after the first ST was higher in the CN group than in the no CN group (11.25% vs. 5.5%, $p < 0.001$). After PSM, the results regarding G-CSF usage did not show any differences. The hospitalization duration at CN was 16.3 ± 11.1 days. Transfusion at CN was performed in 913 patients (53.5%). The transfusion volume per person was 1.4 ± 1.1 packs. The rate of admission without ST or CN was similar between the groups ($p = 0.935$). The number of admissions per person did not significantly differ between groups ($p = 0.075$). The rate of admission within 3 months after CN was 36.0%. Mortality within 3 months after CN occurred in 61 cases.

Overall, 5072 deaths were recorded. The mean time to mortality was 36.7 months (median: 22.3 months, interquartile range [IQR]: 7.7–49.6 months). The mean time to mortality was 32.8 months in the no CN group (median: 20.4 months, IQR: 7.1–44.8 months) and 47.6 months in the CN group (median: 29.2 months, IQR: 9.8–74.1 months). Patients in the CN group showed significantly better OS than those in the no CN group ($p < 0.001$, Fig. 2a). After PSM (1649 patients who did not undergo CN vs. 1649 patients who underwent CN), the CN group was also associated with a higher OS ($p = 0.049$, Fig. 2b).

In the subgroup of patients whose first-line ST was cytokine therapy, 662 did not undergo CN and 486 underwent CN. The mean time to mortality was 46.4 months (median: 26.4 months, IQR: 7.8–69.8 months) in the no CN group and 64.8 months (median: 45.2 months; IQR: 14.7–117.3 months) in the CN group. The CN group had significantly higher OS than the no CN group ($p < 0.001$, Fig. 3a). After PSM (473 patients who did not undergo CN vs. 473 patients who underwent CN), the CN group also showed a significantly higher OS than the no CN group ($p < 0.001$, Fig. 3b).

In the subgroup of patients whose first-line ST was targeted therapy, 3297 did not undergo CN and 889 underwent CN. The mean time to the mortality was 28.4 months (median: 19.8 months, IQR: 6.8–41.1 months) in the no CN group and 29.2 months (median: 20.0 months, IQR: 7.7–40.9 months) in the CN group. No

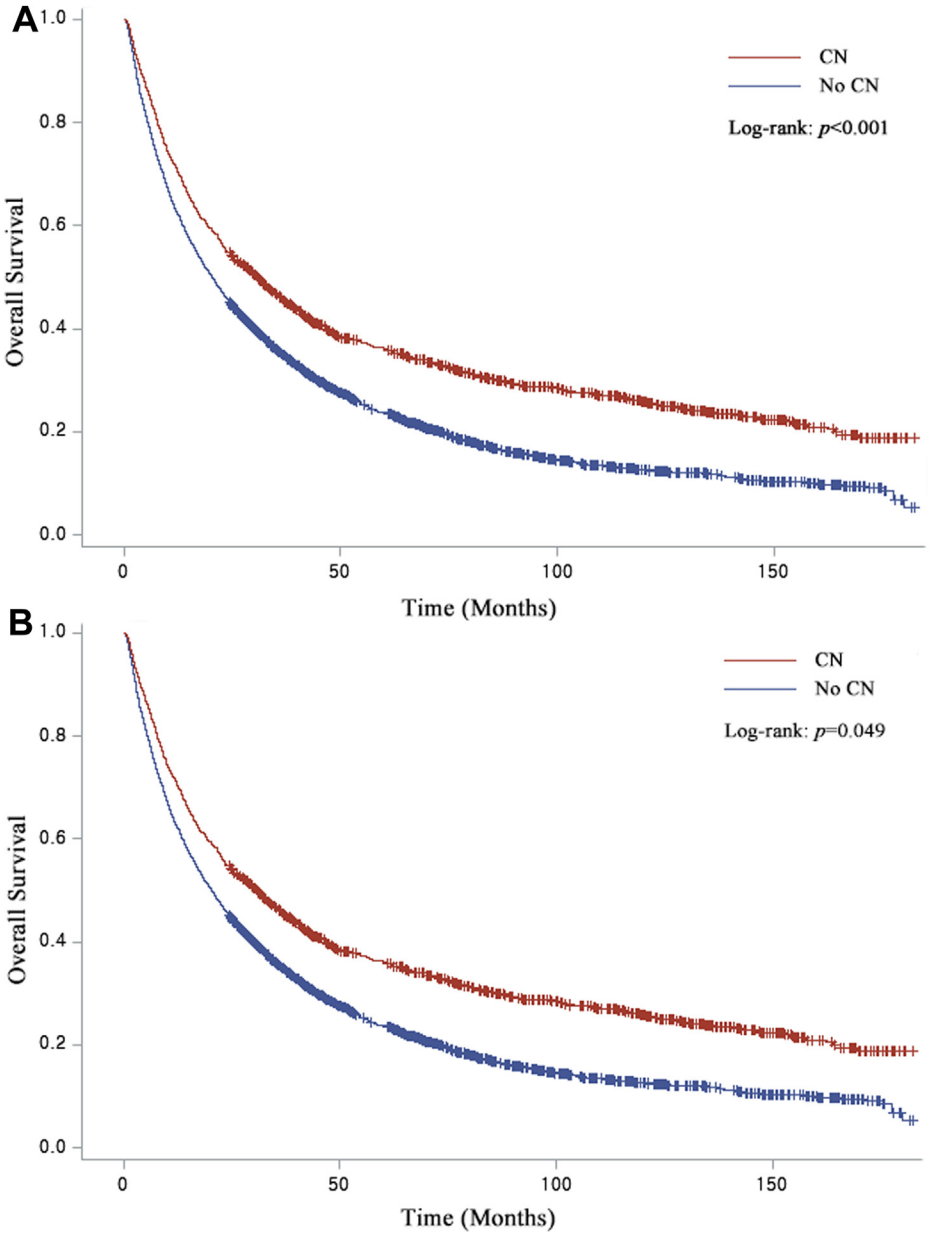

Fig. 2. Kaplan–Meier curve of overall survival before (a) and after (b) propensity score matching in the total cohort
CN, cytoreductive nephrectomy.

significant difference was observed between the no CN and CN groups (p = 0.867, Fig. 4a). After PSM (889 patients who did not undergo CN vs. 889 patients who underwent CN), the two groups also showed similar OS (p = 0.131, Fig. 4b).

In multivariate analysis with adjustments for confounding variables (Table 4), CN was associated with better OS in the total cohort (hazard ratio [HR] 0.819, 95% confidence interval [CI] 0.766–0.875, p < 0.001). CN was associated with better OS in the cytokine therapy subgroup (HR 0.690, 95% CI 0.602–0.792, p < 0.001). However, in the targeted therapy subgroup, CN did not show a significant effect on OS (HR 1.049, 95% CI 0.966–1.140, p = 0.253).

Incremental benefit analyses showed an incremental OS benefit ranging from > +0.98 in patients who survived for <24 months to +2.13 in patients who survived during all periods. However, after adjusting for all covariates, CN was associated with a significantly better OS in patients who survived for <24 months, for <48 months, or during all periods (Table 5).

4. Discussion

In our cohort from a Korean nationwide population-based database, 26.4% of patients with mRCC underwent CN with ST. We assessed the efficacy of CN compared with ST alone in patients with mRCC. In the total cohort and in the subgroup cohort of

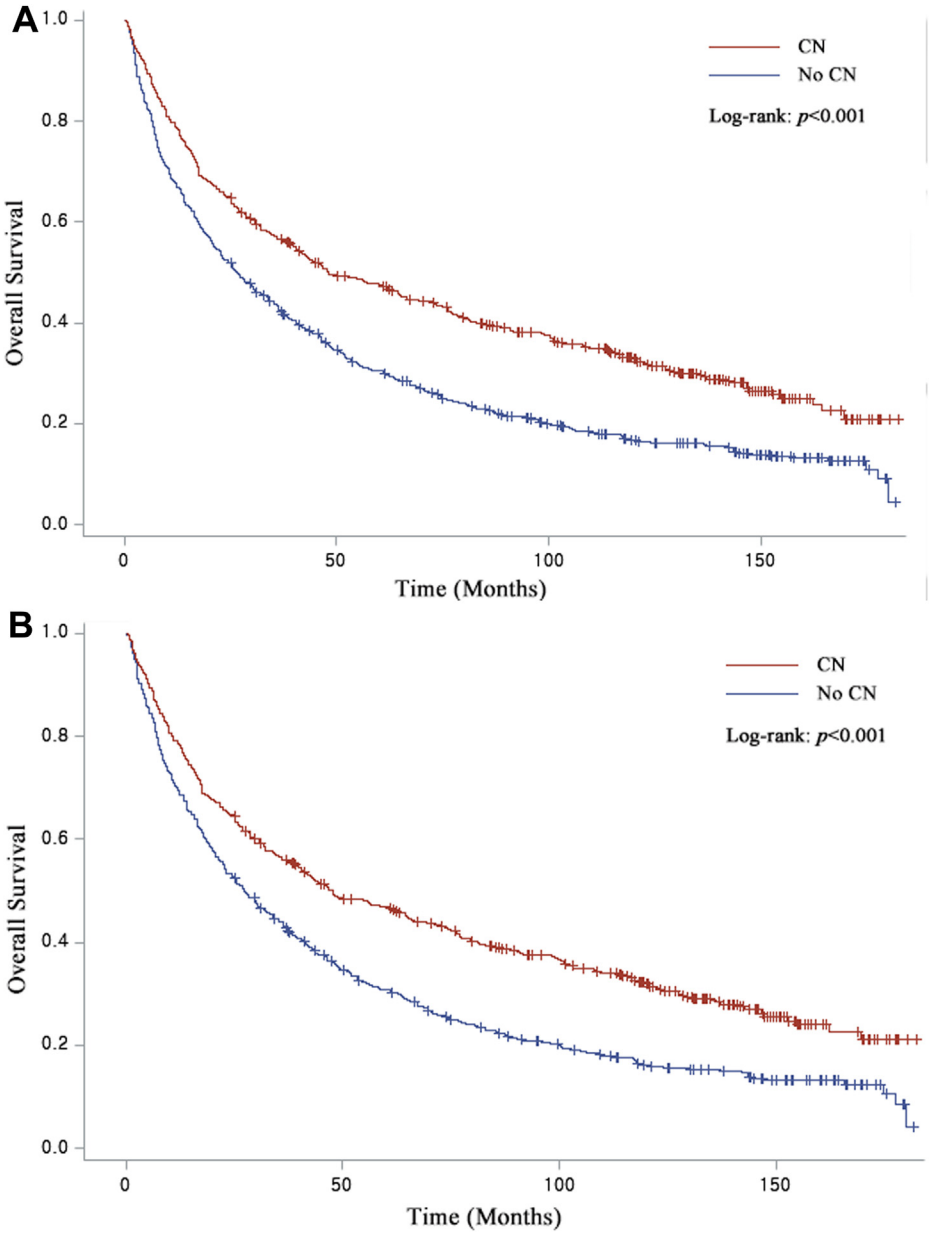

Fig. 3. Kaplan–Meier curve on overall survival before (a) and after (b) propensity score matching in subgroup of cytokine therapy
CN, cytoreductive nephrectomy.

patients who received cytokine therapy, patients who underwent CN showed better OS than those who did not. However, in the subgroup cohort of patients who received targeted therapy, there was no significant difference in OS. This result was similar to that of the CARMENA trial that included patients treated with targeted therapy. The uncertainty about the efficacy of CN in the targeted therapy era led clinicians to hesitate in using CN in the treatment of mRCC. This situation has already been observed in the Surveillance, Epidemiology, and End Results database after the introduction of targeted therapy.[8] In our data, the selection rate of CN decreased from 37.2% in 2004–2006 to 21.9% in 2011–2016. In Korea, the NHIS started to cover sunitinib in 2007 and pazopanib in 2011.

The rationale for CN remains unclear. Nevertheless, CN has a certain role in mRCC management and is still used in the real world. The major hypothesis is that reducing the primary tumor burden will decrease the possibility of new metastases because the primary tumor continuously produces tumor-promoting cytokines or growth factors.[9] RCC is a known immunogenic tumor, which means that it can control the anti-tumor immune mechanism.[10] RCC survives by recruiting angiogenic factors and evading apoptosis.[11] After CN, the inflammatory response decreases and immune activation increases in patients with RCC.[12] The mild acidification after CN affects the peritumoral microenvironment, resulting in the slowing down of metastasis development.[13] The effect of cytokine therapy has been considered unsatisfactory; however, because chemotherapy and radiotherapy are ineffective, cytokine therapy has been used for boosting the immune system.[14] Insights about von Hippel Lindau syndrome and angiogenetic molecular signaling

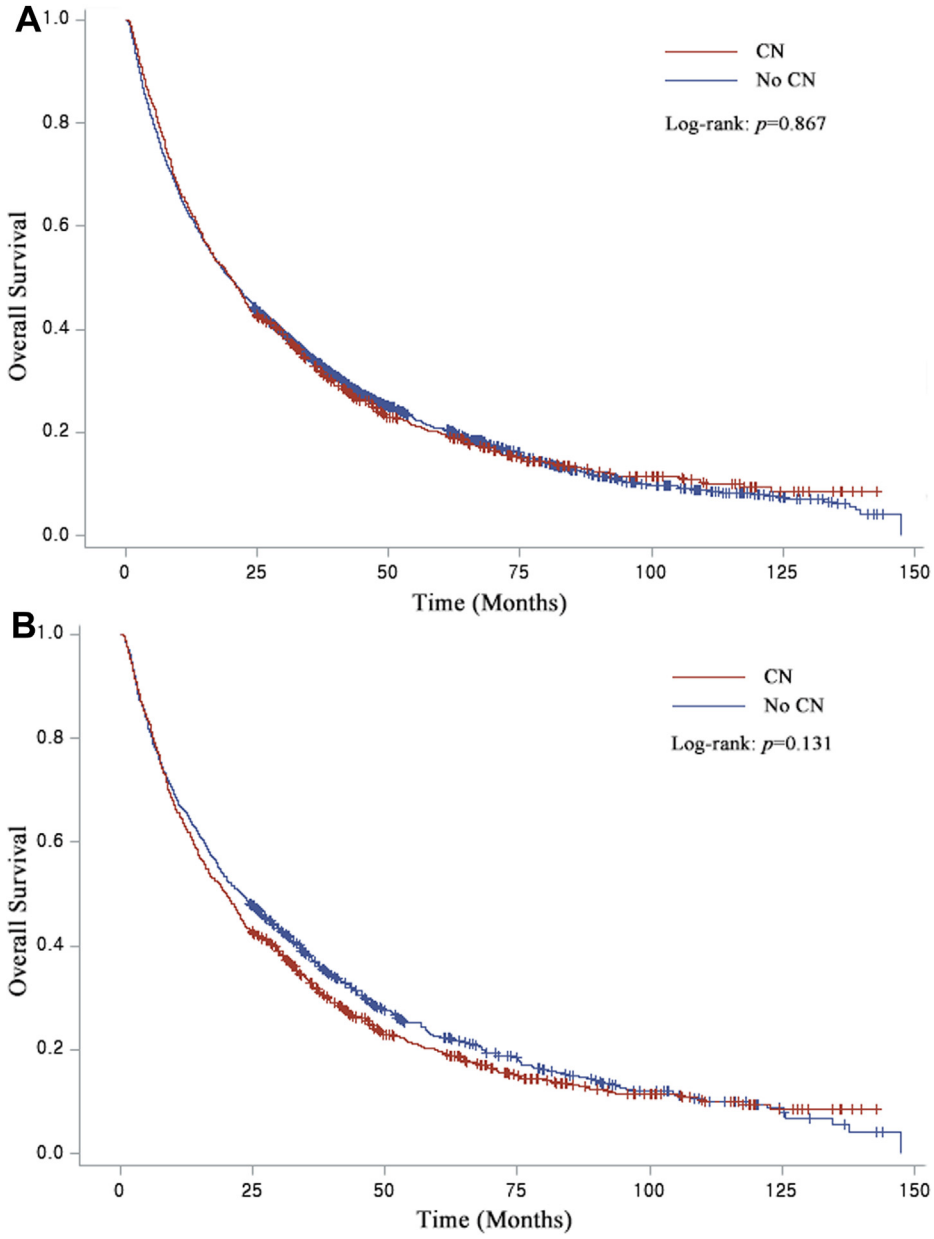

Fig. 4. Kaplan–Meier curve on overall survival before (a) and after (b) propensity score matching in subgroup of target therapy
CN, cytoreductive nephrectomy.

Table 4
Multivariable Cox regression analysis for overall survival.

	Total cohort		Subgroup of cytokine therapy		Subgroup of target therapy	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
CN performed	0.819 (0.766–0.875)	<0.001	0.690 (0.602–0.792)	<0.001	1.049 (0.966–1.140)	0.253
Age	1.021 (1.019–1.023)	<0.001	1.009 (1.003–1.015)	0.005	1.019 (1.015–1.022)	<0.001
Male gender	1.133 (1.063–1.207)	<0.001	1.080 (0.930–1.256)	0.313	1.067 (0.986–1.154)	0.109
Charlson comorbidity index	0.999 (0.987–1.011)	0.904	1.022 (0.987–1.059)	0.226	0.996 (0.982–1.010)	0.539
Diagnosis year	1.007 (0.999–1.016)	0.097	0.902 (0.876–0.929)	<0.001	0.993 (0.980–1.006)	0.281

HR, hazard ratio; CI, confidence interval; CN, cytoreductive nephrectomy.

in RCC have stimulated the widespread use of targeted therapy. However, RCC acquires resistance to targeted therapy through lysosomal sequestration, angiogenic switching, and tumor heterogeneity.[15] As the mechanisms of cytokine therapy and targeted therapy are different, the role of CN in activating the immune reaction may be different between the two therapies. In the impending immune therapy or combination therapy era, the efficacy of CN would change again and would need to be proven. A

Table 5
Incremental survival analyses by stratified survival time in total cohort.

OS (months)	Median OS (months)	Median OS (months)	Incremental benefit (months)	P (log-rank)	HR (95% CI)[a]
	No CN	CN			
<12	5.07 (n = 1770)	5.73 (n = 493)	+0.66	0.168	0.948 (0.856–1.050), p = 0.307
<24	7.80 (n = 2592)	8.78 (n = 772)	+0.98	0.019	0.912 (0.840–0.989), p = 0.027
<36	9.80 (n = 3056)	10.65 (n = 914)	+0.85	0.048	0.941 (0.872–1.015), p = 0.113
<48	10.97 (n = 3349)	12.63 (n = 1022)	+1.66	0.005	0.918 (0.855–0.986), p = 0.019
All	13.90 (n = 3852)	16.03 (n = 1220)	+2.13	<0.001	0.915 (0.857–0.978), p = 0.009

OS, overall survival; CN, cytoreductive nephrectomy; HR, hazard ratio; CI, confidence interval.
[a] Adjusted by age, sex, Charlson comorbidity index, and diagnosis year.

retrospective study has already shown that CN with immune therapy has the potential of providing better OS than immune therapy alone.[16]

We assessed the clinical trends after the treatments (Table 2) and obtained some interesting findings. G-CSF is generally used in neutropenia, and is covered by the NHIS. Sunitinib was reported to induce neutropenia in about 20% and grade 3 or 4 neutropenia in 5–8% of patients.[17] In our data, the rates of G-CSF use were 8.6% and 16.3%, and the rates of use within 3 months after the first ST were 5.5% and 11.2% in the no CN group and the CN group, respectively. Although the number of patients was small, a previous retrospective study reported that patients with RCC with leukopenia after sunitinib therapy showed a higher response rate and longer progression-free survival.[18] In the CN group in our study, the transfusion rate at CN was 53.5%; however, the mean volume per person was only 1.4 packs. Although a 3-month mortality rate of 3.6% after CN was observed, there were no differences in the admission rate and number of admissions between the groups.

In our study, patients who survived for ≥24 months had the possibility of obtaining incremental benefits. Heng et al reported median OS durations of 43.2, 22.5, and 7.8 months, according to the International Metastatic Renal Cell Carcinoma Database Consortium, in the favorable-, intermediate-, and poor-risk groups, respectively.[19] At least an intermediate risk or a favorable risk might be helpful in evaluating the efficacy of CN. The CARMENA and SURTIME trials included patients with an intermediate risk or a poor risk according to the Memorial Sloan Kettering Cancer Center model. These patients may be unsuitable as subjects for the assessment of the efficacy of CN.

Our study had some limitations. First, owing to its retrospective design, the possibility of selection bias could not be avoided. Patient selection for CN was performed by clinicians. Table 1 shows the differences between the groups. We performed PSM to correct the imbalance in baseline characteristics between the no CN and CN groups. Second, indication bias was present in this study, and the type of treatment could be associated with the survival outcomes; however, the survival outcomes might be due to the indication for which the treatment was used such as the treatment period, insurance indication, or clinician's preference. To reduce indication bias, survival between the cytokine and targeted groups was not compared. Instead, survival was compared according to the performance of CN in each sub-cohort of cytokine and targeted therapies. Third, since our large nationwide data did not include detailed results such as the serum laboratory or imaging scan findings, the conditions of the patients or tumors could not be identified. In addition, the cause of mortality could not be confirmed. We adjusted for comorbidities instead of performance status or prognostic risk. Last, the follow-up period of the targeted therapy subgroup might be insufficient compared with that of the cytokine therapy subgroup despite the minimum follow-up period of 2 years. After 2007, targeted therapy has been widely used. We could not directly compare each therapy owing to the discrepancy in the follow-up period. However, this study may be a complete enumeration survey in South Korea because expensive anticancer medicines became much cheaper after coverage by the NHIS. In addition, the cytokine therapy subgroup had a sufficient follow-up period.

5. Conclusion

About a quarter of patients with mRCC from a Korean nationwide database were treated with CN and ST. Patients who received ST and underwent CN had better OS than those who did not undergo CN. OS was favorable in patients who underwent CN in the cytokine therapy subgroup but not in the targeted therapy subgroup. Patients who survived longer obtained incremental OS benefits from CN. The role of CN in mRCC has been changing according to advances in ST. CN is beneficial in specific patients with mRCC. Patient selection is crucial for obtaining the benefit of CN.

Funding

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2019R1C1C1005170) and supported by research grant from Biomedical Research Institute, Chung-Ang University Hospital (2020).

Authors' contributions

Conception and design Se Young Choi, Moon Soo Ha, Acquisition of data Jung Hoon Kim, Byung Hoon Chi, Jin Wook Kim, Analysis and interpretation of data Jeong Woo Lee, Jae Hwan Kim, Drafting of the manuscript Se Young Choi, Moon Soo Ha, Critical revision of the manuscript In Ho Chang, Tae-Hyoung Kim, Soon Chul Myung, Obtaining funding Se Young Choi. Supervision Se Young Choi.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgment

We would like to thank Editage (www.editage.co.kr) for English language editing.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin*. 2018;68:394–424.
2. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975*; 2016. https://seer.cancer.gov/csr/1975_2016/. Accessed December 7, 2020.
3. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a

combined analysis. *J Urol*. 2004;171:1071–1076.
4. Biles MJ, Patel HD, Allaf ME. Cytoreductive nephrectomy in the era of tyrosine kinase and immuno-oncology checkpoint inhibitors. *Urol Clin*. 2020;47:359–370.
5. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med*. 2018;379:417–427.
6. 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*. 2019;5:164–170.
7. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
8. Conti SL, Thomas IC, Hagedorn JC, et al. Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. *Int J Cancer*. 2014;134:2245–2252.
9. Psaila B, Lyden D. The metastatic niche: adapting the foreign soil. *Nat Rev Cancer*. 2009;9:285–293.
10. Finke JH, Rayman P, Edinger M, et al. Characterization of a human renal cell carcinoma specific cytotoxic $CD8^+$ T cell line. *J Immunother*. 1991;11:1–11, 1992.
11. Pindoria N, Raison N, Blecher G, Catterwell R, Dasgupta P. Cytoreductive nephrectomy in the era of targeted therapies: a review. *BJU Int*. 2017;120:320–328.
12. Dadian G, Riches PG, Henderson DC, et al. Immunological parameters in peripheral blood of patients with renal cell carcinoma before and after nephrectomy. *Br J Urol*. 1994;74:15–22.
13. Gatenby RA, Gawlinski ET, Tangen CM, Flanigan RC, Crawford ED. The possible role of postoperative azotemia in enhanced survival of patients with metastatic renal cancer after cytoreductive nephrectomy. *Cancer Res*. 2002;62:5218–5222.
14. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet*. 2009;373:1119–1132.
15. Makhov P, Joshi S, Ghatalia P, Kutikov A, Uzzo RG, Kolenko VM. Resistance to systemic therapies in clear cell renal cell carcinoma: mechanisms and management strategies. *Mol Cancer Therapeut*. 2018;17:1355–1364.
16. Singla N, Hutchinson RC, Ghandour RA, et al. Improved survival after cytoreductive nephrectomy for metastatic renal cell carcinoma in the contemporary immunotherapy era: an analysis of the National Cancer Database. *Urol Oncol*. 2020;38, 604 e609-604 e617.
17. Kollmannsberger C, Soulieres D, Wong R, Scalera A, Gaspo R, Bjarnason G. Sunitinib therapy for metastatic renal cell carcinoma: recommendations for management of side effects. *Can Urol Assoc J*. 2007;1:S41–S54.
18. Fujita T, Wakatabe Y, Matsumoto K, Tabata K, Yoshida K, Iwamura M. Leukopenia as a biomarker of sunitinib outcome in advanced renal cell carcinoma. *Anticancer Res*. 2014;34:3781–3787.
19. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14:141–148.