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# Analysis of pre-operative variables for identifying patients who might benefit from upfront cytoreductive nephrectomy for metastatic renal cell carcinoma in the targeted therapy era

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## Abstract

**Objective:** The aim of the study is to identify pre-operative variables for selection of patients who would benefit from upfront cytoreductive nephrectomy for metastatic renal cell carcinoma.
**Methods:** We reviewed the medical records of 171 patients who were presented with synchronous metastatic renal cell carcinoma and who had received no systemic therapy before enrollment. Of these, 96 underwent cytoreductive nephrectomy followed by targeted therapy (cytoreductive nephrectomy group) and 75 treated with targeted therapy alone (non-cytoreductive nephrectomy group). A Cox proportional hazards regression model was used to estimate the prognostic significance of pre-operative characteristics predicting overall survival in the cytoreductive nephrectomy group. The significant variables were designated as pre-operative factors to identify patients who would benefit from cytoreductive nephrectomy.
**Results:** The median overall survival was 19.9 and 11.7 months in the cytoreductive nephrectomy and non-cytoreductive nephrectomy groups ($P < 0.001$). Karnofsky performance status (<80; hazard ratio 9.497, $P < 0.001$), hemoglobin (less than lower limit of normal; hazard ratio 1.913, $P = 0.025$), neutrophils (greater than upper limit of normal; hazard ratio 6.533, $P < 0.001$) and clinical N stage (N2; HR 2.714, $P = 0.001$) were independent pre-operative risk factors of mortality. Only those patients with risk factor <2 who had undergone upfront cytoreductive nephrectomy had a better median overall survival than patients who received targeted therapy alone (28.2 vs. 18.4 months, $P = 0.018$).
**Conclusions:** Four pre-operative risk factors (Karnofsky performance status, hemoglobin, neutrophils and clinical N stage) were identified as suitable for selection of patients who would not benefit from undergoing cytoreductive nephrectomy.

**Key words:** cytoreductive nephrectomy, metastatic renal cell carcinoma, targeted therapy, survival

## Introduction

In 2008, there were ~274 000 new cases of renal cell carcinoma (RCC) worldwide, with 116 000 deaths (1). Despite advances in RCC imaging and detection followed by stage migration (2), analysis of the Surveillance, Epidemiology and End Results database indicates that 16% of new cases of kidney and renal pelvis cancer during

2004–10 have metastatic disease at diagnosis (3). The prognosis for patients with metastatic RCC (mRCC) has traditionally been poor, with a median survival of ~1 year and a 2-year survival rate of 10–20%, owing to the absence of effective chemotherapy agents and the limited usefulness of radiation therapy (4).

Before the inception of targeted therapy (5–8), cytokine-based immunotherapy was the most effective systemic treatment for patients with mRCC, with upfront cytoreductive nephrectomy (CN) indicated for patients suitable for surgery and with good performance status (9,10). However, the role of CN for patients with mRCC remains controversial in the targeted therapy era (11,12). In the absence of level I evidence (i.e. evidence obtained from at least one properly designed randomized controlled trial), these retrospective studies have suggested the potential benefit of CN in selected patients. Identifying prognostic factors in patients treated with targeted therapy is critical, since it may hold the key to selecting beneficial candidates for CN (11).

We examined a single institutional cohort of patients with mRCC to determine pre-operative variables that might be used to identify patients who would likely benefit from upfront CN.

## Patients and methods

### Patients

The study protocol was approved by the Institutional Review Board of the Asan Medical Center. The medical records of all patients who were presented to the Asan Medical Center from 2006 to 2012 for evaluation or treatment of mRCC were reviewed. During the study period, a total of 177 patients presented with synchronous mRCC and had not received any systemic therapy prior to enrollment. Six patients underwent CN after the start of targeted therapy; palliative surgery due to tumor bleeding and/or pain in three patients, planned CN after presurgical targeted therapy in one patient, intrinsic resistance to targeted agent in one patient and patient's willing in one patient. These six patients were excluded from final analysis. Of the 171 patients included, 96 underwent upfront CN followed by targeted therapy (CN group) and 75 treated with targeted therapy alone (non-CN group).

The medical records of the 171 patients in the two groups were reviewed and information on potential prognostic factors were obtained, including age, sex, targeted agent, presentation (13), time from diagnosis to treatment, side and size of primary renal tumor, histology (14), clinical T and N stage (15), Fuhrman grade (16), sarcomatoid or rhabdoid feature, number and location of metastatic sites, the Memorial Sloan-Kettering Cancer Center (MSKCC) risk factors (17), the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk factors (18) and albumin (19).

### Treatment and evaluation

Staging work-up included chest radiography, computed tomography (CT) of the abdomen and pelvis and a bone scan. If indicated, CT of the chest and/or brain imaging was also performed. Surgery was performed using standardized techniques for open and hand-assisted or pure laparoscopic radical nephrectomy. Biopsy samples for histologic confirmation were taken from primary and/or metastatic lesions. Patients treated with oral sunitinib or sorafenib or pazopanib as mentioned previously (11). Some patients with non-clear cell histology or in the poor risk group treated with intravenous temsirolimus 25 mg once weekly. Dose reduction to manage toxicities was allowed by 5 mg to a dose not <15 mg (8). Treatment was planned to continue until the occurrence of disease progression, unacceptable toxicity or death. Overall survival (OS) was calculated from the time of diagnosis to death from any cause. Patients who were alive were censored at the date of last contact.

### Statistical analysis

Clinicopathologic factors were compared between the CN and non-CN groups, using Pearson's $\chi^2$ test for categorical variables and Student's *t*-test for continuous variables. Kaplan–Meier survival curves were used to estimate OS and compared using log rank tests. Survival was expressed as the median value with 95% confidence intervals (CI). A Cox proportional hazards regression model was used to estimate the prognostic significance of pre-operative characteristics predicting OS in patients received upfront CN followed by targeted therapy. Correlations between outcomes and assessed variables were expressed as a hazard ratio (HR) with 95% CI. Only those variables with $P < 0.05$ in univariate analysis were included in multivariate analysis. The variables that maintained significance on multivariate analysis were designated as pre-operative factors that could be used to identify patients who would benefit from upfront CN. All statistical tests were two sided, with a $P < 0.05$ considered significant. Data were analyzed using IBM SPSS Statistics Version 21 (IBM Corporation, Somers, NY, USA).

## Results

Table 1 shows the clinicopathologic characteristics of the enrolled patients. There were significant imbalances in age, targeted agent, presentation, Karnofsky performance status, neutrophils, corrected calcium, albumin, time from diagnosis to treatment, size of primary renal tumor, histology, venous thrombus, Fuhrman grade, sarcomatoid or rhabdoid feature, number of metastatic sites and bone metastasis between the CN and non-CN groups.

At a median follow-up time of 14.7 months, 133 patients (78%) had died at a median time of 10.7 months (range, 1.5–70.3 months) after diagnosis. Overall, 14 patients (8%) maintained their first-line drug to the time of their last follow-up. Of the remaining 157 patients, 5 had refused to continue taking the drug, 111 discontinued first-line treatment because of disease progression, 25 because of severe adverse events and 16 because of death without radiologic evidence of disease progression. Other two patients were lost from follow-up. The median OS of the entire cohort was 14.8 months; it was 19.9 months (95% CI 12.7–27.1 months) in the CN group and 11.7 months (95% CI 8.8–14.6 months) in the non-CN group ($P < 0.001$) (Fig. 1).

Table 2 shows analysis for pre-operative characteristics predicting OS in patients received upfront CN followed by targeted therapy. We identified nine pre-operative variables that were associated with overall mortality and could be assessed pre-operatively: presentation, Karnofsky performance status, hemoglobin, neutrophils, platelets, corrected calcium, albumin, clinical N stage and number of metastatic sites. In a multivariate Cox proportional hazards model for predicting the probability of overall mortality, the Karnofsky performance status, hemoglobin, neutrophils and clinical N stage were found to be pre-operative risk factors for mortality. The number of pre-operative risk factors was positively associated with overall mortality, and patients with risk factors two or greater in the CN group had a worse OS than patients who were treated with targeted therapy alone (median OS = 8.3 vs. 11.7 months) (Fig. 2).

Comparison of OS between the CN and non-CN groups was carried out following stratification according to the number of pre-operative risk factors (Table 3). In patients without any risk factor, the CN group showed better OS compared with the non-CN group,

**Table 1.** Clinicopathological characteristics of the enrolled patients

| | No. total (%) | No. CN group (%) | No. non-CN group (%) | *P* |
|---|---|---|---|---|
| Mean age ± standard deviation, years | 58.1 ± 11.6 | 56.5 ± 10.4 | 60.2 ± 12.8 | 0.042 |
| Sex | | | | 0.917 |
| Male | 117 (68) | 66 (69) | 51 (68) | |
| Female | 54 (32) | 30 (31) | 24 (32) | |
| Targeted agent | | | | 0.029 |
| Sunitinib | 120 (70) | 60 (63) | 60 (80) | |
| Sorafenib | 33 (19) | 26 (27) | 7 (9) | |
| Pazopanib | 7 (4) | 4 (4) | 3 (4) | |
| Temsirolimus | 11 (7) | 6 (6) | 5 (7) | |
| Presentation | | | | <0.001 |
| Incidental[a] | 23 (13) | 20 (21) | 3 (4) | |
| Local symptom | 53 (31) | 35 (36) | 18 (24) | |
| Systemic symptom | 95 (56) | 41 (43) | 54 (72) | |
| Karnofsky performance status | | | | <0.001 |
| 80 or greater | 132 (77) | 87 (91) | 45 (60) | |
| <80 | 39 (23) | 9 (9) | 30 (40) | |
| Hemoglobin | | | | 0.057 |
| Normal | 59 (35) | 39 (41) | 20 (27) | |
| Less than lower limit of normal | 112 (65) | 57 (59) | 55 (73) | |
| Neutrophils | | | | 0.022 |
| Normal | 152 (89) | 90 (94) | 62 (83) | |
| Greater than upper limit of normal | 19 (11) | 6 (6) | 13 (17) | |
| Platelets | | | | 0.299 |
| Normal | 150 (88) | 82 (85) | 68 (91) | |
| Greater than upper limit of normal | 21 (12) | 14 (15) | 7 (9) | |
| Lactate dehydrogenase | | | | 0.079 |
| 1.5 × upper limit of normal or less[b] | 144 (84) | 85 (89) | 59 (79) | |
| >1.5 × upper limit of normal | 27 (16) | 11 (11) | 16 (21) | |
| Corrected calcium, mg/dl | | | | 0.010 |
| 10 or less | 153 (89) | 91 (95) | 62 (83) | |
| >10 | 18 (11) | 5 (5) | 13 (17) | |
| Albumin | | | | 0.003 |
| Normal | 106 (62) | 69 (72) | 37 (49) | |
| Less than lower limit of normal | 65 (38) | 27 (28) | 38 (51) | |
| Mean time from diagnosis to treatment ± standard deviation, months | 1.7 ± 3.7 | 2.4 ± 4.8 | 0.7 ± 1.1 | 0.001 |
| Side of primary renal tumor | | | | 0.299 |
| Right | 80 (47) | 41 (43) | 39 (52) | |
| Left | 84 (49) | 52 (54) | 32 (43) | |
| Bilateral | 7 (4) | 3 (3) | 4 (5) | |
| Mean size of primary renal tumor ± standard deviation, cm | 8.2 ± 3.3 | 8.7 ± 3.1 | 7.7 ± 3.5 | 0.044 |
| Histology | | | | 0.027 |
| Clear | 156 (91) | 92 (96) | 64 (85) | |
| Non-clear | 15 (9) | 4 (4) | 11 (15) | |
| Clinical T stage | | | | 0.519 |
| T1 | 38 (22) | 19 (20) | 19 (25) | |
| T2 | 29 (17) | 16 (17) | 13 (17) | |
| T3 | 81 (47) | 50 (52) | 31 (42) | |
| T4 | 23 (14) | 11 (11) | 12 (16) | |
| Venous thrombus | | | | 0.014 |
| None | 113 (66) | 65 (68) | 48 (64) | |
| Renal vein | 31 (18) | 22 (23) | 9 (12) | |
| Inferior vena cava | 27 (16) | 9 (9) | 18 (24) | |
| Clinical N stage | | | | 0.262 |
| N0 | 103 (60) | 63 (66) | 40 (53) | |
| N1 | 20 (12) | 10 (10) | 10 (13) | |
| N2 | 48 (28) | 23 (24) | 25 (33) | |
| Fuhrman grade | | | | <0.001 |
| 1 or 2 | 31 (18) | 13 (14) | 18 (24) | |
| 3 or 4 | 98 (57) | 81 (84) | 17 (23) | |
| Unknown | 42 (25) | 2 (2) | 40 (53) | |

*Continued*

**Table 1.** Continued

| | No. total (%) | No. CN group (%) | No. non-CN group (%) | *P* |
|---|---|---|---|---|
| Sarcomatoid or rhabdoid feature[c] | | | | 0.002 |
| No | 142 (83) | 73 (76) | 70 (93) | |
| Yes | 29 (17) | 23 (24) | 5 (7) | |
| No. of metastatic sites | | | | 0.018 |
| 1 | 72 (42) | 48 (50) | 24 (32) | |
| >1 | 99 (58) | 48 (50) | 51 (68) | |
| Bone metastasis | | | | 0.020 |
| No | 110 (64) | 69 (72) | 41 (55) | |
| Yes | 61 (36) | 27 (28) | 34 (45) | |
| Liver metastasis | | | | 0.388 |
| No | 148 (87) | 85 (89) | 63 (84) | |
| Yes | 23 (13) | 11 (11) | 12 (16) | |
| Brain metastasis | | | | 0.779 |
| Yes | 17 (10) | 9 (9) | 8 (11) | |

CN, cytoreductive nephrectomy.

[a]Three patients with an unknown presentation were included in this category.

[b]Twenty-three patients with an unknown lactate dehydrogenase level were included in this category.

[c]The definition of sarcomatoid or rhabdoid feature refers to the presence of any sarcomatoid or rhabdoid feature.

although this difference was marginally significant ($P = 0.084$). When combining each stratum, only patients with risk factor <2 were shown to significantly benefit from upfront CN (median OS = 29.9 vs. 18.1 months; $P = 0.011$) (Fig. 3A). Patients with risk factors two or greater were not shown to benefit from upfront CN compared with patients who had the same risk stratification and treated with targeted therapy alone (median OS = 8.6 vs. 8.2 months; $P = 0.544$) (Fig. 3B).

## Discussion

In 2001, two randomized clinical trials were published in which patients with mRCC were randomly assigned to CN followed by interferon-α treatment, or interferon-α treatment alone (9,10). The results indicated that CN should be used as part of a multimodal treatment strategy and subsequently the use of CN steadily increased. However, a paradigm shift in systemic therapy for mRCC started in 2005, when the US Food and Drug Administration approved the use of tyrosine kinase inhibitors. Because targeted agents each have their own mechanism of action and produce more robust clinical effects than immunotherapy, the evidence from previous clinical trials needs to be verified. Indeed, in a recent retrospective study using the public National Cancer Data Base, Tsao et al. (20) found that the use of CN has decreased since the advent of the targeted therapy era.

Two randomized prospective trials (CARMENA and SURTIME) were specifically designed to evaluate the survival benefit and appropriate timing of CN when used in conjunction with targeted therapy (21,22). Strict criteria for selecting candidates originated from a retrospective study by Fallick et al. (23) in 1997. Namely, both trials include only those patients with a good performance status (Eastern Cooperative Oncology Group 0 or 1), the CARMENA trial excludes patients with symptomatic or untreated brain metastases and the SURTIME trial excludes those with exclusive bone metastases or multiple metastases at one single organ. These stringent inclusion and exclusion criteria mean that upcoming results from these trials will not provide data that are generalizable to real world practice. Therefore, several studies, discussed below, have addressed the impact of CN on OS in a heterogeneous group of mRCC patients, and have identified factors associated with worsened prognosis after CN.

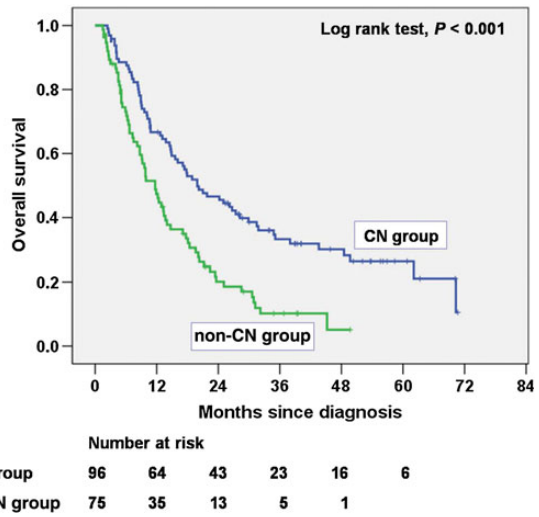


**Figure 1.** Comparison of overall survival (OS) between the cytoreductive nephrectomy (CN) and non-CN groups.

In a study of the University of California-Los Angeles Kidney Cancer Registry, results from 173 patients treated with CN and interleukin-2 immunotherapy were analyzed (24). The authors developed a scoring algorithm to predict survival after nephrectomy and immunotherapy for mRCC, called the SANI score. The SANI scoring algorithm includes lymph node status, constitutional symptoms, location of metastases, sarcomatoid histology and serum thyroid-stimulating hormone level. From the institutional RCC database of the University of Texas MD Anderson Cancer Center, Culp et al. (25) identified seven pre-operative variables that permitted them to distinguish patients who were unlikely to benefit from CN: serum albumin and lactate dehydrogenase levels, clinical stage T3 or T4, symptoms caused by metastatic spread, liver metastasis and radiographic evidence of retroperitoneal or supradiaphragmatic adenopathy. OS of patients who had four or more factors was not different from that of the cohort of patients with mRCC who received medical therapy alone. From the same database, Margulis et al. (19) developed a

**Table 2.** Analysis for pre-operative characteristics predicting OS in patients received upfront CN followed by targeted therapy

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age (continuous variable) | 1.004 (0.980–1.029) | 0.725 | Not assessed | |
| Sex | | | | |
| Female vs. Male | 1.191 (0.703–2.018) | 0.525 | Not assessed | |
| Presentation | | | | |
| Local symptom vs. Incidental | 1.660 (0.768–3.588) | 0.197 | 1.653 (0.746–3.663) | 0.215 |
| Systemic symptom vs. Incidental | 2.511 (1.198–5.261) | 0.015 | 1.697 (0.749–3.846) | 0.205 |
| Karnofsky performance status | | | | |
| <80 vs. 80 or greater | 13.829 (6.030–31.715) | <0.001 | 9.497 (3.795–23.767) | <0.001 |
| Hemoglobin | | | | |
| Less than lower limit of normal vs. Normal | 2.508 (1.477–4.259) | 0.001 | 1.913 (1.087–3.369) | 0.025 |
| Neutrophils | | | | |
| Greater than upper limit of normal vs. Normal | 6.927 (2.904–16.521) | <0.001 | 6.533 (2.404–17.752) | <0.001 |
| Platelets | | | | |
| Greater than upper limit of normal vs. Normal | 3.057 (1.584–5.900) | 0.001 | 0.951 (0.338–2.671) | 0.924 |
| Lactate dehydrogenase | | | | |
| >1.5 × upper limit of normal vs. 1.5 × upper limit of normal or less | 1.324 (0.655–2.678) | 0.434 | Not assessed | |
| Corrected calcium, mg/dl | | | | |
| >10 vs. 10 or less | 7.438 (2.754–20.090) | <0.001 | 1.908 (0.563–6.469) | 0.300 |
| Albumin | | | | |
| Less than lower limit of normal vs. Normal | 2.479 (1.485–4.138) | 0.001 | 1.665 (0.909–3.049) | 0.099 |
| Side of primary renal tumor | | | | |
| Left vs. Right | 0.708 (0.436–1.149) | 0.708 | Not assessed | |
| Bilateral vs. Right | 0.533 (0.127–2.229) | 0.533 | | |
| Size of primary renal tumor (continuous variable) | 1.018 (0.938–1.106) | 0.667 | Not assessed | |
| Clinical T stage | | | | |
| T2 vs. T1 | 0.760 (0.326–1.769) | 0.524 | Not assessed | |
| T3 vs. T1 | 1.073 (0.575–2.004) | 0.825 | | |
| T4 vs. T1 | 2.211 (0.971–5.035) | 0.059 | | |
| Venous thrombus | | | | |
| Renal vein vs. None | 1.479 (0.840–2.604) | 0.176 | Not assessed | |
| Inferior vena cava vs. None | 1.311 (0.588–2.922) | 0.509 | | |
| Clinical N stage | | | | |
| N1 vs. N0 | 2.491 (1.152–5.388) | 0.020 | 1.887 (0.841–4.236) | 0.124 |
| N2 vs. N0 | 3.384 (1.968–5.819) | <0.001 | 2.714 (1.527–4.822) | 0.001 |
| No. of metastatic sites | | | | |
| >1 vs. 1 | 2.049 (1.260–3.333) | 0.004 | 1.505 (0.900–2.515) | 0.119 |
| Bone metastasis | | | | |
| Yes vs. No | 1.510 (0.898–2.539) | 0.120 | Not assessed | |
| Liver metastasis | | | | |
| Yes vs. No | 1.201 (0.590–2.446) | 0.614 | Not assessed | |
| Brain metastasis | | | | |
| Yes vs. No | 1.821 (0.866–3.829) | 0.114 | Not assessed | |

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

pre-operative nomogram, including serum albumin and lactate dehydrogenase levels, to aid identification of patients with mRCC who would or would not benefit from CN.

However, most previous studies have potential biases, such as the inclusion of patients treated with immunotherapy, the use of post-operative variables, and the absence of between-group comparisons within patients with similar baseline characteristics. Accordingly, we focused on patients treated with targeted agents as the first-line drug, and then performed between-group comparisons after controlling for potential confounding clinical variables.

We identified four variables that were determined before CN and that had a negative association with OS: Karnofsky performance status <80, hemoglobin less than lower limit of normal, neutrophils greater than upper limit of normal and clinical N2 stage. In the second part of our analysis, we compared OS between the CN and non-CN groups according to the number of pre-operative risk factors. After adjusting for the number of pre-operative risk factors, an apparent survival benefit of CN is found in patients with risk factors <2.

From recent analysis of the IMDC, Heng et al. (26) found that patients with estimated survival times <12 months or four or more Heng risk may not benefit from CN. It is not surprising that patients in the poor risk group according to the MSKCC or IMDC prognostic models might unlikely benefit from upfront CN (12). The MSKCC and IMDC prognostic models have the merit of being established from large, multicenter study and validated via population-based study. Indeed, three of four risk factors identified in the present study were coincident with components of the IMDC prognostic model. Nevertheless, the IMDC prognostic model has several shortcomings as pre-operative factors to better select patients for CN. First, the IMDC prognostic model was established in the cohort including patients who received with prior

immunotherapy or presented with metachronous metastasis (18). Second, presentation, clinical T and N stage and albumin were not included as potential prognostic factors for analysis. These factors were known to be associated with worsened prognosis after CN (19,24,25,27). In the present study, clinical N2 stage was identified as a pre-operative risk factor. The CI of albumin approached significance (95% CI 0.909–3.049), even if it could not be included in pre-operative risk factors.

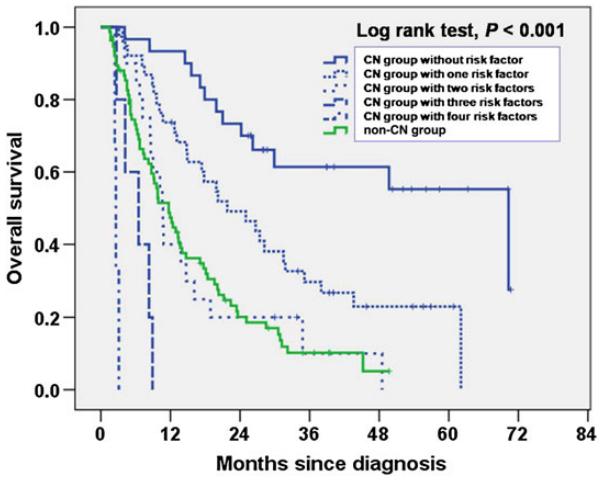


**Figure 2.** OS according to the number of pre-operative risk factors in patients who underwent upfront CN followed by targeted therapy. The green solid line indicates the non-CN group (reference).

**Table 3.** Comparison of OS between the CN and non-CN groups according to the number of pre-operative risk factors

| No. of pre-operative risk factors | CN group | Non-CN group | *P* |
|---|---|---|---|
| | Median OS, months (*n*) | Median OS, months (*n*) | |
| 0 | 70.3 (30) | 19.6 (10) | 0.084 |
| 1 | 21.8 (38) | 18.1 (21) | 0.144 |
| 2 | 10.6 (20) | 9.2 (26) | 0.515 |
| 3 | 6.5 (5) | 5.3 (12) | 0.358 |
| 4 | 2.6 (3) | 2.4 (6) | 0.490 |

OS, overall survival; CN, cytoreductive nephrectomy.

The unfavorable results in patients with risk factors two or greater might, at least in part, be attributable to the rapid disease progression observed in some patients after CN. In the present study, four (17%) patients died of rapid disease progression without radiologic evidence in the CN group with risk factors two or greater. These patients were unable to receive sufficient targeted therapy.

Although the exact mechanisms remain unknown, there are several potential explanations for the unfavorable events observed after CN.

1. A delay in instigating systemic therapy during the post-operative recovery period and any surgery-related complications would be detrimental to the survival of patients who have undergone CN (28).
2. The growth factors released in the process of wound healing after CN may cause the promotion of tumor growth and predominate over the effects of systemic therapy (29).
3. The progression of disease is suggested to be related specifically to the loss of the angiogenesis inhibitor angiostatin by the primary tumor, which suppresses the growth of metastases (30).

Our study has several limitations, the foremost being the retrospective analysis of data collected from a single institution and the small sample size. Thus, our study may be underpowered to detect any potential survival advantage of CN. Another limitation is due to selection bias in the determination of which patients should be given CN before their targeted therapy. This bias has made it difficult to compare OS between the two groups. Fortunately, some patients in the non-CN group did not have any risk factors, so we could compare OS between the CN and non-CN groups according to the number of pre-operative risk factors.

In conclusion, although external validation is required, four pre-operative risk factors (Karnofsky performance status <80, hemoglobin less than lower limit of normal, neutrophils greater than upper limit of normal and clinical N2 stage) identified in the present study can be

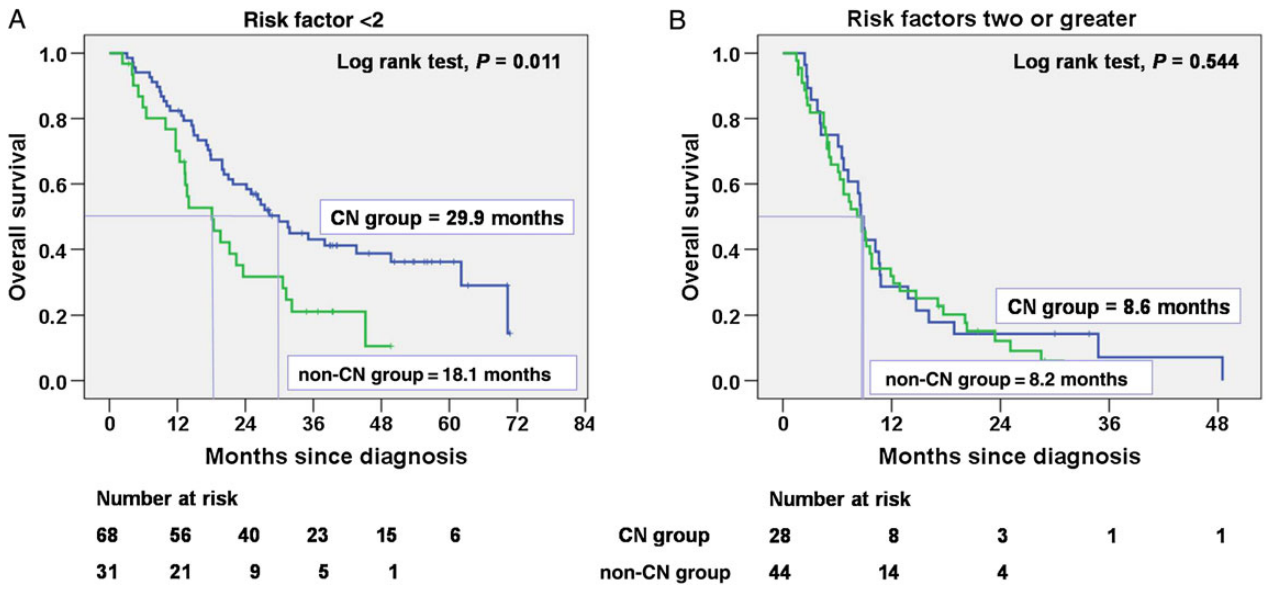


**Figure 3.** Comparisons of OS between the CN and non-CN groups in patients with risk factor <2 (A), with risk factors two or greater (B).

used to identify patients with mRCC who would not benefit from undergoing CN. Patients with two or more pre-operative risk factors should be directed toward targeted therapy alone, thus helping them to avoid the morbidity associated with CN.

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## Conflict of interest statement

None declared.

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