

Effect of Initial Cytoreductive Nephrectomy with Target Therapy versus Target Therapy Alone in Metastatic Renal Cell Carcinoma: A Single Institutional Study

Rasha Mohamed Abdel Latif¹, Kamel Farag Selim²

¹Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt

²Oncology Center, Faculty of Medicine, Mansoura University, Mansoura, Egypt

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*Corresponding author:

Rasha Mohamed Abdel Latif
Clinical Oncology and Nuclear
Medicine Department, Faculty of
Medicine, Mansoura University,
Mansoura, Egypt
Email: rosha20075@yahoo.com

ABSTRACT

Background: The metastatic renal cell carcinoma (mRCC) patients treated with upfront cytoreductive nephrectomy (CN) combined with immunotherapy results in overall survival (OS) improvement. It is unclear whether mRCC patients treated with target therapy will also benefit from CN. The aim of the study was to identify the benefit of upfront CN followed by targeted therapy (TTs) versus TTs alone on OS of patients with mRCC, and to evaluate pre-operative variables for selection of patients who would benefit from CN, and also the response rate (RR) and the progression-free survival (PFS).

Methods: A retrospective study was performed in our Department on patients diagnosed with mRCC within the period of January 2013 to April 2018. Data that were collected included patients and tumor characteristics. Patients were divided into two groups: 1) received upfront CN followed by TTs, and the 2) one treated with TTs alone. Survival analysis was performed using Kaplan-Meier method, univariate analysis with log-rank test was used to estimate predictors of survival in the CN group, and Cox regression was used for multivariate analysis.

Results: The median OS of all patients was 14 months, and was 19 and 10.5 months in CN and non-CN respectively with significant difference ($P < 0.001$). Lower hemoglobin level ($P = 0.012$), high neutrophil count ($P < 0.001$), low albumin level ($P = 0.006$), number of metastatic sites ≥ 3 ($P < 0.001$), and patients with number of risk factors ≥ 3 ($P < 0.001$) have a negative impact on OS in CN group.

Conclusions: Upfront CN before TTs in mRCC carries better survival than TTs alone. Five pre-operative variables (i.e. hemoglobin level, neutrophil count, albumin level, number of metastatic sites, and number of risk factors) were identified as suitable for selection of patients who will benefit from CN.

INTRODUCTION

Renal cell carcinoma (RCC) is the commonest malignancy of kidney representing about 90% [1]. Incidence of RCC varies according to the country as it is higher in Europe and North America than Asia and South America [2]. In Egypt, kidney cancer presented in 1.8/100000 in male and 1.1/100000 in female of all ages, and the numbers increase in older age above 55 years [3].

Around 20% of RCC is presented as metastatic disease synchronous at diagnosis with primary tumor and carries poor prognosis [4, 5]. Treatment of

metastatic renal cell carcinoma (mRCC) was a question of the challenge to researchers, especially in absence of effective chemotherapeutic agents and role of radiation in palliation of metastasis, so they tried to find the optimal treatment for these categories.

Cytoreductive nephrectomy (CN) was considered as an important part in the management of mRCC as a palliative tool in relieving bleeding, pain, compression symptoms, and it is proven to improve overall survival (OS) when being used before immunotherapy, as immunotherapy was the most effective systemic treatment at this time [6-8]. Since the Food and Drug Administration (FDA) has approved target therapy in

treatment of mRCC since 2005, several agents of target therapies were used in aiming to reach the best response and survival of mRCC patients. Target therapy directed to vascular endothelial growth factor and mammalian target of rapamycin (mTOR) have become the treatment of choice for mRCC [9-11].

Researchers compared different target therapies either in comparison to each other or to placebo, and they recorded acceptable results regarding survival [12-18]. After that, the role of CN became controversial. Studies proved that CN reduced risk of death in combination with TTs more than those treated with TTs alone [19, 20].

With the improvement of overall survival (OS) with the addition of CN to TTs in mRCC, some studies reported that selected patients with certain risk factors may benefit from CN than others. These risk factors consist of poor performance status (PS), high c-reactive protein, hemoglobin (Hg) less than normal, high neutrophil-lymphocyte ratio, sarcomatoid dedifferentiation, body mass index (BMI), LDH, serum creatinine, and number of metastatic sites. Patients with 0-2 risk factors only get benefit from upfront CN as regard OS [21-25]. On the other hands, there were studies that reported no benefit of upfront CN in comparison to TTs alone [26, 27].

In this study, we try to evaluate the survival benefit of CN upfront to TTs versus target therapy alone as the primary endpoint. We also try to evaluate risk factors associated with improved survival treated with upfront CN, progression-free survival (PFS) and response rate (RR) as the secondary endpoint.

METHODS

Patients

This study obtained ethical approval from the Institutional Review Board of Mansoura Faculty of Medicine (IRB-MFM). This is a retrospective study performed on patients diagnosed with metastatic renal cell carcinoma (mRCC) who attended the Department of Clinical Oncology & Nuclear Medicine, Mansoura University Hospital, Mansoura, Egypt, within the period of January 2013 to April 2018.

The patients data were collected from files and we recorded age, sex, presentation, performance status, T stage, N stage, Hg, neutrophil count, platelet count, serum calcium, lactate dehydrogenase (LDH) if reported, albumin, side and size of primary tumor, histology, pathological variant, number and sites of metastasis, time of diagnosis to treatment, surgery performed, and type of used target therapies (TTs). Staging procedures included chest radiography, computed tomography (CT) of abdomen and pelvis, bone scan, CT of the chest and/or brain performed if indicated.

Inclusion criteria including age ≥ 18 years, pathologically proven metastatic renal cell carcinoma, metastasis diagnosed radiologically, patients received target therapy (either alone or preceded by CN). As for exclusion criteria including non-clear renal cell carcinoma, synchronous with other malignancies, received systemic chemotherapy, not evaluated during or after treatment, and patients refused target therapy.

Treatment modalities

Surgery was performed if indicated and feasible, the biopsy was taken for pathological confirmation either from the primary or metastatic lesion. Patients were treated with either TTs alone or TTs with CN. Target therapies consisted of 50mg sunitinib once daily for 28 days and discontinued for 14 days, continued to be replaced with everolimus tablet once daily or 800mg/m² pazopanib once daily.

Toxicity assessment

Median follow up period was 13 months (range 2-35 months). Toxicity was assessed according to Common Terminology Criteria for Adverse Events version 3.0. If toxicity was registered, treatment would be discontinued until recovery or return to grade 1 or less with a reduction of dose. If toxicity continued for more than 14 days or after 2 reductions of dose, treatment was stopped. Patients received treatment until progression, toxicity, or death.

Survival outcomes and response assessment

The response was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.0. Complete response (CR) was defined as disappearance of all target, partial response (PR) as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), and PD as at least a 20% increase in the sum of the LD of target lesions. Data was recorded since the treatment started or the appearance of one or more new lesions. Overall survival (OS) was measured from the time of diagnosis of metastasis until loss of follow up or death. Progression-free survival (PFS) was measured from the time of diagnosis of metastasis until progression, the appearance of new lesions, end of follow up, and/or death.

Patients were followed every 6 weeks during the 24-week treatment and every 12 weeks after the 24-week treatment. The evaluation was performed with computerized tomography (CT) of abdomen and pelvis, and chest CT, bone scan if indicated.

Statistical analysis

Data analysis was performed using SPSS version 20.0. The PFS was defined from the time of metastases being diagnosed until disease progression, death, or loss to follow up. Overall survival was calculated from the date of diagnosis to date of death, or loss of follow up.

Qualitative data were presented as number and percent. Non-parametric data were presented as min-max and median. Survival analysis was calculated using Kaplan-Meier method, and the survival rates were compared by the log-rank test. Comparisons between patient groups were performed by the Chi-square test. Multivariate analysis was performed with Cox regression model to estimate the prognostic significance of pre-operative characteristics in predicting OS in patients treated with upfront CN followed by targeted therapy. Only variables with $P \leq 0.05$ in univariate analysis were included in multivariate analysis. All statistical tests were 2 sided with $P \leq 0.05$ considered as significant.

RESULTS

Patients Characteristics

Table 1 shows the clinicopathologic data of the patients. The median age of all patients was 55 years (range 20-76 years), with 67.6% in age group >50 years. Most of the patients were male (70.3%), with male to female ratio of 2.4:1. Twenty-one patients (56.8%) attended with PS 1, with 86.5% associated with comorbidities, mostly in the form of hypertension and diabetes mellitus. Local symptoms were the commonest presentation which found in 25 patients (67.6%).

Median BMI was 27, 31 patients (83.8%) were with BMI in normal range of 19-30 kg/m² and 6 (16.2%) were >30 kg/m². The T2 was the most common stage diagnosed which was found in 19 patients (51.4%), and 18 patients were N+ (48.6%). The median size of the tumor was 9 cm. Rhabdoid and sarcomatoid features were presented only in 4 patients (10.8%). Bone was the most common site of metastasis followed by lung (64.9% and 45.9%, respectively).

The Hg, platelet count, neutrophil count, LDH, albumin level were abnormal in 35.1%, 10.8%, 40.5%, 16.2%, and 21.6% respectively. Corrected serum calcium was not recorded.

Twenty-five patients were treated with CN followed by target therapy, and 12 patients were treated with TTs only (non-cytoreductive nephrectomy; NCN group). Sutent was the most used TTs (59.5%). Thirteen patients (35.1%) were with ≤ 3 risk factors and 24 (64.9%) were diagnosed with >3 risk factors.

There was significant statistical difference between CN and NCN groups in terms of platelet level, T stage, N

stage, Rh and sarcomatoid features, lung metastases, and number of risk factors, but other factors presented no statistical difference between the two groups.

Table 1. Patient's characteristics

Characteristics	Cytoreductive N=25 (67,6%)	Non-cytoreductive N=12 (32,4%)
Age		
Median (range)	54 (20-76)	58 (35-72)
Sex		
Male	16 (64)	10 (83.3)
Female	9 (36)	2 (16.7)
PS		
1	17 (68)	4 (33.3)
2	7 (28)	5 (41.7)
3	1 (4)	3 (25)
Comorbidities		
Yes	3 (12)	2 (16.7)
No	22 (88)	10 (83.3)
Presentation		
Local	16 (64)	9 (75)
Systemic	9 (36)	3 (25)
BMI		
Median	27	27.5
Hg		
N	18 (72)	6 (50)
<N	7 (28)	6 (50)
Neutrophil		
N	17 (68)	5 (58.3)
>N	8 (32)	7 (41.7)
Plat		
N	24 (96)	9 (75)
>N	1 (4)	3 (25)
Alb		
N	21 (84)	8 (66.7)
<N	4 (16)	4 (33.3)
LDH		
Not assessed	20 (80)	8 (66.7)
<1.5ULN	2 (8)	1 (8.3)
>1.5ULN	3 (12)	3 (25)
Side		
Rt	5 (20)	5 (58.3)
Lt	20 (80)	7 (41.7)
T stage		
T1	0 (0)	1 (8.3)
T2	16 (64)	3 (25)
T3	8 (32)	5 (41.7)
T4	1 (4)	3 (25)
N stage		
N0	16 (64)	3 (25)
N+	9 (36)	9 (75)
RH or sarcomatoid		
No	24 (96)	9 (75)
Yes	1 (4)	3 (25)
Size of tumor		
Median	2	2

PS: performance status, BMI: body mass index, Hg: hemoglobin, N: normal, plat: platelet, alb: albumin, LDH: lactate dehydrogenase; Rt: right, Lt: left, RH: rhabdoid.

Table 1. Patient’s characteristics (Continue)

Characteristics	Cytoreductive N=25 (67,6%)	Non-cytoreductive N=12 (32,4%)
Bone mets		
Yes	17 (68)	7 (58.3)
No	8 (32)	5 (41.7)
Liver mets		
Yes	5 (20)	3 (25)
No	20 (80)	9 (75)
Lung mets		
Yes	8 (32)	9 (75)
No	17 (68)	3 (25)
No. of mets		
<3	9 (36)	1 (8.3)
≥3	16 (64)	11 (91.7)
No. of risks		
Median	3	5.5
TTs		
Sutent	15 (60)	7 (58.3)
Affinitor	6 (24)	2 (16.7)
Votriant	4 (16)	3 (25)

mets: metastasis, TTs: target therapies.

Outcomes

The median OS of all patients was 14 months (range 6-38 months), OS rates at 12 and 24 months were 96.3% and 62.8% respectively (**Figure 1**). Median PFS was 12 months (range 2-32 months), with rates of 94.7% and 52% at 12 and 24 months respectively (**Figure 2**). The median overall survival times for CN and NCN groups were 19 and 10.5 months associated with high statistically significant difference ($P<0.001$) (**Figure 3**) and the PFS of CN and NCN were 14 and 8.5 months with significant difference too ($P=0.046$).

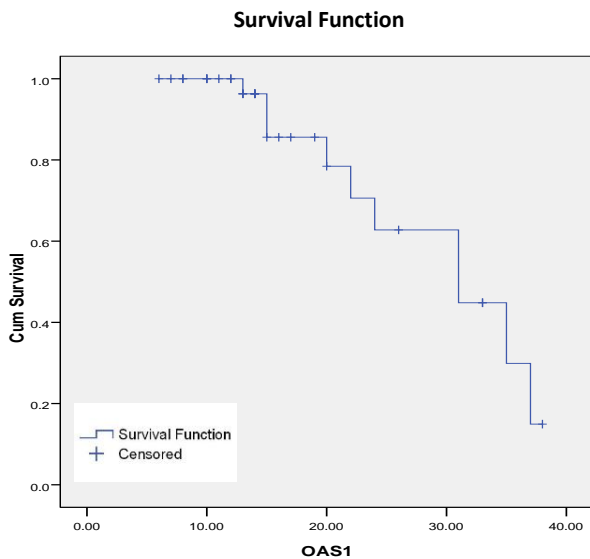


Figure 1. Kaplan-Meier curve for overall survival (OS)

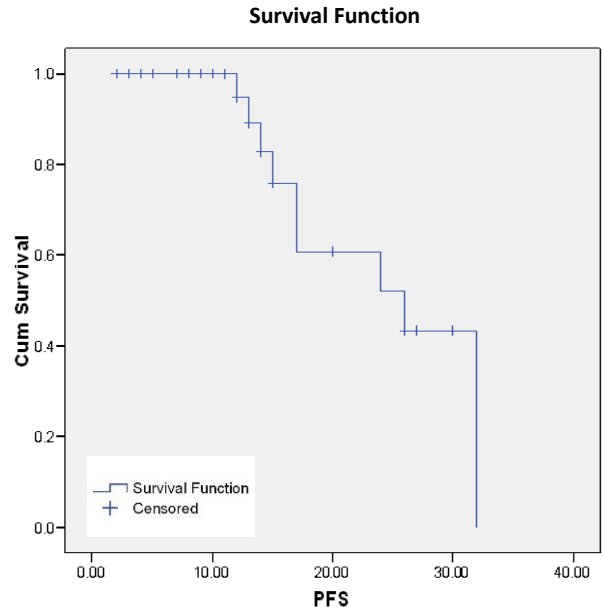


Figure 2. Kaplan-Meier curve for progression free survival

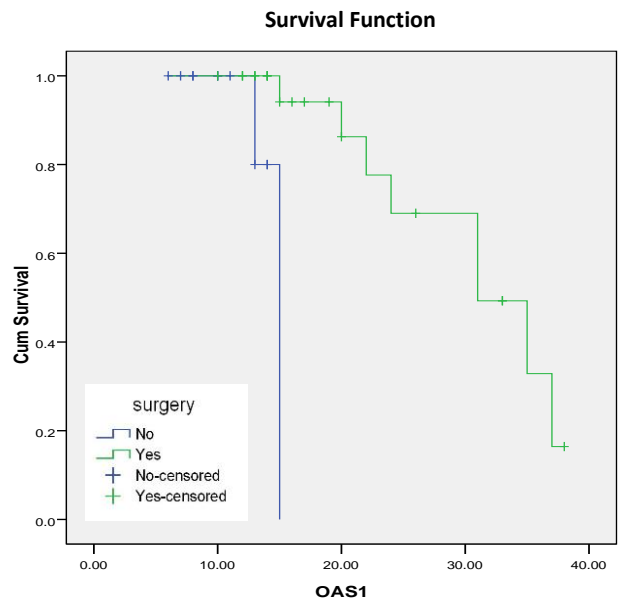


Figure 3. Comparison of overall survival (OS) between the cytoreductive nephrectomy (CN) and non-CN groups

Table 2. Response and fate of patients

Outcome	Cytoreductive N (%)	Non-cytoreductive N (%)
Response		
PR	2 (8)	1 (8.3)
SD	9 (36)	1 (8.3)
PD	14 (56)	10 (83.3)
Fate		
Alive	8 (32)	2 (16.7)
Dead	17 (68)	10 (83.3)

PR: partial response, SD: stable disease, PD: progressed disease.

The response rate was 35.1% (PR+SD) achieved in 13 patients, of which 11 of them were in the CN group but not significant statistically ($P=0.199$). 10 patients (27%) out of 37 were alive at the end of the study, of which 8 of them (80%) were in CN groups and also with no significance ($P=0.326$) (Table 2).

Univariate analysis of prognostic factors

On risk estimation, the overall survival showed improvement with significant difference with normal Hg level (median 18 months, $P=0.001$), normal neutrophil count (median 20 months, $P<0.001$), normal platelet (median 15 months, $P=0.013$), normal albumin (median 16 months, $P=0.034$), negative lymph nodes (median 19 months, $P=0.004$), absence of lung metastases (median 20 months, $P=0.003$), absence of liver metastases (median 15 months, $P=0.024$), and lower number of metastatic sites (median 32 months, $P=0.002$) (Table 3).

The number of preoperative risk factors <3 was statistically high significant ($P<0.000$) predictors of OS.

Similarly, PFS showed improvement with a significant difference in the same previous factors with OS except for platelet which was not associated with a significant difference in survival (Table 3).

On univariate analysis of prognostic factors affecting survival in patients treated with CN and followed by TTs, the median survival was 23 months in patients with normal level of Hg, which is more compared to patients with lower level of Hg that demonstrated the OS was only 14 months and was with significant difference ($P=0.012$). On analysis according to the number of neutrophils, median survival was 24 months with normal count and 13 with elevated number which presented statistically high difference ($P<0.001$). Also, the normal level of albumin was associated with better median survival of 20 months which was significantly longer than that of abnormal level (median 12.5 months; $P=0.006$) (Table 4).

The number of metastatic sites <3 and number of risks <3 were associated with better survival (median 33 and 26 months respectively) than that with ≥ 3 and both showed high statistical significance ($P<0.001$) (Table 4).

Table 3. Prognostic factors in predicting OS and PFS of all patients

Factors	OS median	P	PFS median (95%CI)	P
Age		0.661		0.637
≤50	14		10	
>50	15		12	
Sex		0.629		0.960
Male	14.5		12.5	
Female	14		8	
PS		0.088		0.104
1	17		14	
>1	14		12	
Presentation		0.177		0.205
Local	17.5		14	
Systemic	14		10	
Hg		0.001		0.001
N	18		14.5	
<N	12		5	
Neutrophil		<0.001		<0.001
N	20		15	
>N	12		4	
Plat		0.013		0.082
N	15		13	
>N	10		5	
Alb		0.034		0.006
N	16		13	
<N	11.5		7.5	
LDH		0.300		0.604
<1.5ULN	14		13	
>1.5ULN	12		10.5	

Factors	OS median	P	PFS median (95%CI)	P
BMI		0.934		0.788
N	15		12	
abn	14		11	
Side		0.515		0.205
Rt	13		10.5	
Lt	16		12	
T stage		0.666		0.948
2	15		11	
>2	14		11	
N stage		0.004		0.012
N0	19		14	
N+	12.5		7.5	
Bone mets		0.151		0.118
No	15.5		12.5	
Yes	14		7	
Lung mets		0.003		0.023
No	20		15	
Yes	13		8	
Liver mets		0.024		0.005
No	15		13	
Yes	12		5	
No of met. Site		0.002		0.001
<3	32		25	
≥3	14		9	
No of risk		<0.001		<0.001
<3	26		20	
≥3	13		7	

PS, performance status; Hg, hemoglobin; N, normal; plat, platelet; alb, albumin; LDH, lactate dehydrogenase; BMI, body mass index; abn, abnormal; Rt, right; Lt, left; RH, rhabdoid; mets, metastases; TTs, target therapies.

Table 4. Univariate and multivariate analysis of preoperative factors in patients that received upfront CN followed by TTs

Factors	MOS	Univariate analysis HR(95%CI)	P	Multivariate	P	Factors	MOS	Univariate analysis HR(95%CI)	P	Multivariate	P																													
Age						BMI																																		
≤50	18.5	1.172(0.755-	0.571							N	19.5	1.419(0.618-	0.933																											
>50	19	1.819)								abn	14	3.259)																												
Sex										Side																														
Male	20	0.752(0.498-	0.630							Rt	13	2.139(1.257-	0.134																											
Female	15	1.136)								Lt	20	4.529)																												
PS										T stage																														
1	20	1.315(0.816-	0.431							2	19.5	1.300(0.802-	0.443																											
>1	15.5	2.120)								>2	17.5	2.106)																												
Presentation										N stage																														
Local	18	0.853(0.550-	0.503							N0	20	1.684(1.020-	0.245																											
Systemic	13	1.324)								N+	15	2.780)																												
Hg										Bone mets																														
N	23	1.393(0.801-	0.012							1.832(0.953-							No	22	0.869(0.527-	0.369																				
<N	14	2.423)								2.385)							Yes	18.5	1.433)																					
Neutrophil										Lung mets																														
N	24	1.449(0.857-	<0.001							2.381(1.096-							No	16.5	1.806(1.056-	0.591																				
>N	13	2.449)								4.513)							Yes	8	3.090)																					
Plat										Liver mets																														
N	19.5	2.909(0.526-	0.095							No							10	1.103(0.612-	0.283																					
>N	6	5.087)								Yes							7.5	1.990)																						
Alb										No of met.																														
N	20	1.448(0.699-	0.006							0.985(0.713-													Site		0.001	1.843(1.281-	0.087													
<N	12.5	3.001)								2.163)													<3	33		1.519(1.044-		3.421)												
LDH										No of risk																														
<1.5ULN	20.5	1.333(0.430-	0.635																				>3	14.5	2.209)	0.001		2.364(1.641-	0.009											
>1.5ULN	18	4.134)																					<3	26	2.000(1.341-	3.154)														
																													≥3	14	2.984)									

PS: performance status, Hg: hemoglobin, N: normal, plat: platelet, alb: albumin, LDH: lactate dehydrogenase, BMI: body mass index, abn: abnormal, Rt: right, Lt: left, mets: metastasis.

Multivariate analysis of prognostic factors

On applying Cox regression on predictors associated with improvement in survival on univariate analysis, only normal count of neutrophil and no of risk factors (P=0.024 and 0.009, respectively) were considered as independent factors (Table 4).

DISCUSSION

Cytoreductive nephrectomy (CN) in mRCC was considered as part of treatment in combination with cytokines. But with target therapies (TTs), the role of CN remains questioned. The use of TTs as neoadjuvant to reduce tumor bulk allowed the CN to be proceeded [28]. The combination of TTs and CN was studied with the application of both in different sequences. So, neoadjuvant TTs followed by CN compared with CN alone resulted in an improvement of survival in combination over CN alone [29]. The same benefit was observed in patients treated with CN followed by interferon α in comparison to interferon α alone [6, 7].

Since the approval of TTs in treatment of mRCC achieved better clinical effect than immunotherapy, the role of CN declined [30]. But, CN remains associated

with better survival [31], so, a controversy developed about the role of CN with TTs. There is a study which reported improved overall survival (OS) in patients with mRCC with TTs without CN [27]. However, there was a meta-analysis performed on large sample size in 2016, which registered that patients treated with upfront CN followed by TTs were associated with more than 2 folds prolonged OS compared with targeted therapy alone, but demonstrated no benefit in progression-free survival (PFS), nor increased risk of progression [32]. Same results were obtained by other studies [19, 24].

You et al. [33], reviewed 171 patients with mRCC and reported median OS 19.9 months in CN followed by TTs versus 11.7 months in TTs alone with significant difference (P<0.001). Our results were in agreement with trials that recorded improved survival in CN+TTs versus TTs alone, as the median survival was 19 months in CN group and 10.5 months in NCN group, with high significant difference (p<0.001). Similarly, improvement in PFS was observed which was statistically significant (p=0.046).

On the other hand, there were studies that did not demonstrate survival benefit from upfront CN [27, 34]. Phase III CARMENA trial reported a median survival of 18.4 months in patients treated with sunitinib versus 13.9 months in those treated with CN followed by

sunitinib [27]. The limitation of CARMENA trial was in selecting candidates as it included patients only with good performance status (Eastern Cooperative Oncology Group 0 or 1) and excluded of patients with symptomatic or untreated brain metastases.

Despite improved survival in using upfront CN before TTs, there was a concern surrounding CN in identifying patients suitable for CN. Several studies have identified factors affecting survival after CN. The Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score is useful in predicting patients with mRCC to get the benefit of CN. These factors comprise of Karnofsky performance status, lactate dehydrogenase (LDH) level, hemoglobin level, serum calcium level, and prior nephrectomy [34].

Culp et al. (35) from the institutional RCC database of the University of Texas MD Anderson Cancer Center, identified seven pre-operative variables that permitted them to distinguish patients who were unlikely to benefit from CN, including 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. Overall survival (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 recent analysis of the International Metastatic renal cell carcinoma Database Consortium (IMDC), Heng et al. [36] found that patients with estimated survival times <12 months, or having four or more risks may not benefit from CN. Another large study included 645 patients demonstrated that performance status, calcium level, hemoglobin level, neutrophil count, platelet count, and time from diagnosis can predict survival [9]. Other adverse prognostic factors that were identified in other studies include multiple metastatic sites, sarcomatoid differentiation, elevated alkaline phosphatase, and thrombocytosis [37-39]. Some limitations of these trials are that inclusion criteria included patients treated with immunotherapy, and comparative groups were not performed.

In the present study, we tried to identify the effect of several prognostic factors on the survival of patients treated with CN upfront to TTs in comparison to patients that received only TTs. From univariate analysis we identified five variables determined before CN that had negative effect on survival, namely, lower hemoglobin level than normal ($P=0.012$), high neutrophil count ($P<0.001$) above normal, lower albumin level ($P=0.006$), number of metastatic sites ≥ 3 and number of risk factors ≥ 3 associated with high significant ($P<0.001$), but from multivariate analysis only neutrophil count and number of risk factors showed a significant effect on survival. This is in agreement with results detected by You et al. [33] and Hong et al. [32].

However, there were some limitations in our study. First, some prognostic factors such as calcium level were not recorded, and LDH level was not assessed in 75.7% of patients, sarcomatoid and rhabdoid differentiation was detected only in four patients so they were not analyzed with survival. Second, the retrospective analysis of data collected. Third, small sample size, and lastly, selection bias in determining which patients should be treated with upfront nephrectomy before targeted therapy.

CONCLUSION

Results of our study indicate that cytoreductive nephrectomy combined with target therapy has a significant overall survival advantage in patients with mRCC. However, the evidence is limited due to retrospective nature and small sample size of the present study. Although we detected some significant prognostic factors in predicting survival in patients that received CN, further research should be made to predict factors to help the selection of patients. More large prospective studies are needed to prove these results.

DECLARATIONS

Competing of Interest

The authors declare that they have no competing interests.

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