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Cytoreductive nephrectomy plus targeted therapy in patients with metastatic renal cell carcinoma: Our experience

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ABSTRACT

Introduction: Renal cell carcinoma presents with metastatic disease in approximately 30% of cases. Since the introduction of targeted therapies, they have demonstrated impressive gains in overall survival, progression-free survival and response rates over the previously utilized immunotherapies in cases with mRCC. The rates of cytoreductive nephrectomy have declined since the introduction of targeted therapy. We report our experience with cytoreductive nephrectomy plus targeted therapy. *Materials & Methods:* We retrospectively collected the hospital inpatient and outpatient records of mRCC who had undergone cytoreductive nephrectomy trailed by targeted treatment. Data included demographic, clinical, imaging and laboratory data and those that were found to have prognostic value. Measured outcomes included OS. *Results:* 78 patients (61 males and 17 females) 60.17± 8.76 years was mean age who underwent cytoreductive nephrectomy for mRCC of clear cell type. 43 (55.1%) patients had comorbidity. 78 patients had huge renal masses (mean 10.167±2.756 cms) on CT imaging. All patients were introduced on target therapy four to eight weeks after surgery. The mean overall survival of the patients was 27.98±1.47 months. *Conclusions:* Presently the important role of cytoreductive nephrectomy is not well defined in the ear of targeted therapy. However, in our study patient with good performance statuses do better than patients with existing health risks.

Keywords: Metastatic, Renal cancer, Cytoreductive nephrectomy, Targeted therapy.

1. INTRODUCTION

Of all the epithelial cancers worldwide the renal-cell carcinoma covers around 5% (Biswas et al., 2009). Up to 85% of these cancers are clear-cell renal cell carcinoma (CC-RCC) and 25% of these cancers are metastatic (m) CC-RCC (Murai and Oya, 2004). The 2-year overall survival rate of patients with mCC-RCC is only 10%–20% (Murai and Oya, 2004). There exist reports in the literature that have demonstrated complete resolution of metastases, albeit a

very rare event (0.4–0.8%), in patients with metastatic disease who had undergone nephrectomy without systemic therapy (Marcus et al., 1993).

Cytoreductive nephrectomy was basically kept for the mitigation of indications earlier to the starter of immunotherapy. This comprises of hemorrhage, obstinate pain, unrestrained high blood pressure or hypercalcemia due to paraneoplastic conditions, etc. During the early years of immunotherapy, doubts existed as to whether CN was beneficial. However, studies demonstrated an improved response to immunotherapy in patients undergoing debulking surgery compared with those patients treated with the primary tumor still in place (Fisher et al., 1988; Atkins et al., 1993).

Investigators at Tufts University devised strict criteria as to which patients might benefit from CN prior to systemic therapy: The ability to debulk at least 75% of the tumor burden, absence of brain, liver and bone metastases, an Eastern Cooperative Oncology Group (ECOG) presentation grade of 0 or 1, clear cell histology and adequate cardiac and pulmonary function (Fallick et al., 1997). The authors were able to identify 28 eligible patients based on these criteria and found that 93% of these patients were able to subsequently undergo systemic therapy with IL-2 and importantly, at least 40% demonstrated at least a partial therapeutic response (Fallick et al., 1997).

Two randomized prospective trials (Flanigan et al., 2001; Pantuck et al., 2001) (The European Organization for the Research and Treatment of Cancer trial 30947 and the Southwestern Oncology Group (SWOG) trial 8949) provided Level 1 evidence for the existence profit of CN prior to immunotherapy in patients with mRCC. With the introduction of targeted therapy, the use of nephrectomy in cases with mRCC came into question. Until recently there was no level 1 evidence supporting the use of CN in targeted therapy (TT).

Two large randomized trials were initiated to prospectively examine the role of CN in association with targeted therapy. The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) examined the results of nephrectomy followed by sunitinib treatment in comparison with sunitinib only in patients with mRCC (Culp, 2015). The EORTC Immediate Surgery or Surgery after Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer (SURTIME) assessed the timing of nephrectomy in relation to treatment with sunitinib (Culp, 2015; Nerli, 2013).

In recent years, treatment with molecular-targeted therapies has clearly improved the prognosis in patients with mRCC, with response rates exceeding 30%, resulting in a median overall survival (OS) of up to 2 years (Albiges et al., 2015). It is believed that cytoreductive nephrectomy might pose a vital remedial therapy only if all tumor loads is eliminated. In this study, we report our experience with cytoreductive nephrectomy in patients presenting to us with metastatic RCC who were further treated with targeted therapy at our centre.

2. PATIENTS & METHODS

The patient's data were retrospectively collected from the hospital inpatient and outpatient records with approval obtained from the hospital/institutional review and ethical committee. Patient inclusion criteria were composed of patients with mRCC diagnosis of clear cell type and treatment with a VEGF or mTOR targeted therapy. The age, gender, presenting symptoms, imaging and laboratory data were noted and analyzed. Additional information on co-morbidities was recorded.

The presence of prognostic factors conferring to the Memorial Sloan Kettering Cancer Center (MSKCC) Albiges et al., (2015) were documented at the start of each treatment line, including low (<80%) Karnofsky performance status (KPS), elevated lactate dehydrogenase level (>1.5 more of normal), low haemoglobin (Hb) level (less than the normal limit), elevated corrected calcium (greater than the normal) and the absence of the previous nephrectomy. Using these factors, the patient's individual prognostic risk score was calculated (low risk, 0 risk factor; intermediate risk, 1-2 risk factors; high risk, 3-5 risk factors).

All systemic anticancer treatments (substance, dose, dose modifications and duration) and/or surgeries were documented. The treatment outcome parameters, including the dates of progression and the date of death by any cause, were recorded. Measured outcomes included OS (overall survival) and PFS (progression-free survival).

Statistical analysis

The primary outcome was OS from the initiation of first-line targeted therapy to the date of death or censored at the last follow-up. PFS was defined as the initiation of targeted treatment, drug cessation or censored at the last follow-up. Median OS and PFS distributions were estimated using the Kaplan-Meier method.

3. RESULTS

During the study period Jan 2010 to Dec 2021, a total of 78 patients (61 males and 17 females) bearing 60.17± 8.76 years of mean age underwent cytoreductive nephrectomy for mRCC of clear cell type (Table 1).

Table 1 Patient demographics

Parameter	Total	MSKCC (0)	MSKCC (1-2)	MSKCC (3-5)
Patients	78	30	28	20
Mean Age years	60.17			
≥comorbidity	43 (55.1%)	16	14	13
Histopathology ccRCC	78	30	28	20
KPS<80%		-	1	20
Hb<LLN		-	20	20
Calcium>ULN		-	2	7
LDH>1.5 times ULN		-	5	8

All of these patients had presented with synchronous metastases. Hematuria was the main presenting symptom in these patients. The other symptoms included dragging pain, a sense of illbeing, loss of appetite and pedal edema.

On examination, 6 (7.69%) patients had huge palpable renal masses, 8 (10.2%) patients had left sided varicocele, 3 (3.84%) had bilateral varicocele. Co-morbidity was seen in 43 (55.1%) patients that included hypertension, diabetes mellitus, chronic lung disease, ischemic heart disease and cebero-vascular ischemia. On computed tomography imaging all the 78 patients had huge renal masses (mean 10.16±2.756 cm), visceral metastasis (Figure 1) and the clinical staging was as in (Table 2).

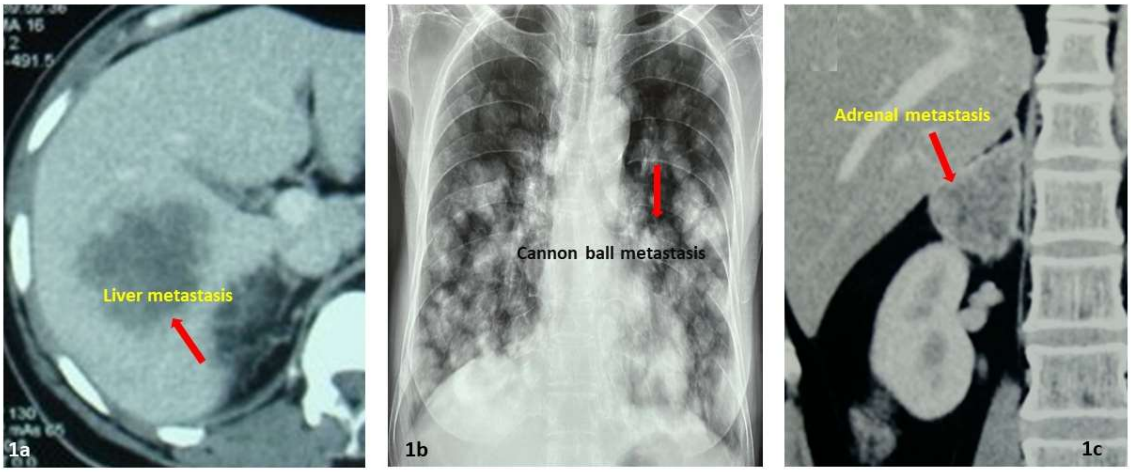

Figure 1 1a) CT showing hypodense lesions suggestive of metastasis from RCC. 1b) Multiple discrete lesions over bilateral lung fields suggestive of metastatic lesion (cannon ball). 1c) CT showing hypodense lesion over the Rt. adrenal gland suggestive of metastasis

Table 2 Clinical staging

No.	Stage	
1	T1b	3
2	T2a	23
3	T2b	28
4	T3a	16 (9 -perirenal invasion, 7 renal vein thrombus)
5	T3b	3 (Tumour thrombus below the diaphragm)
6	T3c	1 (Tumour thrombus above the diaphragm)
7	T4	4 (Tumour invading gerota fascia and extending into ipsilateral adrenals
8	M1	78 (liver -28, contralateral adrenals 4, lungs 38, bones 6, distant lymph nodes 12)

Eleven patients had tumour thrombus extending into renal vein/inferior vena cava and all these patients had removal of tumour thrombus at the time of nephrectomy. All the 78 patients had a smooth post-operative recovery. All patients were initiated on target therapy four to eight weeks after surgery. Twenty-three of them received Sunitinib, thirty-three received Pazopanib and twenty-two others were started on Everolimus as the primary target therapy. The choice of the drug used, was based on the drug clinical trials that were carried out during that period as well as the affordability of the patient. The mean overall survival of the patients was 27.98±1.47 months (Figure 2). The mean survival in patients with MSKCC risk 0 was significantly better than those with MSKCC risk 1-2 and 3-5 (Table 3).

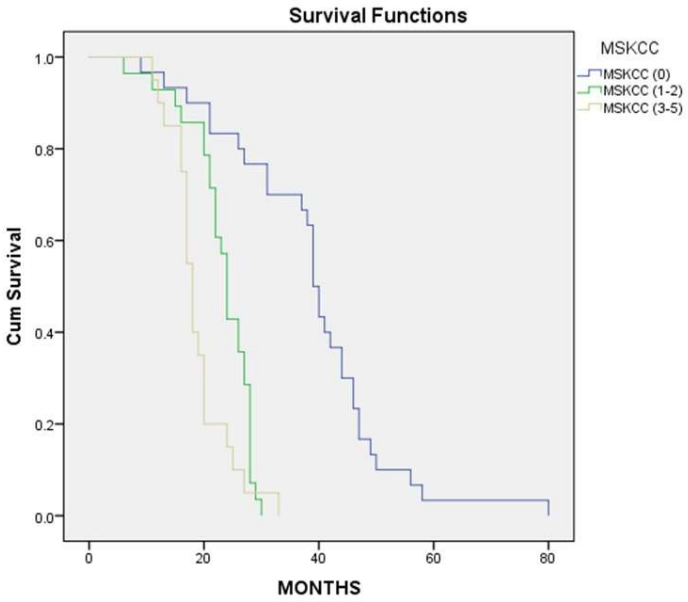

Figure 2 Survival Graph

Table 3 Mean overall survival as per MSKCC risk groups

MSKCC risk group	Estimate	Std Error	95% Confidence interval		Chi-Square	p- value
			Lower bound	Upper bound		
MSKCC (0)	38.56	2.64	33.43	43.71	52.998	0.0001
MSKCC (1-2)	23.14	1.06	21.04	25.23		
MSKCC (3-5)	18.90	1.15	16.63	21.17		
ALL	27.98	1.47	25.10	30.87		

4. DISCUSSION

Cancer of the kidney is more prevalent among the older and the occurrence increases as the age increases with the highest incidence noted between 75 and 85 years, approximately 56/100000 (Scosyrev et al., 2012). Perioperative complications are more often seen in elderly patients, as they have condensed physiological fallback and an amplified occurrence of cardiovascular comorbidities. It is a great challenge to treat these elderly patients although more if they have metastatic disease (Aslam and Mathews, 2014). The exact part of CN in the elderly has been very much defined by the MDACC experience (Kader et al., 2007).

The outcomes were studied in 24 patients who were over 75 years of age and compared with the younger aged patients with alike presentation position, Gender, histology of the tumour, stage of the tumor, grade and size of the tumor. The perioperative deaths were 5 (21%) in elderly patients as associated with 4 (1.1%) in younger patients. However, the intermediate survival between the 2 groups showed no statistically significant difference, contempt the major menace of illness and death. In a selective group of highly motivated elderly patients, cytoreductive nephrectomy can be considered.

The treatment of metastatic RCC has been revolutionized over the last few years. The vast mainstream of clear cell RCCs is known to be as a result of mutations within the VHL gene (Latif et al., 1993). These mutations have effects on hypoxia-inducible factor (HIF) 1 alpha, which leads to the overexpression of manifold hypoxia-responsive proteins that endorse the formation of new blood vessels and promote the growth of the cells within the tumours (Krause and Etten, 2005). Several drugs like sunitinib,

sorafenib, temsirolimus and bevacizumab are known to target the new blood vessel formation pathways which have been altered by mutations in the VHL genes thereby explaining the nature of the action of these targeted therapies (TT).

Several arguments for and against the role of CN have been proposed (Rendon, 2007). The main objectives of CN are to enhance the response to systemic therapy and to improve the quality of life. Additional gains from primary CN include the ability to confirm histology; more accurately assess the tumour stage and provide tissue for the development of vaccine therapies (Sengupta et al., 2005; Mickisch and Mattes, 2005). The constant usage of CN in the multimodal administration of patients with mRCC has been maintained by the element that in studies assessing targeted therapy, the majority (67–100%) of patients had undergone nephrectomy prior to initiation of systemic therapy (Culp, 2015).

In the potential randomized trial evaluating sunitinib *versus* IFNα, a subgroup analysis found that progress-free survival (PFS) was increased in patients undergoing CN compared with patients treated with sunitinib alone (11 *against* the reported 6 months) (Motzer et al., 2007). Treatment with molecularly targeted therapies (TKIs- tyrosine kinase inhibitors and mTOR- mammalian target of rapamycin inhibitors-) has improved the prognosis of mRCC patients, with response rates now exceeding 30% and median OS of up to 2 years (Albiges et al., 2015).

Today many oncologists would like to consider a systemic treatment rather than submitting the patient to CN, given the lack of evidence of the effectiveness of CN in combination with molecularly targeted therapies. Due to this, there has been a decrease in the application of cytoreductive nephrectomy in the VEGFR-TKI era (2006–8) associated with cytokine age (2001-5) (Faba et al., 2017). Results from the SEER database has revealed that there has been a global decrease in usage of CN from 50 to 38% in mRCC patients (Faba et al., 2017). In the United States, specifically, older age, black race, Hispanic ethnicity and treatment with VEGFR-TKI were factors independently associated with a decreased use of CN (Tsao et al., 2012).

Several prominent and pivotal studies have shown that sunitinib improved PFS in the first-line setting (11 vs 5 months; $p < 0.001$; HR 0.42) (Motzer et al., 2007), sorafenib improved PFS in the second-line setting (5.5 vs 2.8 months; $p < 0.01$; HR 0.44) (Escudier et al., 2007), temsirolimus enhanced OS in poor-risk mRCC patients (10.9 vs 7.3 months; $p < 0.008$; HR 0.73) (Hudes et al., 2007), everolimus improved PFS in the second-line setting (4 vs 1.9 months; $p < 0.0001$; HR 0.30) (Motzer et al., 2007) and bevacizumab plus IFN increased PFS in the first-line setting (10.2 vs 5.4 months; $p < 0.0001$; HR 0.63) (Hudes et al., 2007).

Several authors have looked at various factors in order to construct a scoring system that is able to select the best candidates for CN (Adibi et al., 2015; Li et al., 2015). Poor performance status as assessed by means of ECOG or the KPS is widely accepted as an indicator of poor prognosis. The models provided by the Memorial Sloan Kettering Cancer Center (MSKCC) and the International mRCC Database Consortium (IMDC) are the most widely used and were developed on mRCC patients treated with IFN or target therapies (Motzer et al., 1999; Heng et al., 2009).

In the MSKCC scoring system, several factors such as KPS, lactate dehydrogenase (LDH) levels, haemoglobin levels, serum calcium level and time from RCC diagnosis to the start of treatment were utilized to stratify patients into three risk categories (Heng et al., 2009). Similarly, the IMDC group identified four of the original MSKCC criteria as prognostic predictors. In both prognostic models, the presence of three or more risk factors was associated with a worse prognosis. CN is presently endorsed in patients who extant with huge prime tumours, a low metastatic burden and a favorable performance status (PS). In contrast, CN is not indicated in subjects with low-risk disease as per the IMDC or MSKCC prognostic models (Faba et al., 2017).

Presently the results of the two randomized trials to prove the advantage of CN in combination with new systemic treatment options in mRCC patients have been published. A clinical trial was conducted to assess the importance of nephrectomy (CARMENA trial) which was a phase 3 randomized trial comparing CN + sunitinib vs sunitinib alone (AP-Hd, 2009). The study was launched in France in June 2009 with the primary end-point OS. Secondary end-points comprised impartial reply rate, clinical advantage and PFS (Eisenhauer et al., 2009). Sunitinib unaided remained original to be non-inferior to the combination of CN + sunitinib.

The median overall survival in the sunitinib-only group was 18.4 months in comparison to 13.9 months in the combination group. MSKCC intermediate-risk patients had a median overall survival of 23.4 months in the sunitinib-only group versus 19.0 months in the combination group and 13.3 months versus 10.2 months respectively in poor-risk patients (Mejean et al., 2018). Several conclusions were drawn from the CARMENA trial that included that patient selection for CN was vital and that it should not be measured for subjects with intermediate and poor-risk diseases (Bex et al., 2018).

CARMENA trial also supported that CN was ineffective and could be harmful in patients with poor risk mRCC (Heng et al., 2014). The CARMENA trial helped clarify the management of MSKCC intermediate and poor risk mRCC, but did not provide guidance for favorable risk patients. The other phase III trial of the EORTC-SURTIME started in the month of April 2010 in at

various centres in Europe and Canada with the intention of examining the best effectiveness of cytoreductive nephrectomy in relation to systematic treatment with sunitinib (either before or after).

The enrollment was terminated in April 2016 with 99 patients (Bex et al., 2016). The trial was underpowered partly due to strict eligibility criteria. The primary endpoint of progression-free survival was not met and the secondary endpoint of overall survival substantially favored the deferred CN arm, with a median overall survival of 32.4 months versus 15.1 months. The data supported the conclusions, that delaying systemic therapy for immediate CN in patients with intermediate-risk and poor-risk disease, decreased survival.

5. CONCLUSION

In conclusion, systemic therapy has altered the management of patients with mRCC. Cytoreductive nephrectomy offers a survival advantage only when combined with systemic therapy. Upfront CN may delay systemic therapy initiation and may be harmful in patients with more advanced metastatic disease. The CARMENA and the SURTIME trials have shown that upfront CN has worse outcomes in patients with MSKCC intermediate and poor risk disease.

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Author Contributions

VK, MK & RBN Conceptualized and performed the study; RBN & SCG wrote and edited the manuscript; RS, SCG & MBH collected the study material and performed the statistical analysis. All the authors reviewed and approved the manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of the Institutional Ethics Committee (Ethical approval code: KLESKF/20/013).

Informed consent

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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