Is Cytoreductive Nephrectomy Still Relevant in the Era of Targeted Therapy? A Retrospective Survival Study in Metastatic RCC from Nepal

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Abstract

Background: Metastatic renal cell carcinoma (mRCC) accounts for approximately 20-30% of all RCC cases and presents significant treatment challenges, especially in resource-limited settings like Nepal. Although the role of cytoreductive nephrectomy (CN) has been established in the immunotherapy era, its value in the era of targeted therapies remains controversial. This study evaluates overall survival (OS) outcomes among patients with synchronous mRCC treated with sunitinib, with or without prior CN, at a tertiary cancer center in Nepal.

Methods: We conducted a retrospective study of 54 patients with synchronous mRCC who received first-line sunitinib therapy between January 2007 and December 2015 at B.P. Koirala Memorial Cancer Hospital. Patients were divided into two cohorts: those receiving CN followed by sunitinib (CN/TT) and those receiving sunitinib alone (TT). Baseline characteristics, MSKCC risk stratification, and survival outcomes were analyzed. OS was calculated from the start of therapy to death or last follow-up, using Kaplan-Meier analysis and log- rank test for group comparison.

Results: Among the 54 patients included in the study, 17 (31.5%) underwent cytoreductive nephrectomy (CN) followed by sunitinib, while 37 (68.5%) received sunitinib alone. According to the MSKCC risk stratification, most patients in the CN/TT group were intermediate risk (12/17, 70%), while 30% were poor risk. In contrast, most patients in the TT-only group were poor risk (21/37, 57%), with 43% classified as intermediate risk. The median overall survival (OS) for the entire cohort was 6 months (mean ± SD: 12.29 ± 2.35 months). The 1-year, 3-year, and 5-year OS rates for the entire cohort were 29%, 5%, and 2%, respectively. Patients in the CN/TT group demonstrated significantly better survival compared to those in the TT-only group, with a median OS of 13 months versus 4 months. The 1-year, 3-year, and 5-year OS rates in the CN/TT group were 58%, 11%, and 6%, respectively, compared to 15%, 3%, and 2% in the TT group ($p < 0.05$).

Conclusion: This is the first study from Nepal demonstrating a survival benefit of CN in patients with synchronous mRCC treated with sunitinib. Despite limitations of retrospective design and sample size, our findings support the continued role of CN in select patients receiving targeted therapy, particularly in low-resource settings. Prospective studies are warranted to better define patient selection and optimize outcomes.

Keywords: cytoreductive nephrectomy, metastatic renal cell carcinoma, sunitinib, survival, targeted therapy

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Introduction

Renal cell carcinoma (RCC) is the most common histological subtype of kidney cancer and represents a major genitourinary malignancy. Globally, kidney cancer accounts for approximately 2.2% of all cancers, while in Nepal it represents about 0.6% of new cancer cases. According to GLOBOCAN 2022, more than 430,000 new cases of kidney cancer are diagnosed annually worldwide, resulting in nearly 180,000 deaths.[1,2] Approximately 20–30% of patients with RCC present with metastatic disease at diagnosis. Historically, systemic therapy for metastatic RCC (mRCC) was limited to immunotherapeutic agents such as interleukin-2 (IL-2) and interferon-alpha (IFN-α), which achieved modest response rates of 10–22% and were once considered the standard of care.

Two phase III randomized controlled trials, SWOG 8949 and EORTC 30947, evaluated the impact of cytoreductive nephrectomy (CN) followed by INF-α compared to INF-α alone. Both studies concluded that CN combined with interferon therapy resulted in improved survival in patients with metastatic RCC.[2] A pooled analysis of these trials indicated a median overall survival (OS) of 13.6 months in the CN plus INF-α group, compared to 7.8 months in the INF-α-only group.[3] However, with the advent of more effective targeted therapies (TT), particularly vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors (TKI) such as sunitinib, the role of CN has become increasingly controversial, as the survival benefit is not uniform across all patient subgroups. This has necessitated a reassessment of CN in the modern therapeutic landscape.

To date, no study from Nepal has evaluated survival outcomes in patients with mRCC. The present study aims to assess the OS of mRCC patients treated with targeted therapies. Additionally, it will compare survival outcomes in patients with synchronous mRCC who received sunitinib with or without CN.

Methods

This retrospective cohort study was conducted at the Urology Unit of B.P. Koirala Memorial Cancer Hospital (BPKMCH) in Bharatpur, Nepal. As a tertiary cancer care center centrally located in Chitwan, BPKMCH provides accessible oncology services to patients across Nepal, managing approximately 10,000 cancer cases annually, which constitutes nearly half of the estimated 21,000 new cancer cases in the country each year. The study received ethical approval from the Institutional Review Board of BPKMCH.

We reviewed medical records of patients diagnosed with mRCC who initiated first-line sunitinib therapy between January 2007 and December 2015. Inclusion criteria encompassed:

1. Histologically confirmed RCC of any subtype.
2. Presence of synchronous metastases, defined as metastases identified at diagnosis or within three months post-nephrectomy.
3. Administration of sunitinib therapy for a minimum duration of one month.
4. Availability of complete clinical and treatment data.

Patients were categorized into two cohorts: those who underwent CN followed by sunitinib (CN/TT group) and those who received sunitinib without prior CN (TT group).

Exclusion criteria included:

1. Patients with metachronous metastases (metastases occurring beyond three months after initial diagnosis or post-curative surgery).
2. Patients who underwent CN after initiating sunitinib therapy.
3. Patients exhibiting intrinsic resistance to sunitinib.
4. Patients who did not receive sunitinib therapy.

Data extracted from medical records included demographic information (age, gender), clinical presentation, performance status, time from diagnosis to treatment initiation, primary tumor characteristics (side, size, histology, clinical T and N stage, Fuhrman grade), number and sites of metastases, treatment details (type, sequence, dosing of sunitinib), and survival status.

Patients were stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk model, which considers five prognostic factors:[4]

1. Karnofsky performance status score <80.
2. Serum lactate dehydrogenase level >1.5 times the upper limit of normal.
3. Hemoglobin level below the lower limit of normal.

4. Corrected serum calcium level >10 mg/dL.
5. Time from diagnosis to systemic therapy<1 year.

Patients with none of these factors were classified as favorable risk, those with one or two factors as intermediate risk, and those with three or more factors as poor risk.

All patients in this study received sunitinib as first-line therapy, typically initiated at a standard dose of 50 mg daily on a 4/2 schedule (4 weeks on, 2 weeks off), with dose adjustments based on tolerance and adverse events.

A descriptive analysis of all variables was performed. Qualitative data were analyzed by means of absolute and relative frequencies. Quantitative variables were summarized as means, standard deviations and confidence intervals, or by medians and ranges for data without a normal distribution.

The primary endpoint of this study was OS at 1, 3, and 5 years. OS was defined as the time from initiation of definitive treatment to the date of death from any cause or last follow-up. For patients undergoing CN followed by sunitinib, OS was calculated from the date of surgery to the date of death or last follow-up. For patients receiving sunitinib alone, OS was calculated from the date of the first sunitinib dose to the date of death or last follow-up. Survival analyses were performed using the Kaplan–Meier method, and comparisons between groups were conducted using the log-rank test. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 16.

Results

Between 2007 to 2015, altogether we had 101 patients who were diagnosed as mRCC and received sunitinib therapy. However, we excluded 18 patients who had metachronous metastasis and 29 patients who had missing data. The remaining 54 patients with synchronous mRCC who received sunitinib were only included for analysis.

Seventeen patients (31.5%) were in the CN/TT group (CN ≤ 3 months of mRCC diagnosis followed by sunitinib), and 37 patients (68.5%) were in the TT group (sunitinib only). The median age was 61 years (59.98 ± 13.12). The mean age at diagnosis was 59 ± 14.45 years in the CN/TT group and 64 ± 12.63 years in the TT group. Overall, 70.4% had clear cell RCC histology. Baseline characteristics are summarized in Table 1.

Table 1: Baseline characteristics of patients

Patient Particulars	
Age (mean ± SD)	59.98 ± 13.12 years
Sex	Frequency (Percentage)
Male	39(72.2%)
Female	15(27.8%)
Metastatic Sites	
Lung	36(66.67%)
Liver	20 (37.04%)
Bone	18 (33.33%)
Lymph Nodes	19 (35.19%)
Adrenal Gland	6(11.11%)
Brain	3(5.56%)
Spleen	3(5.56%)
Pancreas	1(1.85%)
Testis	1(1.85%)
Peritoneal	4(7.4%)
Histology type	
Clear cell	38(70.4%)
Adenocarcinoma	4(7.4%)
Papillary	3(5.6%)
Sarcomatoid	3(5.6%)
Unknown	6(11.1%)

All patients were classified as intermediate or poor risk according to MSKCC criteria. In the CN/TT group, most were intermediate risk (12/17, 70%), while 30% were poor risk. In the TT group, most were poor risk (21/37, 57%), with 43% intermediate risk. No patients were favorable risk.

The overall median survival from initiation of treatment was 6 months (mean ± SD: 12.29 ± 2.35 months). The 1-year, 3-year, and 5-year OS rates were 29%, 5%, and 2%, respectively. (Figure 1) In the TT group, the 1-year, 3-year, and 5-year OS rates were 15%, 3%, and 2%, respectively (median = 4 months, mean ± SD: 7.96 ± 2.07 months). In the CN/TT group, the 1-year, 3-year, and 5-year OS rates were 58%, 11%, and 6%, respectively (median = 13 months, mean ± SD: 21.52 ± 5.30 months). The difference between group was statistically significant. (Figure 2).

Discussion

To our knowledge, this is the first retrospective study from Nepal to evaluate the impact of CN combined with TT in patients with mRCC. Nepal, a low-income country, faces significant barriers in cancer care delivery. Despite government-backed healthcare financing mechanisms, these are insufficient to protect patients from catastrophic out- of-pocket expenses. The national health insurance scheme remains underdeveloped and inconsistently accessible, particularly for patients requiring prolonged and costly cancer treatments.[5] Access to Sunitinib - a costly, novel VEGFR-TKI has been made possible through a donation program coordinated by the Government of Nepal and the Max Foundation.

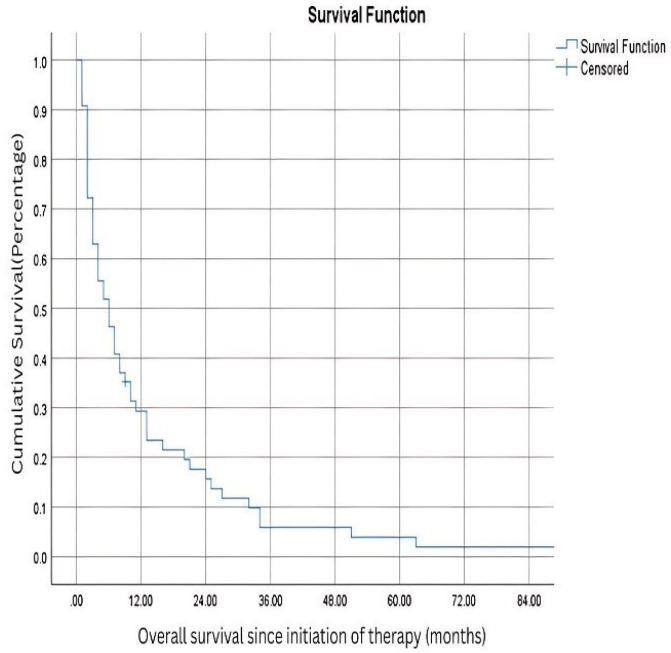

Fig. 1: OS analysis since initiation of therapy

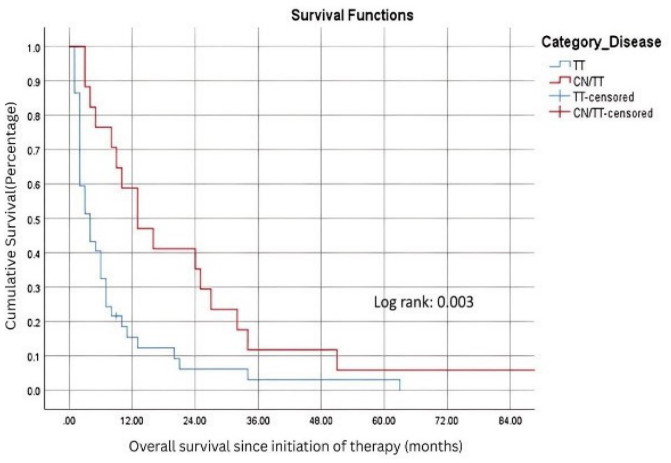

Fig. 2: OS analysis since initiation of therapy between CN/TT group and TT group

This initiative has enabled equitable access to Sunitinib for mRCC patients at our institution, regardless of their surgical status. Our study population included patients with synchronous mRCC, stratified according to the MSKCC risk classification. As expected in a low-resource setting, the majority of patients fell into the intermediate and poor-risk categories. The prognosis of mRCC remains poor despite advances in systemic therapies. Literature reports a 5-year OS ranging from 0 to 20%.[6, 7, 8] In our study, the 1-year, 3-year, and 5-year OS rates were 29%, 5%, and 2%, respectively. The median OS was 6 months (mean ± SD: 1 2.29 ± 2.35 months), reflecting the advanced disease stage at presentation and limitations in supportive care.

Importantly, our results suggest a survival benefit for patients undergoing CN in conjunction with TT. The median OS was 13 months in the CN/TT group compared to 6 months in the TT-only group. This aligns with findings from previous studies. Choueiri et al. (2011) demonstrated that among 314 patients receiving VEGF-targeted therapy, those who also underwent CN had a median OS of 19.8 months versus 9.4 months for those receiving targeted therapy alone.[9] Similarly, Heng et al. (2014), in a large analysis of 1658 patients, reported a median OS of 20.6 months in the CN group versus 9.5 months in the non-CN group, even after adjusting for prognostic variables.[10]

A study by Hanna et al. (2016) involving 15,390 mRCC patients treated between 2006–2013 found a median OS of 17.1 months for those undergoing CN plus TT versus 7.7 months for those receiving TT alone ($p < 0.001$).[11] Furthermore, a meta-analysis confirmed the survival advantage of CN in the TKI era ($p < 0.01$).[12]

Recent data reinforce this benefit. Bakouny et al. (2022) analyzed 4,639 patients 4,202 treated with TKIs and 437 with immune checkpoint inhibitors (ICIs) and found immediate CN was independently associated with improved OS across both groups.[13] Chen et al. (2022) included 30 studies in a meta-analysis and similarly concluded that upfront CN with TT significantly improved OS compared to TT alone.[14] Notably, one study reported median OS of 33.1 months in the upfront CN group versus 11.1 months in the delayed CN group.[15]

Historically, CN was a mainstay of treatment for mRCC, primarily for cytoreduction and symptom relief, including control of hematuria, pain, paraneoplastic syndromes, and improvement in QoL.[8, 16, 17, 18]

The rationale for CN extends to the removal of immunosuppressive tumor burden, possibly enhancing systemic therapy effectiveness. However, the potential benefits must be balanced against perioperative risks, including surgical morbidity, delayed systemic therapy initiation, disease progression and adverse effects on immune function.[19, 20, 21, 22]

The standard role of CN has been recently challenged by randomized controlled trials. The CARMENA trial, a phase III RCT, compared CN followed by sunitinib with sunitinib alone and reported no OS benefit in the surgery arm (13.9 months vs. 18.4 months).[4, 23] However, the trial was heavily criticized for patient selection bias, low accrual rates, and high crossover between arms.[24] Arora et al. questioned the trial's generalizability, noting a disconnect between trial participants and real-world mRCC populations.[25]

The SURTIME trial investigated deferred CN after sunitinib versus upfront CN and found no significant difference in progression-free survival but a trend toward improved OS in the deferred CN group (32.4 vs. 15 months).[4, 23] Like CARMENA, SURTIME trail was underpowered, recruiting only 99 of the planned 458 patients. Both trials suggest a need for careful case selection rather than outright dismissal of CN.

Despite these conflicting results, real-world evidence and retrospective analyses continue to support a role for CN in selected patients with good performance status and low metastatic burden.[10, 26] Current consensus emphasizes individualized decision-making, incorporating prognostic models such as the MSKCC or International Metastatic RCC Database Consortium criteria to guide treatment selection.[27, 28] These models consistently show that patients with poor-risk features experience limited benefit from upfront CN.

Our findings are aligned with several recent studies that have endorsed the continued relevance of CN in the targeted therapy era when applied to carefully selected patients. Kokorovic et al. concluded that CN remains a valuable component of multidisciplinary mRCC management, particularly when integrated with systemic therapy and guided by clinical judgment.[28]

In low-resource settings like Nepal, delayed diagnosis, limited access to diagnostic imaging, lack of genomic profiling, financial barriers to treatment, and absence of timely follow-up limit the efficacy of systemic therapies alone. As such, CN may still play a pivotal role by achieving local disease control, alleviating symptoms, and reducing tumor burden in a resource- constrained environment. Notably, sunitinib was the only targeted agent available and was inconsistently administered due to cost and access issues. The majority of patients did not receive any second-line therapy, and many faced treatment interruptions, making the role of upfront surgical cytoreduction potentially more consequential in this context than in high-income settings.

Limitations

This study is subject to the inherent limitations of retrospective analyses, including incomplete data, and unmeasured confounders. The sample size was small, and some patients were lost to follow-up, which may affect the robustness of survival estimates. Additionally, there was an imbalance in baseline prognostic risk: most patients in the TT group were classified as poor risk, whereas most patients in the CN/TT group were intermediate risk. Nevertheless, our findings offer valuable insights into the treatment of mRCC in low-resource settings and provide real-world evidence supporting the selective use of CN in conjunction with targeted therapies.

Conclusion

This is the first study from Nepal demonstrating a survival benefit of CN in patients with synchronous mRCC treated with sunitinib. Despite limitations of retrospective design and sample size, our findings support the continued role of CN in select patients receiving targeted therapy, particularly in low-resource settings. Prospective studies are warranted to better define patient selection and optimize outcomes.

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