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Prognostic Factors for Survival in Patients Undergoing Surveillance After Cytoreductive Nephrectomy

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Study Need and Importance: A group of patients with metastatic renal cell carcinoma (mRCC) who undergo cytoreductive nephrectomy can be placed on surveillance as opposed to directly receiving systemic therapy. However, there is limited information available regarding the clinical outcomes and predictors of survival in this group of patients. Thus, we performed a single-center retrospective review of patients placed on surveillance after cytoreduction to assess outcomes and identify predictors of survival.

What We Found: We identified 92 patients who underwent cytoreductive nephrectomy and then were placed on surveillance. Systemic therapy–free, intervention-free, cancer-specific, and overall survival were identified. Predictors of systemic therapy–free survival were examined, and the most promising predictors were the presence of ≤1 IMDC (International mRCC Database Consortium) risk factors and ≤2 metastatic organ sites at the time of surgery. Patients with a favorable risk score had longer systemic therapy–free survival (50.6 vs 11.1 months, $P < .01$), intervention-free survival (25.2 vs 7.3 months, $P < .01$), and cancer-specific survival (71.4 vs 46.2 months, $P = .02$; see Figure).

Limitations: Given the retrospective nature of the study, we were unable to identify additional points of stratification like underlying tumor biology to help identify ideal patients for surveillance. Additionally, we could not prospectively and/or more precisely define the criteria about starting a patient on surveillance vs initiating systemic therapy.

Interpretation for Patient Care: A subset of patients with mRCC who undergo cytoreductive nephrectomy may be considered for surveillance as opposed to receiving up-front systemic therapy. Patients who demonstrate ≤1 IMDC risk factor and ≤2 metastatic organ sites may be the best candidates for surveillance as these patients demonstrate the best survival outcomes. This may be an important strategy to limit treatment related toxicities associated with systemic therapy.

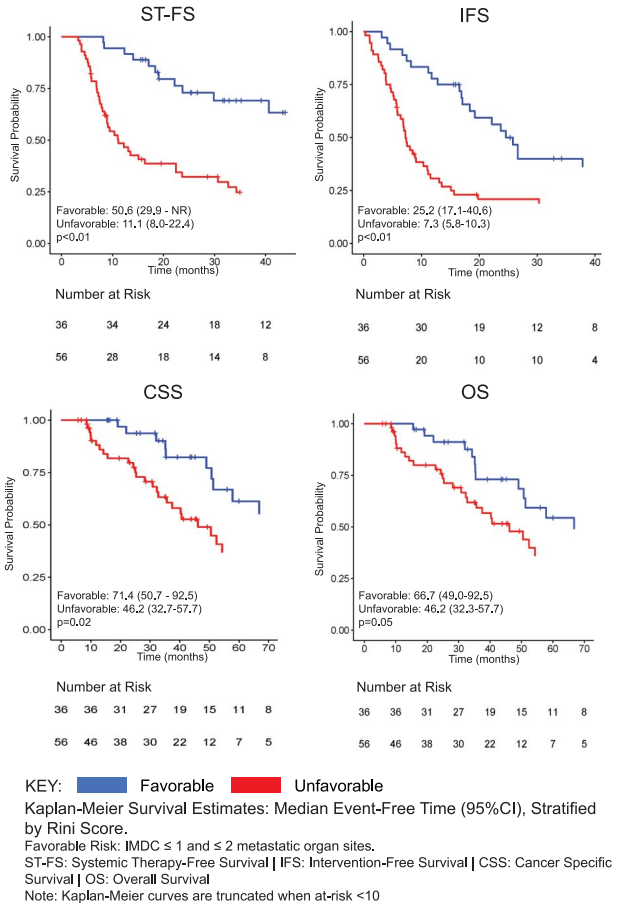

Figure. Kaplan-Meier survival estimates for systemic therapy–free survival (ST-FS), intervention-free survival (IFS), cancer-specific survival (CSS), and overall survival (OS). IMDC indicates International mRCC Database Consortium; NR, not reached.

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Prognostic Factors for Survival in Patients Undergoing Surveillance After Cytoreductive Nephrectomy

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Purpose: The clinical course of patients being placed on surveillance in a cohort of systemic therapy–naïve patients who undergo cytoreductive nephrectomy is not well documented. Thus, we evaluated the clinical course of patients placed on surveillance following cytoreductive nephrectomy and identified predictors of survival.

Materials and Methods: In this large single-institution study, we retrospectively analyzed metastatic renal cell carcinoma patients who underwent cytoreductive nephrectomy followed by surveillance. Predictors of survival were evaluated using the Kaplan-Meier method with a log-rank test. Patients were risk stratified based on IMDC (International mRCC Database Consortium) and number of metastatic sites (Rini score), with IMDC score ≤ 1 and ≤ 2 metastatic organ sites considered favorable risk. Primary end point was systemic therapy–free survival. Secondary end points included intervention-free survival, cancer-specific survival, and overall survival.

Results: Median systemic therapy–free survival was 23.6 months (95% CI: 15.1-40.6), intervention-free survival was 11.8 months (95% CI: 8.0-18.4), cancer-specific survival was 54.2 months (95% CI: 46.2-71.4), and overall survival 52.4 months (95% CI: 40.3-66.8). Favorable-risk patients compared to unfavorable-risk patients had longer systemic therapy–free survival (50.6 vs 11.1 months, $P < .01$), survival (25.2 vs 7.3, $P < .01$), and cancer-specific survival (71.4 vs 46.2 months, $P = .02$).

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Ethics Statement: This study received Institutional Review Board approval (IRB No. 16-199).

Author Contributions: Conception and design: SWR, SK, AS, JC, PR, AAH; Data analysis and interpretation: SWR, SK, AS, AX, LE, AO, SP, JC, RM, RRK, PR, MHV, AAH; Data acquisition: SK, AS, KV-R, AO, MHV, AAH; Critical revision of the manuscript for scientific and factual content: SK, AS, AX, LE, AO, JC, RM, RRK, PR, MHV, AAH; Drafting the manuscript: SWR, SK, AS, KV-R, AO, SP, PR, MHV, AAH; Statistical analysis: SWR, AS, AX, AO, SP, AAH; Supervision: LE, KV-R, AO, JC, RM, RRK, PR, AAH.

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Conclusions: Using risk stratification based on IMDC and number of metastatic sites, surveillance in favorable-risk patients can be utilized for a period without the initiation of systemic therapy. This approach can delay patients' exposure to the side effects of systemic therapy.

Key Words: carcinoma, renal cell; watchful waiting; cytroreduction surgical procedures; nephrectomy; metastasectomy

TREATMENT of metastatic renal cell carcinoma (mRCC) often involves complex management with cytoreductive nephrectomy (CRN) and systemic therapy.[1] With the advent of targeted therapy and immune checkpoint inhibitors, careful patient case selection for CRN is essential,[2] with evidence for benefit in patients with favorable- and intermediate-risk International mRCC Database Consortium (IMDC) score and good performance status.[3-5] CRN may exert its therapeutic effects by removing the major tumor burden responsible for host immune dysfunction and the release of cytokines and growth factors which can contribute to disease progression.[6-8] Additionally, CRN has been shown to improve modifiable IMDC factors[9] and prevent interruption in systemic treatment from bleeding and symptomatic tumor invasion of other organs.[7] In the postoperative period, a treatment strategy involving a period of surveillance prior to starting systemic therapy in mRCC can be a means to minimize therapeutic and financial toxicities associated with treatment.

Despite being a practice utilized in the contemporary management of patients with mRCC, this strategy remains understudied and there is currently a paucity of data to guide clinicians as to which patients may benefit from a period of surveillance after CRN prior to starting systemic therapy.[10] Thus, the aim of our study was to define the outcomes in a large series of patients with residual metastatic disease after CRN who underwent a period of surveillance and to define prognostic factors in this group of patients.

METHODS

Data Source and Patient Selection

We performed a retrospective review of all patients who underwent CRN at our institution between July 1989 and January 2020. We utilized our prospectively maintained institutional database to identify patients 18 years and older who had undergone CRN with residual metastatic disease and then were placed on surveillance. The decision to proceed with CRN as an initial management strategy was based on the discretion of the treating oncologist. Patients were excluded from the study if they had received prior systemic therapy. Patients were placed on surveillance at the discretion of their treating physician. Some patients additionally underwent local therapy to sites of metastatic disease and included surgical resection, thermal ablation, and/or targeted radiotherapy of specific metastatic recurrence sites. Surveillance was continued through the commencement of systemic intervention or death. Institutional Review Board approval (IRB No. 16-199) was obtained before data collection by the Memorial Sloan Cancer Center Institutional Review Board (New York, New York).

Outcomes

The study's primary end point was systemic therapy–free survival (ST-FS). We also examined a novel end point, intervention-free survival (IFS), defined as time on surveillance, measured as time from surgery to the first local therapy, systemic therapy, or death, with patients censored if alive and treatment-free at last follow-up. Patients were risk stratified based on IMDC risk factors and metastatic organ sites. Specifically, patients were considered favorable risk with $\leq$1 IMDC risk factor and $\leq$2 metastatic organ sites, a classification adapted from the one described by Rini et al for patients with mRCC placed on surveillance and for which we have used in this setting and will refer to as the Rini score.[11] We used this to further stratify patients as it was one of the few metrics that was associated with ST-FS on analysis. Secondary end points included IFS, cancer-specific survival (CSS), and overall survival (OS).

Statistical Analysis

Median follow-up was calculated via a reverse Kaplan-Meier method. Univariable Cox proportional-hazard regression analysis was performed to measure the association between clinical and tumor characteristics and ST-FS (Table 1). Time-to-event analyses were performed using the Kaplan-Meier method for outcomes of interest. A log-rank test was used to compare the differences between the outcomes in groups stratified by favorable and unfavorable risk groups (see Figure).

We used multivariable logistic regression analysis to identify factors that were associated with initiating a patient on up-front systemic therapy vs surveillance (Table 2). Variables included in the model were selected a priori based on clinically important variables in the management of patients with mRCC.

SAS Studio 5.2 was used for all statistical analyses. R version 4.2.1 and the *survival* and *survminer* packages were used to generate Kaplan-Meier curves.

RESULTS

Comparison of Patients Who Received Immediate Systemic Therapy vs Surveillance

From July 1989 to January 2020, we identified 414 patients who underwent up-front CRN. Of these patients, 92 (22.2%) underwent surveillance, 295 (71.3%) received immediate systemic therapy, and 27 (6.5%) did not have enough clinical information to be included in the study.

Patients who received immediate systemic therapy after CRN were younger (59.7 vs 66.8 years, $P < .01$), had a lower BMI (27 vs 29.4, $P = .04$), had a larger

Table 1. *Cox Univariate Analysis: Modeling Time to Systemic Therapy*

Clinical characteristics	HR (95% CI)	*P* value
Age	1.0 (0.97-1.03)	.9
Sex (ref = Male)	1.01 (0.56-1.84)	1.0
BMI	1.0 (0.95-1.06)	.9
KPS	0.99 (0.96-1.03)	.6
IMDC risk score		< .01
Favorable	ref	
Intermediate	0.70 (0.21-2.29)	
Poor	3.54 (1.03-12.17)	
Rini score		< .01
Favorable	ref	
Unfavorable	3.35 (1.82-6.15)	
Tumor characteristics		
Size (cm)	1.04 (0.97-1.11)	.3
Sarcomatoid features	1.40 (0.70-2.79)	.3
Clear cell histology (ref = nonclear histology)	1.05 (0.45-2.45)	.9
T-stage at time of cytoreduction		
T1/2	ref	.9
T3/4	0.96 (0.54-1.70)	
Metastatic sites		
Lymph node	0.79 (0.40-1.56)	.5
Bone	1.33 (0.72-2.44)	.4
Lung	1.49 (0.83-2.70)	.2
Viscera	0.77 (0.39-1.52)	.5
Number of metastatic sites	1.21 (0.85-1.73)	.3
Year of surgery	1.0 (0.95-1.04)	.8
Laboratory		
Calcium	6.02 (1.41-25.70)	.02
Hemoglobin	1.50 (0.87-2.53)	.1
Platelets	0.94 (0.40-2.22)	.9
CCI	0.95 (0.86-1.04)	.2
NLR	0.95 (0.88-1.03)	.2

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IMDC, International mRCC Database Consortium; KPS, Karnofsky Performance Status; NLR, neutrophil-to-lymphocyte ratio; ref, reference.

primary tumor size (9.5 vs 8.7 cm, $P < .01$) and had sarcomatoid features on final pathology (48.2% vs 17.4%, $P < .01$). Additionally, the immediate systemic therapy cohort had a lower proportion of clear cell histology (77% vs 89.1%, $P = .01$), had a higher T-stage at time of cytoreduction (86.1% vs 75.0%, $P = .02$), more often had lymph node (47.1% vs 20.7%, $P < .01$) and bone metastases (31.9% vs 20.7%, $P = .04$), and less frequently had only 1 metastasis (35.6% vs 62.0%, $P < .01$; Supplementary Table 1, https://www.jurology.com).

In our multivariable logistic regression model predicting likelihood of receiving immediate systemic therapy as opposed to being placed on surveillance after CRN, older patients had a lower odds of receiving immediate systemic therapy (OR: 0.95, 95% CI: 0.93-0.98, $P < .01$), while patients with sarcomatoid histology (OR: 4.05, 95% CI: 2.19-7.47, $P < .01$), and those with higher T-stage at time of CRN (OR: 2.87, 95% CI: 1.40-5.90,. $P < .01$) had a higher odds of receiving immediate systemic therapy. Treatment year was also associated with a smaller odds of receiving immediate systemic therapy, ie, with increasing years surveillance had a higher odds of being utilized as a management strategy (OR:0.92, 95% CI: 0.87-0.97, $P < .01$; Table 2).

Surveillance Cohort

Patients included in the surveillance cohort had advanced renal cell carcinoma (Table 3). Most patients had clear cell renal cell carcinoma (n = 82, 89.1%) and had a T-stage at time of cytoreduction of either 3 or 4 (n = 69, 75.0%). Pulmonary metastasis was the most common site of metastatic disease (n = 64, 69.6%), followed by lymph nodes (n = 19, 20.7%), bone (n = 19, 20.7%), and viscera (n = 17, 18.5%). Most patients (n = 57, 62.0%) on surveillance had a single organ with metastatic disease. Fourteen (15.2%) of patients received an adjunct intervention either prior to or near the time of CRN. Seventy-three patients (79.3%) underwent an intervention prior to the study's conclusion (Table 3) including radiation of metastatic sites 48 (53.3%), metastasectomy 22 (23.9%), and thermal ablation 3 (3.3%; Table 3).

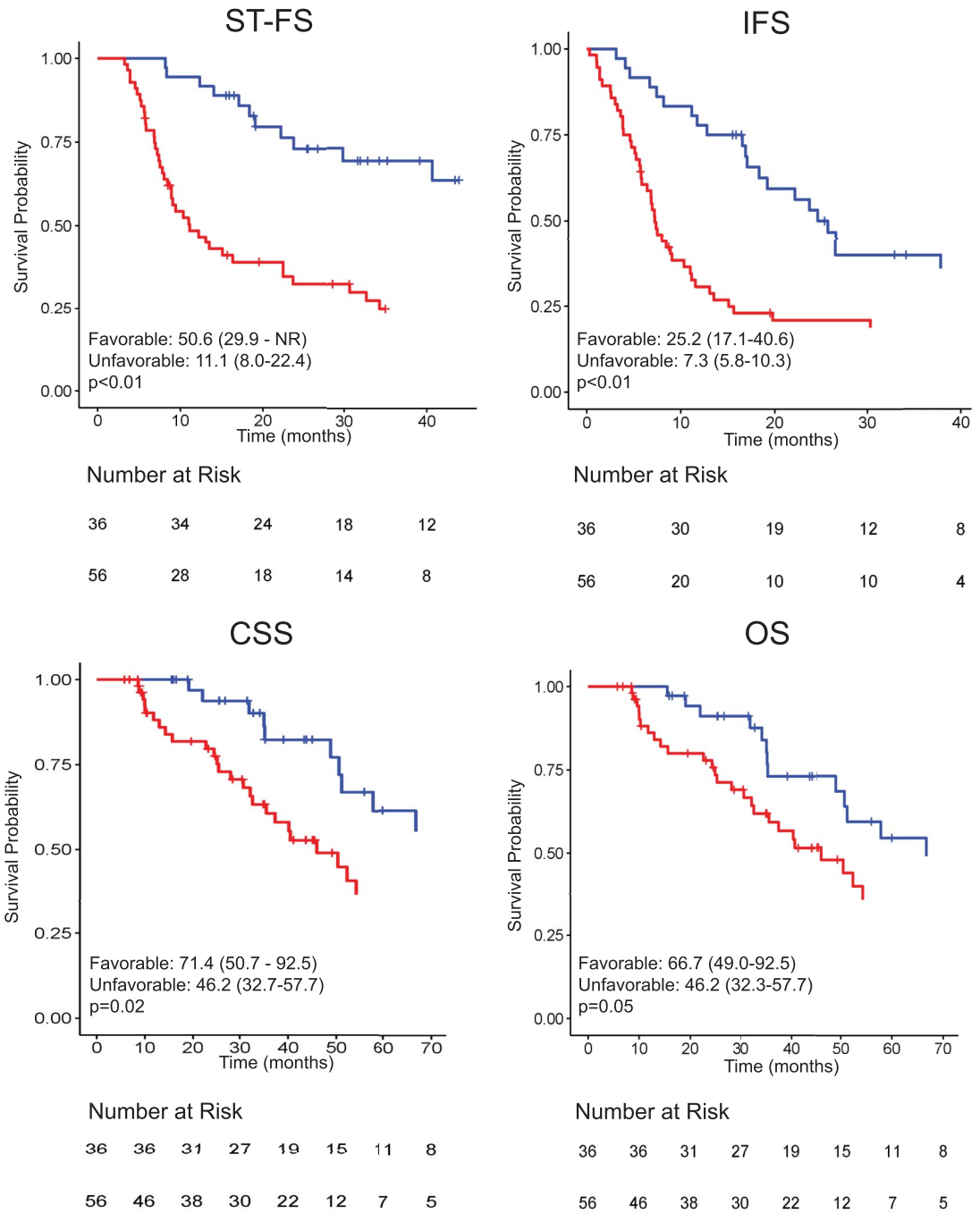
Analysis of Time-to-Event Outcomes

Patients were followed for a median of 54.8 months (IQR: 43.9-73.0). The median ST-FS was 23.6 months (95% CI: 15.1-40.6), IFS was 11.8 months (95% CI: 8.0-18.4), CSS was 54.2 months (46.2-71.4), and the OS was 52.4 (40.3-66.8). The number of events varied by group and included: ST-FS (57), IFS (74), CSS (44), and OS (49). In our Cox univariate analysis modeling time to systemic therapy, unfavorable Rini score (HR: 3.35, 95% CI: 1.82-6.16, $P < .01$), poor IMDC score (HR: 3.54, 95% CI: 1.03-12.17, $P < .01$), and elevated serum calcium (HR: 6.02, 95% CI: 1.41-25.70, $P = .02$) were the only variables associated with an increased time to receiving systemic therapy on surveillance (Table 1). When stratifying patients by favorable vs unfavorable risk groups, favorable-risk patients had longer median ST-FS, IFS, and CSS (ST-FS: 50.6 vs 11.1 months, $P \leq 0.01$; IFS: 25.2 vs 7.3 months, $P < .01$; CSS: 71.4 vs 46.2 months, $P = .02$; OS: 66.7 vs 46.2, $P = .05$; see Figure).

DISCUSSION

Herein we present an extensive experience with systemic therapy–naïve patients placed on surveillance after CRN with residual metastatic disease. Our cohort's median ST-FS was 23.6 months, IFS 11.8 months, and CSS 54.2 months. When stratified by Rini score, favorable-risk patients had significantly longer ST-FS, IFS, and CSS. Overall, our data support the possibility of an initial period of surveillance as a management option after CRN in this select group of patients.

mRCC can have a variable clinical course ranging from indolent to rapidly progressive, and prognosis is variable.[12] Our survival estimates are consistent with recent estimates of OS for patients with mRCC. For example, in the Checkmate 214 trial where approximately 80% of patients received a prior nephrectomy, median OS was 55.7 months in the experimental arm



Kaplan-Meier Survival Estimates: Median Event-Free Time (95%CI), Stratified by Rini Score.

Favorable Risk: IMDC ≤ 1 and ≤ 2 metastatic organ sites.

ST-FS: Systemic Therapy-Free Survival | IFS: Intervention-Free Survival | CSS: Cancer Specific Survival | OS: Overall Survival

Note: Kaplan-Meier curves are truncated when at-risk <10

Figure. Kaplan-Meier survival estimates for systemic therapy–free survival (ST-FS), intervention-free survival (IFS), cancer-specific survival (CSS), and overall survival (OS). IMDC indicates International mRCC Database Consortium; NR, not reached.

Table 2. *Multivariable Logistic Regression Examining Predictors of Receiving Immediate Systemic Therapy vs Surveillance*[a]

Variable	OR (95% CI)	*P* value
Age at surgery	0.95 (0.93-0.98)	< .01
Non–clear cell histology (ref = clear cell)	2.15 (0.95-4.86)	.06
Sarcomatoid histology	4.05 (2.19-7.47)	< .01
Stage T3/4 (ref = T1/2)	2.87 (1.40-5.90)	< .01
Number of met sites	1.90 (1.33-2.72)	< .01
Bone metastases	1.15 (0.59-2.23)	.7
Year	0.92 (0.87-0.97)	< .01

Abbreviations: CI, confidence interval; met, metastatic; OR, odds ratio; ref, reference.
[a]Models odds of receiving immediate systemic therapy.

which is similar to the median OS of 52.4 months in our cohort.[13] Older studies typically have shorter estimates of survival. For example, using the IMDC model, patients treated with anti–vascular endothelial growth factor therapy had an estimated OS of 22 months; 75% of favorable-risk patients were alive at 2 years, while intermediate-risk patients had an OS of 27 months and poor-risk patients had an OS of 8.8 months.[14] Highlighting the importance of patient selection for those undergoing CRN, results from the CARMENA and SURTIME trials demonstrated significantly lower estimates of OS in patients undergoing up-front CRN compared to our cohort, with a median OS less than 20 months.[15,16] Novel scores like the REMARCC score may be helpful in deciding who will do best after CRN.[17] Reasons for longer median CSS and OS times in our cohort may be a function of the utilization of newer therapeutics and careful selection of a subset of patients who are deemed fit enough for surgery and those who experience slower disease progression. Nevertheless, in the appropriately selected patient who undergoes CRN, our data support that a period of surveillance remains an option, and further that the patients with a favorable risk profile may do the best with this strategy.

Table 3. *Demographic and Clinical Information*

Clinical characteristics	AS cohort
Age, median (IQR), y	66.8 (11.7)
Male sex, No. (%)	69 (75)
BMI, median (IQR)	29.4 (6.1)
CCI, median (IQR)	6 (1)
KPS ≥80, No. (%)	86 (93.5)
IMDC risk score, No. (%)	
Favorable	4 (4.4)
Intermediate	67 (72.8)
Poor	21 (22.8)
Rini score, No. (%)	
Favorable	36 (39.1)
Unfavorable	56 (60.9)
Year of surgery, No. (%)	
2015-2019	33 (35.9)
2005-2014	44 (47.8)
1989-2004	15 (16.3)
Tumor characteristics, No. (%)	
Size (cm)	8.7 (4.8)
Sarcomatoid features	16 (17.4)
Clear cell	82 (89.1)
T-stage T3/4 at time of cytoreduction	69 (75.0)
Metastatic sites, No. (%)	
Lymph node	19 (20.7)
Bone	19 (20.7)
Lung	64 (69.6)
Viscera	17 (18.5)
Liver	2 (2.2)
Number of metastatic sites, No. (%)	
1	57 (62.0)
2	27 (29.4)
3	7 (7.6)
4	1 (1.1)
Interventions	
First-line focal interventions, No. (%)	
Radiation	48 (53.3)
Ablation	3 (3.3)
Metastasectomy	22 (23.9)
Adjunct interventions (perioperative period), No. (%)	14 (15.2)
First-line systemic therapy, No. (%)	
TKI/mTOR	44 (77.2)
Immunotherapy	4 (7.0)
Interferon	8 (14.0)
Other	1 (1.8)

Abbreviations: AS, active surveillance; BMI, body mass index; CCI, Charlson Comorbidity Index; IMDC, International mRCC Database Consortium; IQR, interquartile range; KPS, Karnofsky Performance Status; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.
Favorable risk: IMDC score ≤1 and ≤2 metastatic organ sites.

The use of surveillance as a treatment strategy in renal cell carcinoma has been adopted in clinical settings, with the acknowledgement that renal cell carcinoma has a variable presentation and clinical course, with the goal to minimize toxicities from systemic treatments and to target the treatment of those patients only with clinical disease progression. Our institution has a long history of using surveillance prior to initiating therapy in a select group of patients as well as using risk scores to determine prognosis.[18-21] The Motzer criteria[21] is one of the more widely used, however other work has been done to evaluate patients in other clinical settings. For example, Eggener et al found that those patients who recurred after local treatment could be risk stratified based on time to recurrence from surgery, serum hemoglobin, calcium, lactate dehydrogenase, and Karfonsky performance status.[22] Additionally, patients who underwent a metastasectomy demonstrated a survival benefit compared to those who did not.[22,23] Many of the patients in this cohort underwent local treatment and could help explain the long survival times. This paper extends the risk stratification of patients with mRCC to that after cytoreduction and helps clarify which patients may benefit most from a period of surveillance in this clinical scenario.

Surveillance as an initial management strategy has been evaluated in a handful of series in patients after cytoreduction and in the metastatic setting and estimates of survival are consistent with our findings. One study of 15 patients from the National University Hospital, Singapore, found in a series of patients undergoing CRN and then surveillance that at 18 months, 80% of the patients had demonstrated evidence of clinical progression.[24] Other studies examining mRCC patients on surveillance protocols echo similar findings

with respect to OS and ST-FS.[25-29] In general, estimates of clinical outcomes in this patient cohort tend to be longer than expected, suggesting that longer time-to-event in our cohort and other groups studying this patient population likely reflects a subset of metastatic patients with less aggressive disease compared with the average patient with mRCC. Additionally, it suggests that there is a group of patients with relatively indolent disease who can be safely monitored prior to initiating systemic therapy.

Rini et al completed a prospective phase 2 trial of 52 patients placed on surveillance in a cohort of mRCC patients.[11] The primary end point was ST-FS and found, like us, that a select group of patients did well with surveillance. Indeed, median time on surveillance was slightly shorter than in our cohort of patients at 14.9 months, however some patients continued surveillance beyond 2 years. Rini et al identified prognostic risk criteria for time on surveillance as IMDC scores $\leq$1 and $\leq$2 metastatic organ score. Similarly, we found this criterion useful in predicting a group of favorable-risk patients with longer ST-FS, IFS, and CSS. Favorable-risk patients in our cohort initiated systemic therapy at a median time of 49.8 months compared to their finding of 22.2 months, however, in our cohort, our patients were more likely to undergo local treatment which may be the reason for delay in systemic therapy. Other differences in outcomes may reflect the fact that the cohorts were different, as all our patients had up-front CRN and many patients in our cohort had local therapy prior to progressing to systemic therapy. Regardless of the difference, it appears that using the criteria of IMDC scores $\leq$1 and $\leq$2 metastatic organ sites to risk stratify patients is a useful tool when considering whether to place patients on surveillance vs initiate immediate systemic therapy.

Our paper is not without limitations. Retrospective data make it challenging to define the cohort of patients in whom pursuing surveillance would be a safe and reasonable strategy. Additional points of stratification, including a more precise interpretation of tumor biology, could help further classify patients into suitable treatment paradigms. For example, a recently published paper proposed a 2-factor model that predicted time on surveillance in a cohort of patients with mRCC based on genomic alterations in TP53 and SMARCA4.[30] Whether this extrapolates to a large cohort remains to be seen, however such strategies will be important in future lines of work to accurately risk stratify patients. Additionally, we relied on clinician intuition about treatment decisions and thus could not prospectively and/or more precisely define the criteria about starting a patient on surveillance vs initiating focal treatment or systemic therapy.

CONCLUSIONS

Our study supports the use of a period of initial surveillance in patients with mRCC after CRN for a carefully selected subset of patients with residual disease. Our data also support risk stratifying patients into favorable vs unfavorable groups as an aid to identify which patients are most suitable for this approach. Surveillance in the metastatic setting may serve as a harm reduction and cost containment management strategy that can reduce treatment-related toxicity and improve near-term quality of life. Future directions may include more precisely defining which patients are likely to benefit from surveillance through molecular signatures and clarifying the optimal timing of when to initiate systemic therapy, especially in the era of immune checkpoint inhibitors.

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EDITORIAL COMMENT

Metastatic renal cell carcinoma (mRCC) can show a variable clinical course. Delaying systemic therapy in patients with residual M1 disease after up-front cytoreductive nephrectomy (CN) is intriguing, yet potentially hazardous.

In this retrospective study, among 414 patients selected for up-front CN over a 30-year period, 92 (22%) were followed by surveillance and experienced a median systemic therapy (ST)–free survival of 23.6 months, intervention-free survival of 11.8 months, and cancer-specific survival of 54.2 months.[1] Stratified by the Rini score, favorable-risk patients had significantly longer median ST-free survival (50.6 vs 11.1 months), intervention-free survival (25.2 vs 7.3 months), and cancer-specific survival (71.4 vs 46.2 months).

The study incepts the seed of a fascinating idea. However, the complexity of mRCC and the caveats of the study (selection bias, confounding, long time frame) leave us with questions rather than answers.

From biological and clinical standpoints, who are the best candidates for surveillance after up-front CN? What is the best trade-off between the risk of undertreatment and the risk of toxicity from ST? Are the results of the study applicable to contemporary clinical practice?

Notably, ST for mRCC has dramatically evolved during the last decades[2]; therefore, comparing patients treated with CN followed by surveillance vs immediate ST may be conceptually misleading.

The influence of meticulous patient selection in this study is reflected by survival outcomes which were far more favorable as compared to the CARMENA and SURTIME trials.[2] In addition, the purpose and prognostic impact of metastases-directed therapy in patients placed on surveillance remained elusive and warrant further investigation, considering the remarkable evolution of multimodal treatment of metastases in the field of mRCC.[3]

Nowadays, patients with residual disease after CN should be considered for ST. As such, given the current role of up-front CN,[2] the appealing results of the study might be reasonably applied only to highly selected scenarios within the oligometastatic renal cell carcinoma space.

Taken together, the thought-provoking findings reported by Reese et al question whether "less is more" could be safe (at least for a period) in favorable-risk patients after CN, when the risk-benefit trade-off between cancer progression and toxicity from ST is more nuanced.

While the Rini score could be a promising tool for risk stratification, prospective clinical trials and reliable biomarkers are needed to cautiously

integrate surveillance into contemporary decision-making schemes for mRCC.

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REPLY BY AUTHORS

We very much appreciate the insightful commentary by Campi et al and encourage discussion around management strategies in patients with metastatic renal cell carcinoma who undergo surgery. Although at first glance the notion that a period of close surveillance in a patient after cytoreduction may be antithetical to the treating physician, we very much argue that in the appropriate patient this can be an optimal strategy and is supported by management guidelines.[1] Indeed, the very spirit of our paper attempts to confirm and further delineate who might be best served by this strategy.[2]

A balance must be struck between the desire for active intervention in the setting of stage IV disease and the potential benefit of delayed therapy, including improved quality of life and minimization of therapy-related toxicities. Although immune-checkpoint inhibitors are currently our best weapon against metastatic renal cell carcinoma, toxicity remains an important consideration. Indeed, in Checkmate-214, 46% of patients demonstrated grade 3 or 4 toxicities, and there were 8 treatment-related deaths,[3] and in the recently published COSMIC-313, rates of adverse events were even higher.[4]

Although there is theoretical concern that by delaying systemic therapy this strategy may lead to suboptimal results, we currently do not have evidence that immediate administration of systemic therapy leads to improved overall survival outcomes in this patient population. On the contrary, as previously noted, we report excellent survival outcomes, very much an indication that in the right patient, at the right time, close surveillance does not appear to compromise a patient's safety or survival. And to the point that this strategy is an anachronism of a bygone era, we only need to point to the finding that this strategy has been adopted with increasing frequency over the years at our institution.

As always, when engaging in such calculus, we cannot stress enough that sound medical decision-making rests on the bedrock of careful patient selection and a strong physician-patient relationship. As we look to the future, an exciting prospect would be the identification of translational signatures to help further risk stratify patients beyond the current selection factors put forth in our paper. Until then, may we offer the using the Rini score and the great wisdom of time to guide decision-making?

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