

A Prospective Phase II Trial of Active Surveillance in Metastatic Renal Cell Carcinoma

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Research in Context

Evidence before the study:

The biology of metastatic renal cell carcinoma (mRCC) can include patients with indolent progression of disease. Prior case series have documented that some of these patients can be observed prior to the start of systemic therapy. These series, however, were small and retrospective introducing significant bias.

Added value of this study:

The present study is the first prospective assessment of this strategy and demonstrates that some patients with metastatic RCC can be safely observed prior to the start of systemic therapy, many of them for months to years. Clinical characteristics of patients for whom surveillance was a successful strategy were identified, including limited sites of metastatic disease and few adverse prognostic factors. Importantly, CNS progression emerged as a concern, and these data inform a surveillance strategy by suggesting that CNS imaging should be performed routinely during surveillance. Importantly, the present dataset indicates that quality of life, anxiety and depression are not worsened by this approach. Exploratory analysis found that the subpopulation experiencing a long time on surveillance was characterized by a more favorable immune cell repertoire.

Implications of all the available evidence:

Taken together with published retrospective experience, the present study establishes that select patients with mRCC can have prolonged time to cancer

progression with surveillance prior to initiating systemic therapy. Additional experience is necessary to understand the risks and benefits of this approach.

Abstract

Background: A subpopulation of metastatic renal cell carcinoma (mRCC) patients demonstrates indolent growth of metastases. Because of the toxicity and non-curative nature of systemic therapy, select patients may benefit from initial active surveillance. A phase II trial of active surveillance was undertaken in mRCC to characterize the time to initiation of systemic therapy.

Methods: Patients with treatment-naïve, asymptomatic mRCC were enrolled on a prospective phase II trial. Radiographic assessment was performed at baseline, every 3 months for year 1, every 4 months for year 2, then every 6 months. The primary endpoint of the study was time to initiation of systemic therapy. Secondary endpoints included assessment of quality of life, depression/anxiety and peripheral blood immune repertoire. All analyses were per protocol.

Findings: Fifty-two patients were accrued. The median time on surveillance from registration until initiation of systemic therapy was 14.9 months (95% C.I. 10.6-25.0). The median change in tumor burden was 1.3 cm (95% C.I. 0.6-1.8) with a median growth rate 0.09 cm/month (95% C.I. 0.04-0.17). An increased number of International Metastatic Database Consortium (IMDC) adverse risk factors and an increased number of metastatic disease sites were associated with a shorter surveillance period. Quality of life, anxiety and depression did not worsen over

the surveillance period. Patients had a favorable immune cell repertoire at baseline which did not significantly change over the surveillance period.

Interpretation: A subset of mRCC patients can safely undergo surveillance before starting systemic therapy.

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INTRODUCTION

Antiangiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway including sunitinib, sorafenib, and pazopanib, axitinib and bevacizumab benefit patients with metastatic RCC (mRCC), producing objective responses and extending progression-free survival (PFS) and overall survival (OS).¹⁻⁴ Although these agents are considered standard of care for mRCC patients, they are not curative. Further, disease control necessitates chronic therapy, and thus the benefits must be weighed against the overall burden of treatment including toxicity, time commitment and cost.

A subset of patients with mRCC have indolent growth of metastases. This is well-appreciated in clinical practice and reflected by the fact that some patients who present with limited volume oligometastatic disease are successfully managed with surgical resection (metastasectomy). This approach leads to approximately 30% of patients remaining disease-free at 5 years.⁵ There are, however, limited prospective data regarding the natural history of mRCC and the safety of active surveillance as an initial strategy. One study from the late 1980s described a prospective cohort of 73 patients with mRCC who underwent initial observation with radiographs repeated monthly until progression, at which time patients were treated with Bacillus Calmette–Guérin (BCG), mitoxantrone or interferon.⁶ Ten percent of patients had not progressed by 12 months, identifying a subset of patients with slow growth of metastases. Among the cohort who received subsequent interferon, an objective response rate (ORR) of 14% was observed,

identical to the response rate in mRCC patients who receive immediate interferon treatment. These limited data generate the hypothesis that some mRCC patients can safely undergo initial surveillance without compromising response to subsequent systemic therapy. Although current agents have greater activity than interferon alpha, toxicity can be substantial and the drugs can be cost-prohibitive for many patients and health systems. To further define the feasibility and safety of an initial active surveillance approach in the era of modern targeted therapy, a prospective trial was undertaken.

METHODS

Study Design and Participants

Patients 18 years or older (no upper age limit) with histologically- or cytologically-confirmed RCC of any histologic subtype were enrolled. There were no performance status parameter eligibility criteria, but all patients must have been asymptomatic from mRCC. All patients had measurable or evaluable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0.⁷ Patients may have had first documentation (radiographic or histologic) of mRCC up to 12 months prior to registration on study. Patients must not have received any prior systemic therapy for RCC in any setting. Prior radiotherapy (including radiotherapy for central nervous system metastases) and prior surgery (nephrectomy and/or metastasectomy) were permitted but not required. There were no laboratory parameters or comorbidities specified for eligibility. The decision to enroll the patient on study and thus choose active surveillance over immediate systemic therapy was jointly made by the patient and treating physician. The trial was approved by the institutional review board or ethics committee at each institution and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent.

Procedures

Patients underwent a CT scan of the chest, abdomen and pelvis (with contrast if possible) at baseline, every 3 months during year 1, every 4 months during year

2 and every 6 months thereafter. Tumor burden calculation and assessment of objective response and progression was performed by the investigator according to RECIST version 1.0.⁷ Per RECIST guidelines, intravenous contrast agents were given unless contraindicated for medical reasons (e.g. baseline renal dysfunction from prior nephrectomy). Bone scan and CT scan of the brain were required within 12 months of baseline, and afterwards only if abnormal or if clinical signs/symptoms developed. Clinical assessments including ECOG performance status and laboratory evaluation including a complete blood count and serum chemistry were performed at baseline and at each CT scan time point. Patients continued on study until initiation of systemic therapy for mRCC at the discretion of the treating physician and patient. Patients were not required to discontinue surveillance for RECIST-defined disease progression.

Two questionnaires were administered at baseline and at each CT scan time point; the Functional Assessment of Cancer Therapy – Kidney Cancer Index Disease-Related Symptoms (FKSI-DRS), a validated tool developed to measure disease-related toxicity, and the Hospital Anxiety and Depression Scale (HADS) which estimates the severity of anxiety and depression.^{8,9,10} Peripheral blood mononuclear cells were collected at baseline and at each CT scan time point for isolation of immune cell subsets as previously described.¹¹

Outcomes

Time to initiation of systemic therapy was defined as the time from registration on study to the first day of systemic treatment. Change in tumor burden and time to

progression (time from registration to first meeting progressive disease criteria or last follow up) were assessed per RECIST v1.0 criteria using investigator measurements at all CT scan time points. Overall survival was assessed from registration on study to death or last follow up. Changes in quality of life were assessed using FKSI-DRS, where a change of 3 points or greater is considered significant, and anxiety/depression using the HADS, in which scores ≥ 8 indicate the particular condition. Immune repertoire changes were defined as changes in the absolute number of pre-defined peripheral blood immune cell subsets including myeloid-derived suppressor cells, regulatory T cells and interferon gamma-producing CD3⁺ and CD4⁺ T cells.

Statistical Analysis

The primary endpoint of the study was time from the start of surveillance to initiation of systemic therapy. Secondary endpoints included absolute and relative changes from baseline in tumor burden, time to progression, overall survival, changes in quality of life, anxiety and depression and changes in immune repertoire. The accrual goal was set at 50 eligible and evaluable patients in order to estimate the proportion of patients who discontinued surveillance within a specified time (e.g. 12, 18, 24, or 36 months) with 95% confidence intervals that had maximum half-widths of 0.14. Fifty patients also provided statistical power >80% (based on a 2-sided Wilcoxon signed rank test with 5% type I error) to detect changes >0.5 standard deviations in secondary endpoints. The trial was multicenter and therefore the timing of its closure accommodated

each participant's internal processes. To be conservative, trial closure began close to the accrual goal in anticipation that some lead time would be needed by the participants. As a result the final accrual was 52 patients. In addition to assessing changes in immune repertoire in the trial patients, comparisons to two other external cohorts were also performed, one consisting of healthy control subjects and one consisting of patients with mRCC who immediately began systemic treatment previously described.¹¹ Categorical data were summarized as frequency counts and percentages; measured data were summarized as medians and interquartile ranges (IQR). Time-to-event data were summarized using the Kaplan-Meier method. The log rank test and Cox proportional hazards model, and the Wilcoxon signed-rank test and rank sum test were used for univariable analyses of time-to-event data and secondary endpoints, respectively. Proportional hazards models were also used for multivariable analyses of time-to event data. For the multivariable models factors were initially considered if they were statistically significant at $p=.10$ in univariable analysis. Stepwise variable selection with $p=.10$ and $.05$ as the criteria for entry and retention in a model was then used to determine which, if any were independent predictors. SAS version 9.2 (SAS Institute, Cary N.C.) was used for all statistical analyses.

RESULTS

Patients

Between 21 August 2008 and 7 June 2013, 52 patients with mRCC were enrolled. Four patients were excluded from all analyses; three for early withdrawal of consent and one due to ineligibility (non-metastatic disease). Demographics and baseline characteristics were typical of an advanced RCC population with a good performance status and predominantly intermediate International Metastatic Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk scores (Table 1). Patients had typical sites of metastases, with most patients having one organ involved with metastases and a relatively low baseline tumor burden.

Clinical Outcomes

The median follow-up is 38.1 months (IQR 29.4-48.9 months). The median time on surveillance was 14.9 months (95% C.I. 10.6-25.0 months; Figure 1). The percentage (95% CI) of patients remaining progression-free at 12, 18, 24 and 36 months was 41% (27-55%), 22% (11-34%), 17% (8-30%), and 11% (3-24%), respectively. Excluding patients who underwent resection during the surveillance period, the median absolute change in tumor burden during surveillance was 1.3 cm (95% C.I. 0.6-1.8 cm); relative change +31% (95% C.I.14-50%) with a median growth rate of 0.09 cm/month (95% C.I. 0.04-0.17 cm/month). Thirty-nine patients (81%) have come off surveillance, 37 due to disease progression. Overall, 43 patients demonstrated RECIST-defined disease progression (PD), 20

of whom continued surveillance after meeting criteria for RECIST PD. Fourteen of these patients have since initiated systemic treatment while 6 continue on surveillance (Figure 2). The median additional surveillance period for these 20 patients was 15.8 months (95% C.I. 3.0-24.1 months). The median time to RECIST-defined disease progression for the entire cohort was 9.4 months (95% C.I. 7.4-13.4 months). Disease progression occurred as growth in existing sites of metastases in 32 (74%) patients, new sites of disease in 8 (19%), and both a worsening of existing sites plus new sites in 3 (7%). New sites of disease were noted in the lung (n=4), lymph nodes (n=2), bone (n=2), and central nervous system (n=2). Except for the two patients who developed CNS metastases, no patient had symptomatic progression during the surveillance period. The estimated median overall survival from the start of surveillance is 44.5 months (95% C.I. 37.6-not reached) with 22 (46%) patients having died, all from metastatic RCC.

In univariable analysis of the factors in Table 1, the duration of active surveillance was associated the number of organs with metastases (1 versus 2 versus >2, $p=.024$), the location of the metastases (lung only versus non-lung only versus both, $p=.028$), and the number of IMDC ($p=.021$) and MSKCC ($p=.018$) risk factors, but not the associated prognostic groups themselves ($p.4-5$ in the Supplementary Appendix). In multivariable analysis, however, only the number of involved organs ($p=.041$) and number of IMDC risk factors ($p=.040$) were independently prognostic ($p.6$ in the Supplementary Appendix). Based on this

analysis, two prognostic groups were identified through use of a recursive partitioning algorithm – a favourable group consisting of patients with 0 or 1 IMDC risk factors and ≤ 2 organs involved with metastatic disease, and an unfavourable group consisting of all other patients (i.e. more than 1 IMDC risk factor and/or more than two organs with metastases). The favorable group comprised 29 (60%) study patients and had an estimated median surveillance time of 22.2 months (95% C.I. 13.8-33.3 months) while the unfavorable group (19 (40%) patients) had an estimated median surveillance time of 8.4 months (95% C.I. 3.2-14.1 months), $p=.0056$ (Figure 3). Additionally, 10 patients stopped surveillance within 6 months of registration. Baseline characteristics of this short surveillance population that were distinct from the overall population included Karnofsky performance status of 80%, presence of sarcomatoid dedifferentiation in the primary tumor, a greater number of adverse IMDC risk factors and a greater baseline tumor burden.

Univariable and multivariable analyses were also performed for time to progression. The results of the univariable analysis and were similar to those above. In multivariable analysis the number of IMDC risk factors was the only independent prognostic factor (p.4-5 Supplementary Appendix).

Seven patients underwent local therapy during the surveillance period between 7-31 months after registration on study. Six patients underwent resection of metastatic disease (adrenal, $n=2$; renal mass, $n=2$; renal vein thrombosis, $n=1$; abdominal mass, $n=1$), and one patient had radiation to bone disease. Pathology on all resected specimens confirmed metastatic RCC. No patient underwent local

therapy due to symptomatic progression of a lesion. Rather, local therapy was undertaken because other lesion(s) initially felt to be consistent with metastatic RCC did not change during the surveillance period, and thus local therapy to a solitary metastatic site was pursued, consistent with standard clinical practice in metastatic RCC. If local therapy was considered a surveillance failure, however, the median surveillance period is 14.2 months.

Data regarding subsequent systemic therapy are available for 31 of the 39 patients who discontinued surveillance. Most patients received therapy with pazopanib (n=11, 33%), or sunitinib (n=11, 33%). Three patients (9%) received pazopanib or sunitinib in combination with an investigational agent. Other treatments included temsirolimus (n=2, 6%); and axitinib, bevacizumab, nivolumab plus ipilimumab, and celecoxib plus interferon (one patient each). One patient developed brain metastases and died without receiving systemic therapy. Objective responses were documented in 10 (32%) patients who received systemic therapy. The median OS from the start of surveillance for patients who received systemic therapy was 38.6 months (95% C.I. 30.1-not reached).

Quality of life and anxiety/depression

At baseline, seven of 44 patients (16%) had anxiety (scores of ≥ 8) and two patients (5%) had depression (scores ≥ 8) on the HADS questionnaire. Anxiety and depression scores did not change significantly over the period of surveillance (Table 2). Similarly, FKSI scores did not change significantly compared to baseline.

Immune Cell Repertoire

When compared to a separate healthy control population, surveillance patients had a greater number of myeloid-derived suppressor cells (MDSC), fewer regulatory T cells (Treg) and a similar number of IFN-gamma-producing T cells (p.7 in Supplementary Appendix). In addition, compared to a separate cohort of mRCC patients who began immediate systemic therapy¹², the active surveillance group was characterized by significantly fewer MDSC and Treg, with a significantly greater number of IFN-gamma-producing T cells, potentially indicating a less immunosuppressive environment in the surveillance cohort. None of the measured immune cell parameters changed significantly over time in the surveillance cohort or were associated with length of surveillance.

Discussion

The present prospective trial in metastatic RCC patients demonstrates that active surveillance is a viable initial strategy in select patients prior to systemic therapy, with a median surveillance period of greater than one year. No adverse effects in regards to quality of life or anxiety/depression were observed. Patients considered for this approach should have fewer adverse prognostic features and limited organ sites of metastases. Metastatic renal cell carcinoma is a disease characterized by a variable natural history. Numerous prognostic schemas have been developed, with the overall survival of treated patients ranging in poor to good risk patients from 5 to 30 months with interferon-based therapy and from 7 to 43 months with VEGF-targeted therapy.^{13,14} This six-fold difference across the range of outcome highlights the diverse underlying biology of metastatic RCC with or without systemic therapy.

To our knowledge, prospective evaluation of surveillance had previously been lacking. A small, retrospective series (n=15) reported metastatic RCC patients observed after debulking nephrectomy.¹⁵ The median time to disease progression after surgery was 8 weeks, with three patients (20%) progression-free beyond 18 months. A more recent retrospective series (n=62) noted an initial observation period of 18.7 months in a patient population which included 63% IMDC favorable risk patients.¹⁶ A retrospective series of 29 mRCC patients of exclusively IMDC good and intermediate risk patients reported a PFS of 26.1 months with only 9 patients receiving systemic therapy.¹⁷ An additional retrospective series (n=58) reported a median time to disease progression of

12.4 months.¹⁸ Multivariable analysis revealed that performance status < 100%, liver metastases and time from diagnosis to the start of surveillance < 1 year were associated with a shorter time to progression. The present data utilizing a prospectively-defined restaging interval provides a more confident estimate that the median surveillance time in select patients is greater than one year, and can be up to several years in length. Further, a subset of the most favorable patients as defined by 0-1 adverse IMDC risk factors and at most 2 sites of metastatic disease demonstrated a nearly two year surveillance period.

An initial surveillance approach has been prospectively investigated in other malignancies. A trial in low tumor burden follicular lymphoma randomized asymptomatic patients to observation, prednimustine or interferon, demonstrating a freedom-from-treatment interval of 24 months in the observation group and identical overall survival to the initial therapy groups.¹⁹ A more recent study randomized low tumor burden follicular lymphoma to initial observation versus rituximab.²⁰ The estimated median time to starting therapy in the observation group was 31.1 months, with 46% not needing treatment at 3 years and no difference in overall survival. The vast majority of patients had normal baseline scores for anxiety and depression on the HADS questionnaire which did not worsen over time, similar to this RCC cohort. There were significant improvements in the rituximab treatment group in the Mental Adjustment to Cancer scale and the Illness Coping Style scale compared to observation, suggesting some emotional benefit to patients with immediate therapy. The present study measured anxiety, depression and quality of life, with the major

finding being a lack of depression or anxiety at baseline or over the surveillance period, and no negative effect on quality of life.

A subset of patients in this study underwent metastasectomy during the surveillance period. These patients often had multiple suspected metastatic sites at baseline, but over time only one abnormality grew definitively, suggesting that other lesions (e.g. small lung nodules) may not be metastatic RCC. Thus, a period of surveillance in the setting of limited RCC metastases can help select patients in whom metastasectomy may be most appropriately applied. Additionally, initial surveillance may be of benefit in cases where metastases are presumed but not definitively diagnosed, thus avoiding unnecessary treatment of initially equivocal and ultimately benign lesions.

As a gross measure of immune competence, peripheral blood was analyzed for major cellular components including MDSC, regulatory T cells and IFN-gamma-producing T cells. This analysis revealed that surveillance patients had significantly fewer immunosuppressive cells and greater interferon gamma-producing T cells. This phenotype, which would favor an anti-tumor immune response, can be hypothesized to contribute to the relatively indolent nature of tumor growth in these patients. The interaction of this immune phenotype with immunotherapeutics is unknown and requires further study.

The present data should be interpreted in light of other therapeutic options in this disease. High-dose interleukin-2 (IL-2) is an approach also applied to a very select subpopulation of RCC. A recent prospective trial in a population with 19%

MSKCC good risk and 70% intermediate risk patients reported a median PFS of 4.2 months, with 13 patients (11%) progression-free at 3 years and an overall survival of 42.8 months.²¹ The percentage of patients progression-free at three years in the IL-2 trial is identical to the current cohort on active surveillance. Nevertheless, there is an established opportunity for long-term cancer-free survival with IL-2, making this an appropriate strategy for a subset of metastatic RCC patients. A phase 3 trial of sunitinib versus pazopanib in metastatic RCC patients (27% good risk and 58% intermediate risk per MSKCC criteria) reported a median PFS of 9 months and an overall survival of 29 months.¹ The present cohort with a similar distribution of good and intermediate risk patients has comparable clinical outcomes, with the important caveat that patients enrolled on the current trial were highly selected and no direct comparison can be drawn with regards to long-term survival.

This study has several limitations. Patients considered for inclusion in this study were a highly-selected population, with disease characteristics such as tumor burden or pace of disease growth not prospectively defined. Rather, clinical judgement of the treating physician guided which patients were considered for enrollment. It was not possible to more strictly define eligibility criteria in regards to features such as burden or pace of disease given the lack of previous prospective data in this regard. It was felt reasonable to allow the clinician to make a decision to offer enrollment, in the hopes that insight into such features could be elucidated by the present study. Further, the decision to end surveillance and begin treatment was not mandated per objective criteria, rather

left to physician and patient discretion. These study features limit the applicability of this approach. Nonetheless, prospective assessment of this strategy in select metastatic RCC patients provides guidance for physicians in selecting appropriate patients and supports the viability of this approach. Another limitation is the frequent use of non-contrast scans in this population of patients with baseline renal dysfunction due to prior nephrectomy. This could limit the sensitivity of detection of new or worsening disease in certain organs and thus affect determination of progression, although small lesions missed on a non-contrast scan would be unlikely to affect the decision to continue surveillance or not. The number of patients in the final analysis was less than originally planned, although this did not meaningfully affect the statistical considerations. Although anxiety did not increase in this study cohort, three patients withdrew consent early. Thus it is possible that anxiety over surveillance led to this decision, although the specific reason for consent withdrawal is not known. Immune parameters measured did not include the tumor cell infiltrate, and thus are at best an indirect measure of the anti-tumor immune competence of patients. Importantly, two patients under surveillance developed new central nervous system metastases. While baseline CNS imaging was required, CNS imaging during surveillance was not mandated. As a result of this experience, all patients remaining on trial are undergoing annual CNS imaging and this should be incorporated into future active surveillance protocols in RCC.

In conclusion, the present study suggests that active surveillance as an initial strategy in select patients with metastatic renal cell carcinoma is safe, and is

associated with an extended period free of systemic therapy in many patients. For these select patients, active surveillance may be the optimal approach, avoiding the certain toxicity of systemic therapy without clearly compromising the benefit of therapy when initiated. Appropriate selection of patients and adequate monitoring, which should include CNS surveillance, is critical in application of this approach. Additional investigation into the risks and benefits of surveillance with the development of novel therapies is warranted.

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Table 1. Baseline demographics and clinical characteristics

Characteristic (n=48)	
Age, years	
Median (interquartile range; IQR)	67 (62-75)
Gender	
Male	36 (76%)
Female	12 (24%)
Karnofsky performance status	
100	30 (63%)
90	15 (31%)
80	3 (6%)
Histology ^a	
Clear cell	46 (96%)
Chromophobe	2 (4%)
Sarcomatoid dedifferentiation ^b	6 (13%)
Median (IQR) time from diagnosis to metastatic disease (months)	5.1 (0.7-25.7)
Prior nephrectomy	47 (98%)
IMDC risk factors ²²	
0 (favorable)	11 (23%)
1–2 (intermediate)	36 (75%)
3 or more (poor)	1 (2%)
MSKCC risk factors ^c	

0 (favorable)	11 (24%)
1–2 (intermediate)	35 (76%)
Site of metastatic disease ^d	
Lung	34 (71%)
Lymph Nodes	12 (25%)
Bone	10 (21%)
Kidney	9 (19%)
Adrenal	6 (12%)
Liver	2 (4%)
Number of organ sites with metastases	
1	25 (52%)
2	15 (31%)
3	6 (13%)
4	2 (4%)
Median (IQR) Tumor Burden at Baseline (sum in centimeters of RECIST tumor measurements) ^e	3.2 (1.5-6.7)

^a Histology determined by nephrectomy in all patients except for one, in which it was determined by renal mass biopsy.

^b Missing for 3 patients; patients with sarcomatoid dedifferentiation are also counted according to underlying histology and thus the total for histology sums to > 100%.

^c Missing for 2 patients

^d Percentages sum to >100% because some patients had >1 organ with metastases

^e 43 patients had measurable disease

Table 2: Anxiety/Depression and Quality of Life Questionnaire Scores

A. Hospital Anxiety and Depression Scale – Anxiety^a

	N	Median (IQR) Score	Median (IQR) Change from Baseline	p^b	No. patients with a score ≥8
Baseline	44	3 (1-5)			7 (16%)
Month 6	32	2 (1-5)	0 (-2 - 1)	.53	5 (16%)
Month 12	22	3 (1-6)	0.5 (-2 - 1)	.86	4 (18%)
Final Assessment	29	3 (1-5)	-1 (-2 - 1)	.14	3 (10%)

B. Hospital Anxiety and Depression Scale – Depression^a

	N	Median (IQR) Score	Median (IQR) Change from Baseline	p^b	No. patients with a score ≥8
Baseline	44	1 (1-5)			2 (5%)
Month 6	32	1 (0-3)	0 (-2 - 1)	0.11	1 (3%)
Month 12	22	2 (1-4)	0 (-2 - 1)	0.52	2 (9%)
Final Assessment	29	2 (1-3)	0 (-2 - 1)	0.87	2 (7%)

C. Functional Assessment of Cancer Therapy–Kidney Cancer Index Disease-Related Symptoms

	N	Median (IQR) Score	Median (IQR) Change from Baseline²	p^b	No. of patients with ≥ 3 point change^c	No. of patients with improvement (≥3 point decline)	No. of patients with decline (≥3 point increase)
Baseline	44	3 (0-14)					
Month 6	32	3 (0-16)	0 (-8 - 4)	.76	10 (31%)	6 (19%)	4 (12%)

Month 12	22	3 (0-13)	0 (-5 -10)	.52	10 (45%)	4 (18%)	6 (27%)
Last Assessment	28	4 (0-22)	1 (-7 -16)	.46	16 (57%)	8 (29%)	8 (29%)

^a Scores ≥ 8 on a subscale indicate anxiety or depression

^b Wilcoxon signed rank test

^c A change of ≥ 3 points is considered significant²³

Figure 1: Kaplan-Meier curves for time on active surveillance (A), progression-free survival (B), and overall survival (C) Tick marks are censored patients. *22 patients died, two were lost to follow-up, and two withdrew consent.

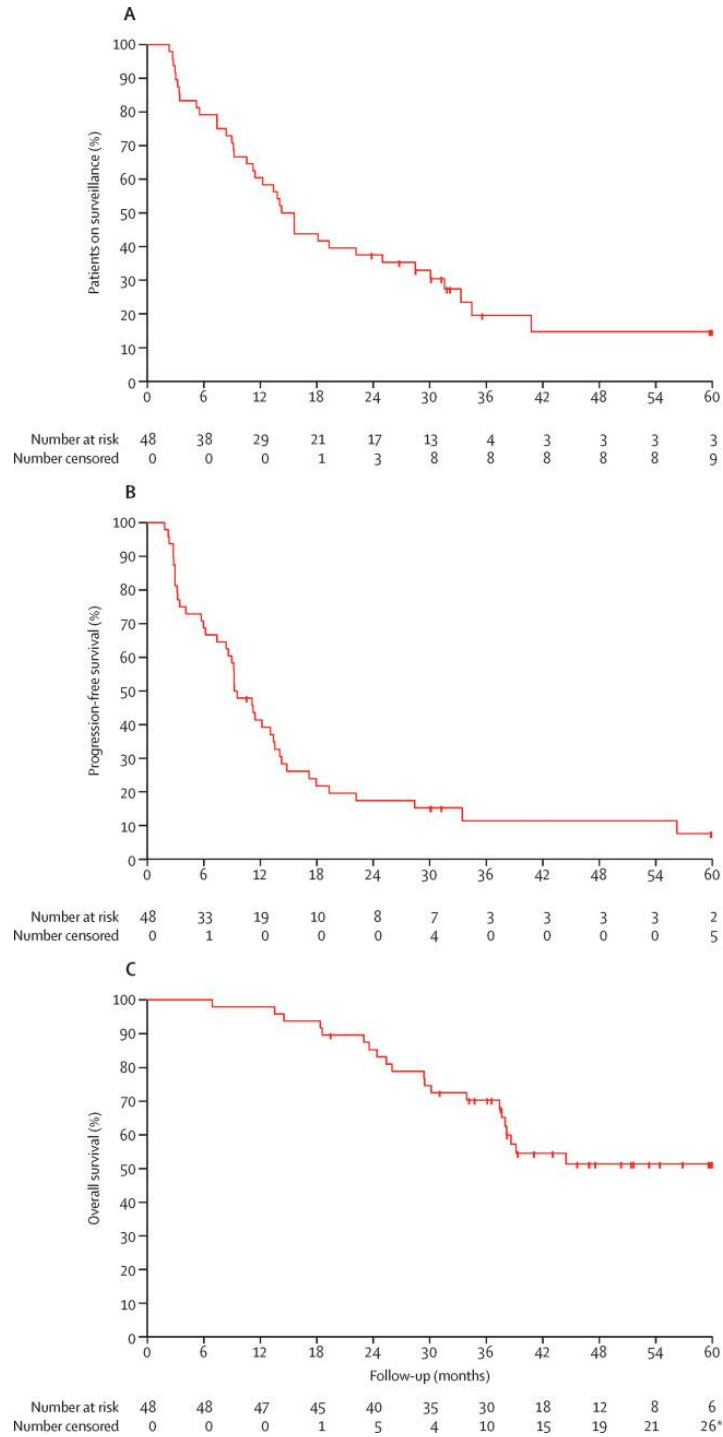


Figure 2: Swimmer's plot of time on active surveillance. For patients who progressed by RECIST criteria but continued to be observed, the endpoint of their bar represents discontinuation of surveillance. RECIST=Response Evaluation Criteria in Solid Tumors.

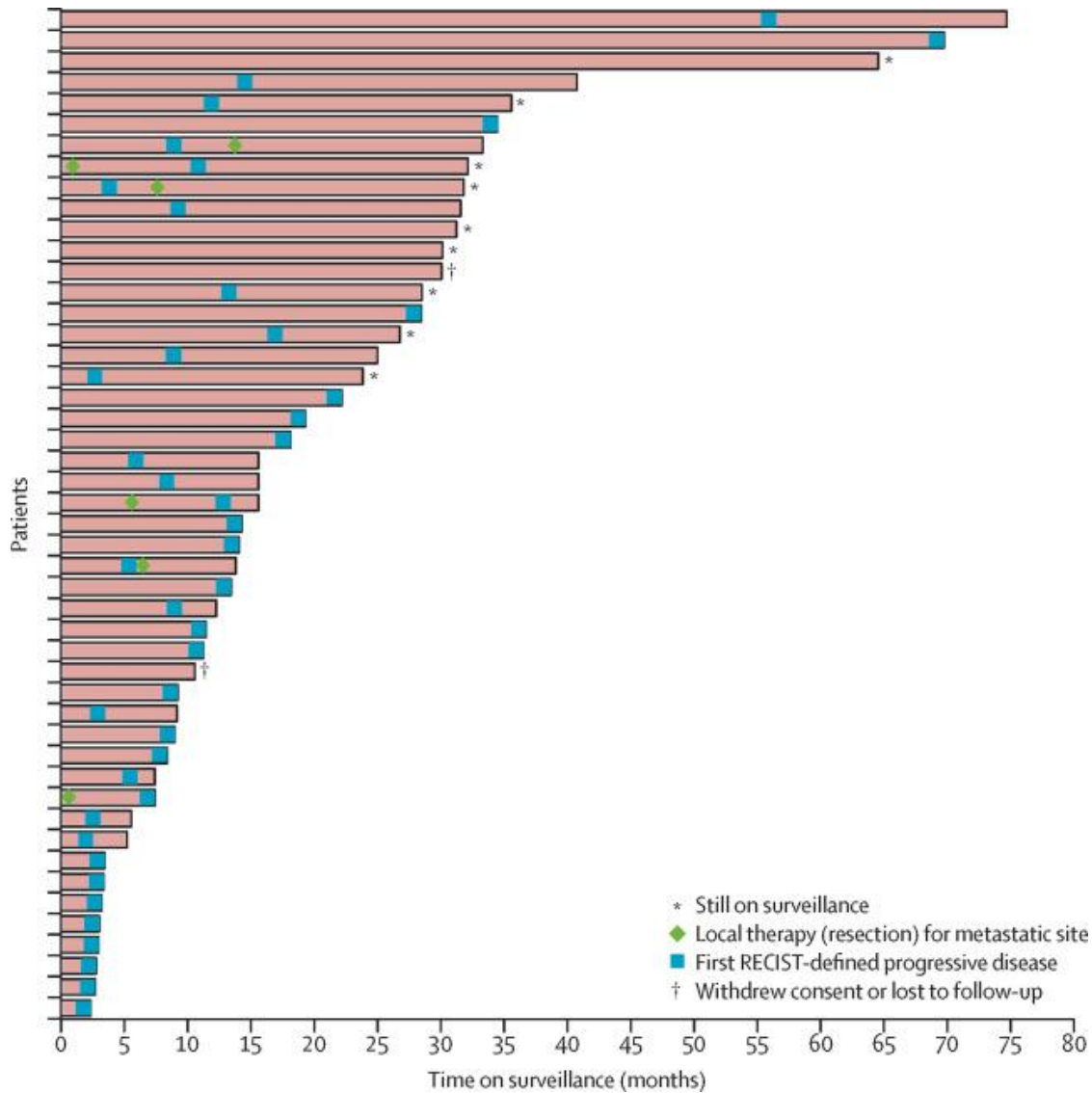
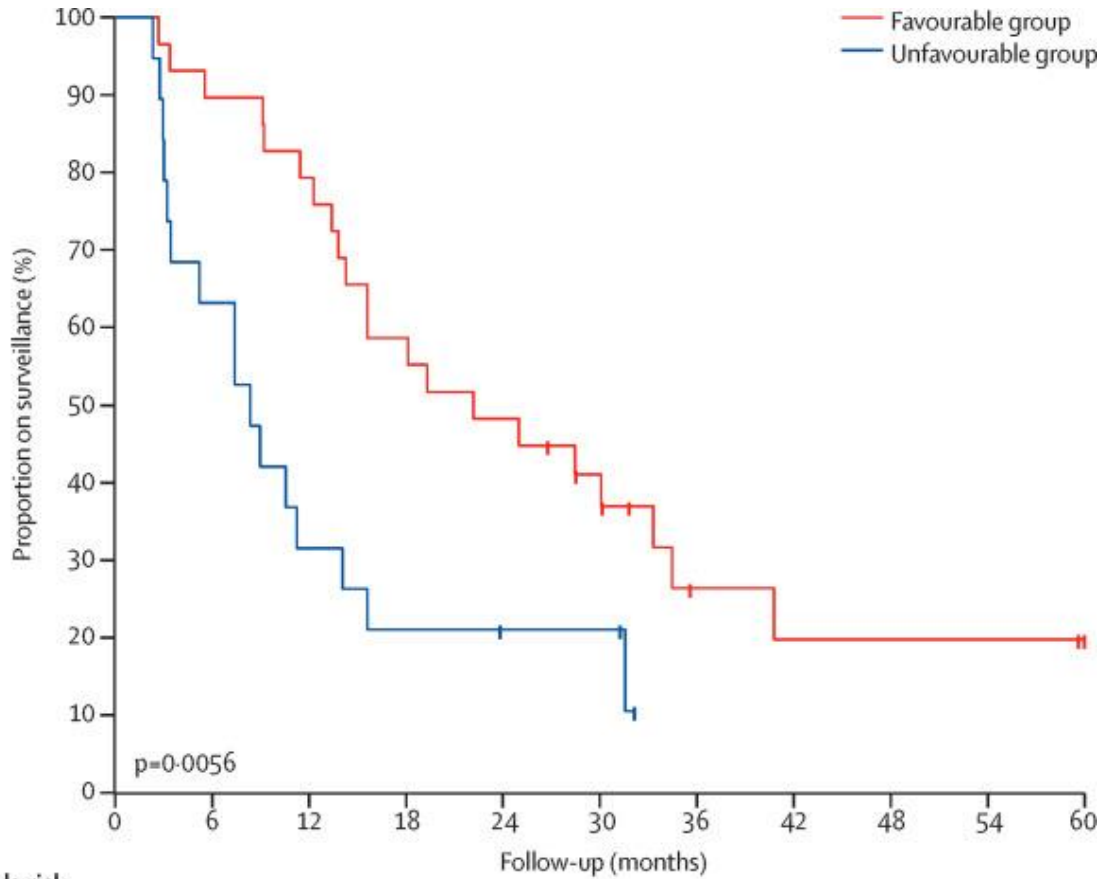


Figure 3: Active surveillance in patients with 0–1 IMDC risk factors and two or less organs involved with metastatic disease (favourable group) compared with all other patients (unfavourable group). Tick marks are censored patients. IMDC=International Metastatic.



	0	6	12	18	24	30	36	42	48	54	60
Favourable risk											
Number at risk	29	26	23	17	14	10	4	3	3	3	3
Number censored	0	0	0	0	2	5	5	5	5	5	6
Unfavourable risk											
Number at risk	19	12	6	4	3	3	0	0	0	0	0
Number censored	0	0	0	1	1	3	3	3	3	3	3

Author Contributions

Professor Brian I. Rini, MD: conception and design of the work, acquisition, analysis and interpretation of the data, drafting the work and revising it for content, manuscript writing, final approval of the manuscript, agreement to be accountable for all aspects of the work

Tanya B. Dorff, MD: conception and design of the work, accrual of patients, interpretation of the data, manuscript writing, final approval of the manuscript

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