Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial

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Summary

Background **A subset of patients with metastatic renal-cell carcinoma show indolent growth of metastases. Because of the toxicity and non-curative nature of systemic therapy, some of these patients could benefit from initial active surveillance. We aimed to characterise the time to initiation of systemic therapy in patients with metastatic renal-cell carcinoma under active surveillance.**

Methods **In this prospective phase 2 trial, we enrolled patients with treatment-naive, asymptomatic, metastatic renal-cell carcinoma from five hospitals in the USA, Spain, and the UK. Patients were radiographically assessed at baseline, every 3 months for year 1, every 4 months for year 2, then every 6 months thereafter. Patients continued on observation until initiation of systemic therapy for metastatic renal-cell carcinoma; a decision that was made at the discretion of the treating physician and patient. The primary endpoint of the study was time to initiation of systemic therapy in the per-protocol population. The follow-up of patients is ongoing.**

Findings **Between Aug 21, 2008, and June 7, 2013, we enrolled 52 patients. Median follow-up of patients in the study was 38·1 months (IQR 29·4–48·9). In the 48 patients included in analysis, median time on surveillance from registration on study until initiation of systemic therapy was 14·9 months (95% CI 10·6–25·0). Multivariate analysis showed that higher numbers of International Metastatic Database Consortium (IMDC) adverse risk factors (p=0·0403) and higher numbers of metastatic disease sites (p=0·0414) were associated with a shorter surveillance period. 22 (46%) patients died during the study period, all from metastatic renal-cell carcinoma.**

Interpretation **A subset of patients with metastatic renal-cell carcinoma can safely undergo surveillance before starting systemic therapy. Additional investigation is required to further define the benefits and risks of this approach.**

Funding **None.**

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Introduction

Antiangiogenic drugs that target the vascular endothelial growth factor (VEGF) pathway, such as sunitinib, sorafenib, and pazopanib, axitinib, and bevacizumab, can produce objective responses and extend progression-free and overall survival in patients with metastatic renal-cell carcinoma.[1–4] Although these drugs are considered standard of care, they are not curative. Furthermore, 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 metastatic renal-cell carcinoma show indolent growth of metastases; this is understood 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). Surgical resection leads to approximately 30% of patients remaining disease free at 5 years.[5] However, there are few prospective data for the natural history of metastatic renal-cell carcinoma and the safety of active surveillance as an initial strategy. One study from the late 1980s described a prospective cohort of 73 patients with metastatic renal-cell carcinoma who underwent initial observation with radiographs monthly until progression, at which time patients were treated with BCG vaccination, mitoxantrone, or interferon alfa.[6] 10% of patients had not progressed by 12 months. Among the cohort who received subsequent interferon alfa, 14% had an objective response, identical to the proportion of patients who received immediate interferon treatment. These limited data generate the hypothesis that some patients with metastatic renal-cell carcinoma can safely undergo initial surveillance without compromising response to subsequent systemic therapy. Although modern drugs have greater activity than interferon alfa, toxicity can be substantial and the drugs can be cost-prohibitive for many patients and health systems. We aimed to further define the feasibility and safety of an initial active surveillance approach in the era of modern targeted therapy.

Methods

Study design and participants

In this phase 2 prospective trial, we enrolled patients 18 years or older (no upper age limit) with histologically or cytologically confirmed renal-cell carcinoma of any histological subtype. The protocol is available online. Patients were enrolled through referral by their clinician to centres in three hospitals in the USA, one in Spain,

For the **protocol** see http://my.clevelandclinic.org/ccf/media/Files/Cancer/Pubs/case4808-cc508-protocol.pdf?la=en

Research in context

Evidence before the study

A subset of patients with metastatic renal-cell carcinoma has indolent progression of disease. We searched PubMed using the terms "metastatic renal cell carcinoma" and "surveillance" and "observation" for papers published between Jan 1, 1980, and Oct 30, 2015. Based on this search, previous case series have shown that some of these patients can be observed for a period of time before the start of systemic therapy. However, these series were small and retrospective, which can introduce substantial bias.

Added value of this study

To our knowledge, this is the first prospective assessment of observation for patients with metastatic renal-cell carcinoma. We show that some patients with metastatic renal-cell carcinoma can be safely observed before the start of systemic therapy, many of them for months to years. We identify clinical characteristics of patients for whom surveillance was a successful strategy, including having 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 the CNS should be routinely imaged 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 present trial cohort was characterised by a more favourable immune-cell population.

Implications of all the available evidence

Taken together with published retrospective data, our findings show that select patients with metastatic renal-cell carcinoma 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.

See Online for appendix

and one in the UK (appendix p 8). We did not stipulate any performance status eligibility criteria, but all patients must have been asymptomatic from metastatic renal-cell carcinoma. All patients had measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.[7] Patients could have had first documentation (radiographical or histological) of metastatic renal-cell carcinoma up to 12 months before registration on study. Patients who received any previous systemic therapy for renal-cell carcinoma in any setting were excluded, but previous radiotherapy (including radiotherapy for CNS metastases) and surgery (nephrectomy or metastasectomy) was permitted. We did not specify any laboratory parameters or comorbidities for eligibility. The decision to enrol the patient on the study and thus choose active surveillance over immediate systemic therapy was made jointly by the patient and treating physician. The study was approved by the institutional review board or ethics committee at each institution. All patients provided written informed consent.

Procedures

Patients underwent a CT scan of the chest, abdomen, and pelvis at baseline, every 3 months during year 1, every 4 months during year 2, and every 6 months thereafter. Study investigators calculated tumour burden and assessed objective response and progression according to RECIST version 1.0.[7] As per RECIST guidelines, intravenous contrast agents were given unless contraindicated for medical reasons (eg, 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 or symptoms developed. Clinical assessments at baseline and at each CT scan time-point included Eastern Cooperative Oncology Group (ECOG) performance status and laboratory evaluation with a complete blood count and serum chemistry. Investigators administered the Functional Assessment of Cancer Therapy—Kidney Cancer Index Disease-Related Symptoms (FKSI-DRS) and the Hospital Anxiety and Depression Scale (HADS) at baseline and at each CT scan timepoint.[8–10] Peripheral blood mononuclear cells were collected at baseline and at each CT scan timepoint as previously described.[11] We also aimed to do an exploratory genomic analysis of samples from baseline nephrectomy of consenting patients.

Patients continued on observation until initiation of systemic therapy for metastatic renal-cell carcinoma; a decision that was made at the discretion of the treating physician and patient. Patients were not required to discontinue surveillance because of RECIST-defined disease progression.

Outcomes

The primary endpoint of the study was time from the start of surveillance (defined as registration on study) to initiation of systemic therapy (defined as the first day of systemic treatment). Secondary prespecified endpoints were changes from baseline in tumour burden, quality of life (including anxiety and depression), and immune cell populations; analysis for protein expression in the tumour tissue; and best overall response and progression-free survival in patients who received systemic therapy. Overall survival and progression-free survival in the overall cohort were exploratory outcomes.

Change in tumour burden and time to progression (time from registration to first meeting of progressive disease criteria or last follow-up) were assessed per RECIST version 1.0 criteria using investigator measurements at all CT scan timepoints. Changes in quality of life were assessed using FKSI-DRS, where a change of

3 points or more is considered significant. Changes in anxiety or depression were assessed with the HADS, in which scores of 8 or higher suggest the possible presence of anxiety or depression. Immune population changes were defined as changes in the absolute number of predefined peripheral blood immune cell subsets including myeloid-derived suppressor cells, regulatory T cells, and interferon-γ-producing CD3 and CD4 T cells. Overall survival and best overall response after therapy were defined from registration on study to the patient's death or last follow-up.

Statistical analysis

We aimed to enrol 50 eligible and evaluable patients to estimate the proportion of patients who discontinued surveillance within a specified time (eg, 12, 18, 24, or 36 months) with 95% CIs that had maximum half-widths of 0·14. Inclusion of 50 patients also provided statistical power higher than 80% (based on a two-sided Wilcoxon signed-rank test with 5% type I error) to detect changes of more than 0·5 standard deviations in secondary endpoints. The trial was multicentre and therefore the timing of its closure accommodated each participant's internal processes. To be conservative, trial closure began early in anticipation that some lead time would be needed by the participants. As a result, the final accrual was higher than 50 patients.

All analyses were done in the per-protocol population, defined as all eligible patients who did not withdraw consent. We summarised time-to-event data with the Kaplan-Meier method. Wilcoxon signed-rank test and rank-sum test were used for assessments of secondary endpoints. We did a multivariable analysis of time-to-event data to identify prognostics factors for duration of surveillance and time to progression. We used log-rank test and Cox proportional hazards models for univariable analyses of factors. Factors were entered in the Cox proportional hazards models for multivariable regression if they were statistically significant (p>0·10) at univariable analysis. Stepwise variable selection with p>0·10 as the criteria for entry and p>0·05 as the criteria for retention in a model were then used to determine which, if any were independent predictors of length of surveillance.

In addition to assessing changes in immune cell populations, we also compared these populations to reported data from two other external cohorts[11]—one consisting of healthy control participants and one of patients with metastatic renal-cell carcinoma who immediately began systemic treatment after diagnosis as previously described.[11] We used SAS version 9.2 for all statistical analyses.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

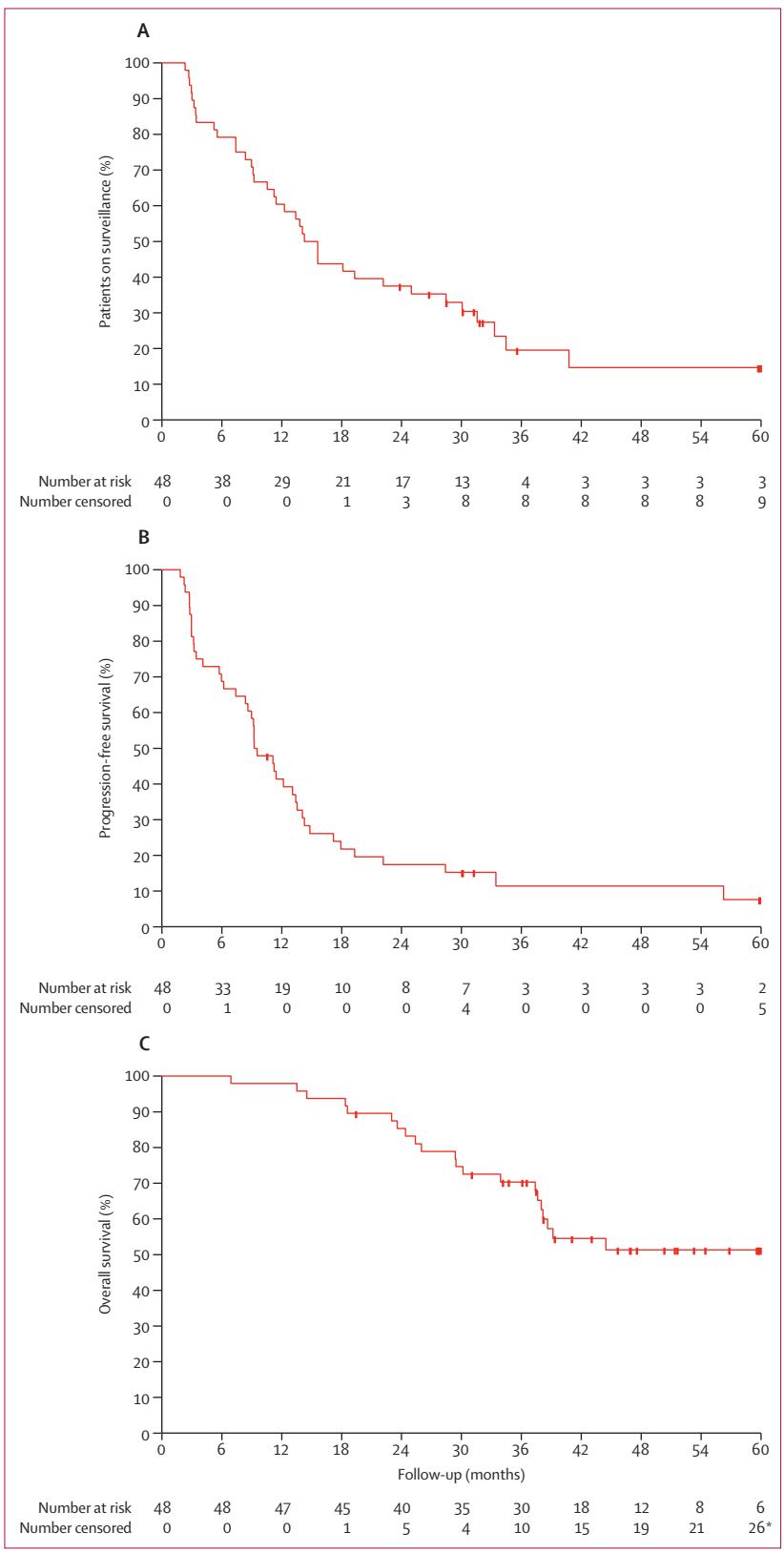
Results

Between Aug 21, 2008, and June 7, 2013, we enrolled 52 patients with metastatic renal-cell carcinoma. Four patients were excluded from all analyses: three because of early withdrawal of consent and one because of ineligibility (non-metastatic disease), leaving 48 patients in the per protocol population. Demographic and baseline characteristics were typical of populations with advanced

	Patients (n=48)
Age (years)	67 (62–75)
Sex	
Male	36 (75%)
Female	12 (25%)
Karnofsky performance status	
100	30 (63%)
90	15 (31%)
80	3 (6%)
Histology*	
Clear cell	46 (96%)
Chromophobe	2 (4%)
Sarcomatoid dedifferentiation†	6 (13%)
Time from diagnosis to metastatic disease (months)	5·1 (0·7–25·7)
Prior nephrectomy	47 (98%)
IMDC risk factors[12]	
0 (favourable)	11 (23%)
1–2 (intermediate)	36 (75%)
3 or more (poor)	1 (2%)
MSKCC risk factors‡	
0 (favourable)	11 (24%)
1–2 (intermediate)	35 (76%)
Site of metastatic disease§	
Lung	34 (71%)
Lymph nodes	12 (25%)
Bone	10 (21%)
Kidney	9 (19%)
Adrenal	6 (13%)
Liver	2 (4%)
Number of organ sites with metastases	
1	25 (52%)
2	15 (31%)
3	6 (13%)
4	2 (4%)
Tumour burden at baseline (sum in cm of RECIST tumour measurements)¶	3·2 (1·5–6·7)

Data are n (%) or median (IQR). IMDC=International Metastatic Renal-Cell Carcinoma Database Consortium. MSKCC=Memorial Sloan Kettering Cancer Center. RECIST=Response Evaluation Criteria in Solid Tumors. *Histology determined by nephrectomy in all patients except for one, in whom it was determined by renal mass biopsy. †Missing for three patients; patients with sarcomatoid dedifferentiation are also counted according to underlying histology and thus the total for histology sums to more than 100%. ‡Missing for two patients. §Percentages sum to more than 100% because some patients had more than one organ with metastases. ¶43 patients had measurable disease.

Table 1: **Baseline demographics and clinical characteristics**



renal-cell carcinoma (table 1). Patients had typical sites of metastases, with most having one organ with metastases and a relatively low tumour burden at baseline.

Patients were followed up for a median of 38·1 months (IQR 29·4–48·9). The median time on surveillance (from registration until initiation of treatment or withdrawal of consent) was 14·9 months (95% CI 10·6–25·0; figure 1).

43 (90%) of 48 patients met criteria for RECIST-defined disease progression at some point in the study and 37 of these patients started systemic therapy, while six continued on surveillance. Median time to progression for the entire cohort was 9·4 months (95% CI 7·4–13·4; figure 1). 23 (53%) of 43 patients who had progressive disease immediately started systematic therapy after progression and 20 (47%) continued on surveillance (median additional surveillance period for these patients was 15·8 months; 95% CI 3·0–24·1). At the time of paper submission, 14 of the 20 patients who initially continued on surveillance have initiated systemic treatment; six continue on surveillance (figure 2). Three patients did not have any RECIST disease progression during the study, and two patients came off surveillance due to withdrawal of consent (n=1) or loss to follow-up (n=1).

Of the 43 patients with disease progression, 32 (74%) had growth in existing sites of metastases, eight (19%) had new sites of disease, and three (7%) had both a worsening of existing sites plus new sites. New sites of disease were noted in the lung (n=4), lymph nodes (n=2), bone (n=2), and the CNS (n=2). No patient had symptomatic progression during the surveillance period excluding the two patients who developed new CNS disease. 22 (46%) patients died, all from metastatic renal-cell carcinoma. In an exploratory analysis of the whole population, progression-free survival at 12 months was 41% (95% CI 27–55%), falling to 22% (11–34%) at 18 months, 17% (8–30%) at 24 months and 11% (3–24%) at 36 months (figure 1). The estimated median overall survival from the start of surveillance was 44·5 months (95% CI 37·6 to not reached; figure 1).

In the 42 patients who did not undergo resection during the surveillance period, the median absolute change in tumour burden during surveillance was 1·3 cm (95% CI 0·6–1·8); relative change 31% (14–50) with a median growth rate of 0·09 cm per month (0·04–0·17).

In univariable analysis of baseline prognostic factors, the length of active surveillance was associated with the number of organs with metastases (one *vs* two *vs* more than two; p=0·0239), the location of the metastases (lung only *vs* other organs only *vs* both; p=0·0280), and the number of International Metastatic Database Consortium (IMDC; p=0·0213) and Memorial Sloan Kettering Cancer

***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.

Center (MSKCC; p=0·0184) risk factors, but not the associated prognostic groups themselves (appendix pp 4–5). In multivariable analysis, only the number of involved organs (p=0·0414) and number of IMDC risk factors (p=0·0403) were independently prognostic (appendix p 6). On the basis of this analysis, we identified two prognostic groups through use of a recursive partitioning algorithm—a favourable group consisting of patients with no or one IMDC risk factors and two or fewer organs with metastatic disease, and an unfavourable group consisting of all other patients. The favourable group comprised 29 (60%) patients and had an estimated median surveillance time of 22·2 months (95% CI 13·8–33·3), whereas the 19 (40%) patients in the unfavourable group had an estimated median surveillance time of 8·4 months (3·2–14·1; p=0·0056; figure 3).

In a post-hoc analysis of the ten patients who stopped surveillance within 6 months of registration, distinctive baseline characteristics included Karnofsky performance status of 80%, presence of sarcomatoid dedifferentiation in the primary tumour, a greater number of adverse IMDC risk factors, and a greater baseline tumour burden (data not shown).

At univariable analysis, numbers of IMDC (p=0·0011) and MSKCC (p=0·0045) risk factors were significantly associated were reduced time to RECIST progression. In multivariable analysis, the number of IMDC risk factors was the only independent prognostic factor (appendix p 6).

Seven patients underwent local therapy which included resection or radiation during the surveillance period (range 2–31 months after registration). Six patients underwent resection of metastatic disease (two for adrenal disease, two for renal mass, one for renal vein thrombosis, and one for an abdominal mass), and one patient had radiotherapy to treat metastasis to the bone. Pathology on all resected specimens confirmed metastatic renal-cell carcinoma. No patient underwent local therapy due to symptomatic progression of a lesion. Rather, local therapy was undertaken because other lesions initially felt to be consistent with metastatic renal-cell carcinoma 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 renal-cell carcinoma). The median time from the start of the surveillance period to local resection was 14·2 months (95% CI 9·2–22·2).

Data for subsequent systemic therapy are available for 31 of the 39 patients who discontinued surveillance. Most patients received therapy with pazopanib (n=11 [35%] of 31 patients), or sunitinib (n=11 [35%]). Three patients (10%) received pazopanib or sunitinib in combination with an investigational drug. Other treatments included temsirolimus (n=2 [6%]); and axitinib (n=1 [3%]), bevacizumab (n=1 [3%]), nivolumab plus ipilimumab (n=1 [3%]), and celecoxib plus interferon (n=1 [3%]). One patient developed brain metastases and died without

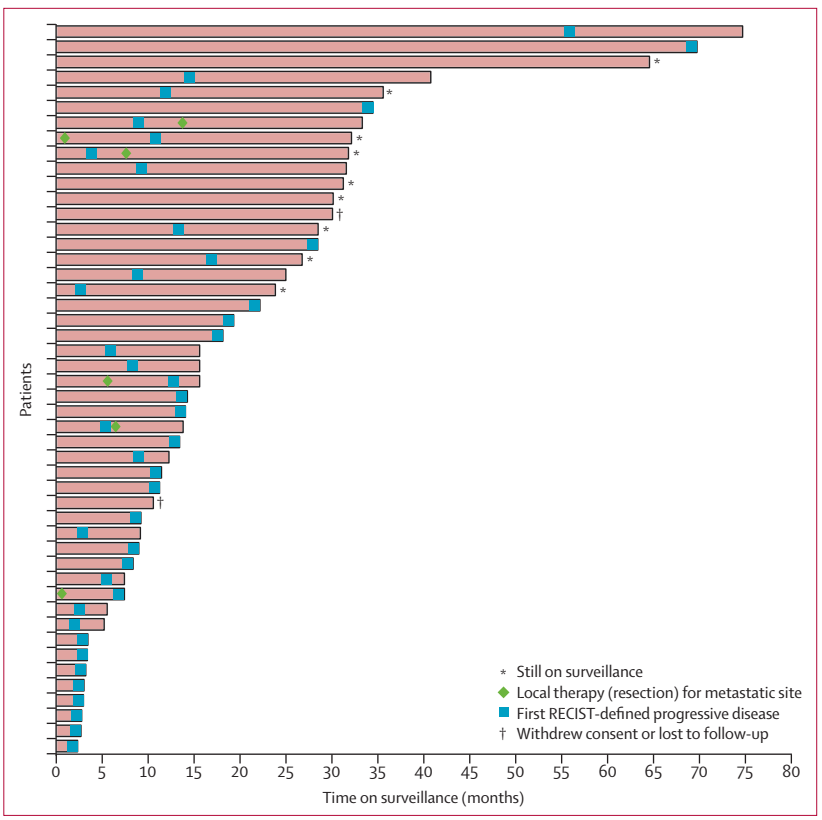


Figure 2: **Swimmer's plot of time on active surveillance**
For patients who progressed by RECIST criteria but continued to be observed, the endpoint of their bar represents discontinuation of surveillance. RECIST=Response Evaluation Criteria in Solid Tumors.

receiving systemic therapy. Objective partial responses were documented in ten (32%) patients who received systemic therapy. The median overall survival from the start of surveillance for the 31 patients who received systemic therapy was 38·6 months (95% CI 30·1 to not reached). Progression-free survival for patients who discontinued surveillance was not assessed.

At baseline, seven (16%) of 44 patients had scores suggestive of anxiety and two (5%) had scores suggestive of depression on the HADS questionnaire (table 2). Anxiety and depression scores did not change significantly over the period of surveillance (table 2). Similarly, FKSI scores for quality of life did not change significantly compared with baseline.

When compared with a healthy control population, patients on surveillance in the study (n=40) had a greater number of myeloid-derived suppressor cells, fewer regulatory T cells, and a similar number of interferon-γ-producing T cells (appendix p 7). Compared with a separate cohort of patients with metastatic renal-cell carcinoma who began systemic therapy immediately[14] the active surveillance group had significantly fewer myeloid-derived suppressor cells and regulatory T cells, and a significantly greater number of interferon-γ-producing T cells. These results potentially indicate a less immunosuppressive environment in the

surveillance cohort, compared to patients who received systemic therapy immediately. None of the measured immune cell populations changed significantly over time in the surveillance cohort or were associated with length of surveillance (appendix p 7). Protein expression in tumour tissue is not reported because it has not yet been assessed.

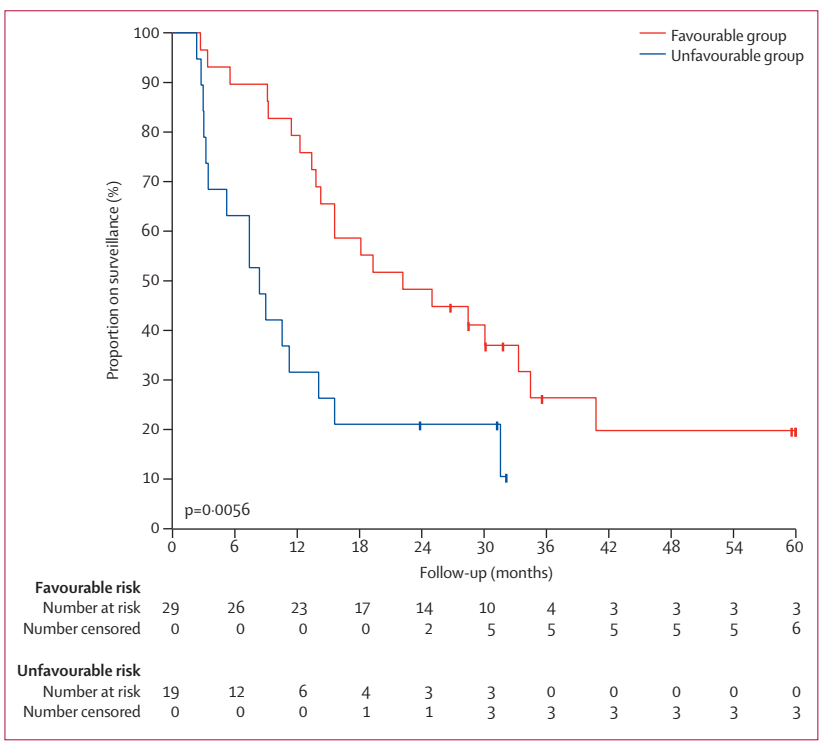


Figure 3: **Active surveillance in patients with 0–1 IMDC risk factors and two or less organs involved with metastatic disease (favourable group) compared with all other patients (unfavourable group)**
Tick marks are censored patients. IMDC=International Metastatic Database Consortium.

Discussion

Findings from our prospective trial show active surveillance to be a viable initial strategy in some patients with metastatic renal-cell carcinoma. The median surveillance period before start of systematic therapy was greater than 1 year, with no observed adverse effects on quality of life, anxiety and depression. Our multivariate analysis also showed that patients considered for this approach should be those with fewer adverse prognostic features and limited organ sites of metastases.

Metastatic renal-cell carcinoma is a disease characterised by a variable natural history. Many prognostic schemas have been developed, with the overall survival of patients ranging from 5 months in poor-prognosis patients to 30 months in good-prognosis patients after interferon-based therapy, and from 7 months to 43 months, respectively, after VEGF-targeted therapy.[15,16] This six-fold difference across the range of outcomes highlights the diverse underlying biology of metastatic renal-cell carcinoma with or without systemic therapy.

To our knowledge, very little prospective evaluation has been done of surveillance. A small retrospective series reported findings for 15 patients with metastatic renal-cell carcinoma observed after debulking nephrectomy.[17] 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[18] (n=62) noted an initial observation period of 18·7 months until systemic therapy in a patient population that was composed of 63% IMDC-favourable-risk patients. An additional

	N	Score	Change from baseline	p*	Patients with a score ≥8	Patients with ≥3 point change	Patients ≥3 point decrease	Patients with ≥3 point increase
Hospital Anxiety and Depression Scale–Anxiety†								
Baseline	44	3 (1 to 5)	..	..	7 (16%)	..	..	..
Month 6	32	2 (1 to 5)	0 (–2 to –1)	0·53	5 (16%)	..	..	..
Month 12	22	3 (1 to 6)	0·5 (–2 to –1)	0·86	4 (18%)	..	..	..
Final assessment	29	3 (1 to 5)	–1 (–2 to –1)	0·14	3 (10%)	..	..	..
Hospital Anxiety and Depression Scale–Depression†								
Baseline	44	1 (1 to 5)	..	..	2 (5%)	..	..	..
Month 6	32	1 (0 to 3)	0 (–2 to –1)	0·11	1 (3%)	..	..	..
Month 12	22	2 (1 to 4)	0 (–2 to 1)	0·52	2 (9%)	..	..	..
Final assessment	29	2 (1 to 3)	0 (–2 to 1)	0·87	2 (7%)	..	..	..
Functional Assessment of Cancer Therapy–Kidney Cancer Index Disease-Related Symptoms‡								
Baseline	44	3 (0 to 14)	..	..	..	..	..	..
Month 6	32	3 (0 to 16)	0 (–8 to 4)	0·76	..	10 (31%)	6 (19%)	4 (13%)
Month 12	22	3 (0 to 13)	0 (–5 to 10)	0·52	..	10 (45%)	4 (18%)	6 (27%)
Last assessment	28	4 (0 to 22)	1 (–7 to 16)	0·46	..	16 (57%)	8 (29%)	8 (29%)

Data are median (IQR) or n (%), unless otherwise stated. *Wilcoxon signed-rank test. †Scores ≥8 on a subscale are suggestive of the presence of anxiety or depression. ‡A change of ≥3 points is considered significant.[13]

Table 2: **Anxiety and depression and quality-of-life questionnaire scores**

retrospective series of 29 patients with metastatic renal-cell carcinoma of exclusively IMDC good-risk and intermediate-risk groups reported a progression-free survival of 26·1 months with only nine patients receiving systemic therapy.[19] An additional retrospective series (n=58) reported a median time to disease progression of 12·4 months.[20] Multivariable analysis showed that Karnofsky performance status of less than 100%, liver metastases, and time from diagnosis to the start of surveillance of less than 1 year were associated with a shorter time to progression. Our data use a prospectively-defined restaging interval to provide a more confident estimate that the median surveillance time was greater than 1 year, and can be up to several years in length in some patients. Furthermore, a subset of the most favourable patients in our cohort, as defined by one or fewer adverse IMDC risk factors and at most two sites of metastatic disease, demonstrated a nearly 2 year surveillance period, although these results must be interpreted with caution due to small patient numbers (figure 3).

An initial-surveillance-based approach has been prospectively investigated in other malignancies. A trial in patients with low-tumour-burden follicular lymphoma randomly assigned asymptomatic patients to observation, prednimustine, or interferon therapy and showed a freedom-from-treatment interval of 24 months in the observation group and an identical overall survival to the initial therapy groups.[21] A 2014 study[22] randomly assigned patients with low-tumour-burden follicular lymphoma to initial observation versus rituximab. 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 compared with the rituximab group. Most patients had normal baseline scores for anxiety and depression on the HADS questionnaire, which did not worsen over time, similar to in our renal-cell carcinoma cohort. Patients in the rituximab group had better scores on the Mental Adjustment to Cancer scale and the Illness Coping Style scale, compared with observation, suggesting some emotional benefit to patients with immediate therapy. However, we did not note a significant change with time in anxiety, depression, and quality of life in our study.

Six patients in our 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 (eg, small lung nodules) might not have been metastatic renal-cell carcinoma. Thus, a period of surveillance in the setting of limited renal-cell carcinoma metastases can help to select patients in whom metastasectomy might be most appropriate. Additionally, initial surveillance could be of benefit in patients in whom metastases are presumed but not definitively diagnosed, avoiding unnecessary treatment of initially equivocal and ultimately benign lesions.

Our analysis of overall immune competence revealed that patients in our surveillance cohort had significantly fewer immunosuppressive cells and higher numbers of interferon-γ-producing T cells than a cohort of patients with metastatic renal-cell carcinoma who began systemic therapy immediately. This phenotype, which would favour an anti-tumour immune response, could be postulated to contribute to the relatively indolent nature of tumour growth in these patients. The interaction of this immune phenotype with immunotherapeutic drugs is unknown and needs further study.

The present data should be interpreted in light of other therapeutic options in this disease. High-dose interleukin 2 has been given in a very select subpopulation of patients with renal-cell carcinoma who had clear-cell histology and a good performance status. A 2015 prospective trial[23] in 23 (19%) patients that were MSKCC good risk and 84 (70%) that were intermediate risk reported a median progression-free survival of 4·2 months, with 13 patients (11%) progression free at 3 years, and an overall survival of 42·8 months. The proportion of patients who were progression-free at 3 years in the interleukin 2 trial is identical to that in our trial. Nevertheless, there is an opportunity for long-term cancer-free survival with interleukin 2, making this an appropriate strategy for a subset of patients with metastatic renal-cell carcinoma. A phase 3 trial[1] of sunitinib versus pazopanib in patients with metastatic renal-cell carcinoma (303 [27%] good risk and 470 [58%] intermediate risk per MSKCC criteria) reported a median progression-free survival of 9 months and an overall survival of 29 months. The present cohort with a similar distribution of good-risk and intermediate-risk patients has comparable clinical outcomes, with the important caveat that patients enrolled on our trial were highly selected and no direct comparison can be drawn for long-term survival.

Our study has several limitations. Patients considered for inclusion were a highly selected population, with disease characteristics such as tumour burden or pace of disease growth not prospectively defined. Rather, clinical judgment of the treating physician guided which patients were considered for enrolment. It was not possible to more strictly define eligibility criteria for features such as burden or pace of disease, given the lack of previous prospective data in this regard. We felt it reasonable to allow the clinician to make a decision to offer enrolment, in the hopes that insight into such features could be elucidated by the present study. Furthermore, the decision to end surveillance and begin treatment was not mandated per objective criteria, and was instead left to physician and patient discretion. These study features limit the applicability of this approach. Nonetheless, prospective assessment of this strategy in selected patients provides guidance for physicians about how to select appropriate patients and

supports the viability of this approach; further study is required to validate this guidance. Another limitation is the frequent use of non-contrast scans in this population of patients with baseline renal dysfunction due to prior nephrectomy. This method 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. Although the specific reason for consent withdrawal is unknown, it is possible that anxiety about surveillance led to this decision. Immune parameters measured did not include the tumour-cell infiltrate, and thus are at best an indirect measure of the anti-tumour immune competence of patients. Importantly, two patients under surveillance developed new CNS metastases. Although baseline CNS imaging was required, regular CNS imaging during surveillance was not mandated. As a result of this development, all patients remaining on trial are now undergoing annual CNS imaging and this should be incorporated into future active surveillance protocols for renal-cell carcinoma studies.

In conclusion, for some select patients with metastatic renal carcinoma, active surveillance might be the optimum approach to avoid 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 crucial in application of this approach. Additional investigation into the risks and benefits of surveillance with the development of novel therapies is warranted.

Contributors

All authors contributed to the design and concept of the trial. TBD, CSR, DS, LW, JH, Y-NW, JMGL, JAG, and ERP accrued patients. BIR acquired and analysed data, with all authors contributing to data interpretation. BIR drafted and revised the manuscript for content, with all authors contributing to writing of the text. All authors approved the final manuscript.

Declaration of interests

JHF received grants from Pfizer and GlaxoSmithKline outside the submitted work. All other authors declare no competing interests.

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