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Economic burden of metastatic clear-cell renal cell carcinoma for French patients treated with targeted therapies

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Conflict of interest :

Dr Thiery-Vuillemin Antoine and Dr Mouillet Guillaume serve as consultants for different companies. Amelie Anot received non-financial support from companies. But these conflicts of interest are not directly related to the content of the article.

Other authors declare that they have no conflict of interest.

ABSTRACT

Background: Targeted therapies have transformed the treatment of metastatic clear-cell renal cell carcinoma (mccRCC). Despite the importance of mccRCC, studies evaluating its economic burden in daily practice are sparse. The purpose of this retrospective study was to evaluate cost-of-illness for 224 patients with diagnosed mccRCC included in the cohort published by Thiery-Vuillemin *et al.*, and then to determine the explanatory factors of cost-of-illness.

Methods: The study was performed from the French Public Healthcare System perspective with lifetime horizon. Only direct medical costs were included. Multiple linear regression was used to search for explanatory factors of cost-of-illness. The robustness of results was assessed.

Results: The mean cost-of-illness was estimated at €71,185 ±52,683. Outpatient/inpatient treatment and hospitalization represented 76.0% and 19.7% of this cost, respectively. After adjustment, five explanatory factors were identified: time of disease control for the metastatic first-line treatment ≥ 6 months, number of lines of treatment > 2 , nephrectomy at metastatic stage, lack of metastases at presentation, age at metastatic diagnosis < 65 years. Individually, they increased cost-of-illness by 128%, 95%, 53%, 53% and 23%, respectively.

Conclusions: Although it is difficult to transpose our EE results to those obtained in other countries, it should be noted that our findings were consistent with them and robust. To our knowledge, our study was the first to accurately identify explanatory factors of cost-of-illness. Identifying them could enable us to predict the budgetary impact on a regional level of managing patients who began their first-line treatment with a targeted therapy.

Key words: cost-of-illness; explanatory factors, metastatic clear-cell renal cell carcinoma; targeted therapy.

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Background

Kidney cancer accounts for 3.4% of all newly diagnosed cancers, with an overall estimate of 115,174 cases, causing 48,991 deaths (5.0%) in Europe for the year 2012 [1]. It is the third most frequent urologic cancer after prostate and bladder cancers [1]. Among various histologic entities of kidney cancers, clear-cell carcinoma is the most common accounting for approximately 70% of renal-cell carcinomas (RCC) [2]. To date, nine targeted therapies (through inhibition of angiogenesis or the mTOR pathway) have been evaluated in randomized, controlled phase III clinical trials in patients with metastatic RCC, and they have been approved by regulatory authorities in Europe [3–11]. Large randomized studies have shown significant benefit with targeted therapies, which has been confirmed by various cohorts [12–14].

These targeted therapies have transformed the treatment of metastatic clear-cell RCC (mccRCC) and have largely outperformed cytokines as the first-line standard of care [14–17].

On the other hand, clinical and economic studies in daily practice are sparse [18–27]. A previous retrospective multicenter study was conducted to assess the effectiveness of targeted therapies in real life settings [28]. All patients with histologically confirmed mccRCC who received targeted therapies in first-line treatment were included. Three prognostic factors influencing overall survival were identified in first-line treatment: MSKCC favorable and intermediate risks, metastasectomy and lack of lymph node metastasis). In second-line treatment, three different prognostic factors predicted long survival: toxicity for first-line treatment, time of disease control in first-line and MSKCC favorable and intermediate risks. These real-life data not only confirmed the positive impact of targeted therapies in the mccRCC setting, but also highlighted the importance of considering many factors to better estimate patient prognosis.

Antineoplastic drugs have had a major and growing impact on health insurance expenditures. In France, in 2015, antineoplastic drug expenditure for inpatients reached €1,696 million, targeted therapies representing more than 54% of this figure (€923 million) [29]. In comparison, antineoplastic drug expenditure for outpatients, reimbursed by the general fund – which covers 85% of the French population – reached €1,646 million (i.e. 8.6% of overall drug expenditure for outpatients) and targeted therapies represented €885 million [29,30]. In 2015, 5.1% and 4.4% of antineoplastic drug expenditure for outpatient treatment were respectively associated with everolimus and sunitinib, both being used to treat patients with mcrRCC [29].

In the context of rational decision-making in health care, the economic evaluation (EE) of health care products has become a necessity. One of the major challenges is to provide cost-effectiveness data that are relevant to daily practices and may be required to optimize consumption of healthcare resources. Decision-making for coverage and reimbursement of new drugs is being increasingly supported by EE in many countries including Australia, Canada, and the UK [31,32]. Furthermore, it's essential to estimate the economic burden of cancer and its management. However, despite the importance of mcrRCC, data concerning its economic burden are few. Thus, the purpose of this retrospective study was to evaluate the cost-of-illness for 224 patients with diagnosed mcrRCC included in the cohort published by Thiery-Vuillemin *et al.*, and then to determine the explanatory factors of cost-of-illness [28].

Patients and Methods

Patient population and treatment

From January 2007 to March 2015, all consecutive patients with histologically confirmed mcrRCC who started their first-line treatment with a targeted therapy in 3 main oncology treatment sites of the Institut Régional Fédératif du Cancer de Franche-Comté were included in the analysis. ~~The selection procedure of 224 patients with histologically confirmed mcrRCC who started their first line treatment with a targeted therapy was previously presented by Thiery-Vuillemin *et al.* [28].~~ Each anticancer drug was given until disease progression, toxicity or death and was routinely administered according to

guidelines and the summary of product characteristics. Some patients might have received drugs as part of clinical trial; in that case, drug was given following the clinical study protocol.

Cost-of-illness study

This EE was performed from the French Public Healthcare System perspective. Only direct medical costs, from the start of metastatic first-line treatment until death from any cause or to last follow-up for survivors (lifetime horizon), were included in our analysis, i.e. costs related to outpatient and inpatient treatment, hospitalization, outpatient consultations and healthcare travel. Minor costs and costs considered to be independent of the treatment were not taken into account (such as premedication, outpatient treatment of adverse events). Nor were indirect medical and intangible costs. Costs are expressed in Euros (€) (reference year 2015). All of these cost items were collected by reviewing each patient's medical and pharmaceutical records, completed by the French hospital discharge system for hospitalization data.

Inpatient and outpatient treatment

For reimbursed drugs administered in hospital (bevacizumab, temsirolimus) and ambulatory (axitinib, everolimus, pazopanib, sorafenib, sunitinib, cytokine and interferon) settings, we determined the exact number of milligrams per prescription and per patient and then multiplied this quantity by the purchase price of each drug. Unit prices of drugs were obtained from wholesale price lists from our hospital and from official tariffs for outpatient treatment.

Hospitalization

We identified each hospitalization for nephrectomy, anticancer drug administration, serious adverse event management, radiotherapy, metastasectomy and best supportive care. Hospital resource costs were based on the French public Diagnosis-Related Group (DRG) database, which is used to fund each hospital stay and does not include expensive drugs such as bevacizumab and temsirolimus (<http://atih.sante.fr>). All resources were therefore

included for each hospital with the exception of these expensive drugs. For instance, the DRG for chemotherapy is estimated at €410.67.

Outpatient consultations

An outpatient consultation was performed every month for each patient (€28, according to the French Public Healthcare System) (<http://ameli.fr>).

Healthcare travel

Healthcare travel costs were estimated for each patient based on the total number of hospital admissions and the number of outpatient consultations. Patient traveling costs were based on one return trip by light medical vehicle per hospital admission or outpatient consultation, using the distance from home to hospital, according to the French Public Healthcare System (<http://ameli.fr>).

Base case and sensitivity analyses

Because direct medical costs were measured over a period exceeding one year for the majority of patients, an annual discount rate was applied at a 4% annual rate according to recommendations of the department of Economics and Public Health Assessment of the French Haute Autorité de Santé [33].

The robustness of the cost-of-illness study, i.e. the base-case result, was assessed through a series of deterministic one-way sensitivity analyses. Firstly, the anticancer drugs are the most important cost driver of cost-of-illness; thus, the cost of each reimbursed anticancer drug was reduced by 30%, but also increased by 30% to take into account the potential advent of generic anticancer drugs onto the European market in future years as well as intra-country price variability. Secondly, an annual discount rate of 0% and 5% were used instead of 4% to take into account uncertainty related to the basic methodological choice and transferability of results.

Statistical analysis and determination of the explanatory factors of cost-of-illness

Continuous variables were described by mean $\pm$ standard deviation and range, and qualitative variables by size and percentage. The Wilcoxon rank-sum test (Mann-Whitney

U test) or the Kruskal-Wallis test was used to compare continuous variables. Association between quantitative variables was measured on the Spearman rank-order correlation, nonparametric measure of association based on the ranks of data values (Spearman correlation coefficient (θ), *p-value*).

Multiple linear regression was used to search for explanatory factors of cost-of-illness for patients with diagnosed mccRCC (patient-related variables, mccRCC-related variables and treatment-related variables). To determine which variables were candidates for explanatory factors of cost-of-illness in multiple linear regression, their association with cost-of-illness was previously explored in a univariate way using the Mann-Whitney U test and the Spearman rank-order correlation, like the correlation between candidate variables. All variables with $p < 0.15$ entered into the multiple linear regression. The data was tested for the assumption of normality for the variable of cost-of-illness using the Shapiro-Wilk test. If the distribution is found to be skewed, this may lead to problems with statistical estimation such as heteroscedasticity in the model. Thus, the natural logarithm of cost-of-illness was used as the dependent variable for further analyses. Because the dependent variable was log-transformed, the coefficient estimates are semi-elasticities for which coefficient interpretation requires some care. Thus, for a dichotomous explanatory variable, such as MSKCC risk group (favorable = 1 and intermediate/poor = 0), the coefficient estimate represents the factor by which cost would be higher or lower for the favorable risk as opposed to the intermediate/poor risk. By exponentiating the estimated coefficient and subtracting 1, it is possible to interpret the result as a percentage change from the reference group. Using the delta method, we estimated and reported the standard error associated with the estimated coefficient for the switching status variable (explanatory variable) [33,34].

All tests were two-tailed and significant at an alpha threshold of 5% (p). Statistical analysis was performed with SAS[®] software version 9.1.3.

Several variables were then studied to determine their impact on cost-of-illness. They included:

- patient characteristics: gender (female *versus* male), age at metastatic diagnosis (< 65 *versus* ≥ 65 years);

- metastases at presentation (yes *versus* no);
- MSKCC prognostic risk (favorable *versus* intermediate *versus* poor, favorable or intermediate *versus* poor) at metastatic diagnosis;
- nephrectomy at metastatic stage (yes *versus* no);
- metastasectomy (yes *versus* no);
- radiotherapy (yes *versus* no);
- participation in therapeutic clinical trial (yes *versus* no);
- injectable metastatic first-line treatment (yes *versus* no);
- time of disease control (defined by the time interval between initiation of treatment to progression of disease) for the metastatic first-line treatment (< 6 *versus* ≥ 6 months);
- Number of metastatic lines of treatment (1 or 2 *versus* > 2).

The robustness of the base-case model was assessed through a series of deterministic one-way sensitivity analyses, the same as for the cost-of-illness study.

Results

Cost-of-illness study

The mean cost-of-illness of 224 patients with diagnosed metastatic clear-cell renal cell carcinoma was estimated at €71,185 ± 52,683 with arange from €1,235 to €263,405 (Table 1). Interestingly, outpatient/inpatient treatment and hospitalization represented 76.0% and 19.7% of this cost, respectively. The mean cost of first-line treatment was estimated at 39,843 ± 36,253€, i.e. 56.0% of the cost-of-illness (Table 2). The deterministic one-way sensitivity analysis confirms the robustness of these results, with the economic impact of the cost of reimbursed anticancer drugs (Table 3).

Explanatory factors of cost-of-illness

Results of the univariate analysis are summarized in Table 4. Seven potential explanatory factors were significantly associated with higher cost-of-illness: MSKCC prognostic risk at metastatic diagnosis (p-value < 0.0001), time of disease control for the metastatic first-line treatment (p-value < 0.0001), number of metastatic lines of treatment (p-value < 0.0001), metastasectomy (p-value = 0.003), metastases at presentation (p-value = 0.02), nephrectomy at metastatic stage (p-value = 0.08) and age at metastatic diagnosis (p-value = 0.10).

After adjustment, multiple linear regression with log-transformed cost-of-illness as the dependent variables demonstrated significant associations between time of disease control for the metastatic first-line treatment ≥ 6 months, number of lines of treatment > 2 , nephrectomy at metastatic stage, lack of metastases at presentation, age at metastatic diagnosis < 65 years and cost-of-illness (Table 5). Individually, they increased cost-of-illness by 128% (± 22), 95% (± 19), 53% (± 19), 53% (± 17), and 23% (± 12), respectively, explaining up to 47% of cost-of-illness variability. Thus, the extent of cost-of-illness can range from €15,465 (lack of explanatory factors) to €198,670 (all explanatory factors).

Discussion

Despite the importance of mcrRCC, studies evaluating its economic burden are sparse [18–27]. Most of them were conducted before 2011 and before targeted therapies appeared on the market [18–22]. However, targeted therapies for mcrRCC have brought both new hope and new challenges, considerably expanding the number of treatment options for this indication. Because we have come to question the clinical and economic impact of systematically/routinely using these targeted therapies for patients with mcrRCC, we decided to assess their effectiveness and cost-of-illness [28]. Thus, all patients with mcrRCC treated over an eight-year period in three main oncology treatment centers of our Franche-Comté region were included in this retrospective study. It has estimated a mean cost-of-illness of €71,185 ± 52,683, to look at it against mean follow-up time after treatment initiation estimated at 25.6 ± 23.6 months [0.3 – 111.1], i.e. around €2,780 per patient per month, from the payer's perspective. Indirect and intangible medical costs were not taken into account as costs for loss of productivity were not included. Because of this, the cost-of-illness may have been underestimated. Nevertheless, it seems unlikely given the mean age at metastatic diagnosis of patients (67 ± 11 years). The largest cost driver of cost-of-illness was inpatient and outpatient anticancer treatment (76% of cost-of-illness). The second largest cost driver was hospital stays (20% of cost-of-illness). The cost of first-line treatment represented 56% of cost-of-illness.

Few EE conducted in Europe and North America have estimated the economic burden of mcrRCC for patients treated with targeted therapies [23–27]. In France, in 2013, Maroun *et al.* assessed the economic burden among patients with mcrRCC treated by targeted therapies from first-line of treatment to the last follow-up or death, from a hospital perspective, at €22,318 (year 2013) [23]. Only 16% (against 63% in our study) of patients had received at least one administration of bevacizumab or temsirolimus; this can explain the difference with our results taking into account only hospital costs (around €30,000). Four years later, in 2017, Maroun *et al.* assessed direct medical costs from the payer's perspective among patients with mcrRCC treated in first-line by targeted therapies, from treatment initiation until the last follow-up or death [24]. Patient characteristics (age at metastatic diagnosis, gender and sites of metastases) are similar to those of our patient

cohort, except for MSKCC risk group which was unknown. Direct medical costs were estimated at €5,546 (i.e. year 2016) per patient per month and treatment costs reached €2,327 per patient per month. In comparison with our study, supplementary costs, i.e. laboratory and imagery were included which, again, may explain the difference with our results (€71,185 with a follow-up of 25.6 months or €2,780 per patient per month). Both the first and second cost drivers were cost treatment (in- and outpatient) and hospitalization, representing 46% and 40% of total cost, respectively. We identified these same cost-drivers. Differences in terms of patient distribution among MSKCC group risk can account for the discrepancy in the results of the two studies.

Although it is difficult to transpose our EE results to those obtained in other countries, using the same inclusion and exclusion criteria, perspective and lifetime horizon, it should be noted that our findings were consistent with them [25–27]. Thus, a Dutch study published in 2017 by De Groot *et al.* estimated mean cost-of-illness at €65,620 ± 11,031 (year 2014). Supplementary costs (only healthcare travel) in our study can explain the observed difference [25]. A Canadian study published in 2016 by Nazha *et al.* estimated the mean treatment cost of the first three lines of treatment (taking into account only drug acquisition and hospitalisation for administration) with targeted therapy at \$100,078 (i.e. €83,629, year 2016) from the payer's perspective [26].

It is not surprising to find treatment as the first cost-driver, as previous EE identified treatment as the main cost-driver for overall mcrRCC burden [24,27]. Thus, for example, Choueri *et al.* performed a retrospective review of patients treated with an angiogenesis inhibitor in first-line treatment in two tertiary oncology centres in the United States [27]. They concluded that first-line treatment cost (i.e. year 2008) for patients treated with sunitinib, sorafenib and bevacizumab represented 71%, 74% and 90% of cost-of-illness, respectively. This cost included out- and inpatient treatment, hospitalization, outpatient consultations and healthcare travel.

It should be noted that sensitivity analysis showed robustness of results. Indeed, knowing that treatment is the main cost-driver, variation in the cost of treatment has a direct impact on overall cost. Thus, robustness of results makes it possible to minimize the impact of intra-country price variability over time, taking into account the potential advent of generic anticancer drugs on the market in the years to come.

Not surprisingly, the cost of first-line treatment is the highest when compared with other lines of treatment, correlated to the duration of first-line treatment. Indeed, increasing overall survival brings about an increase in the cost of treatment. Moreover, this result was expected given the fact that nephrectomy is recommended in mccRCC treatment [35,36]. Metastasectomy also increased first-line cost, because it was performed for 43 out of 54 patients as first-line treatment. These results are similar to those of international cohorts and in agreement with standard mccRCC treatment [26,37]. Thus, a Canadian study by Nazha *et al.* showed a lower median cost according to the line of treatment (\$55,986, \$27,328 and \$16,764 (year 2016) in first-, second- and third-line treatment, respectively) [26].

Our results underscore the originality and the strength of our study on the determination of explanatory factors of the economic burden of mccRCC. Additionally, to our knowledge, our study was the first to accurately identify these explanatory factors. The results with high external validity, but low internal validity, identified five explanatory factors: time of disease control for the metastatic first-line treatment ≥ 6 months (increasing cost-of-illness by 128%), number of lines of treatment > 2 (95%), nephrectomy at metastatic stage (53%), lack of metastases at presentation (53%) and age at metastatic diagnosis < 65 years (23%). Two factors, time of disease control greater than 6 months and lack of metastases at presentation, have already been identified as prognostic factors of overall survival in the Thiery-Vuillemin *et al.* study [28]. Indeed, improving overall survival could increase the duration of treatment and therefore the cost-of-illness. Likewise, nephrectomy influences overall survival, and consequently the cost-of-illness [38,39]. Interestingly, MSKCC prognostic risk was not related to the cost-of-illness, although it is the main prognostic factor of overall survival in the Thiery-Vuillemin *et al.* study [28].

Identifying explanatory factors could enable us to develop a dynamic model of the economic burden of mccRCC. Such a model could, in turn, predict the budgetary impact on a regional level of managing patients who began their first-line treatment with a targeted therapy (i.e. Franche-Comté). The findings could then perhaps be extrapolated on the national level, from the French healthcare perspective. Additionally, the model could predict different profiles of patients and enable us to compare their therapeutic strategies. Although this model explains the cost drivers of mccRCC, it does not take into account the

notion of cost-effectiveness. The perspective of this study is to create a longitudinal model including time effect (through the line of treatment). This model will allow us to conduct an economic analysis to identify the best treatment sequence in patients treated at Franche-Comté region. With the advent of immunotherapy on the market and its impact on overall survival, another analysis will be performed to determine its economic impact on the management of patients with mcrRCC.

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Table 1 Cost-of-illness of 224 patients with diagnosed metastatic clear-cell renal cell carcinoma

Cost items (€)	mean $\pm$ standard deviation	minimum – maximum	percentage
Outpatient and inpatient treatment	54,070 $\pm$ 47,906	673 – 253,313	76.0
<i>Inpatient treatment</i>	15,826 $\pm$ 26,586	0 – 195,339	29.3
<i>Outpatient treatment</i>	38,244 $\pm$ 45,538	0 – 253,313	70.7
Hospitalization	14,016 $\pm$ 9,974	0 – 42,834	19.7
<i>Nephrectomy</i>	2,504 $\pm$ 4,297	0 – 28,265	3.5
<i>Anticancer drug administration</i>	4,287 $\pm$ 6,668	0 – 40,870	6.0
<i>Serious adverse event management</i>	715 $\pm$ 1,934	0 – 11,936	1.0
<i>Radiotherapy</i>	730 $\pm$ 1,278	0 – 6,053	1.0
<i>Metastasectomy</i>	1,166 $\pm$ 2,383	0 – 11,273	1.7
<i>Best supportive care</i>	4,614 $\pm$ 5,557	0 – 28,789	6.5
Outpatient consultations	421 $\pm$ 412	0 – 2,003	0.6
Healthcare travel	2,679 $\pm$ 2,972	29 – 17,392	3.7
Cost-of-illness (€)	71,185 $\pm$ 52,683	1,235 – 263,405	100.0

Table 2 Cost per line of treatment for 224 patients with diagnosed metastatic clear-cell renal cell carcinoma

Line of treatment	Number of patients (percentage)	Follow-up (months)				Cost (€)
		mean $\pm$ standard deviation	minimum – maximum	mean $\pm$ standard deviation	minimum – maximum	
1	224 (100.0)	11.7 $\pm$ 13.0	0.2 – 109.6	39,843 $\pm$ 36,253	1,235 – 263,405	
2	189 (84.4)	8.1 $\pm$ 9.6	0.1 – 41.6	22,752 $\pm$ 23,185	1,021 – 123,933	
3	109 (48.7)	6.8 $\pm$ 9.2	0.3 – 66.9	18,301 $\pm$ 22,030	346 – 153,155	
4	52 (23.2)	5.1 $\pm$ 6.5	0.3 – 36.6	14,870 $\pm$ 17,036	213 – 80,603	
5	21 (9.4)	6.6 $\pm$ 8.7	0.4 – 39.8	15,985 $\pm$ 21,674	272 – 93,897	
6	12 (5.4)	3.8 $\pm$ 3.1	0.59 – 10.6	9,709 $\pm$ 7,361	137 – 27,714	
7	6 (2.7)	2.0 $\pm$ 1.7	0.4 – 4.8	5,366 $\pm$ 6,108	105 – 13,796	
8	1 (< 1.0)	3.1	/	/	345	
All	224 (100.0)	25.6 $\pm$ 23.6	0.3 – 111.1	71,185 $\pm$ 52,683	1,235 – 263,405	

Abbreviation: SD = Standard Deviation

Table 3 Deterministic one-way sensitivity analysis

	Cost-of-illness (€)	
	mean $\pm$ standard deviation	minimum – maximum
Base-case analysis	71,185 $\pm$ 52,683	1,235 – 263,405
30% cost reduction of reimbursed anticancer drugs	54,964 $\pm$ 38,713	1,033 – 187,411
30% cost increase of reimbursed anticancer drugs	87,406 $\pm$ 66,824	1,437 – 339,399
Discount rate of 0% instead of 4%	81,565 $\pm$ 68,378	1,237 – 378,784
Discount rate of 5% instead of 4%	68,945 $\pm$ 49,539	1,234 – 241,063

Abbreviation: SD = Standard Deviation

Table 4 Univariate analysis of explanatory factors of cost-of-illness for patients with diagnosed metastatic clear-cell renal cell carcinoma

Potential explanatory factors	Number of patients (percentage)	Cost-of-illness (€)		p-value
		mean $\pm$ standard deviation	minimum – maximum	
Gender				0.67
Male	159 (71.0)	71,646 $\pm$ 55,623	2,250 – 263,405	
Female	65 (29.0)	70,056 $\pm$ 45,067	1,235 – 202,819	
Age at metastatic diagnosis, years				
Spearman correlation coefficient	224 (100.0)	-0.20		0.003
< 65	96 (42.9)	79,538 $\pm$ 58,791	1,235 – 263,405	0.10
$\geq$ 65	128 (54.1)	64,920 $\pm$ 46,859	1,602 – 238,293	
Metastases at presentation				0.02
Yes	120 (53.6)	66,511 $\pm$ 55,382	1,235 – 244,047	
No	104 (46.4)	76,578 $\pm$ 49,099	2,370 – 263,405	
MSKCC prognostic risk at metastatic diagnosis				<0.0001
Favorable	26 (11.6)	93,079 $\pm$ 46,372	34,692 – 232,084	
Intermediate	141 (63.0)	76,403 $\pm$ 54,928	2,370 – 263,405	
Poor	57 (24.4)	48,292 $\pm$ 41,537	1,235 – 186,052	
Favorable or intermediate	167 (74.6)	79,001 $\pm$ 53,902	2,370 – 263,405	
Poor	57 (24.4)	48,292 $\pm$ 41,537	1,235 – 186,052	

Nephrectomy at metastatic stage				0.08
Yes	68 (30.4)	83,300 ± 60,984	9,219 – 244,047	
No	156 (69.5)	65,904 ± 47,887	1,235 – 263,405	
Metastasectomy				0.003
Yes	55 (24.6)	89,151 ± 57,188	21,962 – 263,405	
No	169 (75.4)	65,338 ± 49,929	1,235 – 244,047	
Radiotherapy				0.20
Yes	74 (33.0)	74,217 ± 48,486	13,390 – 263,405	
No	150 (67.0)	69,690 ± 54,730	1,235 – 244,047	
Participation in therapeutic clinical trial				0.26
Yes	33 (14.7)	75,427 ± 46,734	9,219 – 232,084	
No	191 (85.3)	70,452 ± 53,722	1,235 – 263,405	
Injectable metastatic first-line treatment				0.53
Yes	99 (44.2)	70,986 ± 56,121	1,235 – 244,047	
No	125 (55.8)	71,343 ± 50,023	1,602 – 263,405	
Time of disease control for the metastatic first-line treatment, months				<0.0001
Spearman correlation coefficient	224 (100.0)	0.88		
< 6	101 (45.1)	44,145 ± 39,732	1,235 – 232,084	
≥ 6	123 (54.9)	93,392 ± 51,737	17,603 – 263,405	

Number of metastatic lines of treatment				<0.0001
Spearman correlation coefficient	224 (100.0)		0.48	
1 or 2	115 (51.3)	51,048 ± 44,548	1,235 – 263,405	
> 2	109 (48.7)	92,433 ± 52,433	21,664 – 244,047	

Abbreviations: MSKCC = Memorial Sloan Kettering Cancer Center

Table 5 Factors associated with cost-of-illness for patients with diagnosed metastatic clear-cell renal cell carcinoma using multiple linear regression analysis

Explanatory factors	Parameter estimate β	Standard error S_β	p-value	Percentage Difference θ	Standard error S_θ
Time of disease control for the metastatic first-line treatment, months					
≥ 6 versus < 6	0.82463	0.09848	<0.0001	1.28104	0.22464
Number of lines of treatment					
> 2 versus 1 or 2	0.66791	0.09604	<0.0001	0.95016	0.18729
Nephrectomy at metastatic stage					
Yes versus no	0.42591	0.12481	0.0008	0.53098	0.19108
Metastases at presentation					
No versus yes	0.42355	0.11378	0.0003	0.52737	0.17378
Age at metastatic diagnosis, years					
< 65 versus ≥ 65	0.21105	0.09677	0.0303	0.23497	0.11951
Adjusted R-square	0.4692				

Legend: $\theta = \exp(\beta) - 1$ (percentage increase in cost-of-illness for switch inter independent variable); $S_\theta = \exp(\beta) \times S_\beta$ (Standard error of the percentage difference)