RESEARCH ARTICLE

# Efficacy and Toxicity of Sunitinib in Metastatic Renal Cell Carcinoma Patients in Egypt

**Wael Abdelgawad Edesa*, Raafat Ragaey Abdelmalek**

## Abstract

**Background: To evaluate our results in terms of response, survival and toxicity profile of sunitinib among Egyptian patients with metastatic renal cell carcinoma. Materials and Methods: Between January 2010 and December 2013, 44 patients with metastatic renal cell carcinoma who received sunitinib at an oncology center of Cairo university hospitals were enrolled in this retrospective analysis. Results: The median age of the patients was 53 years, 22 (50%) having localized disease at presentation ,while the remaining half of the patients presented with metastasis. At a median follow up of 19 months, 9 (21%) patients achieved partial remission, while disease was reported stable in 20 cases (45%) and progressive in 7 (16%), 4 (9%) being lost to follow up, and 4 (9%) had discontinued therapy due to toxicity. The median overall survival was 23 months (95%CI 15.2 - 30.9), while progression free survival was 12 months (95%CI 11.6 - 12.3). The most commonly reported non hematological grade 3 adverse events included mucositis (15.9%), hand-foot syndrome (13.6%), and fatigue (9%), while the predominant grade 3 or 4 laboratory abnormalities were neutropenia (6.8%), followed by anemia in 4.5% of patients. Conclusions: Our efficacy data were comparable to the published literature in terms of progression free survival and overall survival , while toxicity profile is different from Asian and western countries. However, sunitinib adverse events were manageable and tolerable in most of our Egyptian patients**

**Keywords:** Renal cell carcinoma - sunitinib - toxicity - efficacy - Egyptian cases

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## Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all adult cancers, (Herrmann et al., 2010). At diagnosis, a third of the patients present with locally advanced or metastatic disease and a third of patients undergoing nephrectomy will eventually develop metastasis, (Athar and Gentile, 2008).

RCCs can evoke an immune response, which occasionally results in sustained remissions. Various immunotherapeutic strategies have been used to treat advanced disease. High-dose, bolus interleukin-2 (IL-2) or interferon-alpha can induce durable remissions in about 10 to 20 percent of patients, but its use is limited by severe toxicity, (Law et al., 1995; Negrier et al 1998).

Understanding the molecular pathogenesis of RCC has identified many targets for therapeutic intervention. In clear cell carcinoma which accounts for the majority of RCC, Von-Hippel-Lindau (VHL) gene is found to be deleted, mutated or altered in up to 80% of the patients, (Na et al., 2003).

Inactivation of the VHL gene causes persistent stimulation of the HIF-alpha, which then leads to activation of HIF and consequently, tumor angiogenesis, tumor growth, and metastasis (Turner et al., 2002).

Another pathway implicated in RCC is mediated by the mammalian target of rapamycin (mTOR), which is downstream of the phosphoinositide 3-kinase and Akt and is regulated by the PTEN tumor suppressor gene. Inhibition of this pathway leads to decreased protein translation and inhibition of both angiogenesis and tumor cell proliferation (Rini et al., 2009).

The rapid development of agents blocking the vascular endothelial growth factor (VEGF) pathway (eg, Pazopanib, Axitinib, Sunitinib, Sorafenib, Bevacizumab) or the mTOR pathway (Temsirolimus, Everolimus) has established molecularly-targeted therapy as the preferred treatment approach for most patients with advanced clear cell renal cell carcinoma, (Rini and Small., 2005; Escudier et al., 2007; Escudier et al., 2007). The benefit of Sunitinib was shown in a phase III trial of 750 patients with largely good- or intermediate-prognosis metastatic clear cell RCC who had not received prior systemic therapy, (Motzer et al., 2007; Motzer et al., 2009).

Here we present our data regarding the efficacy and toxicity of Sunitinib among Egyptian patients with metastatic RCC. This is the first experience with Sunitinib in Egypt.

*Kasr Alaini Center of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt *For correspondence: wael_gawwad@hotmail.com*

## Materials and Methods

Between January 2010 and December 2013, 44 Patients with metastatic RCC who received Sunitinib at the oncology center of Cairo university hospitals (tertiary care center) either in the first or the second line setting were enrolled in this retrospective analysis.

The medical records were reviewed, and data on both the patient and tumor characteristics were collected.

The patients were analyzed with respect to the demographic profile, MSKCC (Memorial Sloan Kettering Cancer Center) risk scoring system, dose of Sunitinib, response rate, adverse events, and survival .Patients were assessed clinically on day one with each treatment cycle.

Clinical Response to treatment (complete remission, partial remission, stable disease, and progressive disease) was assessed by Response Evaluation Criteria in Solid Tumors (RECIST criteria). Response evaluation by CT scan was done every 2 cycles of Sunitinib. Adverse events were assessed according to the common terminology criteria for adverse effects (CTCAE) version 3.0

*Statistical analysis*

All data were tabulated and statistically studied by descriptive analysis as well as survival analysis in relation to different prognostic factors.

Progression free survival (PFS) was calculated from the date of diagnosis of metastatic disease till the date of progression or death from any cause. Overall survival (OS) was calculated from the date of diagnosis of metastatic disease till the date of death due to any cause. Patients alive at last date of follow up were censored for analysis.

Survival analysis was done according to Kaplan-Meier method and compared by log-rank test for significance. The Cox proportional hazards regression method was performed to determine factors affecting PFS and OS. Differences were considered significant if p value was less than 0.05.

## Results

The median age of the patients was 53 years (range 18-79), Only 11 patients were above 60 years. Ninety three percent had ECOG (Eastern Cooperative Oncology Group) performance status of 0-1. The majority (73%) were males, 22 patients (50%) had localized disease at presentation and underwent radical nephrectomy while the remaining half of the patients had metastatic disease at presentation. Fifteen of these patients underwent cytoreductive nephrectomy before starting Sunitinib. The baseline patient characteristics are listed in Table (1)

Among the whole group, 35 patients (80%) received Sunitinib as the first line of therapy, 9 patients (20%) as the second line. Of the 35 patients who received Sunitinib as first line, 17 patients were metastatic at presentation, and 18 patients relapsed after radical nephrectomy; while for the second line, 5 patients were metastatic compared to 4 patients presented initially with localized disease. The agents used prior to Sunitinib were interferon alpha (6 patients), while Sorafenib, Temsirolimus and Bevacizumab-Everolimus were administrated in one patient each.

Clear cell carcinoma was the most common pathological type encountered (91%). The lung was the most common site of metastasis (66%), lymph nodes, bone and liver were involved in 36%, 32%, 25% respectively

According to MSKCC scoring, 66% of patients ranked in the intermediate category, while 25% in the favorable risk, and in 9% the poor risk category

*Response*

At a median follow up of 19 months (range 4.5 - 54.5), 9 (21% ) patients achieved partial remission, while disease was reported stable in 20 cases (45%) and progressive in 7 patients (16%), 4 (9%) lost follow up, and 4 patients (9%) had discontinued therapy due to toxicity. The cause of discontinuation was Fatigue grade3 or Hand and Foot syndrome grade 3. At the time of the analysis (September 2014), treatment was ongoing among 9 patients, 9 patients had second line therapy due to progressive disease (7 received Everolimus and 2 received Sorafenib), 4 lost follow up, while 22 patients died.

The median overall survival was 23 months, (95%CI 15.2 - 30.9)( Figure 1), while progression free survival

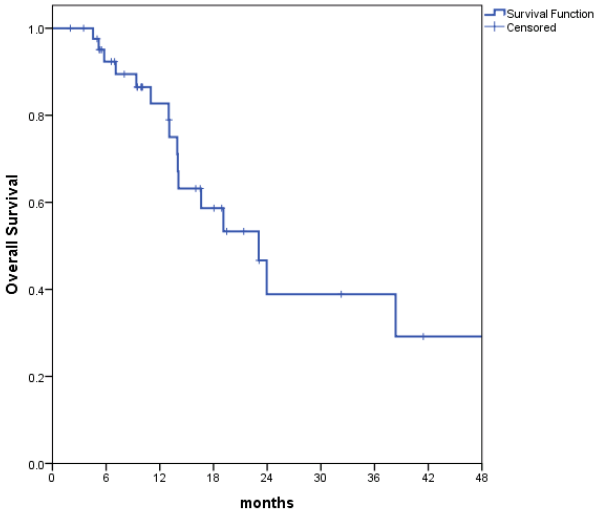


**Figure 1. Overall Survival for Patients with Metastic Disease**

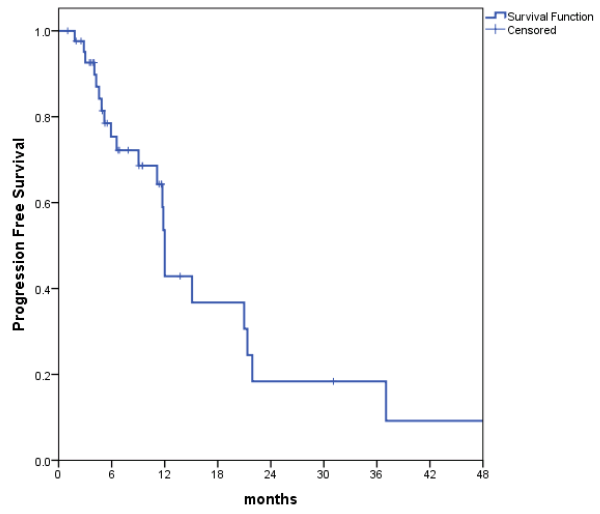


**Figure 2. Progression free Survival**

was 12 months (95%CI 11.6 - 12.3) (Figure 2). According to MSKCC scoring, the intermediate risk had statistically significant difference compared to the poor risk in terms of PFS (p=0.05), this was not shown with the favorable risk mostly because of low numbers (Figure 3).

In a univariate Cox regression analysis to determine prognostic indicators affecting PFS, only metastatic status at presentation was statistically significant (p= 0.035) (Table 2 and Figure 4). As for factors affecting Overall survival, metastatic status at presentation as well as Nephrectomy were significantly affecting OS using univariate Cox regression analysis but not in multivariate analysis (Table 3 and Figure 5).

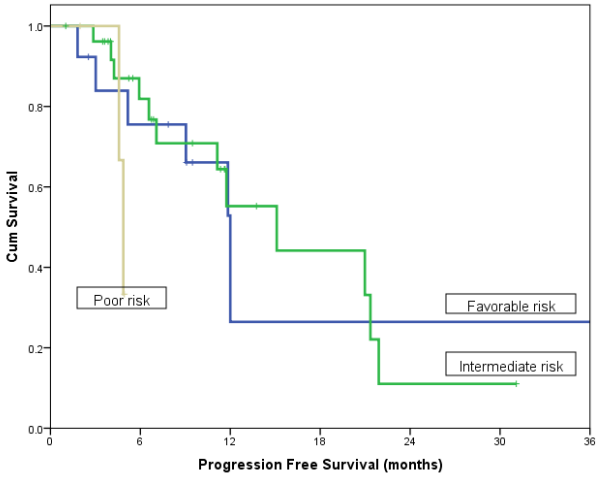


**Figure 3. PFS According to Memorial Sloan Kettering Cancer Centre Score**

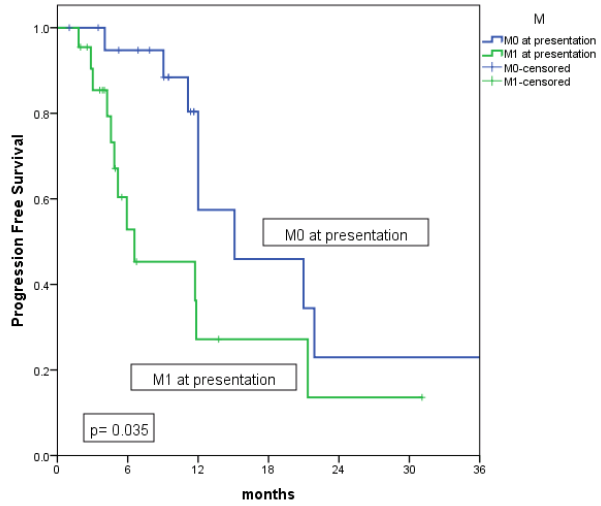


**Figure 4. PFS According to Status at Presentation**

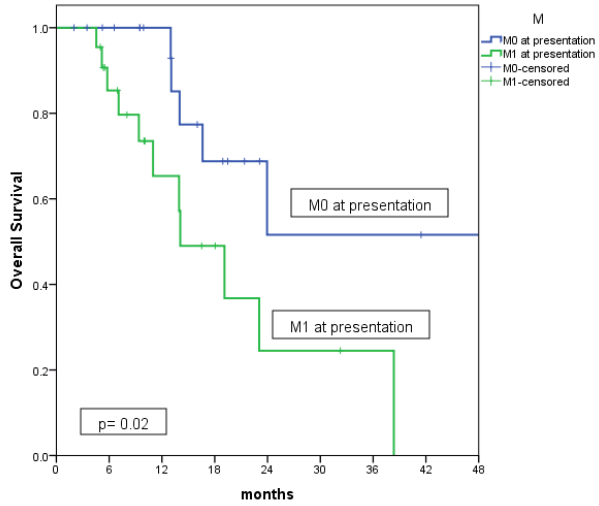


**Figure 5. OS According to Status at Presentation**

*Sunitinib dose and adverse events*

All patients started Sunitinib at the standard dose 50 mg orally once daily on a 4 weeks on, 2 weeks off dosing schedule. The median treatment duration was 8.75 months, dose reduction was necessary in 21 (47.7%) patients. The dose was decreased to 37.5 mg/day in 18 (86%) patients and to 25 mg/day in 3 (14%) patients. Sunitinib was interrupted in 4 patients due to grade 3 toxicity. Most of the patients had their dose reduction at the second cycle (70%) followed by the third one (20%).

The most commonly reported non hematological Sunitinib-related grade 3 adverse events included mucositis (15.9%), hand-foot syndrome (13.6%), fatigue (9%) and diarrhea (7%). None of these adverse events occurred with grade 4 severity. Hypertension was observed as any grade and grade 3 in 17 (38.6%), and 1

**Table 1. Baseline Patients Characteristics**

| characteristics | | n (%) |
|---|---|---|
| Sex: | male | 32 (73) |
| | female | 12 (27) |
| Age: | ≤ 40 | 8(18) |
| | 41-60 | 25 (57) |
| | > 60 | 11 (25) |
| | Median (range) | 53 (19-78) |
| Pathological type | | |
| | Clear cell | 40 (91) |
| | Papillary | 1 (2) |
| | Sarcomatoid | 3 (7) |
| ECOG P.S: | | |
| | 0-1 | 41(93) |
| | 2 | 3 (7) |
| Cytoreductive nephrectomy | | 37 (84) |
| Present with metastasis | | 22 (50 ) |
| Prior therapy | | |
| | Interferon alpha | 6(14) |
| | Sorafenib | 1(2) |
| | Temsirolimus | 1(2) |
| | Bevacizumab-Everolimus | 1(2) |
| *Site of metastasis | | |
| | Lung | 29 (66 ) |
| | Bone | 14 (32) |
| | Liver | 11(25) |
| | Lymph node | 16 (36) |
| | Brain | 3(7) |
| | *Local recurrence | 3(7) |
| Number of disease sites | | |
| | 1 | 15 |
| | 2 | 14 |
| | >3 | 15 |
| MSKCC scoring | | |
| | Favorable | 11 (25) |
| | Intermediate | 29 (66) |
| | Poor | 4 (9) |

**Table 2. Univariate Analysis for Factors Affecting Progression free Survival**

| | P value | Hazard rartio | 95%CI |
|---|---|---|---|
| Age (<40 *vs* >40) | 0.14 | 2.49 | 0.72-8.6 |
| Gender (male *vs* female) | 0.46 | 0.68 | 0.24-1.88 |
| Histological subtype (clear cell *vs* others) | 0.67 | 0.73 | 0.16-3.17 |
| T stage | 0.25 | 0.91 | 0.77-1.07 |
| N stage | 0.137 | 2.4 | 0.76-7.61 |
| Metastatic at presentation | 0.035 | 2.65 | 1.07-6.57 |
| Grade | 0.14 | 2.34 | 0.75-7.24 |
| Nephrectomy | 0.99 | 0.99 | 0.22-4.37 |
| MSKCC score | 0.96 | 0.96 | 0.21-4.33 |

**Table 3. Univariate Analysis for Factors Affecting Overall Survival**

| | P value | Hazard ratio | 95%CI |
|---|---|---|---|
| Age (<40 *vs* >40) | 0.71 | 1.26 | 0.36-4.45 |
| Gender (male *vs* female) | 0.37 | 1.6 | 0.56-4.53 |
| Histological subtype (clear cell *vs* others) | 0.99 | 0.99 | 0.22-4.4 |
| T stage | 0.83 | 1.1 | 0.43-2.78 |
| N stage | 0.43 | 1.63 | 0.47-5.64 |
| Metastatic at presentation | 0.028 | 3.3 | 1.13-9.59 |
| Grade | 0.63 | 0.69 | 0.15-3.16 |
| Nephrectomy | 0.013 | 4.52 | 1.37-14.86 |
| MSKCC score | 0.16 | 2.6 | 0.67-10.24 |
| Lung metastasis | 0.56 | 1.45 | 0.41-5.16 |
| liver metastasis | 0.34 | 1.71 | 0.57-5.12 |
| Bone metastasis | 0.95 | 0.96 | 0.31-3.02 |

**Table 4. Treatment Related Adverse Events and Selected Lab Abnormalities**

| Adverse events | All grades n (%) | Grade 3-4 n (%) |
|---|---|---|
| Fatigue | 25 (65.8) | 4 (9) |
| Vomiting | 22 (50) | 3 (6.8) |
| Mucositis | 21 (47.7) | 7 (15.9) |
| Hand and foot syndrome | 20 (45.4) | 6 (13.6) |
| Hypertension | 17 (38.6) | 1 (2.2) |
| Diarrhea | 16 (36.3) | 3 (6.8) |
| Heart burn | 11 (25) | 0 |
| Skin rash | 10 (22.7) | 0 |
| Nausea | 9 (20.4) | 0 |
| Hypothyroidism | 4 (9) | 0 |
| Bleeding | 3 (6.8) | 0 |
| Decline in ejection fraction | 2 (4.5) | 0 |
| Lab abnormalities | | |
| Anemia | 22 (50) | 2 (4.5) |
| Leucopenia | 21 (47.7) | 1 (2.2) |
| Neutropenia | 12 (27.2) | 3 (6.8) |
| Thrombocytopenia | 7 (15.9) | 1 (2.2) |
| Liver enzymes elevation | 4 (9) | 1 (2.2) |

(2.2%) of patients respectively. Hypothyroidism has been associated with Sunitinib treatment; it was reported in 9% of patients. Eight patients (4.7%) experienced a decline in left ventricular ejection fraction; however, none of them developed congestive heart failure

The predominant grade 3 or 4 laboratory abnormalities were neutropenia (6.8%), followed by anemia in 4.5% of patients; there was no report of febrile neutropenia or sepsis. The adverse events are summarized in Table 4.

## Discussion

Targeted therapy using tyrosine kinase inhibitors (TKI) is widely used in the treatment of advanced renal cell carcinoma in the first or second line setting. Sunitinib inhibits the VEGF receptor tyrosine kinase as well as other TKI associated with the platelet derived growth factor (PDGF) receptor and c-kit oncogene.

The efficacy of Sunitinib in previously untreated patients with metastatic RCC was shown in a large multicenter international trial in which 750 patients with metastatic RCC (all risk) clear cell carcinoma were randomized1:1 to receive either sunitinib or interferon alpha, (Motzer et al., 2007). The patients selected for the trial had no prior therapy with systemic treatment, good performance, and measurable disease. The primary end point was PFS, while the secondary end points were response rate and overall survival and safety. Approximately, 90% of the trial had favorable or intermediate risk according to MSKCC criteria. The median PFS was 11 months for Sunitinib versus 5 months for interferon alpha, the objective response rate as assessed by independent review was 31% for Sunitinib versus 6% for interferon. Severe adverse events were acceptable, with neutropenia (12%), thrombocytopenia (8%), hyperamylasemia (5%), diarrhea (5%), hand and foot (5%) and hypertension (8%) being noteworthy in the Sunitinib arm, while fatigue more common in the interferon arm (12% *vs*. 7%).

Updated results demonstrated a strong trend towards overall survival advantage of Sunitinib over interferon alpha in the first line setting (26.4 *vs* 21.8 months) with P value 0.051, (Motzer et al., 2009 )

Results from expanded access trial revealed that Sunitinib possesses an acceptable safety profile and has activity in subgroups of patients with brain metastasis, non clear histology and poor performance status, (Gore et al., 2009). The objective response rate (ORR) was 17%, median PFS was 10·9 months, and OS was 18·4 months.

Sunitinib also has shown anti-tumor activity in the second line after progression on cytokine therapy, (Motzer RJ et al., 2006; Motzer., 2006). It has also been reported that there is limited cross-resistance between Sunitinib and Sorafenib, and that patients who experience treatment failure with Sorafenib as first-line therapy might benefit from Sunitinib therapy, (Porta et al., 2011 ).

In the current analysis, we studied the response and toxicity profile of Sunitinib in our Egyptian patients. To our knowledge, no other data from Arab region or African nation have been published. In the present study, the median age and sex distributions were typical for this type of cancer .The median age was 53 years, with the majority (75%) were under the age of 60, with male to female ratio 2.5:1, half of our study patients presented with metastasis, 68% of them had cytoreductive nephrectomy. Only 9% had none clear cell type, which is lower than the reported literature, (Ahmet et al., 2013; Hashmi et al., 2014; Inamoto et al., 2014).

In terms of efficacy, the clinical benefit rate (CR-PR-SD) of our study (66%) is similar to the published trial by Krishna et al from India (65%), (Krishna et al., 2013), and from Turkey (68%) (Dirican A et al. ,2013), but lower to other Asian people, where it was reported as higher as 86% in Korea (Changhoon et al., 2010 ), 87% in China (He Zhisong et al., 2014 ) and also lower than the western literature (79%), (Motzer et al., 2006). The estimated progression free survival in our trial was 12 months (95%CI 11.6 - 12.3) while median overall survival was 23 months (95%CI 15.2 - 30.9). These Figures coincide with published literature. However differences in response rate could be attributed to different patient population, small number of patients, retrospective nature of the analysis, and logistic reasons in terms of drug availability which is not documented properly in our data base. Another important point is the missing data due to lost follow up patients; this observation deserves reconsidering the administration and data management system of our institute to overcome the defects and improve patient compliance, follow up and documentation.

Dose reduction due to adverse events was comparable to some studies, (Changhoon et al., 2010) while higher than others (Motzer et al., 2007; Krishna et al., 2013; He et al., 2014 ), Dose modification was not based only on grade 3or 4 toxicity but also on the cumulative grade 1 and 2 adverse events. However, Sunitinib discontinuation (8%) was relatively lower than the landmark study by Motzer et al. (2007) (10%), and Krishna et al. (2013) (18%), these results could be explained by small patient number and probably non adherence to the guidelines.

In the present analysis, treatment related adverse events were mostly grade 1 and 2, and only few grade 3 toxicities were observed. The most common hematological adverse events in our study population was anemia 50%, and leucopenia 48% where neutropenia and anemia represent the most prevalent grade 3 and 4 toxicity, 6.8% and 4.5% respectively.

The most common non hematological adverse events in our Egyptian patients including all grades were fatigue 66%,vomiting 50%, mucositis 48%,and hand and foot syndrome 45%,while the most frequent grade 3 and 4 toxicity were mucositis 16% and hand and foot syndrome 13.6%.

Our toxicity profile is quite different from the western literature, where diarrhea was the dominant adverse event 61%, while hypertension 12% and fatigue 11% were the most frequent grade 3 non hematological toxicity. Neutropenia and lymphopenia (16% each) were the most common hematological adverse events encountered, (Motzer et al., 2009).

Different toxicity profile were seen in Asian population where the most common adverse events were fatigue (81%), stomatitis (60%), thrombocytopenia (56%), anemia (55%) and hand-foot syndrome (48%). Grade 3 or 4 events were for hand-foot syndrome 16%, thrombocytopenia 16% and stomatitis 10% (Changhoon et al., 2010). These adverse events were similar to other published trials in Asian patients. (Hong et al., 2009; Uemura et al., 2010). Thrombocytopenia in particular was very common (75% and 69%) of Asian patients treated with Sunitinib as reported by Kim et al., 2011 and He et al., 2014 respectively.

Tyrosine kinase inhibitors have a different toxicity profile compared to the conventional chemotherapy. In our study, hypothyroidism was seen in 9%, routine monitoring of thyroid function tests was performed to our patients, this result is lower than the reported literature (Motzer et al., 2009; Krishna et al., 2013) 14%, and 23% respectively. Reduction in ejection fraction has been observed in 4.5% of our patients compared to 13% as reported by Motzer et al., 2009, none of our patients had grade 3 toxicity.

It seems that the toxicity profile in our Egyptian patients is more close to the Asian people rather than the western countries, a phenomenon that obviously needs further validation by a large prospective trial. Different toxicity profile due to ethnic discrepancies is well known (Cheng AL et al., 2009; Se-Hoon et al., 2014) polymorphisms in specific genes encoding for metabolizing enzymes, efflux transporters, and drug targets have been suggested as a possible mechanism of Sunitinib-related toxicities (van Erp et al., 2009). Another study has shown that polymorphisms in VEGFR3 and CYP3A5*1 could define a subset of patients with decreased Sunitinib response and tolerability. (Garcia-Donas et al., 2011).

In conclusion, our efficacy data were comparable to the published literature in terms of progression free survival and overall survival, while toxicity profile is different from the Asian and western countries, however Sunitinib adverse events were manageable and tolerable in most of the Egyptian patients.

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