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Sequential Use of Targeted Therapies (TT) in Metastatic Renal Cell Cancer (mRCC): Overall Results of a Large Experience

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1. Introduction

Renal cell carcinoma accounts for 80% of all kidney cancers -worldwide; the tumor staging at diagnosis ranges from small, low-stage tumors to more advanced neoplasms [1-5]. The survival rate has increased in recent years: nowadays, patients with localized disease have a 5-year survival >80% but in those with distant metastatic RCC, 5-year survival is <10% [6-8]. The increase in overall survival was due, at least in part, to improved surgical techniques [9,10]. Until recently cytokines (interleukin-2 or interferon-alpha), were the mainstay of systemic treatment despite low response rates and significant toxicity [11,12].

Since 2005, six targeted therapies for advanced/metastatic RCC were approved by both the FDA and EMA: three are multitargeted tyrosine kinase inhibitors (TKIs), sorafenib (SO), sunitinib (SU) and pazopanib (PZ), two are oral mTOR inhibitors, temsirolimus (TS) and everolimus (EV) and one is the anti-VEGF monoclonal antibody bevacizumab (BV), administered in combination with IFN-alpha [13]. These new agents improved the progression free survival (PFS) and the overall survival (OS) in several subgroups of patients; however, expert opinion on the optimal therapeutic strategy is divided.

Two main therapeutic approaches—use of these new agents in combination or sequentially—have been studied to increase efficacy and tolerability. Sequential therapy is the current standard of care in the treatment of advanced RCC as existing combination regimens have a high incidence of adverse events without a substantial increase in efficacy. The use of sequential therapy provides a number of important advantages: patients who are refractory to one or more targeted agent(s) may benefit from treatment with a different agent; there is no/limited cross-resistance between agents and patients experiencing disease progression with one anti-angiogenic agent can subsequently benefit from treatment with another [14,15].

The results of recent phase III randomized controlled trials (RCTs) prompted the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) to update their clinical practice guidelines for the treatment of metastatic RCC [16,17]. The EAU recommended SU as a first-line therapy in low- and intermediate-risk patients and

concluded that SO is effective as second-line treatment after failure of cytokine therapy or in patients unfit for cytokines [18]. Clinical evidence supports the efficacy of sequential treatment with SU/SO [19]; however, the optimal sequence for SO and SU is still under debate, and additional evidence on the optimal use of sequential targeted therapies is advocated.

In this retrospective study – the preliminary results of which have been previously presented [20] - the safety and efficacy of different sequential schemes of targeted therapies, in patients with advanced/metastatic RCC were studied.

2. Methods

2.1 Patients

This retrospective study was conducted at the 'Istituto Nazionale Tumori of Milan' (National Institute of Tumors, Milan, Italy) – one of the most important Italian institutions for cancer diagnosis and treatment - between January 2004 and July 2010. Patients were patients aged ≥18 years with advanced/metastatic RCC and a life expectancy of >3 months who had been treated with antiangiogenic therapy (one or more) were eligible for enrollment in this retrospective study. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2 were included. A number of patients enrolled in this study had previously taken part in a range of prospective trials including TARGET , the EU-ARCCS , RECORD-1 , AXIS , AVOREN and ROSORC at our centre.

3. Treatment

Patients received a range of different systemic agents – SO, SU, BV, EV, TS and axitinib (AX) alone or in combination, and could have received a previous treatment with cytokines. SO was administered orally at a dose of 400 mg twice daily and SU at a daily dose of 50 mg orally with a 4 weeks on 2 weeks off schedule. BV was administered iv at 10 mg/Kg every 2 weeks in combination with Interferon-a subcutaneously, EV was administered orally at 10 mg daily continuously, TS iv weekly at 25 mg/dose and AX at 10 mg/daily orally continuously. Patients received systemic therapy until disease progression or the presence of serious adverse events.

4. Study assessments

Study assessments were conducted at baseline and once a month thereafter. Baseline characteristics were taken ≤28 days after the start of treatment. Drug safety and tolerability were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCTCA version 3). Efficacy was assessed by progression-free survival (PFS) and overall survival (OS) according to the Motzer classification [21]. PFS was defined as the time from start of systemic treatment to death or disease progression whichever occurred first. Disease progression was evaluated using the Response Evaluation criteria in Solid Tumours (RECIST, version 1.0) by the treating physician. Assessments were performed monthly (every 3 weeks for patients on sunitinib, due to the schedule of administration for this drug). Patients with Bellini duct RCC were excluded from the efficacy analysis, due to the different histology of the tumor.

5. Statistical analyses

All clinical and instrumental variables and toxicity data were analyzed by descriptive statistics: mean, standard deviation, minimum, and maximum values for continuous variables, and absolute and relative frequencies for categorical variables. Curves relevant to OS (overall, Motzer and according to therapy option) were estimated by the Kaplan–Meier method and compared by means of the log-rank test. Reports of AEs were categorized according to type, severity, and outcome. A p value <0.05 was considered statistically significant.

6. Results

A total of 310 patients with metastatic RCC were observed, and followed-up for a median of 37 months (range 21–49 months). Patient characteristics at baseline are shown in **Table 1**.

Patients included in database	310	
Median age (years)	62	
Range	55–69	
Male	229	(74%)
Female	81	
ECOG PS		
0	168	(54%)
1	123	(40%)
2	19	(6%)
Histology		
Clear-cell	268	(86.4%)
Papillary	27	(8.7%)
Bellini	7	(2.2%)
Chromophobe	6	(1.9%)
Oncocytoma	1	(0.3%)
UNK	1	(0.3%)
Previous nephrectomy, %	273	(88.1%)
Fuhrman grade, %		
1	15	(5.58%)
2	93	(34.57%)
3	118	(43.87%)
4	43	(15.99%)
Missing	41	
Motzer criteria		
High	64	(20.6%)
Low	100	(32.3%)
Intermediate	146	(47.10%)
Targeted therapies %		
1	163	(52.6%)
2	113	(36.5%)
3	30	(9.7%)
4	4	(1.29%)

Number of disease sites		
1	121	(39.0%)
2	107	(34.5%)
3	67	(21.2%)
4	12	(3.9%)
5	3	(0.9%)
Sites of disease (n=599)		
Bone	88	(28.39%)
Brain	16	(5.16%)
Liver	59	(19.03%)
Lung	204	(65.81%)
Lymph nodes	119	(38.39%)
Pancreas	15	(4.84%)
Thyroid	4	(1.29%)
Other	94	(30.32%)

Table 1. Patient characteristics at baseline

Overall the majority of patients (163; 53.9%) received one treatment line with systemic agents while 113 (36.5%) received two, 30 (9.7%) received three line and four patients (1.3%) received four. One-sided analysis of variance showed that the Motzer classification/score was predictive regarding the number of therapy lines (Fisher 8.49, $p<0.01$) with the mean number of treatments significantly lower in the high-risk group ($p<0.05$) than in the low/intermediate risk groups (t-tests). Overall the majority of patients 196/310 received SO as first line followed by SU in 96 cases or SU, in 63 cases followed by SO in 13 cases). The remaining 51/310 received other systemic agents in sequence (BV, TS, AX alone or in sequence/combination with SO and SU).

Median OS was 22 months and the 5-year OS was 23.4% (95% CI 16.7, 30.0%) (**Figure 1**).

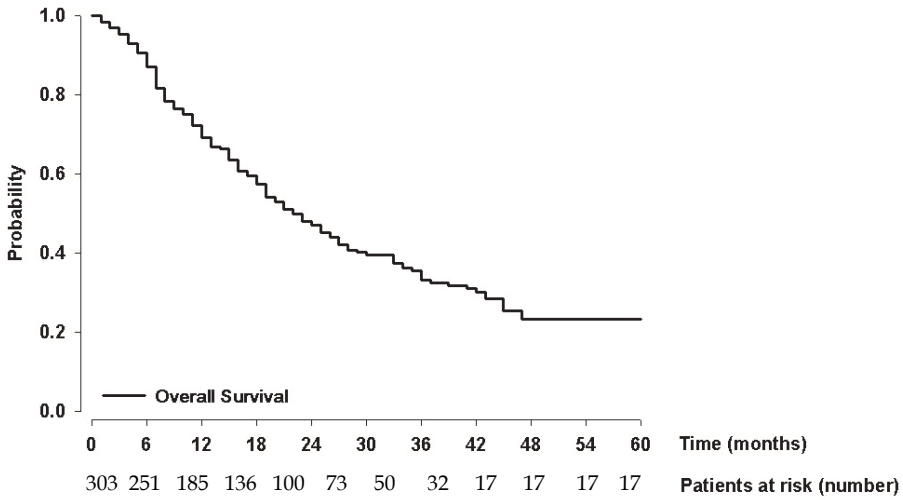


Fig. 1. Overall survival

The Motzer criteria were validated as prognostic factors in both the uni- and multi-variate analysis ($p<0.001$). The median and 5-year OS was 43 months and 42.8% in low-risk patients, 21 months and 15.9% in intermediate risk patients and 8 months in patients with poor risk (**Figure 2**).

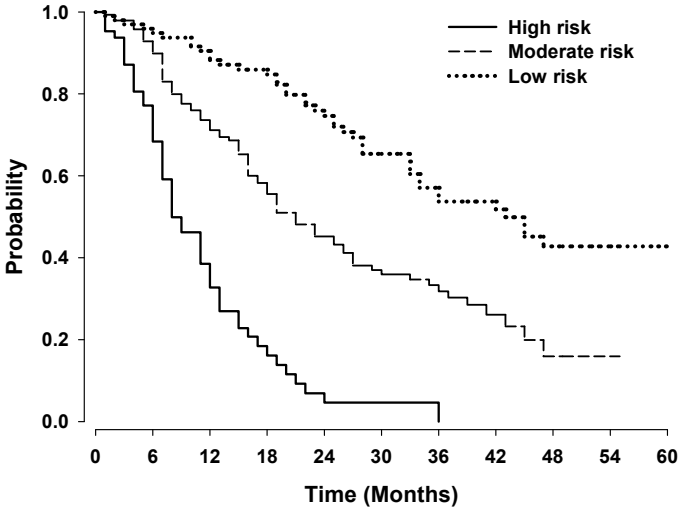


Fig. 2. Overall survival according to Motzer classification

Interestingly in both the multi- and uni-variate analysis there were no significant differences in the hazard ratios when SO+SU are compared with SU+SO and with other therapies (**Table 2, 3 and Figure 3**).

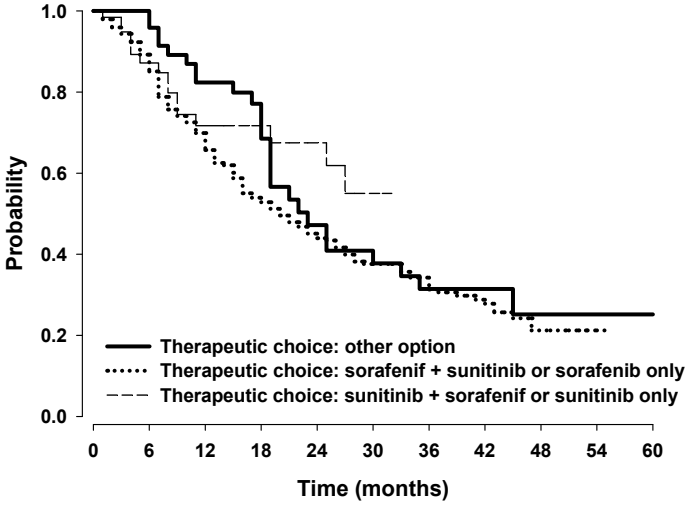


Fig. 3. Overall survival with sorafenib and sunitinib compared with other therapies

In detail, the PFS was 17 months with the specific sequence of SO+SU (9 months + 8 months) and 16 months with SU+SO (12 months + 4 months). The median PFS of first line treatment with either SO or SU was 10.5 months.

Furthermore in the multivariate overall survival analysis un-adjusted for the Motzer classification (**Table 3**) the risk was nearly 1.5 times higher in those patients who had previously been treated with cytokines compared with those who had not received cytokines (p<0.033).

	Hazard ratio (95% CI)	**p**
Age		
10 years increasing	0.98 (0.86; 1.11)	0.735
Sex		
Male vs. female	1.09 (0.77; 1.55)	0.635
ECOG PS		
1 vs. 0	1.69 (1.25; 2.29)	**<0.001**
2 vs. 0	2.62 (1.39; 4.95)	
Cytokine		
Yes vs. no	1.28 (0.95 ; 1.72)	0.101
Histology		
Papillary vs. clear cell	1.39 (0.85; 2.27)	0.247
Non clear cell vs. Clear cell	1.47 (0.75; 2.89)	
Nephrectomy		
Yes vs. no	0.41 (0.26; 0.65)	**<0.001**
Motzer criteria		
Intermediate vs. low risk	2.30 (1.57; 3.35)	**<0.001**
High vs. low risk	7.90 (5.07;12.31)	
Therapeutic choice		
Other option vs. Sorafenib+sunitinib	0.77 (0.51;1.17)	0.212
Sunitinib+sorafenib vs. sorafenib+sunitinib	0.69 (0.41;1.16)	

ECOG PS = Eastern Cooperative Group Performance Score

Table 2. Univariable overall survival analysis

7. Adverse events

The most commonly reported treatment-related all grade adverse events (AEs) were typical of those reported with TKIs including asthenia, hand-foot syndrome, hypertension, diarrhea, mucositis, hypothyroidism and most of these were mild or moderate in intensity (Grade 1 or 2). Overall, 61 (19.68%) patients experienced AEs Grade ≥3 (**Table 4**) and there were a total of 65 Grade ≥3 AEs, and three patients experienced a Grade 4 event (two patients receiving SU+SO had cardiac failure and one receiving SO+SU had a cardiac stroke). The percentage of patients experiencing adverse events Grade ≥3 was similar in patients treated when SO was given as in those treated first with SU then SO (18.88 and 17.46%). In those treated with other systemic therapies there was a tendency to a higher incidence of AEs (25.5%). Furthermore the nature and severity of AEs groups did not differ if SO or SU was given first.

	Adjusted for Motzer criteria		**Not adjusted for Motzer criteria**	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age				
10 years increasing	0.98 (0.85; 1.12)	0.767	0.91 (0.80; 1.04)	0.180
Sex				
Males vs. females	0.91 (0.62; 1.32)	0.611	1.09 (0.76; 1.59)	0.631
ECOG PS				
1 vs. 0	1.09 (0.78; 1.54)	0.838	1.53 (1.11; 2.12)	**0.003**
2 vs. 0	0.95 (0.48; 1.89)		2.42 (1.27; 4.59)	
Cytokine				
Yes vs. no	1.26 (0.91; 1.75)	0.169	1.41 (1.03; 1.94)	**0.033**
Histology				
Papillary vs. clear cell	1.35 (0.81; 2.24)	0.478	1.42 (0.86; 2.35)	0.285
Non clear cell vs. clear cell	1.19 (0.60; 2.39)		1.38 (0.69; 2.74)	
Nephrectomy				
Yes vs. no	0.59 (0.35; 0.98)	**0.041**	0.40 (0.24; 0.67)	**0.001**
Motzer criteria				
Intermediate vs. low risk	2.15 (1.44; 3.21)	**<0.001**	-	-
High vs. low risk	7.23 (4.42; 11.83)		-	
Therapeutic choice				
Other options vs. sorafenib+sunitinib	0.84 (0.55; 1.29)	0.388	0.85 (0.56; 1.30)	0.675
Sunitinib+sorafenib vs. Sorafenib+sunitinib	0.70 (0.40; 1.23)		0.85 (0.49; 1.47)	

ECOG PS = Eastern Cooperative Group Performance Score

Table 3. Multivariable overall survival analysis

Adverse event	**N**	**% (N/310)**
Asthenia	36	11.61
Hand-foot syndrome	13	4.19
Anemia	4	1.29
Cardiac failure	2	0.65
Hypertension	2	0.65
Mucositis	2	0.65
Abdominal pain	1	0.32
Cardiac stroke	1	0.32
Fever	1	0.32
Macroematuria	1	0.32
Nausea	1	0.32
Rash	1	0.32

Table 4. Adverse events Grade ≥3 (patients may have experienced one or more events)

8. Discussion

Despite improvements in therapy, RCC eventually progresses during therapy and other agent(s) need to be administered in an attempt to control the disease.

This large-scale retrospective analysis was carried out to investigate the effects of systemic therapy in general and in particular to compare the efficacy and safety of different sequential approaches with targeted therapies in controlling the disease progression of patients with RCC. Importantly, our results show that treatment with TKIs improves survival. In fact the median OS for patients with advanced RCC has increased from around 13 months before the introduction of TKIs to around 22 months in the last decade and the median OS of 22 months observed in the present study provides further evidence to support the importance of use of TKI in patients with advanced RCC. In addition, to our knowledge most studies have considered PFS, and not OS, as the major determinant of clinical efficacy of any sequential therapy for the treatment of RCC: our study provides new evidence on OS even in a large unselected population from a single institution. Of note, a relevant proportion of patients received sorafenib as a first-line agent, despite current recommendations suggest this molecule as a second-line treatment, and sunitinib at progression of disease. This therapeutic strategy did not result in any worsening of clinical outcomes and in a similar tolerability with respect to the other therapeutic strategies assessed. Even if this study was not designed to evaluate the feasibility of sorafenib as a first-line agent, and therefore we are unable to draw any conclusion, we believe that this finding could be of some interest in the current therapeutic scenario of RCC patients.

In addition, the Motzer criteria resulted significant prognostic factors in both the uni- and multi-variate analysis. On this basis, we suggest that these criteria should – at present - be regarded to as the most useful tool for the definition of prognosis and, as a consequence, for the optimization of therapy for every single patient.

Of note, the findings reported in the present report were obtained in a real-life scenario, on a large population of unselected patients: it has been suggested that observational trials can expand upon outcomes of randomized controlled trials, which are necessarily conducted in highly-selected patients [22].

In most patients with advanced RCC the objective of treatment is to stabilize disease and prolong survival and there is good evidence that this can be achieved with sequencing systemic agents. The use of this therapeutic approach, in fact, may determine a relevant benefit in terms of OS and quality of life, independently from the specific sequence of targeted therapies used.

Our study confirms the suitability of a TKI sequential therapy. This finding is in line with recent evidence, albeit collected in retrospective studies, which seems to support that the use of SO before SU, rather than vice versa may be more effective in extending PFS (**Table 5**). In addition, some studies suggest that SO may be associated with a more favorable safety profile than more potent SU, in terms of incidence of changes in blood counts and anemia [23,24].

The major limitations of the current study was that the sample size was not randomized and the data were collected retrospectively. In addition the study populations were very hoeterogenous with much patients received the sequence TKI followed TKI and only few cases treated with bevacizumab, everolimus, temsirolimus and axitinib.

Source	*n*	1st PFS (months)	2nd PFS (months)
Sorafenib→Sunitinib			
Eichelberg et al.	30	8.7	10.3
Dudek et al.	29	5.1	18.0
Porta et al.	83	9.8	8.4
Procopio et al.	50	9.5	8.3
Sablin et al.	68	6.0	6.5
Zimmerman et al.	22	11.5	5.0
Sunitinib→Sorafenib			
Dudek et al.	20	5.8	8.5
Porta et al.	87	8.3	3.7
Sablin et al.	22	5.1	3.9
VEGFi→Sorafenib			
Garcia et al	48	8.7	3.7

PFS = progression-free survival; TTP = time to progression.

Table 5. Summary of sorafenib and sunitinib sequence data (reproduced from ref 24)

In conclusion, despite the major breakthrough introduced by targeted therapies, further research is necessary to shed new lights on the most effective use of these drugs in clinical practice: in particular, the optimal sequence of TKIs has yet to be established.

Our study supports – however - the importance of TKI treatment in RCC patients to improve OS. In addition, it suggests that factors other than the specific sequence of treatment, like the Motzer classification, influence the OS in a large unselected population from clinical practice collected in a single institution. On the basis of these results and of current evidence reported in literature is now clear that there is not one therapy that will benefit all patients and treatment should be tailored to meet individual circumstances and needs. Physicians should therefore base their treatment decisions not only on data from RCTs but also on clinical experience and judgment

9. References

[1] Lindblad P. Epidemiology of renal cell carcinoma. *Scand. J. Surg.* 93(2), 88–96 (2004).
[2] Chow WH, Devesa SS, Warren JL, Fraumeni Jr JF. Rising incidence of renal cell cancer in the United States. *JAMA*. 281(17), 1628–1631 (1999).
[3] Bos SD, Mellema CT, Mensink HJ. Increase in incidental renal cell carcinoma in the northern part of the Netherlands. *Eur. Urol*. 37 (3), 267–270 (2000).
[4] Mevorach RA, Segal AJ, Tersegno ME, Frank IN. Renal cell carcinoma: incidental diagnosis and natural history: review of 235 cases. *Urology*, 39 (6), 519–522 (1992).
[5] Hock LM, Lynch J, Balaji KC. Increasing incidence of all stages of kidney cancer in the last 2 decades in the United States: an analysis of surveillance, epidemiology and end results program data. *J. Urol*. 167 (1), 57–60 (2002).
[6] Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. *J. Urol*.166 (5), 1611–1623 (2001).
[7] Atzpodien J, Royston P, Wandert T, Reitz M. Metastatic renal carcinoma comprehensive prognostic system. *Br. J. Cancer* 88 (3), 348–353 (2003).

[8] Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am. J. Surg. Pathol. 27 (5), 612–624 (2003).

[9] Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer. J. Clin.* 54(1), 8–29 (2004).

[10] Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. *J. Urol.* 163 (2), 408–417 (2003).

[11] Oudard S, George D, Medioni J et al. Treatment options in renal cell carcinoma: past, present and future. *Ann. Oncol.* 18 (suppl 10), 25–31 (2007).

[12] Atkins MB, Regan M, McDermott D. Update on the role of interleukin 2 and other cytokines in the treatment of patients with stage IV renal carcinoma. *Clin. Cancer. Res.* 10 (suppl), 6342–6346 (2004).

[13] Hutson TE. Targeted Therapies for the Treatment of Metastatic Renal Cell Carcinoma: Clinical Evidence. *The Oncologist.* 16 (suppl 2), 14–22 (2011).

[14] Dudek AZ, Zolnierek J, Dham A, Lindgren BR, Szczylik C. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. *Cancer*. 115 (1), 61–67 (2009).

[15] Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 372 (9637), 449–456 (2008).

[16] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. V. 2.2010. Available at http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf. Accessed March 22, 2011.

[17] Ljungberg B, Cowan N, Hanbury DC et al. European Association of Urology Guidelines on Renal Cell Carcinoma. 2010. Available at http://www.uroweb.org/gls/pdf/Renal%20Cell%20Carcinoma%202010.pdf. Accessed March 22 2011.

[18] Hutson TE, Bukowski RM, Cowey CL, Figlin R, Escudier B, Sternberg CN. Sequential use of targeted agents in the treatment of renal cell carcinoma. *Crit. Rev. Oncol. Hematol.* 77 (1), 48–62 (2011).

[19] Beck J,Procopio G,Bajetta E et al. Final results of the European Advanced Renal Cell Carcinoma Sorafenib (EU-ARCCS) expanded-access study: a large open-label study in diverse community settings. *Ann. Oncol.* 2011; Epub ahead of print.

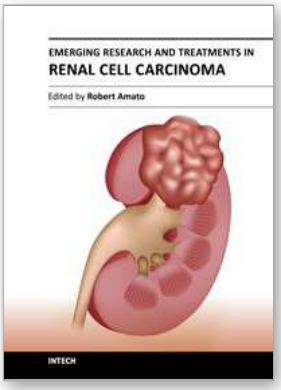
[20] Procopio G,Verzoni E, Guadalupi V, Pietrantonio F, Salvioni R, Nicolai N, et al. Sequential use of sorafenib (So) followed by sunitinib (Su) in metastatic renal cell cancer (mRCC): a single-institution experience [abstract]. Genitourinary Cancers Symposium. Orlando, FL, February 26–28; 2009 [Abstract 319].

[21] Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J. Clin. Oncol.* 17 (8): 2530-40 (1999).

[22] Silverman SL. From randomized controlled trials to observational studies. *Am. J. Med.* 122 (2), 114-20 (2009).

[23] Grünwald V, Heinzer H, Fiedler W. Managing side effects of angiogenesis inhibitors in RCC. *Onkologie* 30, 519–524 (2007).

[24] Ivanyi P, Winkler T, Ganser A, Reuter C, Grünwald V. *Dtsch. Arztebl. Int.* 105 (13): 232–237 (2008).



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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

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