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Oncology Gold Standard™ practical consensus recommendations 2016 for treatment of advanced clear cell renal cell carcinoma

Authors OGS RCC Group (in Alphabetical Order) Coordinating Committee: Batra U, Parikh PM, Prabhash K, Tongaonkar HB and Expert Group Members: Chibber P, Dabkara D, Deshmukh C, Ghadyalpatil N, Hingmire S, Joshi A, Raghunath SK, Rajappa S, Rajendranath R, Rawal SK, Singh Manisha, Singh R, Somashekhar SP, Sood R

Abstract

The Oncology Gold Standard (OGS) Expert Group on renal cell carcinoma (RCC) developed the consensus statement to provide community oncologists practical guidelines on the management of advanced clear cell (cc) RCC using published evidence, practical experience of experts in real life management, and results of a nationwide survey involving 144 health-care professionals. Six broad question categories containing 33 unique questions cover major situations in the routine management of RCC. This document serves as a ready guide for the standard of care to optimize outcome. The table of "Take Home Messages" at the end is a convenient tool for busy practitioners.

Key words: Guidelines, immuno-oncology, kidney cancer, mammalian target of rapamycin inhibitor, targeted therapy, tyrosine kinase inhibitors, vascular endothelial growth factor

Introduction

The Oncology Gold Standard (OGS) Expert Group on renal cell carcinoma (RCC) met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines on the management of advanced clear cell (cc) RCC. Their discussions were based on the scenario as exists currently in India. The mandate was to develop practical consensus recommendations (PCRs) applicable globally with emphasis on countries with limited resources. The expert group members included members of Indian Cooperative Oncology Network Trust, Molecular Oncology Society, Indian Society of Medical and Pediatric Oncology, Urology Association of India (USI), and Mumbai Urological Society.

The manuscript is developed with the help of domain expertise of the expert group (by invitation), published evidence, and practical experience in real life management of such patients. Results of a nationwide survey involving 144 health-care professionals managing advanced RCC was also taken into consideration by the expert panel. Secretarial, academic, and educational support were provided by OGS.

The core expert group discussed over several sessions and arrived at a consensus on the methodology to be used, as well as develop the survey questionnaire. The series of multiple choice questions included key practical issues and management challenges. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use PCR for advanced RCC. The OGS PCR 2016 will therefore serve to optimize the management of advanced cc RCC in conjunction with evolving literature, good clinical judgment, and individual patient characteristics and preferences.

As a part of the background work, current published evidence and landmark papers were provided to the expert group panel members for review.[1-4] The experts were also provided the analysis of the survey data involving 144 health-care professionals actively treating RCC (medical oncologists, genitourinary oncologists, urologists, radiation oncologists, and surgical oncologists). These were spread across 17 cities in India – 38% of respondents being from metro cities. The geographical distribution across the country indicated that 42% of respondents were from the North, 22% from the West, 21% from East, and 15% from the South. Members of the core and extended panel were encouraged to share their personal experiences, take into consideration the unique features particular to countries with limited resources, make comments, and record dissent while voting for the consensus statements.

A total of six broad question categories containing 33 unique questions were the part of the expert group discussions [Table I].

This manuscript is the outcome of the expert group consensus arrived at on Saturday, March 12th, 2016. The OGS PCR shall be updated from time to time as and when significant new developments impact management of cc RCC.

Defining Clinical Cohort and Practice of Expert Group Panel Members

Urological malignancies form 20% of all cancers in India.[5] Globally RCC forms about 338,000 new cases[6] annually with 50% death rate. In India, the incidence of new cases with malignant neoplasms of the kidney is 15–22 per 100,000 per year. This amounts to 2% of all cancers. The median age at diagnosis is 52 years. The age-adjusted incidence of RCC in metro cities varies from 2.1 to 3.4 per 100,000 of the population [Table II].[7]

Its incidence is increasing significantly in India, as well as globally.[8] The population-based cancer registry of Indian Cancer Society has documented that the incidence of kidney cancer in the four cities of Mumbai, Pune, Nagpur, and Aurangabad is 408 new cases in the year 2011 and trends indicate that it will increase by 50% when we are in the year 2020 – within the next 4 years.[9]

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Correspondence to: Dr Purvish M. Parikh, Department of Precision Oncology, Asian Cancer Institute, Somaiya Hospital, Sion East, Mumbai. E-mail: purvish1@gmail.com

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Up to 30% of patients present with the involvement of lymph nodes (LNs) or metastatic disease at initial diagnosis. Moreover, 20–40% of patients with the localized disease will develop metastasis during the course of their management. With the 5 year survival of Stage III RCC being only 50% and dropping to 8% as the disease progresses to Stage IV, this is an unmet need that needs urgent attention.[10] With several effective targeted agents becoming available in the last 5 years and the emerging role of immune-oncology, it is important that therapy is personalized to optimize outcome and patient benefit. Our primary objective therefore was to develop a consensus document for community oncologists and urologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the current practice of the survey participants, and the group panel members provided their domain expertise and insights to finalize the recommendations.

Since cc RCC forms 70–85% of all RCCs, this PCR is limited to advanced stage of cc RCC only.[11]

Investigations

To the question about minimum information required in the histology report in advanced cc RCC, the answers are shown in Table III.

While all the options in Table III are important under usual circumstances, the situation is different with metastatic disease. Here, besides the histologic subtype, the other minimum information required is presence or absence of LN metastasis as identified by imaging. This is because bulky LNs are associated with inferior outcome. Therefore, if cytoreductive surgery is contemplated, such patients should also undergo removal of such LNs [Table IV].[12-14]

As far as imaging is concerned, computed tomography (CT) scans of chest and abdomen are sufficient in the metastatic setting. Other imaging tests should be done only under specific conditions. All the four blood tests mentioned are routinely recommended. It needs to be stressed that CBC must be done in all cases.

Table I: Question categories addressed by the Oncology Gold Standard practical consensus recommendation expert group

Serial number	Broad question category – advanced cc RCC	Number of questions
1	Investigations	2
2	Surgery	2
3	Systemic therapy general	4
4	Systemic therapy - first line	14
5	Systemic therapy - change and sequencing	5
6	Systemic therapy - second line	6
Total		33

RCC=Renal cell carcinoma

Table II: Incidence of renal cell carcinoma in Indian metro cities (2010)

Metro city	Incidence per 100,000 of population
Delhi	3.4
Mumbai	3.3
Bengaluru	3.0
Kolkata	2.6
Chennai	2.1

Surgery

Cytoreductive surgery is to be contemplated only if there is a reasonable chance that at least two-thirds of the primary tumor can be removed. In the tyrosine kinase inhibitors (TKI) era, survival benefit might exist with this approach, especially for patients with symptomatic bulky primary [Table V].[15,16]

When the patient has already undergone nephrectomy on one side and now develops a tumor in the other kidney, the majority of survey answers (92%) were for partial excision (nephron-sparing surgery) as the treatment of choice, which was also the expert group consensus. The choice of radical surgery (selected by 2% in the survey) is applicable only when partial nephrectomy is not possible, and the plan is to place the patient on dialysis for 1 year followed by a renal transplant. This approach is not applicable in the metastatic setting. Radiofrequency ablation and cryosurgery are other alternatives that can also be considered if surgery is not possible.

Systemic therapy general

Advances in our understanding of metastatic RCC (mRCC), as well as the availability of effective cancer-directed systemic therapy, have converted this from an acute to chronic illness.

Table III: Question 1 - In your opinion, what is the minimum information required in the histology report (biopsy/surgical specimen)?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Histologic subtype	97
Completeness of resection	83
LN metastasis	77
Histologic differentiation	72
Perinephric spread	69
Sarcomatous component	66
IVC involvement	59
Capsule/fascia involvement	56
Adrenal involvement	53
Expert group consensus: In mRCC, the minimum information required is histologic subtype and presence or absence of LN metastasis as identified by imaging	

mRCC=Metastatic renal cell carcinoma, IVC=Inferior vena cava, LN=Lymph node

Table IV: Question 2 - As per your opinion, what should be the optimal laboratory/imaging investigation required for newly diagnosed clear cell renal cell carcinoma?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Imaging related	
CT scan of chest + abdomen	76
CT scan abdomen only	13
Whole body PET CT scan	47
X-ray pelvis/chest	8
Bone scan	47
Blood related	
Biochemistry	77
Serum calcium	72
Thyroid function test	24
CBC	20
Expert group consensus: CT scan of chest and abdomen are sufficient in the metastatic setting. All the four blood tests mentioned are routinely recommended in all cases	

CT=Computed tomography, PET=Positron emission tomography, CBT=Complete blood count

Patients are now surviving for several years with good quality of life. Earlier, cytokine-based therapy was associated with a median progression-free survival (PFS) of 3–5 months and median overall survival (OS) of up to 17 months. With targeted therapy, the median OS is up to 29 months.[17] Of the multi-targeted TKIs currently available in India, the most commonly used ones are pazopanib, sunitinib, and sorafenib. We also have available kinase inhibitors of mammalian target of rapamycin (mTOR), of which the commonly used ones include everolimus and temsirolimus [Table VI].

Systemic therapy is recommended for all patients with mRCC, as well as those with recurrence or progressive disease. It should not be used only if specifically contraindicated. Adjuvant systemic therapy is also recommended for all patients.[18] For instance, pazopanib has been shown to be effective in the adjuvant setting. On the other hand, vascular endothelial growth factor (VEGF) TKIs are not recommended in the adjuvant setting for routine use.[19-21] It should be used only if upfront resection is not possible due to large tumors, bilateral disease, or involvement of IVC [Table VII].

Expert group consensus regarding prognostic markers and predictive modeling is that they should be taken into consideration in all patients. Since only 60% of the survey answers to this question were yes, there is an urgent need to educate the health-care professionals in the value and importance in implementing this in daily practice.

Any one of the existing criteria (Memorial Sloan Kettering Cancer Center [MSKCC], modified MSKCC and Heng Prognostication Criteria) can be taken into consideration while starting systemic therapy. Recently, it has been validated that hemoglobin, performance status (PS), neutrophil count, and time from diagnosis to treatment were independent predictors of survival in different risk category groups in mRCC in both the first-line and second-line setting.[22,23]

There is potential confusion created by MSKCC criteria since they use five parameters in the first-line setting and three parameters in the second-line setting. It also shows that its validity is not robust. Hence, the six-factor Heng Prognostication Criteria is the recommended tool for practical decision making [Table VIII].

Active surveillance is not recommended since 80% ultimately have progression of RCC, as well as the fact that patients do not follow instructions regarding careful and timely re-evaluation. If active surveillance is at all used, it should be limited to those with normal laboratory indices, good PS, limited single-organ-system metastasis, and assurance of diligent follow-up [Table IX].

When considering predictive systemic modeling, PS indirectly includes the effect of comorbidities-both of which (together) have rightly been selected by almost all as the most important factor(s), which is very right. Together they cover 69% of respondents. Feasibility of safe nephrectomy, number and site of metastasis, and socioeconomic status are factors that may be considered in few patients. Fractional tumor volume is no longer of any importance in most patients.

For non-cc RCC, there is no currently available standard therapy (though NCCN guidelines include all the targeted agents used for cc RCC). In case the disease is of mixed histology, the patient can be treated as if having cc RCC. Best supportive care should be given to all patients, in addition to the cancer-directed systemic therapy.

Conventional chemotherapy drugs have no benefit and should not be used in cc RCC.

Table V: Question 3 - In which circumstances do you feel that cytoreductive surgery is indicated?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Upfront	57
After systemic therapy	08
Both of above	43
Recurrence - local	35
Recurrence - systemic	08
Expert group consensus: Cytoreductive surgery is to be contemplated only if there is a reasonable chance that at least 2/3rd of the primary tumor can be removed	

Table VI: Question 5 - What are the indications for commencing systemic therapy for a patient with cc renal cell carcinoma?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Neoadjuvant	29
Adjuvant	19
Metastatic	100
Recurrence	75
Progressive disease	76
Expert group consensus: Neoadjuvant systemic therapy is not standard of care	

Table VII: Question 6 - What are the important prognostic markers used in practice while taking the decision to start systemic therapy?

Options	Percentage of surveyed health-care professionals giving affirmative answer
History of prior nephrectomy	51
Serum calcium level	50
Serum LDH	54
Hemoglobin level	59
WBC count	19
Serum protein/albumin	19
Other	8
Expert group consensus: Any one of the existing prognostication criteria can be used	

WBC=White blood cell, LDH=Lactate dehydrogenase

Table VIII: Heng/International Metastatic Renal Cell Carcinoma Database Consortium Criteria

	Parameters
1	Karnofsky Performance Status <80%
2	Hemoglobin < lower limit of normal
3	Time from diagnosis to treatment < 1 year
4	Corrected calcium > upper limit of normal
5	Platelet count > upper limit of normal
6	Neutrophils > upper limit of normal
Factors applicable to the patient	**Risk**
0	Favorable
1-2	Intermediate
3 or more	Poor

Systemic therapy first line

Bevacizumab, interferons, and interleukin to be mentioned only to categorically state that they are no longer recommended in current first-line management of mcc RCC [Table X]. It is good to note that this is well understood among the experts surveyed.

Earlier guidelines and recommendations used to define treatment to the category of patients who were previously treated with and found to be refractory to cytokine therapy. Such a statement is consciously omitted from this PCR since such cytokine therapy is neither used nor recommended at present.

Both pazopanib and sunitinib are standard treatment options in the first-line setting. Two factors must be considered while selecting the most appropriate drug in a particular patient.

a. In a disease which is going to require lifelong treatment, the quality of life (QoL) is a vital consideration, especially if equally efficacious treatment options are available. When data from all phase III trials are compared [Table XI], the PFS for pazopanib (11.1 months) and sunitinib (11 months) is comparable. When considering two equally efficacious treatment options, toxicity profile is the most important consideration. Figure 1 is a forest plot that compares the adverse events (AEs) between pazopanib and sunitinib. A total of 19 AEs were higher with sunitinib, whereas six were greater with pazopanib. Some AEs affect QoL, a factor determined solely by patients. Other AEs affect important clinical and treatment decisions as determined by the treating oncologist since they can impact health and/or illness without patient being aware of them in its initial phase (neutropenia, thrombocytopenia, anemia, hand-foot syndrome, and hypothyroidism). These need to be proactively managed. Figure 2 documents that both patients (70%) and physicians (61%) prefer pazopanib over sunitinib.[28,29]
b. Temsirolimus is a treatment option for the first-line management of mcc RCC, especially for poor risk cases based on the ARCC trial.[30] There are sufficient data to indicate that everolimus is equally good, interchangeable, and more convenient. Hence, practical consensus is that everolimus is standard of care in the first line.[31]

Dose Intensity and Starting Dose: Questions regarding dose schedule used in practice showed that a significant number of patients were initiated with a suboptimal dosage/schedule. This ranged from 10% to 50%. Such a practice is strongly condemned. Compromising dose/schedule is based on the fear of dealing with adverse effects and actually provides an inferior outcome. For instance, the SCAN 2015 guideline initially allowed the use of sunitinib at 37.5 mg continuous schedule. Such a use was subsequently documented to have an inferior outcome. Standard schedule of 50 mg 4/2 was statistically superior to 37.5 mg once daily with respect to time to deterioration, as well as a composite end point of death, progression, and disease-related symptoms[32,33]

Even the recently presented data from Austria emphasize the use of labeled therapeutic starting dose of everolimus. STEPAUT Study (Start of mTOR inhibition with Everolimus after Progression on endocrine therapy in advanced breast cancer in clinical routine practice in Austria) is an Austrian noninterventional study conducted to collect real world data on the efficacy and safety of everolimus + exemestane, and

Table IX: Question 8 - Rank the patient factors important for appropriateness of predictive systemic modeling (1 is most important and 6 is least important) in percentage

Rank	1	2	3	4	5	6
Comorbidities	3	29	25	16	15	4
PS	66	18	9	5	4	0
No and site of metastasis	16	19	33	15	15	5
Feasibility of safe nephrectomy	7	15	14	21	37	8
Socioeconomic	8	16	6	25	17	27
Fractional tumor volume	0	2	13	19	12	56

Expert group consensus: Performance status and comorbidities are the factors to be considered while doing systemic modeling

Table X: Question 9 - In routine practice, what is the first-line systemic therapy preferred by you?

Options	Percentage of surveyed health-care professionals giving affirmative answer
IFNs	0
Interleukins	0
Bevacizumab plus interferon	1
Sorafenib	15
Pazopanib	41
Sunitinib	43

Expert group consensus: IFNs, interleukins and bevacizumab should no longer be considered as options for standard first-line systemic therapy

IFNs=Interferons

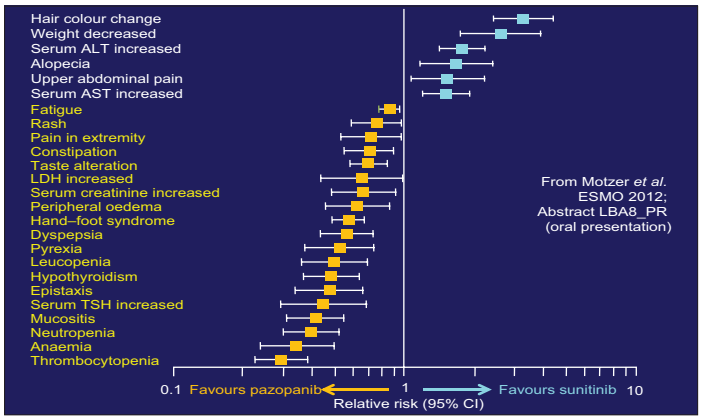

Figure 1: COMPARZ study relative risk of adverse events (occurrence ≥10% in either arm)

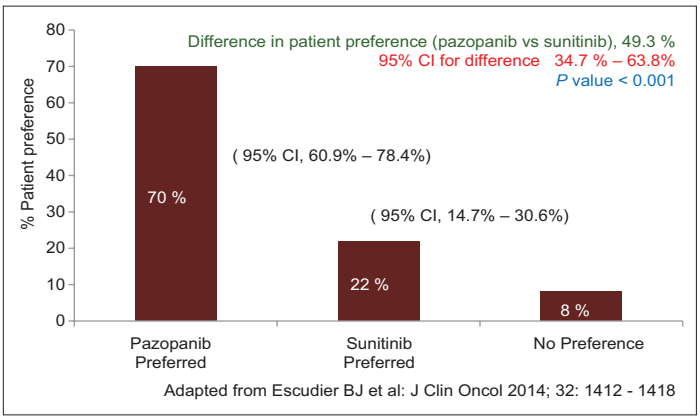

Figure 2: PISCES primary endpoint - Pt preference primary analysis population

Table XI: Phase III trials in first-line setting for metastatic renal cell carcinoma

	Trial	Drug in first line	PFS (months)	OS (months)
1	Sternberg *et al*., 2010[23]	Pazopanib Rx naïve	11.1	22.9
		Pazopanib Cytokine pretreated	7.4	
2	Motzer *et al*., 2013 (COMPARZ)[24]	Pazopanib arm	8.4	28.3
		Sunitinib arm	9.5	29.1
3	Motzer 2007[25]	Sunitinib	11	26.4
4	Hutson 2013[26]	Axitinib arm	10.1	20.1
		Sorafenib arm	6.5	19.2
5	Escudier *et al*., 2009[27,28]	Sorafenib	5.7	

Expert group consensus: First-line Phase III trials show best PFS with pazopanib and sunitinib. Choice between the two should be based on avoiding toxicity, improving QoL and patient preference

PFS=Progression-free survival, QoL=Quality of life, OS=Overall survival

data were presented at EBCC 2016.[34] A total of 150 patients have been enrolled so far in this study, of which 134 were evaluable for safety and efficacy. The two groups included 89 (60.14%) received a starting daily dose of EVE 10 mg, and 59 patients (39.86%) started treatment with EVE 5 mg. Interestingly, 54 patients (40.30%) in the EVE 10 mg group and 37 (27.61%) in the EVE 5 mg group did not have a dose change until the end of the study. The median PFS in the subgroup of patients receiving a 10 mg EVE dose was 9.83 months as opposed to a median of 4.97 months for patients receiving 5 mg. In addition, patients starting and continuing with EVE 5 mg until the end of the study were found to have more visceral metastases, worse Eastern Cooperative Oncology Group status, more prior therapies, and more treatment interruptions compared to those who started treatment with EVE 10 mg.

Hence, the initial starting dose should be the labeled dose for patients with mRCC. What is necessary is that patients are given counseling or reference material to ensure that AEs are prevented, recognized early, and promptly reported to the concerned oncologist.[35]

When asked specifically, what was the rationale for starting at a suboptimal dosage, the answers in the survey are shown in Table XII. Other than poor PS, none of the factors require initiation of therapy at less than recommended doses. Current first-line TKIs do not require starting at reduced doses even in renal impairment.

It is possible that dose adjustment shall be required during the course of treatment, after starting at the right dose and scheduling. It is important to remember that this is not required in the majority of patients. If required, the common causes identified are shown in Table XIII.

There are specific guidelines on dose adjustment with TKIs which need to be followed. Hypertension should be treated with appropriate doses with two antihypertensive agents before TKI dose reduction is done.[35]

Avoiding hot water, use of moisturizing cream, wearing thick gloves, etc., can be used in the proactive management of hand-foot syndrome.[36]

When such recommendations are followed diligently, the majority of patients can be treated without compromising on dose intensity.

Selection of appropriate co-prescription medication to proactively prevent adverse reactions is also important. For instance, the prophylactic use of dexamethasone mouthwash (10 mL of alcohol-free dexamethasone 0.5 mg/5 mL oral solution) results in the majority (almost 80%) not developing stomatitis at all compared to 33% in BOLERO-2 study (where such a strategy was not used).[37] Such effective AE management strategies need to be capitalized upon.

One reason is that common toxicity criteria (CTC) grading and criteria for AE documentation and reporting are not uniformly used. The survey showed that only 79% actually used them. The expert group consensus is that CTC should be used to guide dose adjustment when required. The Common Terminology Criteria for AE reporting v4.0 is the most recent one. More than half (53%) of the experts surveyed felt that proper documentation of AE using CTC was not possible due to time constraints, it being cumbersome or the criteria not being easily accessible [Table XIV]. The expert group consensus is that medically significant AEs should be clearly documented along with the corrective course of action to be followed till its resolution.[38]

Table XII: Question 17 - What are the reasons for starting at lower than standard recommended dose and schedule in daily practice?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Poor PS	79
Renal impairment	40
Cardiac disorder	4
Hepatic disorder	3
Low BSA	1*
Other	1*
All options	2*

Expert group consensus: Current first-line TKIs do not require starting at reduced doses for any reason other than poor PS

*Absolute numbers. BSA=Body surface area, PS=Performance status, TKIs=Tyrosine kinase inhibitors

Table XIII: Question 18 - In routine practice, when does adjustment is actually done for?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Any Grade 3 or 4 toxicity	94
Hand-foot syndrome	38
Mucositis	30
Hypertension	22
Raised LFT	17

Expert group consensus: Follow specific guidelines for dose adjustment with TKIs. Hypertension should be treated with appropriate doses of two antihypertensive drugs before TKI dose reduction is done

TKIs=Tyrosine kinase inhibitors, LFT=Liver function test

Monitoring of patients while on TKI showed a lot of gray areas – both in the opinion of what is required, as well as their actual implementation in clinical practice [Table XV]. Clinical examination, blood pressure monitoring, routine blood tests, and thyroid function tests are to be repeated as routinely required. A bone scan is required only for response evaluation when patients have significant bony involvement. Electrocardiogram and two-dimensional echocardiogram are no longer required for routine follow-up. They should be used only if patients have significant cardiac-related symptoms or is clinically indicated. CT scan, activated partial thromboplastin time/international normalized ratio should be done when clinically indicated.

Systemic therapy change and sequencing

Table XVI defines the inculcations for change from first to second line systemic therapy. Failure of efficacy (progressive disease or resistance) was selected by 99%, which is appropriate. AEs were selected by 70%. This is a healthy trend. AEs should be managed with appropriate measures (co-prescriptions, symptomatic therapy, and dose adjustments) before considering shifting to second-line therapy.

Majority of the polled doctors prefer TKI – mTOR – TKI sequencing [Table XVII]. RECORD-4 study in purely second-line setting using everolimus after the failure of one prior VEGF-directed therapy showed median PFS of 7.8 months and OS of 23.8 months.[39] This can be explained on the basis of change in the mechanism of action of mTOR inhibition which will target downstream activation, translating to efficacy, and differentiated safety profile as compared to cumulative toxicity with may occur with sequential use of TKI.[40]

It is important to keep in mind that almost a quarter of patients will not be in a position to receive 3rd line therapy (due to poor PS, significant comorbidities, unwillingness, etc.). Hence, the choice of the second-line therapy should not be made with the intention of reserving a drug for the 3rd line. Finally, no head-to-head comparison trials are likely to be initiated in the future. Hence, the currently existing data need to be extrapolated for real life decisions. Table XVIII shows the cross-trial comparison of outcome after the second-line therapy in mRCC using data from key trials.

While selecting the most appropriate choice of cancer-directed systemic therapy, several factors are important in the Indian setting. These factors are also applicable in other countries (low- and middle-income countries, as well as uninsured patients in all countries). The majority correctly rely on results of clinical trials. However, it must be borne in mind that such results are directly applicable only to that population which falls into their respective inclusion criteria. For instance, elderly patients or those with significant comorbidities are often excluded from trials but form a chunk

Table XIV: Question 22 - What prevents the use of common toxicity criteria for adverse event reporting?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Not easily accessible	10
Time constraints	33
Cumbersome	10
Not required	7
Other (not specified)	1*
Expert group consensus: Medically significant adverse events should be documented	

*Absolute numbers

Table XV: Question 19 and 20 - what are the minimum tests required for optimal monitoring while the patient is on tyrosine kinase inhibitors?

Options	Percentage of surveyed health-care professionals giving affirmative answer	
	Opinion	Actual practice
CBC/LFT/RFT	94	95
BP monitoring	78	68
CT scan	60	54
Thyroid function tests	52	48
Clinical examination	57	32
Bone scan	37	26
ECG/ECHO	63	35
APTT/INR	13	9
Expert group consensus: Clinical examination, BP monitoring, routine blood tests and thyroid function tests are to be repeated as routinely required. Other tests are not routinely necessary and should be done only when clinically indicated		

TKIs=Tyrosine kinase inhibitors, CBC=Complete blood count, BP=Blood pressure, LFT=Liver function test, RFT=Renal function test, INR=International normalized ratio, ECG=Electrocardiogram, APTT=Activated partial thromboplastin time, ECHO=Echocardiogram, ECG=Electrocardiogram

Table XVI: Question 23 - What is the most important factor in practice for shift from first-line to second-line systemic therapy?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Progressive disease	89
Resistance	10
Intolerance	36
Grade 3 or 4 toxicity	34
Expert group consensus: Progressive disease and resistance related to failure of efficacy. Intolerance and Grade 3 and 4 toxicity related to adverse events. Both groups are important and are reasonable reason to shift to second-line systemic therapy	

Table XVII: Question 24 - What is your preferred selection of sequencing of systemic therapy?

Options	Percentage of surveyed health-care professionals giving affirmative answer
TKI >mTOR >TKI	63
TKI >TKI >mTOR	37
No preference	1*
Expert group consensus: Pure second-line data demonstrate best PFS with everolimus. Since 24% of patients never get the third line therapy, choice of second-line therapy should not be based on reserving a drug for the third line	

*Absolute numbers. TKI=Tyrosine kinase inhibitor, PFS=Progression-free survival, mTOR=Mammalian target of rapamycin

Table XVIII: Cross trial comparison of drugs used in "pure" second-line therapy for metastatic renal cell carcinoma

Drug	Trial acronym	PFS (months)	OS (months)
Everolimus	Record - 4	7.8	23.8
Axitinib	Axis	6.7	20.1
Sorafenib	Target	5.5	17.8

PFS=Progression-free survival, OS=Overall survival

of real life patients. Furthermore, once the patient exits a trial, they will continue to receive treatment outside of the trial setting. Crossover to the active drug is also permitted in most trials. Hence, difference in overall outcome (e.g., survival) is actually more with the active drug than is documented in published literature.

The other aspect to be taken into consideration is the cost. This has been identified as an important influence in two-thirds of cases [Table XIX]. Hence, counseling should focus on providing the information, and then respecting the patient's right to decide about his or her treatment.

Table XX documents the factors that influence the selection of second-line therapy. Contrary to expectations, the efficacy of the drug did not emerge as the most important factor. Longer duration of response to first-line therapy predicts a better prognosis irrespective of what is selected as the second-line therapy.

Selecting the right sequence of drugs shall therefore strive to optimize overall benefit for the patient – converting an acute illness to a chronic one, while providing best likelihood of reduced relative risk and/or longer OS and/or better QoL. The risk of discontinuation and interruptions due to clinically significant toxicity will form an important consideration [Figure 2].[41,42]

Threshold for stopping current line of therapy (and proceeding to a newer agent/next line) may be lowered (any toxicity, stable disease at first scan, etc.) in selected cases.

Systemic therapy second line

It is very unlikely that any head-to-head comparison trials are going to be initiated in the second-line setting with. Hence, the decision will need to be made based on cross-trial comparison, even if this is not an ideal situation [Table XVIII, vide supra].

Since the best PFS and OS are with everolimus, it is not surprising that the majority of health-care professionals surveyed selected this option [Table XXI].

Longevity is increasing steadily. Hence, also are expectations from medical management. Hence, dose intensity should not be compromised simply because the patient belongs to the geriatric age group. It is the biological age and fitness that matter. Table XXII shows the common reasons for compromise of dose intensity in the real world.

Additional considerations

At present, there are no trials for mRCC in the third line setting. Hence, there is no standard of care. Oncologists should select cancer-directed systemic therapy in the third line setting on the basis of individual patient requirement.

Advances in molecular oncology are playing an increasing role in precision oncology and personalized care. For instance, 2–3% of all RCC are hereditary, whereas 50% are diagnosed incidentally. Von Hippel-Lindau (VHL) tumor-suppressor gene inactivation (dep 3p-) is seen in familial VHL cancer syndrome and in more than 80% of sporadic RCCs. Other changes seen are t (3;8)(FHIT gene) and t (3;11). WHL mutations are also important since they lead to overexpression of VEGF and dysregulation of hypoxia-inducible factors.

Other pathway molecular alterations include mTOR, FGF, FGFr, and Akt. When RCCs are driven by mTOR pathway,

Table XIX: Question 26 - What are the data that influence your selection of systemic therapy of choice?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Clinical trial results	89
Cost	67
Toxicity profile	62
Effects of comorbidities	33
Other (reliability of patient)	1*
Expert group consensus: Clinical trial results need to be interpreted in the correct context for each individual patient. Treatment decisions are based on all factors applicable to the patient - with a personalized approach	

*Absolute numbers

Table XX: Question 27 - What is the most important prognostic marker that will influence your selection of second-line systemic therapy?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Duration of response to first-line systemic therapy	67
PS	34
Response rate of second-line drug	29
Other (cost)	3*
Expert group consensus: Duration of response to first-line systemic therapy is a general good prognostic marker. Choice of the second-line drug will depend on its likely response rate and the ability of the patient to tolerate it	

*Absolute numbers. PS=Performance status

Table XXI: Question 28 - What is the most common second-line systemic therapy actually used in your practice?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Everolimus	53
Axitinib	23
Sorafenib	23
Pazopanib	2*
Expert group consensus: Based on cross-trial comparison (since there will not be any head to head comparison), everolimus gives the best PFS and OS in the second-line setting and is therefore recommended as the drug of choice for second-line therapy of mRCC, unless otherwise contraindicated	

*Absolute numbers. mRCC=Metastatic renal cell carcinoma, PFS=Progression-free survival, OS=Overall survival

Table XXII: Question 33 - In which patient will you start with lower than recommended dose for second-line systemic therapy?

Options	Percentage of surveyed health-care professionals giving affirmative answer
Poor PS	69
Compromised organ function	53
Poor tolerability to first-line systemic therapy	46
Elderly	31
Expert group consensus: Chronological age of the patient should not be a reason to initiate second-line therapy at suboptimal doses. If the other three factors mentioned above do not exist, elderly patients tend to tolerate full recommended doses like their younger counterparts	

PS=Performance status

they have elevated pS6, pAKT, elevated lactate dehydrogenase, and specific mutations. In the future, some of them have the potential to become useful prognostic and/or predictive biomarkers.

The other area that is the focus of interest is the high individual variations in drug effect due to PK and PD variability. Some of these are specifically due to genetic differences in how drugs are metabolized in the body. Single nucleotide polymorphisms affecting the activity of key enzymes are therefore being studied to fine tune management in individual patients.

Immuno-oncology is recognized as the most important advance for the year 2015. Its application has spread to a host of organ-specific tumors that were hitherto not considered to be immune susceptible. Immune strategies have been used in RCC since long, and we expect that better such strategies will be available in the near future.

We believe that we are living in exciting times. Such advances will resolve many of the key gaps in our knowledge that exists today. PCRs like these will ensure that such insights are made available to the health-care professionals in the community as an effective education tool as soon as possible.

Conclusion

The OGS PCR2016 expert group for advanced cc RCC had the specific mandate to develop PCRs for easy application by the community oncologist. It took into consideration data, as well as the current practices in India, in addition to international data that conventional panels look at, making it the perfect blend of evidence, clinical expertise, and real life preference.

The options for treatment of such patients include pazopanib, sunitinib, sorafenib, everolimus, temsirolimus, axitinib, nivolumab, and cytokine molecules.

Common factors to be considered while selecting therapy in individual patients include previous therapy, disease-free interval, tumor biology, molecular markers, number and sites of metastasis, underlying medical and social issues (age, PS, and comorbidities), patient preferences (convenience vs. compliance), risk of toxicities, and their implications.

This PCR allows for optimal sequencing of the effective therapeutic interventions available today [Table XXIII]. While both VEGF as well as mTOR result in the better outcome as compared to their control arms, the magnitude of clinical benefit, as well as the robustness of currently available data, favors the use of mTOR inhibitor, everolimus. The benefit to individual patients can be optimized (response as well as the quality of life) by paying adequate attention to proactively minimizing toxicity.

Unresolved issues of importance will be addressed in the updated version of this document as more data become available and the group makes insightful revisions. Therefore, the group encourages gathering real world evidence on efficacy and safety of various treatment options in Indian patients. All those interested in contributing are requested to contact us through E-mail.

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Conflicts of interest

There are no conflicts of interest.

Table XXIII: Take home messages

	Parameters
1	Cytoreductive surgery is to be contemplated only if there is a reasonable chance that at least 2/3rd of the primary tumor can be removed
2	For first-line systemic therapy, the Phase III trials show best PFS with pazopanib and sunitinib. Choice between the two should be based on avoiding toxicity, improving QoL, and patient preference
3	PISCES study showed that 70% of patients and 61% of physicians prefer pazopanib over sunitinib
4	Current first-line TKIs do not require starting at reduced doses for any reason other than poor PS
5	Hypertension should be treated with appropriate doses of two antihypertensive drugs before TKI dose reduction is done
6	Optimal monitoring of patients on TKIs require clinical examination, BP monitoring, routine blood tests, and thyroid function tests. Other tests should be done when clinically indicated
7	Since 24% of patients never get the third line therapy, choice of second-line therapy should not be based on reserving a drug for the third line
8	Pure second-line data demonstrate best PFS with everolimus
9	Chronological age of the patient should not be the default reason to initiate second-line therapy at suboptimal doses

PFS=Progression-free survival, PS=Performance status, QoL=Quality of life

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