Review

Assessing the impact of evolving evidence in renal cell carcinoma treatment: An update of the Renal Cell Carcinoma Appropriateness-based Treatment Toolkit (ReCATT)


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Abstract The appropriateness of the numerous therapeutic options available for patients with advanced or metastatic renal cell carcinoma (RCC) was evaluated in 2011, using the RAND/University of California, Los Angeles (UCLA) appropriateness methodology to match treatment suitability to a range of patient scenarios. However, the RCC therapeutic area evolves rapidly and a body of new clinical data has accrued in the intervening years; as a result the exercise was repeated in 2013 using the same methodology, expert panel and patient scenarios. The aim of the updated assessment was to update the guidance to clinicians and use it to develop an interactive web-based application, the Renal Cell Carcinoma Appropriateness-based Treatment Toolkit (ReCATT).
This round of assessment achieved greater concordance concerning the appropriateness of treatments/interventions for the clinical scenarios tested; this higher level of agreement is likely to reflect the body of scientific evidence accrued since the previous assessment exercise. Many of the areas of disagreement in 2011 related to the suitability of pazopanib or sunitinib treatment; in the 2013 assessment both agents were considered appropriate treatment options for many of the clinical scenarios assessed. Uncertain scenarios often are related to the optimal management of metastatic RCC with clear cell histology. The use of the RAND/UCLA RCC assessment findings to develop the ReCATT support tool will help to disseminate expert opinion concerning best treatment practice and guide the clinical management of RCC patients treated in the community setting.

1. Introduction

In 2011 the RAND/University of California, Los Angeles (UCLA) appropriateness methodology [1] was used to integrate clinical efficacy data and expert opinion, to evaluate the suitability of treatments for patients with advanced or metastatic renal cell carcinoma (RCC) [2]. The RCC therapeutic area evolves rapidly [3,4] and since 2011 a new agent has been licensed and a body of new data has accrued regarding existing therapies. The RAND/UCLA-based assessment exercise was therefore repeated.

The objective of this study was to update the RAND/UCLA assessment and the resulting RCC treatment algorithm. Repeating the assessment, using the same methodology and expert panel, allowed the evolution of expert opinion to be tracked. The 2013 data have been used to support the Renal Cell Carcinoma Appropriateness-based Treatment Toolkit (ReCATT), an interactive application to guide clinicians regarding the most suitable treatment for their patient.

2. Methods

The RAND/UCLA method combines evidence-based review with the practical experience of leading clinicians. The assessment was conducted by an expert RCC panel, who evaluated the applicability of various treatment strategies to 34 clinical scenarios; the panel members and scenarios used were those from the previous RAND/UCLA assessment [2]. Treatments were identified by updated systematic literature review to January 2013.

2.1. Literature review

Systematic review of the literature considering treatments/interventions for locally-advanced/metastatic RCC involved updating the original MEDLINE search to include English language articles published from July 2010 to January 2013 using the terms: kidney cancer, metastatic renal cell carcinoma, carcinoma renal cell and clinical trial; bibliography search of articles identified additional publications. Abstracts from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and European Association of Urology (EAU) websites were also reviewed. The literature review identified data relating to the safety and efficacy of RCC treatments.

2.2. Consensus panel

The expert panel was the same as that involved in the 2011 assessment [2] and comprised recognised European RCC experts, with nine oncologists and two urologists from eight countries. All were clinical researchers who regularly publish on RCC management.

Case histories and supporting materials for the 34 scenarios and the literature review were sent to each panel member; panel members used the materials to score the treatment/intervention choices applicable to each scenario. The scoring results were discussed at a panel meeting.

2.3. Clinical scenarios

The 34 hypothetical RCC scenarios from the 2011 RAND/UCLA assessment [2] were used for this updated exercise, to ensure consistency in approach. The scenarios were based on patient characteristics considered to have a material effect on treatment decisions. Patient characteristics comprised: tumour histology (clear cell or non-clear cell), Memorial Sloan-Kettering Cancer Centre (MSKCC) score, surgical risk, tumour staging, prior systemic therapy, and prior nephrectomy; additional information concerning and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score was included in the 2013 assessment.

2.4. Classifying and grading the appropriateness of treatments for RCC patients

The 34 clinical scenarios and 575 treatment/interventions were grouped based on 6 generic descriptions (locally-advanced tumour; metastatic RCC with in-situ primary tumour and prior therapy; metastatic RCC...
with in situ primary tumour and no prior therapy; metastatic RCC with prior nephrectomy and prior therapy; and metastatic RCC with prior nephrectomy and no prior therapy) before scoring. For this updated assessment, treatment within a clinical trial (as included in the 2011 exercise) was not a therapy option, to ensure relevance to practice outside of specialist centres. Panel members scored the appropriateness of each treatment/intervention for each scenario on a scale of 1 (most inappropriate) to 9 (most appropriate).

Median scores for each treatment/intervention for each scenario were classified as:

1. **Appropriate**: A median score of 7–9, without disagreement.

2. **Uncertain**
   a. A median score of 4–6,
   b. ‘Disagreement’ (at least 4 panelists scoring low [1–3] and at least 4 panelists scoring high [7–9]).

3. **Inappropriate**: A median score of 1–3, without disagreement.

Areas of disagreement were discussed at the panel meeting, as per the RAND/UCLA methodology [1]; after discussion contentious options were re-scored.

### 2.5. Assessing the impact of evidence on expert opinion

Papers identified by literature search were graded using the Scottish Intercollegiate Guidelines Network (SIGN) system [5]. Analyses quantified and graded the evidence and explored associations between new grade 1 and 2 evidence and concurrence regarding treatment recommendations; the comparison was informal and subjective, with no statistical tests being used.

Further analyses compared the findings with those from the 2011 assessment and evaluated the impact of evidence changes on expert opinion; potential correlation between treatments/interventions where opinion changed and the level of evidence was explored.

### 2.6. Renal Cell Carcinoma Appropriateness-based Treatment Toolkit

The ReCATT toolkit was updated based on the recommendations from this assessment. The ReCATT toolkit is currently in development and comprises an interactive, web-based application into which clinicians can enter patient information relating to tumour histopathology and stage and the treatment being considered; ReCATT then provides the user with information regarding optimal treatment for the individual, based on the 2013 RAND/UCLA RCC treatment/intervention appropriateness assessment, and gives advice as to whether the treatment under consideration is suitable.

### 3. Results

#### 3.1. The evidence base

Literature search identified 65 reports cited as part of the previous assessment (February 2005–July 2010) and an additional 61 publications. A total of 123 manuscripts reported sufficient data to be included in the assessment, including: 24 sunitinib studies, 27 sorafenib studies, 14 bevacizumab studies, 7 temsirolimus studies, 15 everolimus studies, five pazopanib studies, 10 interferon alpha (IFNα) studies, nine interleukin-2 (IL-2) monotherapy studies, four studies with combination IL-2 and IFNα, 28 studies with an IFNα combination and 19 studies with an IL-2 combination. Literature details are presented as Supplementary Data. Table 1 summarises the clinical benefits (objective response rate [ORR], complete response [CR], progression-free survival [PFS] and overall survival [OS]) achieved by the RCC treatments assessed.

In September 2012 the tyrosine kinase inhibitor (TKI) axitinib was approved in the EU as second-line treatment for patients with advanced RCC. At the time of the literature search for this assessment, data from the Phase III AXIS trial [6] showed that axitinib achieved an ORR of 19% with no complete responses and median PFS of 6.7 months. The data presented by this first report were not considered sufficient to support inclusion of axitinib in the formal RAND/UCLA assessment; axitinib does however represent a novel RCC treatment and a more substantial body of data will be considered in future assessments.

Overall, 101 peer-reviewed publications supported this assessment, with 26 considered grade 1 evidence using the SIGN criteria [5]. The numbers and grading of publications identified for the 2013 and 2011 assessments are summarised in Fig. 1.

#### 3.2. Appropriateness of the treatment options

Fig. 2 summarises treatment preferences for RCC patients with locally-advanced clear cell tumours, and shows surgical intervention with no targeted therapy to be appropriate. The 2013 assessment identified some scenarios where TKIs were a potential treatment option for patients with bad surgical risk. For the purpose of the RAND/UCLA assessment an attempt was made to standardise surgical risk using the American Society of Anesthesiologists (ASA) classification system [7] which considers risk in terms of the patient’s physical status; good surgical risk was defined as ASA category 1 or 2 and bad surgical risk as ASA category 3 or 4. Surgical risk depends on the expertise of the surgeon.
and the surgical setting at the treating institution; assessing the impact of these factors was beyond the scope of this exercise.

Table 1
Systematic review of the efficacy of interventions for the management of renal cell carcinoma.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cumulative no of patients</th>
<th>No of trials</th>
<th>Objective response rate (ORR), % (range)</th>
<th>Complete response (CR), % (range)</th>
<th>Median progression-free survival (PFS), months (range)</th>
<th>Median overall survival (OS), months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>7857</td>
<td>24</td>
<td>41.9 (17.0, 58.1)</td>
<td>3.5 (1.0, 6.0)</td>
<td>9.6 (5.5, 16.3)</td>
<td>23.2 (5.5, 36.3)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>5642</td>
<td>27</td>
<td>15.9 (5.0, 50.0)</td>
<td>1.8 (1.0, 2.5)</td>
<td>8.2 (2.1, 23.9)</td>
<td>24.4 (4.3, 52.1)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2761</td>
<td>14</td>
<td>24.1 (11.0, 52.0)</td>
<td>2.3 (1.0, 4.0)</td>
<td>9.0 (3.9, 11.3)</td>
<td>24.8 (17.2, 52.1)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>2154</td>
<td>15</td>
<td>15.3 (1.0, 51.6)</td>
<td>–</td>
<td>7.3 (2.9, 29.0)</td>
<td>24.2 (6.6, 43.0)</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>1460</td>
<td>7</td>
<td>9.8</td>
<td>–</td>
<td>5.9 (2.6, 9.1)</td>
<td>30.7 (9.6, 52.1)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>1115</td>
<td>5</td>
<td>30.0</td>
<td>–</td>
<td>8.7 (5.0, 13.0)</td>
<td>52.1</td>
</tr>
<tr>
<td>Interferon alpha (IFNα)</td>
<td>3311</td>
<td>10</td>
<td>13.8 (4.8, 3.1)</td>
<td>1.8 (1.0, 3.0)</td>
<td>4.9 (3.0, 8.0)</td>
<td>14.4 (6.3, 31.0)</td>
</tr>
<tr>
<td>IL2</td>
<td>1042</td>
<td>9</td>
<td>15.6 (6.5, 23.2)</td>
<td>5.7 (3.0, 23.2)</td>
<td>11.3 (3.1, 19.5)</td>
<td>16.5 (11.5, 23.0)</td>
</tr>
<tr>
<td>Interleukin-2 (IL2) + IFNα</td>
<td>294</td>
<td>4</td>
<td>9.3 (4.9, 16.6)</td>
<td>3.3</td>
<td>6.7 (3.1, 10.4)</td>
<td>12.75 (12.5, 13.0)</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>1447</td>
<td>3</td>
<td>19</td>
<td>5</td>
<td>12</td>
<td>40.2 (15.0, 57.6)</td>
</tr>
</tbody>
</table>

Fig. 3 summarises treatment preferences for patients with metastatic clear cell RCC and prior nephrectomy. Pazopanib and sunitinib were considered appropriate for most scenarios; for non-clear cell RCC, sunitinib was considered more appropriate than other TKIs.

Fig. 4 summarises treatment preferences for patients with metastatic clear cell RCC with prior targeted therapy, for whom everolimus and TKIs were generally considered appropriate. For patients with prior sunitinib or pazopanib therapy, systemic everolimus was considered most appropriate; pazopanib was generally viewed as most appropriate for patients with prior cytokines, everolimus or temsirolimus.

There was discordance of opinion regarding the role of surgery in high-risk patients. When surgery is not indicated the systemic treatment of choice for metastatic disease with clear cell histology with/without prior nephrectomy remained unclear; possible options were pazopanib, sunitinib, sorafenib, everolimus or temsirolimus. This discordance of opinion may reflect the need...
for thorough clinical examination of such patients to further evaluate the best therapeutic approach.

3.3. New opinions regarding the appropriateness of treatment options

The 575 treatments/interventions and 34 clinical scenarios used in 2011 were reassessed in 2013. The update was generally in-line with the 2011 findings but the 2013 assessment demonstrated three trends for changing expert opinion: fewer treatments were considered appropriate; greater consensus was seen between experts; and pazopanib and sunitinib were considered equally suitable for most clinical scenarios.

Forty-one treatment options were considered appropriate in 2013, as opposed to 78 in 2011; 24 cases previously considered appropriate in 2011 were reassessed as inappropriate in 2013.

### Fig. 3. Appropriate treatment options for patients with metastatic renal cell carcinoma with prior nephrectomy.

- **Green** = appropriate treatment option.
- **Red** = inappropriate treatment option.
- **Yellow** = treatment options of uncertain appropriateness.

(The TNM classification represents stage of disease; surgical risks are according to American Society of Anesthesiologists (ASA) classification.)

### Fig. 4. Appropriate treatment options for patients with metastatic renal cell carcinoma with an in situ primary tumour.

- **Green** = appropriate treatment option.
- **Red** = inappropriate treatment option.
- **Yellow** = treatment options of uncertain appropriateness.

(The TNM classification represents stage of disease; surgical risks are according to American Society of Anesthesiologists (ASA) classification.)
ously deemed appropriate were considered inappropriate by the 2013 assessment and 23 cases previously deemed appropriate were regarded as of uncertain suitability. As a result, 439 treatments were considered inappropriate in 2013 (compared with 372 in 2011). In 2013, 95 of 575 (17%) treatments/interventions were classified as of uncertain appropriateness compared with 125 of 575 (22%) in 2011.

Greater concordance between experts was also apparent: in 2011 there was disagreement between panel members regarding 26 treatments/interventions; in 2013 scoring disagreement concerning 15 treatments was resolved during panel discussion. Most cases of disagreement related to sunitinib (7 scenarios) and pazopanib (5 scenarios); for sunitinib there was a substantial increase in the volume of data available (9 manuscripts in 2011; 24 in 2013); for pazopanib there was a dearth of data in 2011, with the evidence base increasing substantially by 2013 (from 2 to 5 manuscripts).

4. Discussion

This 2013 RAND/UCLA assessment of RCC treatments/interventions identified that: surgery was generally appropriate for patients with locally-advanced clear cell tumours; pazopanib and sunitinib were appropriate for most cases of metastatic clear cell RCC with prior nephrectomy; sunitinib was preferred over other TKIs for non-clear cell RCC with prior nephrectomy; everolimus and the TKIs were generally appropriate for metastatic clear cell RCC and prior targeted therapy. The panel considered pazopanib and sunitinib to be equally appropriate for most scenarios, reflecting the impact of the COMPARZ study [8].

The findings of the 2013 assessment have been used to update the ReCATT toolkit. ReCATT will provide guidance on suitable RCC treatment options for an individual, taking into account patient characteristics, to inform clinicians not located in specialist centres.

4.1. Appropriateness of treatment

Compared with the 2011 exercise, this assessment achieved greater concordance between panelists with regard to the appropriateness of treatments/interventions for the clinical scenarios tested. This is likely to reflect the larger body of scientific evidence accrued since 2010, with the findings of a number of clinical trials being reported in the intervening two years.

In the 2013 assessment, 17% of treatments/interventions were considered of uncertain appropriateness, slightly lower than the 22% identified in 2011 [2]. Most uncertainty related to metastatic clear cell RCC with or without nephrectomy, where there was a lack of clarity as to whether pazopanib, sunitinib, sorafenib, everolimus or temsirolimus was most efficacious. Though increased certainty is likely to relate to data accrued since 2010, it is also possible that decreased ‘uncertainty’ is in part due to increased familiarity with the RAND/UCLA methodology; this is a potential confounder when trying to identify factors driving changing expert opinion.

4.2. Change in expert opinion

Of the 78 treatment scenarios considered appropriate in 2011, opinion on 47 options (60% of those previously deemed appropriate) has changed over the intervening two years. This change reflects greater specificity regarding treatments/interventions considered appropriate to different RCC scenarios. The greater concordance achieved in 2013 can be attributed to new evidence that clearly demonstrates clinical benefit, particularly for the newer targeted therapies.

It is interesting to note the correlation between change in expert opinion and change in evidence. Of the 26 treatment options for which there was disagreement in 2011, 7 concerned the use of sunitinib; the lack of disagreement in 2013 corresponds to the availability of an additional 15 manuscripts of which 12 were evidence grade 1 or 2 (Fig. 1).

Changing expert opinion is not unexpected in a situation where evidence has accrued over time. This 2013 assessment facilitated identification of changing opinion, using the quantitative though non-statistical RAND/UCLA methodology. Having findings from the 2011 and 2013 assessments, in which the same expert panel considered the same clinical scenarios and treatment options, demonstrates how changes in treatment preference correlate with the availability of high-quality trial data.

4.3. Validation of the RAND-UCLA methodology

Validation of the semi-quantitative RAND-UCLA methodology is critical to ensuring repeatability of the exercise and credibility of the RCC treatment-assessment model as a decision tool. RAND-UCLA uses two areas of input, clinical evidence identified by systematic review and expert opinion. By examining the dynamics of change over time, findings that validate use of the methodology in the RCC setting can be identified.

The RAND/UCLA methodology proved reproducible when assessing RCC treatments, with the level of consensus between experts increasing over two years. The greater specificity of the 2013 recommendations can be correlated with the increased volume of published evidence. The RAND/UCLA methodology allows rapid integration of new evidence and expert opinion, to mirror ongoing trends in treatment preferences. The correlation between the volume and quality of the
evidence and expert opinion, indicates the validity of the RAND/ULCA methodology as a formalised decision-making tool for identifying appropriate treatments for individual RCC patients.

Seven new RCC treatments have been licensed in recent years [4,9]. The responsiveness of the RAND/UCLA assessment tool to changing clinical data and the ease of the assessment process, mean that the methodology is ideally suited to developing treatment algorithms in rapidly changing clinical settings such as RCC. Though the availability of numerous treatments facilitates development of tailored therapy regimens [10,11], a broad understanding of the evidence base is required to enable selection of the agent best suited to the individual [9]. Selection of the most appropriate treatment, necessitates that the efficacy and safety of different therapies are considered in the light of RCC disease characteristics and patient comorbidities [12]; the RAND/UCLA methodology takes into account patient characteristics, disease status and prior treatment.

Incorporating the RAND/UCLA RCC treatment assessment findings into an online support tool, in the form of ReCATT, will facilitate dissemination of best-practice from expert centres into the wider clinical-oncology community; the ReCATT tool will guide community oncologists as to suitable RCC management regimens for the individual, by taking into account patient-specific factors that impact on treatment suitability.

5. Conclusions

During the 2013 consensus meeting concordance was reached regarding 26 treatment options for which there was disagreement during the 2011 exercise. Many areas of disagreement in 2011 related to the suitability of pazopanib or sunitinib treatment; in the 2013 assessment these agents were both considered appropriate to many clinical scenarios. Areas of uncertainty among RCC experts still exist. For instance, when surgery is not indicated the systemic treatment of choice for metastatic clear cell disease with or without prior nephrectomy remains unclear.

The availability of data from large clinical trials has a rapid impact on how RCC experts treat patients; however advances may not translate into general oncology practice. The use of the RAND/UCLA RCC assessment findings to develop the online ReCATT support tool will help disseminate expert opinion on management practices and ensure that RCC patients treated in the community receive optimal therapy.

Role of the funding source

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Conflict of interest statement

Martin Gore has been on the speaker bureau and on advisory boards for Roche, GSK, Novartis, Bayer, Pfizer, Schering Plough, Bristol Myers Squibb, Aveo, AstraZeneca and Astellas and is funded by the NHRI Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London, United Kingdom.

Joaquim Bellmunt has received lectures fee and honoraria as advisor for GSK, Pfizer, Bayer Healthcare and Roche.

Tim Eisen has Astra Zeneca shareholding (£30 K), is on an advisory board for Bayer, Pfizer, Roche, GSK, AVEO. Has been involved in corporate-sponsored research by Astra Zeneca, GSK, Pfizer, Bayer, has received fees from Roche, Bayer, Pfizer, GSK, AVEO.

Bernard Escudier has been an advisor for most of the drug companies involved in RCC treatment including Pfizer, Bayer, Novartis, GSK, Roche, Aveo, and has received honoraria for this activity.

Gerald Mickisch has served as a consultant/speaker for a number of companies over the last 2 years including Astra-Zeneca, Antigenics, Pfizer, Roche, GSK, Novartis, Sanofi, Astellas, Ipsen, Takeda, Bayer, Dendreon and Wyeth.

Jean-Jacques Patard has acted as a consultant for Pfizer and GSK.

Camillo Porta has acted as a consultant and/or as a speaker for GSK, Pfizer Oncology, Hoffman La Roche, Bayer-Schering Pharma, Novartis Pharma and Boehringer Ingelheim. Furthermore, he has received research grants from Bayer-Schering Pharma and Novartis Pharma.

Alain Ravaud is a member of Global, European and/or French boards for Pfizer, Novartis, GSK, Bayer Schering, BMS on urological tumours. He has received institutional research grant/support from Pfizer, Novartis, Roche and accommodation and transport for meetings from Novartis, Pfizer, Bayer, Amgen.

M. Schmidinger has received honoraria for lectures from and/or acted as an advisor for Pfizer, GSK, Roche, Novartis, Astellas.

Patrick Schöffski has received scientific grants for translational research projects from GSK, Pfizer, Bayer, Novartis, has received honoraria for educational activities in collaboration with Astellas, GSK, Pfizer,
Bayer, Novartis, has given scientific advice to GSK, Pfizer, Bayer, Novartis, Roche.

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