The Oncologist®

Algorithms in the First-Line Treatment of Metastatic Clear Cell Renal Cell Carcinoma—Analysis Using Diagnostic Nodes

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. With the advent of targeted therapies, many treatment options in the first-line setting of metastatic clear cell renal cell carcinoma (mccRCC) have emerged. Guidelines and randomized trial reports usually do not elucidate the decision criteria for the different treatment options. In order to extract the decision criteria for the optimal therapy for patients, we performed an analysis of treatment algorithms from experts in the field.

Materials and Methods. Treatment algorithms for the treatment of mccRCC from experts of 11 institutions were obtained, and decision trees were deduced. Treatment options were identified and a list of unified decision criteria determined. The final decision trees were analyzed with a methodology based on diagnostic nodes, which allows for an automated cross-comparison of decision trees. The most common treatment recommendations were determined, and areas of discordance were identified.

Results. The analysis revealed heterogeneity in most clinical scenarios. The recommendations selected for first-line treatment of mccRCC included sunitinib, pazopanib, temsirolimus, interferon-α combined with bevacizumab, high-dose interleukin-2, sorafenib, axitinib, everolimus, and best supportive care. The criteria relevant for treatment decisions were performance status, Memorial Sloan Kettering Cancer Center risk group, only or mainly lung metastases, cardiac insufficiency, hepatic insufficiency, age, and "zugzwang" (composite of multiple, related criteria).

Conclusion. In the present study, we used diagnostic nodes to compare treatment algorithms in the first-line treatment of mccRCC. The results illustrate the heterogeneity of the decision criteria and treatment strategies for mccRCC and how available data are interpreted and implemented differently among experts. *The Oncologist* 2015;20:1–8

Implications for Practice: The data provided in the present report should not be considered to serve as treatment recommendations for the management of treatment-naïve patients with multiple metastases from metastatic clear cell renal cell carcinoma outside a clinical trial; however, the data highlight the different treatment options and the criteria used to select them. The diversity in decision making and how results from phase III trials can be interpreted and implemented differently in daily practice are demonstrated.

Introduction

Progress in understanding the molecular biology of metastatic clear cell renal cell carcinoma (mccRCC) [1, 2] has led to the development and approval of several molecularly targeted treatments in the past decade, supplementing the initially limited repertoire of immunotherapies [3, 4]. These new drugs have shown improvement in disease control, progression-free survival (PFS), and overall survival [5–11]. However, the opulence of therapeutic options has caused uncertainty and

debate regarding the optimal first-line treatment and the best sequence of treatments for mccRCC. Importantly, no predictive biomarkers are available for anti-vascular endothelial growth factor, anti-mammalian target of rapamycin, or immunotherapy.

Data from randomized trials inform about the efficacy of treatments. However, large phase III trials cannot provide information for all possible clinical scenarios or patient and disease characteristics. Only a few cancer patients are eligible for clinical trials [12], and restrictions on eligibility cast doubt on the generalizability of trial results. Yet, data from trials are the basis for establishing guidelines [13–15], and these guidelines are then used in treatment decisions for patients who would not have been eligible for the trials [16]. When high-level evidence is not available for treatment decisions, personal experience or the medical community might provide guidance [17]. The RAND/UCLA methodology aims to develop a formalized process by which expert opinions can be integrated with clinical data and used as an additional source of information [18, 19].

The objective consensus method based on diagnostic nodes (Dodes) allows automated comparison of multiple recommendations and provides information on agreement and disagreement in treatment strategies [20, 21]. Predominant recommendations and minority opinions can be mapped. The goal of the present project was to investigate the treatment strategies for mccRCC in centers of expertise and compare them. It was not the scope of the present analysis to provide treatment recommendations, give guidance, or advocate certain drug choices, but rather to illustrate the diversity in decision making and assess practice patterns.

Materials and Methods

Medical oncology experts in the field of RCC, representing 13 centers in Austria, France, Germany, Great Britain, Italy, Norway, Switzerland, and the United States, were selected according to their track record in RCC and previous interaction. Eleven decided to participate. They were asked to provide their algorithm for the treatment of treatment-naïve patients with multiple metastases from mccRCC outside a clinical trial. We were interested in the choice of initial management in terms of first-line systemic treatment and best supportive care (BSC) and in the criteria for this choice. For the purposes of the present analysis, nephrectomy, metastasectomy, and surveillance with a view to later treatment were not considered.

Decision trees can serve in decision support and are representations of decision criteria and their implications. Decision trees can be constructed by connecting several nodes from a starting point, each element representing a possible patient or disease characteristic and value (diagnostic node) [22]. General treatment recommendations and decision criteria, without providing specific clinical examples or constraints on criteria used, were obtained by electronic mail as text or figures and manually converted into draft decision trees, initially using a simple graphics editor and later with a dedicated tool. To enable cross comparisons of algorithms, compatible criteria are a prerequisite; therefore, all decision trees were reviewed, and the treatment options and decision criteria were identified and harmonized (e.g., decision criteria were omitted if used by two or fewer experts). The trees were then exported

as images and distributed to the submitting participants. After discussions and possible corrections, the trees were finalized and confirmed by each center by October 2014. The decision trees were then analyzed to determine the most common recommendations for each possible combination of parameters. Subsequently, the most common (mode) recommendation could be determined. This analysis was performed semi-automatically with specifically designed web-based software, developed in Java programming language using a BigTable database and ran on the Google Cloud Platform AppEngine (Google, Inc., Mountain View, CA, http://www.google.com). Input was provided manually through a website interface, which was built using Google Web Toolkit Framework. For visualization of the decision trees, a free JavaScript library called JIT InfoVis was used [20].

Results

Eleven decision trees were analyzed and compared. The treatments selected for first-line treatment of mccRCC were interferon-α combined with bevacizumab (IFN-α+BEV), high-dose interleukin-2 (HD IL-2), sunitinib (SUN), pazopanib (PAZ), sorafenib (SOR), axitinib (AXI), everolimus (EVE), temsirolimus (TEM), and BSC.

The parameters considered relevant for the treatment decision and mentioned by at least three experts were performance status (PS) according to the World Health Organization, Memorial Sloan Kettering Cancer Center risk group (MSKCC) [23], only or mainly lung metastases (OLM), cardiac insufficiency (CI), hepatic insufficiency (HI), and age. Among the decision criteria proposed by the experts, several included indicating a need for tumor response owing to the extent of disease or symptoms. This urgency was expressed differently by the experts (aggressiveness, tumor volume or burden, bulky disease, symptomatic, shrinkage needed, response required) and was summarized under the newly implemented term "zugzwang." Zugzwang (ZZ) is a German word and implies the compulsion to move [24]. Laboratory parameters and comorbidities, which were considered relevant by fewer than three experts, were omitted. The treatment selection criteria implemented and the summary of all treatment options are listed by center in Figure 1. Three generic decision trees are displayed in Figure 2 and differ in complexity. High consensus among the 11 participating centers was seen in patients with MSKCC good or intermediate risk, PS 0 or 1, no ZZ, no HI or CI, old age, and not OLM: 82% choose PAZ for this patient group (Fig. 3).

Similarly, SUN would be given by 9 of 11 centers to patients with MSKCC good or intermediate risk, PS 0 or 1, ZZ, HI but no CI, and not OLM, irrespective of age. In one center, both PAZ and SUN would be options according to the implemented criteria (Fig. 4).

In contrast, the treatment options are very heterogeneous for patients with MSKCC intermediate risk, PS 0, ZZ, no HI but CI, old age, and OLM. The therapeutic options for this patient group included PAZ at four centers, SUN at two, SOR at two, IFN-α+BEV in one, and EVE in one center. One expert would prescribe PAZ or SUN (Fig. 5).

IFN-α+BEV was only used in 4 of the 11 participating centers. We found 100% agreement of these centers in treating MSKCC good-risk patients, PS 0, no ZZ, no comorbidities,

Figure 1. Treatment selection criteria implemented and a summary of all treatment options.

Abbreviations: AXI, axitinib; BSC, best supportive care; CI, cardiac insufficiency; EVE, everolimus; HD IL-2, high-dose interleukin-2; HI, hepatic insufficiency; IFN-α+BEV, interferon-α combined with bevacizumab; MSKCC, Memorial Sloan Kettering Cancer Center; OLM, only or mainly lung metastases; PAZ, pazopanib; PS, performance status; SOR, sorafenib; SUN, sunitinib; TEM, temsirolimus; ZZ, zugzwang.

young, and OLM with IFN-α+Bev. IFN-α+BEV would also be considered for patients with other characteristics; however, less agreement was present among the centers (e.g., old patients or patients with comorbidities, such as CI). Hepatic insufficiency and MSKCC poor risk are universal exclusion criteria for IFN-α+BEV (Fig. 6).

Treatment with HD IL-2 would be considered in three centers. Among these centers was agreement to offer HD IL-2 to MSKCC good- and intermediate-risk patients, PS 0, no ZZ, and no CI nor HI—a patient group that would receive IFN-α+BEV at the other four centers. In clinical situations with ZZ, one of the three centers would rather choose PAZ; however, the other two would consider HD IL-2 anyway (Fig. 6).

TEM is one of several treatment options in MSKCC poor-risk patients. Most centers (6 of 11) would treat MSKCC poor-risk and PS 2 patients with TEM. However, depending on other criteria, additional choices are SUN, PAZ, EVE, and BSC (Fig. 7).

In addition to the more widely used drugs, AXI, EVE, and SOR are part of the treatment repertoire for only some of the participating centers. Although AXI is licensed for the treatment of advanced RCC after the failure of one previous

systemic therapy, it is the drug of choice for patients with HI for first-line treatment at one center. EVE is given to MSKCC good- and intermediate-risk patients with CI in one center and to MSKCC poor-risk patients, irrespective of other criteria, at the same center.

SOR is a first-line treatment in two centers for patients with the comorbidities of CI or HI, or both, old age, or poor PS.

DISCUSSION

This is the first report on a comparison of treatment algorithms for mccRCC. We performed a survey among 11 medical oncology experts in the field of RCC. We obtained nine different treatment options for first-line treatment of mccRCC and selected seven criteria for treatment choice; these had been mentioned by at least three experts. Subsequently, we used Dodes for the analysis of agreement and disagreement among the experts.

The selection of the 11 experts was biased and a limitation of our analysis; however, even this limited sample has demonstrated considerable heterogeneity in the treatment selection criteria and treatment choice. Although nephrectomy, metastasectomy, and surveillance are relevant in the management of mccRCC, we focused on drug therapy and did not include the other topics, because none have been prospectively analyzed in a randomized trial, and the decision trees would have become too complex.

Decision criteria relevant to fewer than three experts were omitted, including avoidance of skin and bone marrow toxicity, scheduling, and route of administration preference. In addition, to make the decision trees more comprehensive, we excluded comorbidities other than CI and HI, specifically excluding hemodialysis, autoimmune disease, diabetes mellitus, chronic obstructive pulmonary disease, and pulmonary fibrosis. The definition of CI and HI was at the discretion of the experts and therefore could have differed substantially. All the experts used the MSKCC risk score rather than the Heng classification [25], despite the validation of the latter in the era of targeted therapies [26].

Zugzwang was chosen as a decision criterion to summarize different facets mentioned by the experts. This pressure to move could, however, apply in a different context to HD IL-2: if a patient is currently suitable for HD IL-2 but might not be for much longer, this could be interpreted as ZZ to give HD IL-2 [27]. Nevertheless, the experts who consider HD IL-2 unanimously chose clinical situations without ZZ present.

PAZ is used in all the centers and was chosen more frequently by the experts than SUN. The preference for PAZ was even more apparent for older patients. We hypothesized that this is a result of a trial assessing patients' and physicians' preferences [28] and the comparison of the two drugs in a randomized noninferiority trial [29]. These trials, however, have been criticized for their conduct (e.g., time of assessments likely to favor PAZ). Also, despite the favorable safety and quality-of-life profiles for PAZ relative to SUN, treatment was discontinued because of adverse events in 24% of patients receiving PAZ compared with 20% receiving SUN. The validity of the noninferiority trial raises concerns, given that results of the intention-to-treat analysis differed from the per-protocol analysis [30].
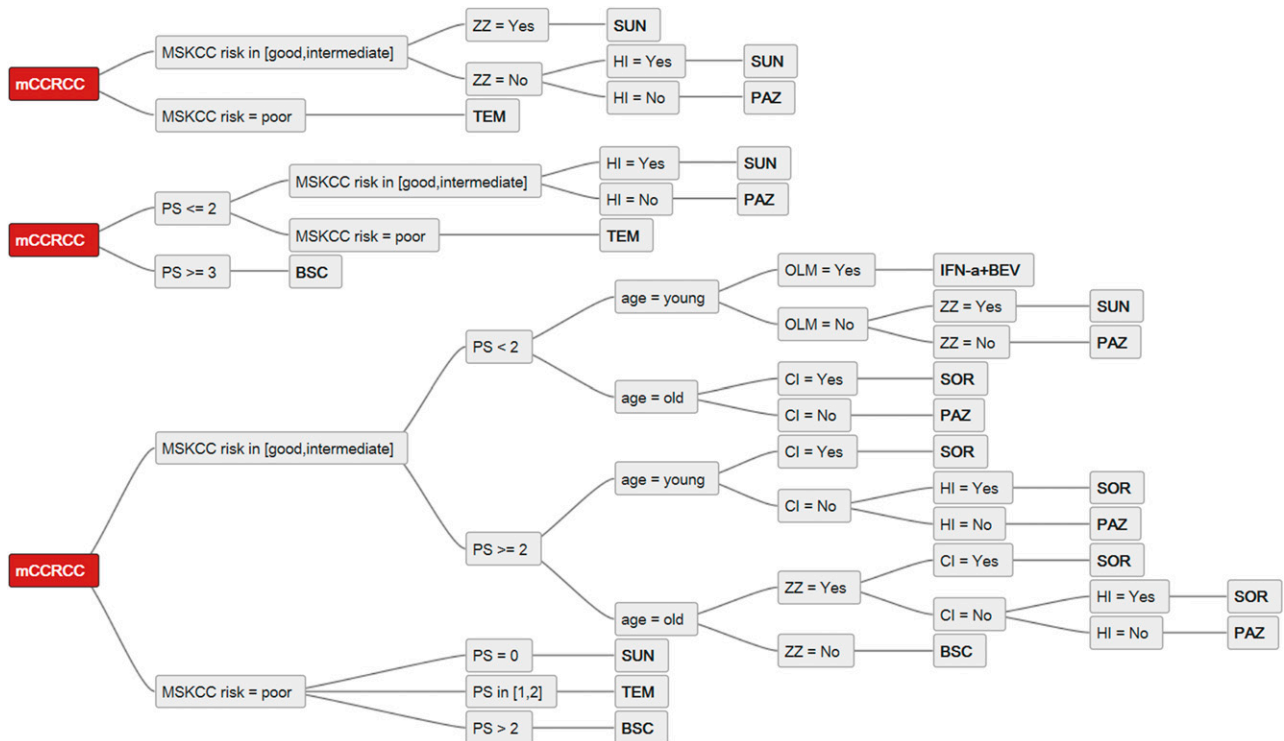
Figure 2. Three generic decision trees illustrating the input from centers for the analysis.

Abbreviations: AXI, axitinib; BSC, best supportive care; CI, cardiac insufficiency; EVE, everolimus; HD IL-2, high-dose interleukin-2; HI, hepatic insufficiency; IFN-α+BEV, interferon-α combined with bevacizumab; mccRCC, metastatic clear cell renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; OLM, only or mainly lung metastases; PAZ, pazopanib; PS, performance status; SOR, sorafenib; SUN, sunitinib; TEM, temsirolimus; ZZ, zugzwang.
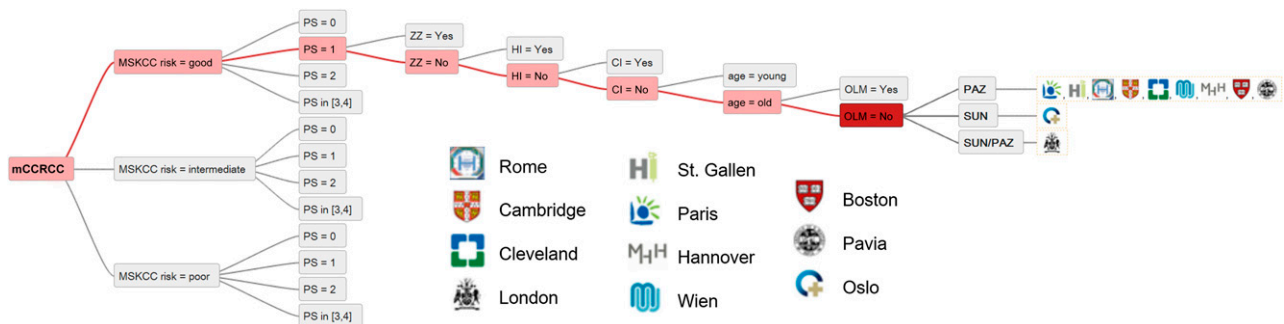

Figure 3. All 11 treatment recommendations for patients with MSKCC good or intermediate risk, PS 0 or 1, no ZZ, no HI and CI, old age and not OLM.

Abbreviations: CI, cardiac insufficiency; HI, hepatic insufficiency; mccRCC, metastatic clear cell renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; OLM, only or mainly lung metastases; PAZ, pazopanib; PS, performance status; SUN, sunitinib; ZZ, zugzwang.

In patients with MSKCC good and intermediate risk, PS 0 or 1, and no comorbidities, young age, not OLM, and ZZ, SUN would be selected rather than PAZ, despite the Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma (COMPARZ) data, which indicated a higher response rate with PAZ than with SUN [29]. This might have resulted from the discrepancy in the response rates to SUN in COMPARZ (25%) compared with that in the final analysis of the SUN versus IFN trial (47%). Evidence has shown that early tumor shrinkage is prognostic in mccRCC [31, 32]. However, the question remains whether superior tumor shrinkage represents a favorable treatment effect or merely tumor biology [33].

Data on the efficacy of first-line treatment with IFN-α+BEV was first published in 2007 (Phase III Trial of Bevacizumab Plus Interferon Alfa-2a in Patients With Metastatic Renal Cell Carcinoma; AVOREN) and 2008 (Cancer and Leukemia Group B 90206 trial). In an indirect comparison, no significant PFS difference was found between IFN-α+BEV and TKIs in first-line treatment of mccRCC [34]. Nevertheless, most experts do not use IFN-α+BEV routinely. This implies that additional selection criteria are considered, such as practicability (route of administration), tolerability, adverse event management [35], and therapy sequencing.

Similarly, HD IL-2 is considered in two centers in the United Kingdom, both of which refer their patients to a single center
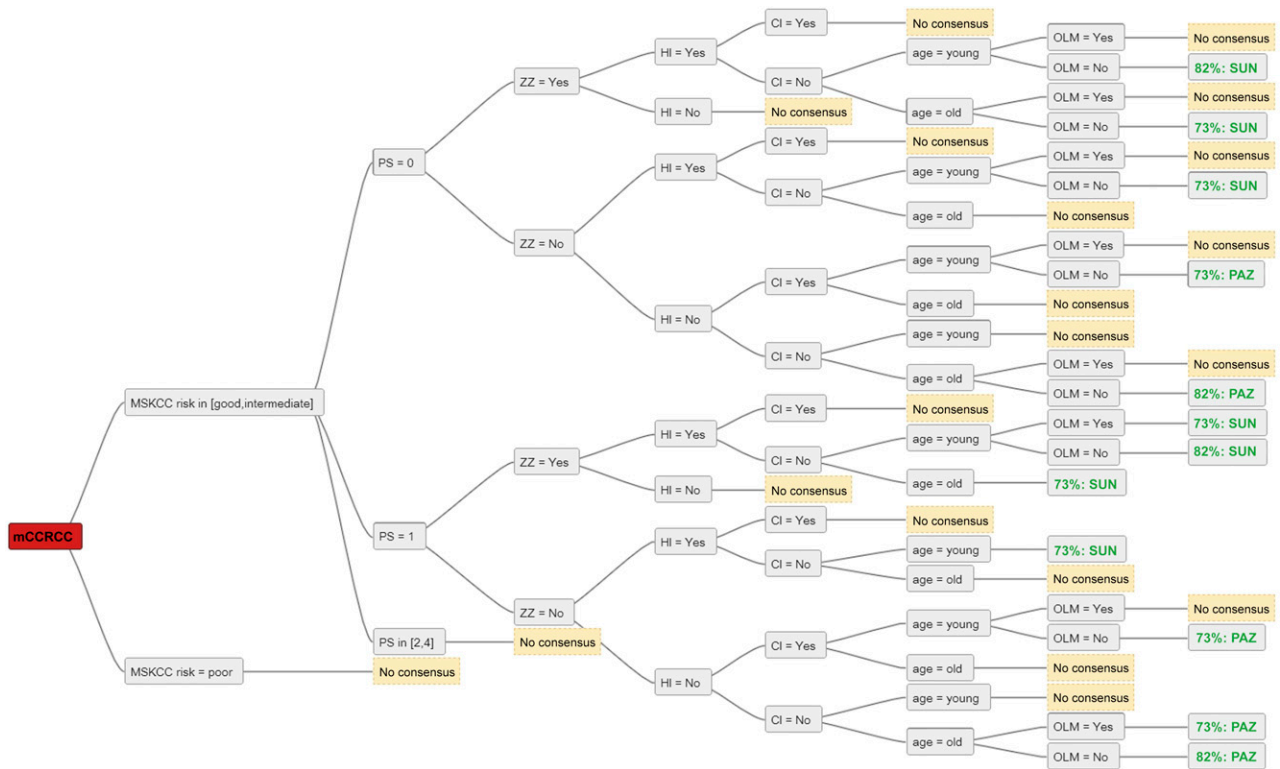
Figure 4. Most common (mode) recommendations for all treatment options for which a consensus of at least 73% (8 of 11) was achieved.
Abbreviations: CI, cardiac insufficiency; HI, hepatic insufficiency; mccRCC, metastatic clear cell renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; OLM, only or mainly lung metastases; PAZ, pazopanib; PS, performance status; SUN, sunitinib; ZZ, zugzwang.
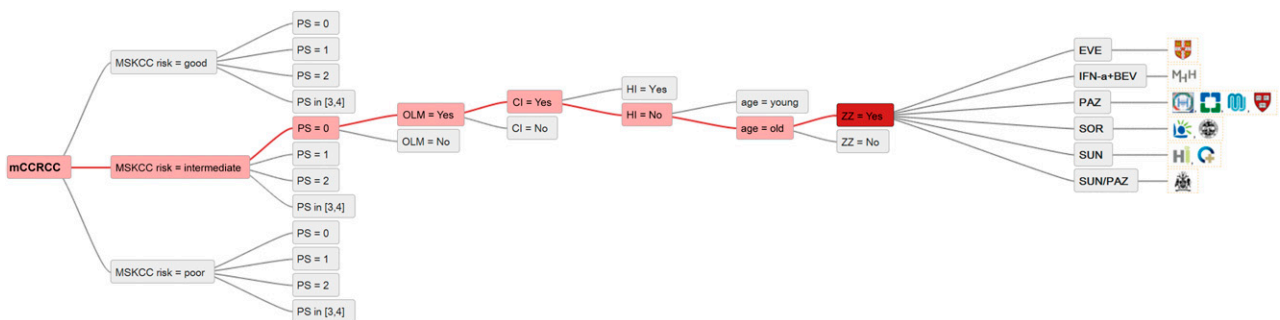

Figure 5. Therapeutic options for patients with MSKCC intermediate risk, PS 0, ZZ, no HI but CI, old age, and OLM.
Abbreviations: CI, cardiac insufficiency; EVE, everolimus; HI, hepatic insufficiency; IFN-α+BEV, interferon-α combined with bevacizumab; mccRCC, metastatic clear cell renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; OLM, only or mainly lung metastases; PAZ, pazopanib; PS, performance status; SOR, sorafenib; SUN, sunitinib; ZZ, zugzwang. A key to the centers shown is given in Fig. 3.

in Manchester; only one center in the United States would consider HD IL-2. HD IL-2 might not be a treatment option in other countries because of a lack of experience with management or drug registration. Although, in contrast to the results achieved with HD IL-2 [4], treatment with TKIs does not usually produce long-term remissions, patients develop a relapse when therapy is discontinued [36], and resistance to treatment inevitably develops during therapy [37]. Recent clinical trials exploring monoclonal antibodies targeting programmed death-1 (PD-1), PD ligand 1, and cytotoxic T-lymphocyte antigen 4 pathways in the treatment of mccRCC have shown that immunotherapy could still play a key role in

the future management of kidney cancer [38] and add to the cornucopia of options. Data demonstrating the efficacy of the PD-1 immune checkpoint-blocking antibody nivolumab are maturing [39, 40].

BSC was chosen as a treatment by five centers. Obviously, it is debatable whether BSC is a treatment option in the narrower sense and whether systemic treatment should entail an anticancer drug. Most experts would probably use BSC for certain patients. However, using the decision criteria outlined in our study, some experts believed BSC to be the preferred treatment choice, and others decided to be more active. We decided neither to omit BSC from the decision trees nor to
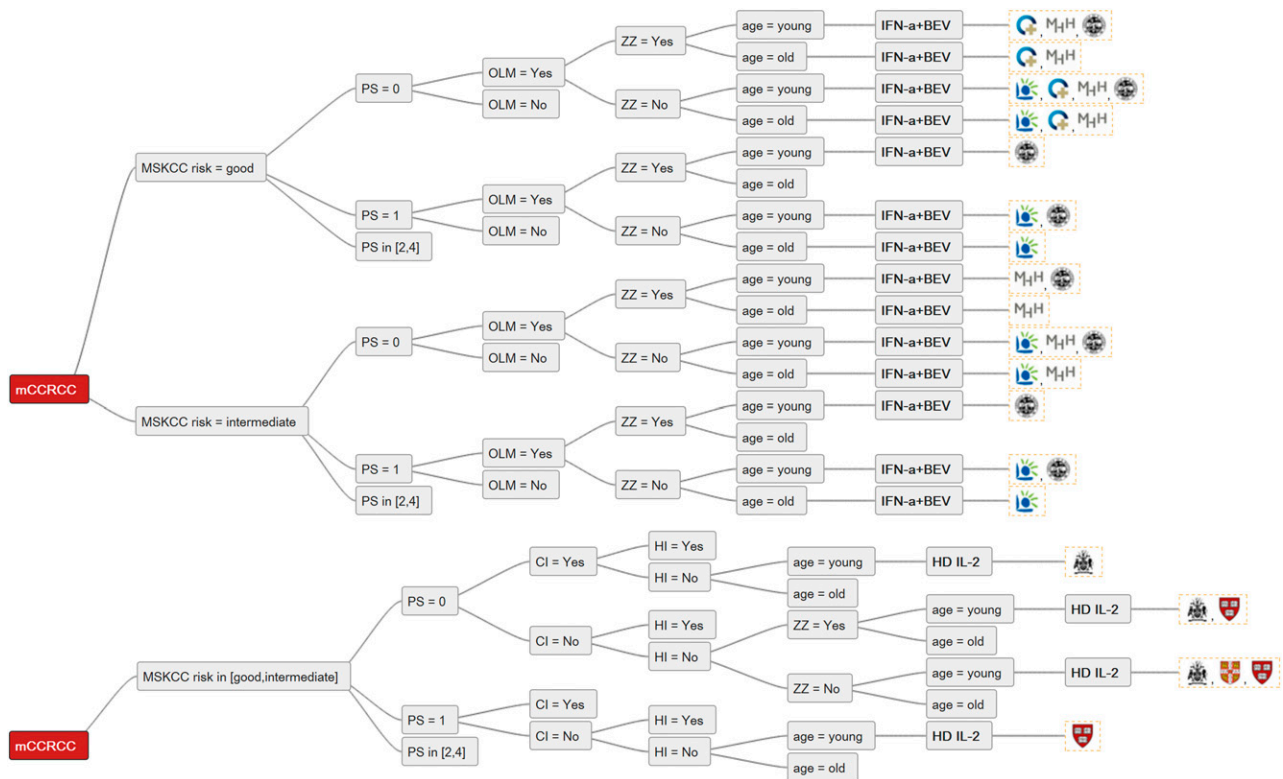
Figure 6. Criteria for selection of IFN-α+BEV and HD IL2.

Abbreviations: CI, cardiac insufficiency; HD IL-2, high-dose interleukin-2; HI, hepatic insufficiency; IFN-α+BEV, interferon-α combined with bevacizumab; mccRCC, metastatic clear cell renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; OLM, only or mainly lung metastases; PS, performance status; ZZ, zugzwang. A key to the centers shown is given in Fig. 3.

include BSC in the algorithms if the experts had not included it themselves to demonstrate the variety of opinions.

We are aware that some of the treatment choices given by the experts are unconventional and not according to published guidelines. So much the more is it interesting to show the spectrum reflecting the reality in clinical practice. For example, the choice of first-line treatment with everolimus is not supported by published high-level evidence. In a phase II study (Renal Cell Cancer Treatment With Oral RAD001 Given Daily; RECORD-3), the primary endpoint, PFS noninferiority of first-line everolimus compared with first-line sunitinib, was not met: the median PFS was 7.9 months for first-line everolimus and 10.7 months for first-line sunitinib [41].

This is a snapshot of real-world scenarios in tertiary centers across countries with different rules and distinct drug labels. Given that clinical trials cannot answer all the relevant questions, wide labels allow experienced physician to go beyond and sometimes even against guidelines. Randomized controlled trials can provide the least biased estimates to compare treatments. However, their results do not always correspond to what is seen in daily practice, where physicians apply the results among a broader range of patients [42].

Guidelines from medical societies are intended to provide recommendations for the best standards of cancer care [43]. The results obtained are limited to the specific decision criteria implemented and for the otherwise fit patient. It was possible to determine multiple criteria used by experts and to reveal their influence in the collected algorithms.

One limitation of the present analysis was the lack of information for why certain treatments were considered in some centers and not in others. This disparity might reflect the availability of drugs in the different participating countries; however, it also mirrors experience, convenience, and personal preference.

Given the similar efficacy of the drugs discussed, one could hypothesize that the treatment choice is of less importance, provided the management of application, dispensing, and toxicities are not issues. Patients with a good prognosis will usually receive several lines of treatment. However, retrospective data have shown that only 59% of patients receive second-line treatment after SUN, 52% after SOR, and 79% after BEV [44]. The MSKCC classification and first-line agent were significant predictors for receiving second-line treatment. Similarly, in an Italian retrospective analysis of targeted therapies, only 13% of patients received third-line treatment [45]. This suggests that the first choice of drugs could be crucial and decisive. This might be especially relevant in the patient group with ZZ, in which additional disease progression will disable the patient to undergo further treatments owing to the deterioration of clinical conditions. Although the debate on the best first-line treatment is especially relevant to patients and physicians, it could also be of interest to stakeholders of pharmaceutical companies, who create marketing strategies.

In the present analysis, we did not address the question of drug sequencing, also a debated topic [46, 47]. Instead we concentrated on the initial treatment choice, which could be crucial for the further course of the disease.
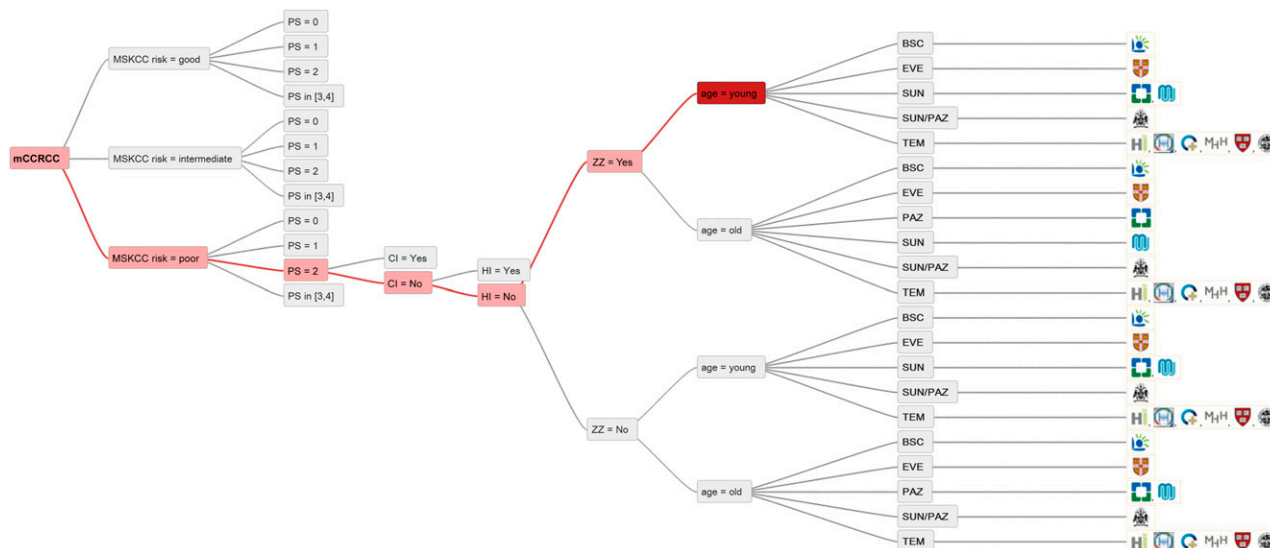
Figure 7. Treatment options for MSKCC poor-risk patients.

Abbreviations: BSC, best supportive care; CI, cardiac insufficiency; EVE, everolimus; HI, hepatic insufficiency; mccRCC, metastatic clear cell renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; OLM, only or mainly lung metastases; PAZ, pazopanib; PS, performance status; SUN, sunitinib; TEM, temsirolimus; ZZ, zugzwang. A key to the centers shown is given in Fig. 3.

Conclusion

We believe the presented data will be of interest to clinicians. Our findings illustrate the heterogeneity of the decision criteria and treatment strategies and how differently the available data are interpreted and implemented by experts. The range of treatment options for mccRCC, given multiple proven agents in randomized trials, reflects the rapidly evolving field in cancer therapy in general and alludes to the opportunities and dilemmas resulting from this development. When many treatments are available, choice will be driven by experience, comfort, convenience, cost, and personal preference.

Author Contributions

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