World Journal of Urology (2021) 39:2831–2841
https://doi.org/10.1007/s00345-021-03632-6

TOPIC PAPER

Comorbidity and frailty assessment in renal cell carcinoma patients

Jean Courcier[1,2] · Alexandre De La Taille[1] · Nathalie Lassau[2,3] · Alexandre Ingels[1,2]

Received: 13 November 2020 / Accepted: 5 February 2021 / Published online: 22 February 2021

Abstract

Purpose Renal cell carcinoma (RCC) incidence has considerably increased during the last decades without any real impact on age-standardized mortality. It questions the relevance of aggressive treatments carrying potential side effects. Conservative management should be considered for frail patients. Comorbidity and frailty assessment in RCC patients is paramount before engaging a treatment.

Methods Narrative, non-systematic review based on PubMed and EMBASE search with the terms "renal neoplasm", "elderly, frail", "comorbidities", "active surveillance", "metastatic". The selection was restricted to articles written in English.

Results Comorbidity and frailty assessment go along with the cancer-specific aggressivity and intervention risks assessment. In localized disease, several standardized algorithms offer patient health evaluation to define how suitable the patient would be for curative treatment. The pre-operative American Society of Anesthesiologists and the age-adjusted Charlson's scores are the most widely used. At the metastatic stage, drug combinations based on immunotherapies and targeted therapies improved cancer outcomes at the price of significant toxicities. Frail patients are not always suitable for such strategies. Commonly used scores like the International Metastatic RCC Database Consortium or Memorial Sloan Kettering Cancer Center integrate features to define patients' risk groups, more specifically the Karnofsky Performance Score is an easy way to document the frailty.

Conclusions Comorbidity and frailty have to be assessed at any stage of the RCC disease based on a standardized scoring system to define the most suitable treatment strategy ranging from surveillance to aggressive treatment.

Keywords Renal cell carcinoma · Frailty · Comorbidity · Active surveillance · Adverse events

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2% of global cancer diagnoses and deaths [1, 2]. Despite a doubling incidence (from 7.1/100,000 in 1975 to 14.9/100,000 in 2016), mostly due to incidental diagnosis of asymptomatic renal masses on routine imaging, the age-standardized mortality in 2016 (3.6/100,000) was the same as in 1975 when the statistic was first reported [3]. The 5-year survival rate in the US has increased remarkably from 46.8% in 1977 to 76.5% in 2016 according to the Surveillance, Epidemiology and End Results Program (SEER) from the National Cancer Institute [4]. This discrepancy questioned the necessity of aggressive treatment that might be more harmful than the original disease. The first step was the development of nephron-sparing surgery to preserve potential kidney function while removing the tumor [5], then the concept of active surveillance (AS) emerged for small renal masses management [6]. On another level, many systemic treatments have recently been approved to treat metastatic RCC (mRCC) leading to significant survival improvement [7–11]. However, these treatments combine immunotherapies (IO) or immunotherapy and vascular endothelium growth factor targeted tyrosine kinase inhibitors (VEGFR-TKI) with potential toxicity [12].

Therefore, a thorough assessment of patients' comorbidities and frailties at any stage of the disease is paramount to balance the benefits and the risks of any treatment. In this

✉ Alexandre Ingels
alexandre.ingels@gmail.com

1 Department of Urology, University Hospital Henri Mondor, APHP, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France

2 Biomaps, UMR1281, INSERM, CNRS, CEA, Université Paris Saclay, Villejuif, France

3 Department of Imaging, Institut Gustave Roussy, Villejuif, France

study, we reviewed the different systems of evaluation for localized and metastatic RCC.

Comorbidity and frailty assessment in local renal masses

Rationale: the place of active surveillance

AS is gaining interest in small renal masses (SRM) management due to their rarely-aggressive nature [13]. SRM is defined by a less than 4 cm, mostly solid enhancing renal tumor. Those are quasi systematically asymptomatic. On the one hand, about 20% of SRM presumed to be malignant happened to be benign on biopsy or surgical specimen histology [14]. On the other hand, the median age at SRM diagnosis is 65 years old with often associated comorbidities [15]. It was also reported that active treatment of SRM after 75 years old might not impact overall survival because of competing cardiovascular and other non-cancer conditions [16]. Therefore, the concept of AS appears as a rationale option for patients harboring SRM over a certain age and for whom the surgery would be particularly risky. Such a strategy requires a good evaluation of the tumor aggressivity and patient's competing risk factors unrelated to cancer. Smaldone et al. reported tumor size and growth rate as valuable markers of tumor aggressivity and predictor of metastatic progression: small renal masses with metachronous metastases ($n=18$) were compared to non-metastatic progressing tumors ($n=281$). With similar follow-up, the first group had significantly larger tumor diameter at diagnosis (4.1 cm vs 2.3; $p<0.001$) and faster mean linear growth rate (0.80 cm vs 0.30 cm/year; $p<0.001$) [17]. The histology subtype, characterized with a biopsy is also a good predictor of SRM evolution. Finelli et al. recently reported outcomes from the largest series of biopsy-proven RCC under AS, Among the 136 patients included, the 5-year progression rate (volume doubling time < 1 year and/or tumor size ≥ 4 cm) was 54%. Clear-cell (ccRCC) tumors were more aggressive representing 73% of the progressing masses. The average diameter growth rate was 8% per year and significantly faster for ccRCC than other subtypes (0.25 vs 0.02 cm per year for the papillary type 1 subtype, $p=0.0003$). All the six patients who developed metastases harbored ccRCC [18]. An increase in growth rate and, a fortiori, clinical progression should be arguments to consider a curative strategy in the elderly under AS [12].

The role of AS for larger renal masses, per se cT1b and cT2, is marginal. However, expectant management remains an option when surgery would be particularly risky and thermal ablation probably inefficient because of the tumor size. Mehrazin et al. reported on 68 patients presenting over 4 cm localized renal masses (T1b or greater) managed with AS with a median follow-up of 32 months. While only 10 patients (14.7%) had stable disease during follow-up, no metastatic progression nor cancer-specific death occurred and 9 (13%) patients died of an unrelated cause. Forty-five (66%) patients remained on AS and 23 (34%) were subsequently operated. AS maintenance was associated with an older age (77 vs 60 years old, $p=0.0002$) and slower linear tumor growth (0.37 vs 0.73 cm/year, $p=0.02$) [19].

Patients over 70 years old managed with AS for SRM present limited rates of conversion to curative treatment and low cancer-specific mortality: in a systematic review highlighting four retrospective studies Cheung et al. showed a low conversion rate (4%, 4%, 9% and 26%), the higher last could be explained by a significatively longer follow-up (29, 51, 39.9 and 91.5 months, respectively) [20]. AS has to be distinguished from watchful waiting: while the first one requires regular imaging to monitor the tumor size to trigger an active treatment in case of progression, the second one concerns contraindicated patients for active treatment due to their comorbidities, they do not require imaging follow-up unless clinically indicated [12].

Therefore, comorbidities and frailties have to be evaluated correctly at the time of SRM diagnosis to inform the patient correctly and eventually make the right decision between an active treatment, AS or watchful waiting.

Surgical risks

Age should not be the only criteria to consider when choosing SRM management, indeed acceptable surgical outcomes have been reported for the elderly: Lowrance et al. showed in a retrospective study on 1712 pts an existing but small association between aging and risk of complication [OR for 10-year increase in age 1.17; 95% CI (1.04; 1.32) $p=0.009$ in multivariate analysis] [21]. Surgical outcomes in the elderly were also reported in a smaller cohort by Sirithanophol et al. in which 101 pts went principally on open radical nephrectomy. Patients aged over 65 years old had a comparable operative time and a slightly increased overall complication rate (22% vs 12%), mainly related to comorbidities more than organ injury or bleeding [22]. Those results are mainly related to open surgery. Therefore, comorbidities represent the main surgical and perioperative risks, increasing the risk of cardiac or respiratory issues during anesthesia and mechanical ventilation.

Physical status score of American Society of Anesthesiologists (ASA) is a composite score used by anesthesiologists to categorize patients function based on their preoperative health status. An ASA score ≥ 3 should alarm the practitioner to reconsider the benefits expected in light of the risks [23].

Surgical management present constitutive risks of complications, particularly for partial nephrectomies, compared to radical nephrectomies, with a slightly increased likelihood

of postoperative complications such as severe hemorrhage (3.1% vs 1.2%), reoperation (4.4% vs 2.4%) or urinary fistulae (4.4% vs 0%) [24, 25]. Those differences showed a similar distribution in a large population of 2277 elderly patients [26].

The surgical risk of ablative treatments (cryoablation or radiofrequency), the alternative technique to radical or partial nephrectomies, remains unclear. The current European Association of Urology guidelines recommend reserving this treatment for frail and comorbid patients with SRM and to inform them of the higher risk of local recurrence [12]. However the level of evidence is low with mixing results from the literature regarding complications rates and oncologic outcomes, most of the comparative studies are biased with more comorbid patients selected for ablative techniques [12].

The cancer-specific mortality competing with comorbidity and frailty

As frailty might appear like a straightforward concept, it has to be standardized to aim for reproducible patient management. It is distinct from comorbidity or disability.

The standardized Fried criteria aim to measure it [27]. The presence of three or more of the following criteria define the frailty and one or two of them are predictive of increased risk of becoming frail over 3 years: unintentional weight loss (4.5 kg in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Every patient in the situation of frailty must be investigated for comorbidities to define the interventional risk. An accurate balance of risks and benefits expected must be done before any treatment consideration.

When assessing frailty and comorbidities, it is important to identify the modifiable risks: high blood pressure [28], obesity, poor physical activity, poor fruit and vegetable diet, smoking [29], diabetes [30], alcohol consumption [31], and regular use of the nonsteroidal anti-inflammatory drug [32].

Other conditions like age, liver, and chronic kidney diseases [33] cannot be modified. We can add that age is an evolving condition and the risk of frailty goes hand in hand with aging: the Cardiovascular Health Study (published in 1991, Fried et al.) included 5317 over 65 years old patients and 61.9% were aged over 75 years old among frail patients vs 23.9% among not frail [34]. Interestingly, cancer was the only affection among prevalent diseases at baseline that did not differ in frail patients.

Specialized geriatric assessment can also help in the therapeutic decision when frailty is suspected by the practitioner. Urologists or oncologists can use simple questionnaires like the G-8 screening tool, to discriminate in aged patients those with increased risks for geriatric deficiency [35]. Seven questions and the patient's age give 0, 1, 2 or 3 points each, the addition giving a total score: loss of appetite, loss of weight, mobility, neuropsychological problems, body mass index, polypharmacy, perceived health condition. A score under 14 points should lead the patient to be referred to a gerontologist or a specialist in geriatric oncology. It will allow a global assessment of the patient, with a more systemic approach such as comprehensive geriatric assessment (CGA) which is much time consuming and is the prerogative of specialists [36]. Other validated screening tools are also available like Triage Risk Screening Tool (TRST) or the Vulnerable Elders-13 Survey (VES-13) [37, 38].

Several algorithms are reported in the literature to balance the comorbidities-related and the cancer-specific risks to determine the relevance of an intervention.

The Charlson comorbidity index score is a tool created to summarize and categorize the comorbidities of patients (based on the International Classification of Diseases) with a ponderation (1–6) directly based on the adjusted risk of mortality. The sum gives a single comorbidity score. This last estimates the 10 years overall survival probability [39] from sixteen variables [40]. The age-adjusted Charlson's comorbidity index adds age categories weighing and might be a valuable tool to predict long-term survival in non-metastatic RCC patients [41] (Table 1).

Kutikov et al. proposed a nomogram to assess the competing risk of death after surgery in patients affected with localized RCC [42] (Fig. 1). It is represented by several graduated scales including the associated variables: ethnic group, gender, age, and tumor size, each of which has three distinct sections (non-cancer, kidney cancer, and other cancer). The graduations of the scales depending on the section concerned. Adding up the length of all the scales gives a total of points, which can be related to the 5 years probabilities of three different cause of death (renal cancer, other cancer or noncancer). The five years competing probabilities of death are therefore determined using patients' common characteristics, making it an easy-to-use tool. For example, a 70 years old white non-Hispanic man with a localized 5 cm renal mass gets 75 points. The corresponding 5-year probabilities of death are 7–10%, 3–6% and around 1%, respectively, for non-cancer, kidney cancer, and other cancer. RCC-specific risk overcoming the others should help tip the scales in favor of a curative strategy.

The modified Glasgow prognostic score integrates nutritional (albumin level) and inflammation (C-reactive protein) information [43]. A meta-analysis confirmed its reliability to predict survival in RCC patients with poorer overall survival and cancer-specific survival for patients presenting a high score [44].

Principal findings for the localized RCC setting are synthetized in Table 2.

Table 1 Charlson's comorbidity index score

Variable	Points
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular accident or transient ischemic attack	1
Dementia	1
Chronic obstructive pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Mild liver disease	1
Uncomplicated diabetes	1
Hemiplegia	2
Moderate to severe chronic kidney disease	2
Diabetes with end-organ damage	2
Localized solid tumor	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumor	6
AIDS	6
Comorbidity-age combined risk score	Predicted 10 years survival (%)
0	99
1	96
2	90
3	77
4	53
5	21
6	NC

The Charlson's index score is obtained by summing the points corresponding to the variables observed in the patient. For the aged-adjusted Charlson's comorbidity index score, add 1 point every decade to patients aged over 40 years, with a maximum of 4 points

AIDS Acquired Immuno Deficiency Syndrome

Comorbidity and frailty assessment for metastatic disease

The place of active surveillance in metastatic disease

Metastatic RCC disease can be asymptomatic despite some active growth of lesions. Because of the systemic treatment toxicity, AS has been considered as an option for elderly, weak patients with reduced global performance status and comorbidities [45]. The financial cost of systemic treatments in metastatic RCC could be another argument to consider AS with regards to a patient's social coverage.

Rini et al. reported in 2016 a prospective phase II trial evaluating active surveillance for mRCC patients [46]. The patients enrolled were treatment naïve and asymptomatic. The decision of systemic treatment initiation was based on the physician's discretion. Fifty-two patients were included. The median time from inclusion to initiation of systemic therapy (primary endpoint) was 14.9 months with a median follow-up of 38.1 months. The authors concluded that AS might be safe for a subgroup of patients with no International Metastatic RCC Database Consortium (IMDC) risk factor and two or fewer metastatic organs affected, with a median time of AS of 22.2 months.

Another prospective study reported on a "watch and wait" protocol after cytoreductive nephrectomy for synchronous metastatic RCC: a third of patients had over 6 months progression-free interval, the median overall survival was 25 months [47]. Preoperative predictive factors for non-progression were the absence of abnormal laboratory indices, single-site metastases, and good performance status.

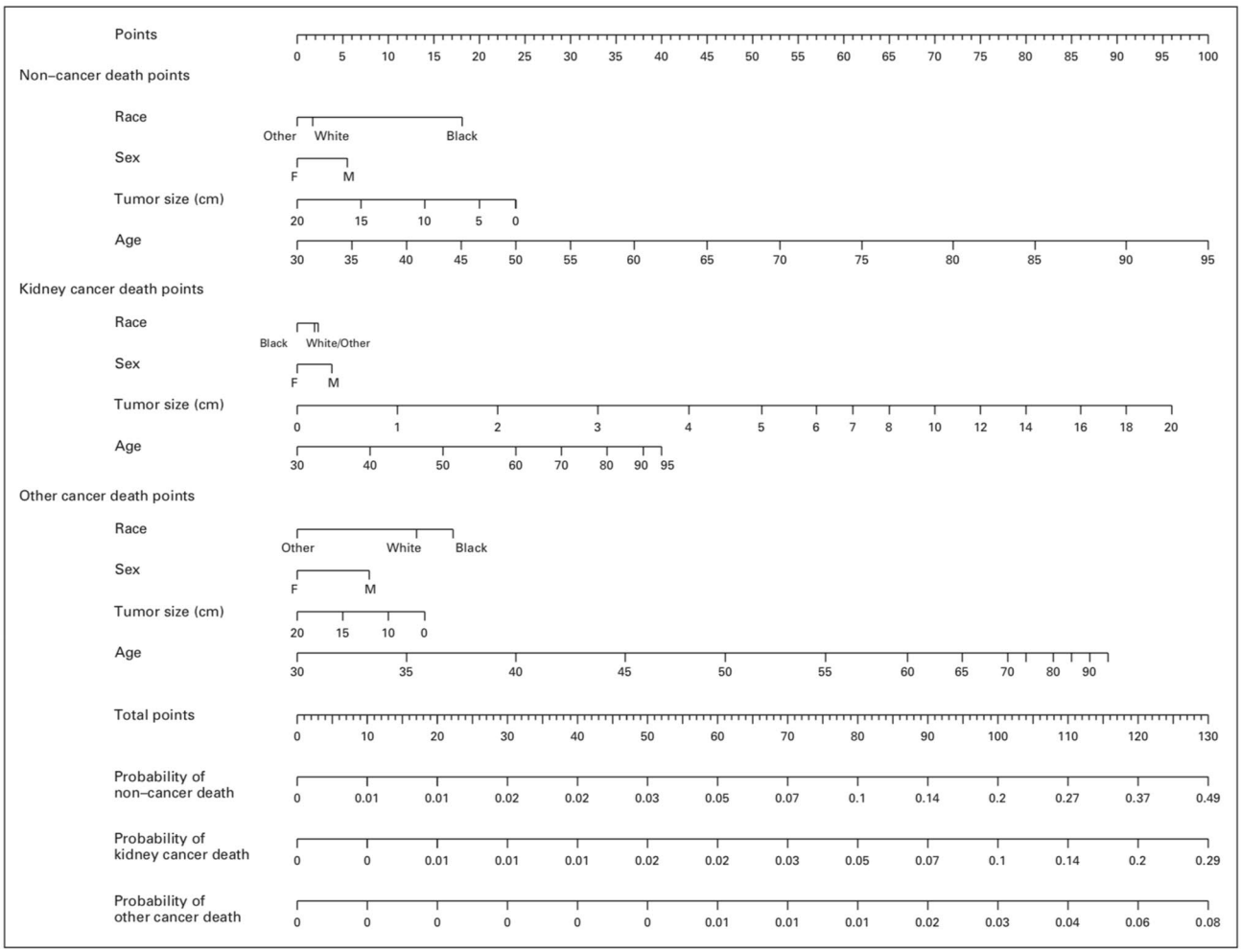

Fig. 1 Kutikov's nomogram

Table 2 Summary of the findings in localized renal masses setting

Active surveillance
Systematically consider AS for a > 75 year old patient with < 4 cm renal mass [13–16]
Tumor growth rate should influence the decision of treatment [17, 18]
AS can be an option in comorbid and/or frail > 70 years old patients with T1b/T2[a] renal mass [19, 20]
Surgical risks
Biological age should not be a counterindication for surgery in selected patients: over-risks in elderly is tenuous [21–23]
Specific complications related to nephron sparing surgery may not differ in elderly patients [24–26]
Ablatives techniques remains a good approach for surgery-unfit patients with limited renal masses [12]
Balance between cancer and comorbidities
The search for comorbidities should be systematic in uro-oncology to identify modifiable risks [27–34]
Screening tools (like G-8) for frailty assessment are valuable and easy-to-use in elderly [36–38]
Algorithms like Charlson comorbidity index or Kutikov nomogram may help balancing the comorbidities and cancer-specific risks [41, 42]

AS active surveillance

[a]According to the TNM classification

A retrospective study conducted in Canada compared the characteristics of two metastatic RCC patients cohorts: the first was managed with initial AS for minimum 6 months after metastatic diagnostic and had over 1-year overall survival while the other was treated immediately or before 6 months after metastatic diagnosis [48]. Patients under AS had a higher rate of metastasectomy, fewer metastatic sites, and greater overall survival. The median time on AS was 14.2 months. The authors concluded that AS is a coherent strategy for some patients.

Despite those studies, the precise subset of patients who could benefit the most of AS is still unknown. However, the number and localization of metastasis should systematically be taken into account [49, 50]. Interestingly, these studies were all reported during the VEGFR-TKI era. The recent surge of IO becoming the new backbone of metastatic RCC treatment has led to significant improvements in patients' prognosis with complete responses and prolonged survival [51]. This better management questioned the idea of postponing an intervention with the risk of missing a chance of a curative treatment [49, 52].

Toxicity of systemic treatments

Targeted therapies VEGFR-TKI was the main option for first-line metastatic RCC treatment [53] until the surge of IO [11]. They are still used in association with IO [54–57], as a second line after progression under IO or when those are contraindicated [12].

Although VEGFR-TKIs present a high response rate, they are associated with a non-negligible toxicity profile.

Bhojani et al. reported a systematic review of side effects associated with sunitinib, sorafenib and temsirolimus [58]. Overall side effects ranged from < 1 to 72%. Grade 3–4 side effects ranged from < 1 to 13% for Sorafenib and < 1 to 16% for sunitinib. The most common grade 3–4 adverse events reported were lymphopenia (13%), hypophosphatemia (13%), elevated lipase (12%), mucositis/stomatitis (6%), hand-foot syndrome (6%), fatigue/asthenia (5%), dyspnea (4%), hypertension (4%) for sorafenib and elevated lipase (16%), lymphopenia (12%), neutropenia (12%), thrombocytopenia (8%), hypertension (8%), fatigue/asthenia (7%), diarrhea (5%), hand-foot syndrome for sunitinib.

More recently, Manz et al. reported a network meta-analysis to compare the safety of approved first-line VEGFR-TKI in metastatic RCC [59]. They concluded that cabozantinib, sunitinib, pazopanib and tivozanib did not significantly differ in their efficacy but tivozanib was associated with a more favorable safety profile in terms of grade 3–4 toxicities.

These detailed toxicities and level of grade 3–4 adverse events have to be known when considering VEGFR-TKI treatment for frail patients to prevent and anticipate the potential deterioration of their comorbidities.

Immune checkpoint inhibitors The currently approved IO in metastatic RCC target lymphocytes checkpoint inhibitors to reactivate the anti-tumoral immune response. These targets are the cytotoxic T lymphocyte antigen-4 (CTLA-4), and programmed cell death protein 1 (PD-1) and its ligand (PD-L1). This disinhibition of T-cell function can lead to many auto-immune and inflammatory side effects [60]. Translational research investigated the pathophysiology of these immune-related adverse events (irAE) and depicted a combination of pathways involving autoreactive T cells, autoantibodies, and cytokines [61].

The incidence of irAEs is much higher when combinations are used [62, 63]. The incidence of any-grade irAE in trials including patients with multiple solid tumor types has been reported at 72% with ipilimumab monotherapy [64] and 66% with anti–PD-1/anti–PD-L1 monotherapy [65]. The mortality rates associated with CTLA-4; PD-1; PD-L1; and combination blockade are 1.08%; 0.36%; 0.38% and 1.23% respectively [66]. The most common causes of irAE mortality are colitis (70%) with anti-CTLA-4 therapies and pneumonitis (35%), hepatitis (22%), or neurotoxicity (15%) with anti–PD-1/anti–PD-L1. For combinations, the most common causes of deaths are colitis (37%) and myocarditis (25%).

The most frequent toxicities reported are dermatologic: rash, dermal hypersensitivity reactions, dermatomyositis, sweet syndrome, pyoderma gangrenosum, bullous disorders, drug reaction with eosinophilia, and systemic symptoms. Other reported toxicities are colitis, hepatitis, endocrine affection with dysthyroidism, and hypophysitis with subsequent dysfunctions of adrenal, thyroid, and gonadal axis [67].

While most of these complications can usually be managed with treatment holds and steroids prescriptions in the case of grade 3–4 irAE, these potential risks have to be considered for frail patients.

Recent phase 3 trials have demonstrated the superiority of the combinations of avelumab + axitinib or pembrolizumab + axitinib over sunitinib [55, 56]. Unfortunately, due to an under-representation of the elderly in these studies, there is no strong data on the adverse effects of ICI + TKI in this population [68]. The proportion of patients who discontinue treatment due to side effects stays around 10% in ICI monotherapy trials (similar rates were observed with TKI). No significant differences were observed among age subgroups [68].

Treatment recommendations should be applied with caution in an elderly and potentially frail population, with data extrapolated from a younger population.

Balancing the cancer-related risk with other comorbidities

Several algorithms integrate frailty assessment and cancer-related prognostic factors to categorize patients' risk. The

two most important are the international metastatic RCC database consortium (IMDC) and the Memorial Sloan Kettering cancer center (MSKCC) score.

The MSKCC classification is derived from a 2002 retrospective study of metastatic RCC patients formerly treated with interferon [69] 70. It is composed of five equally weighted criteria: 2 clinicals [< 1 year from the time of diagnosis to systemic therapy and Karnofsky performance index status (KPS) < 80%] and 3 biologicals (lactates dehydrogenase and corrected calcium over upper limit and hemoglobin under the lower limit) (Table 3). The estimated median OS for good, intermediate, and high-risk groups were 20, 10, and 4 months respectively in a pre-targeted therapy era.

The IMDC classification was initially derived from a 2009 retrospective study of metastatic RCC patients treated with VEGFR-TKI [71, 72]. It relies on the same 2 clinical and 4 biological criteria (platelet count, neutrophil count, and corrected calcium over upper limit and hemoglobin under the lower limit) which are related to overall survival. The score categorizes three prognostics groups: favorable (0 criteria), intermediate (1 or 2) and poor (3 or more) with related estimated median OS of 43.2, 22.5, and 7.8 months respectively (Table 4). The IMDC classification has also subsequently been validated in patients treated with IO [73].

Pal et al. retrospectively analyzed survival outcomes and prognostics factors in patients treated with VEGFR-TKI for advanced RCC comparing 2 cohorts: one from the early (2006–2009) and the second from the late (2010–2012) targeted therapy era [74]. Comorbidities rates in the 6 months preceding the initiation of therapy were similar between the two groups. With a median age of 68 years old, the main comorbidities in the late group were hypertension (82.4%), cardiovascular disease (54.9%), diabetes (44.1%), renal failure (39.8%), chronic pulmonary disease (27.8%) and liver disease (4.5%). The same group subsequently analyzed the treatment patterns and adverse events from a large American

Table 3 Memorial Sloan Kettering Cancer Center (MSKCC) risk factors criteria for metastatic renal cell carcinoma

Risk factors	
Karnofsky performance status < 80%	
Lactate dehydrogenase > 1.5 ULN	
Hemoglobin < LLN	
Corrected serum calcium > ULN	
Time from diagnosis to systemic treatment > 1 year	
Risk groups	Number of factors
Good	0
Intermediate	1 or 2
High	3 to 5

ULN upper limit of normal, *LLN* lower limit of normal

Table 4 International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk factors criteria

Risk factors	
Time from diagnosis to systemic treatment > 1 year	
Karnofsky performance status < 80%	
Hemoglobin < LLN	
Corrected serum calcium > ULN	
Neutrophils > ULN	
Platelets > ULN	
Risk groups	Number of factors
Favorable	0
Intermediate	1 or 2
Poor	3 to 6

ULN upper limit of normal, *LLN* lower limit of normal

Table 5 Summary of findings in mRCC setting

Active surveillance
AS in mRCC setting might be considered initially for asymptomatic patients [45–48]
AS could delay adverse effects of systemic therapy and reduce financial cost without reducing overall survival in selected patients
AS in the new immune checkpoint inhibitors era remains unknown and data relies on the TKI era
Drugs toxicity
Adverse effects seem not to be more frequent in elderly but special precautions should be taken due to a potential greater impact
Profiles of toxicity of TKI and ICI are different. Nevertheless, overlapping toxicity could occur
Balance between cancer and comorbidities
Scores such as IMDC, MSKCC, ECOG PS etc.… are used to categorize each patient and help in choosing between systemic treatments according to standardized guidelines
Adverse effects of systemic treatments should be closely monitored to stay up to the expected benefits

mRCC metastatic renal cell carcinoma, *AS* active surveillance, *TKI* tyrosine kinase inhibitor, *ICI* immune checkpoint inhibitor, *IMDC* International Metastatic RCC Database Consortium, *MSKCC* Memorial Sloan Kettering Cancer Center, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

database in a real-world setting with 1992 metastatic RCC patients mostly treated with VEGFR-TKI from 2011 to 2015. They reported a relatively lower rate of comorbidities in this population [75]. The median age was 62 years old. The most common comorbidities were diabetes (27%), chronic kidney disease (20%), followed by liver disease (18%) and chronic obstructive pulmonary disease (12.6%).

According to the latest European association of urology guidelines, the choice of first-line systemic therapy in metastatic RCC patients relies on the IMDC classification. In this classification, the frailty assessment is based on the KPS scale, where 100 is the maximal score representing "perfect" health and 0 representing death. The threshold to consider a patient frail is 80%, concretely, it means that the patient is unable to carry on normal activity or to do active work.

Another score to assess patients' general condition is the Eastern Cooperative Oncology Group scale of performance status (ECOG PS) ranging from 0 for asymptomatic, 1 for symptomatic but completely ambulatory, 2 < 50% of the time in bed during the day, 3 > 50% of the time in bed during the day, 4 bed bounded patient, to 5 death. An excellent agreement between the two scores has been reported [76].

In the United States, 80% of patients over 65 years old cancer patients present at least one comorbidity requiring a medication [77]. Metastatic RCC patients frequently present multiple comorbidities. Therefore, the indication for systemic treatment in frail or aged patients should be thoroughly balanced in regard of intrinsic toxicity and risk of decompensation. Although severe adverse effects rates seem comparable in the elderly and the general population, their impact is usually greater with more dose diminution or treatment discontinuation, they need to be particularly anticipated and closely monitored [78].

Principal findings in the mRCC setting are synthetized in Table 5.

Conclusion

Comorbidity and frailty assessment are of utmost importance at both localized and metastatic stages of the disease. For localized RCC, this evaluation will lead the treatment decision toward surgery, focal therapy, surveillance or watchful waiting. It relies on standardized evaluations like ASA score or the Charlson's index to better balance the intervention and the cancer risks. For metastatic disease, the recent surge of effective systemic treatment based on combinations of immunotherapies and targeted therapies improved the cancer outcomes at the price of significant toxicity. Comorbidities and frailty should be assessed before starting such treatments. Integrated scores like the IMDC allow to categorize patients in risk groups to better select the appropriate therapeutic strategy.

Author contributions J Courcier: manuscript writing; A De La Taille: manuscript editing; N Lassau: manuscript editing; A Ingels: project development, manuscript writing/editing.

Funding None.

Compliance with ethical standards

Conflict of interest Jean COURCIER None. Alexandre DE LA TAILLE Intuitive Surgical. Nathalie LASSAU Jazz Pharmaceuticals. Alexandre INGELS Intuitive Surgical, Bristol-Myers Squibb.

Research involving human participants and/or animals None.

Informed consent Not applicable.

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