REVIEW

Renal cell carcinoma (RCC): fatter is better? A review on the role of obesity in RCC

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Abstract

Obesity represents a well-known risk factor for renal cell carcinoma development. Several studies evaluated the relationship between obesity and outcome in patients with non-metastatic and metastatic renal cell carcinoma using different parameters such as BMI, visceral fat area and s.c. fat area. These studies suggest that obesity is associated with a better prognosis in renal cell carcinoma patients. This phenomenon is called obesity paradox and it was found in other diseases in which obesity represents an established risk factor such as heart failure, diabetes, atrial fibrillation, hypertension and coronary heart disease. The purpose of this review is to analyze the mechanisms by which obesity increases the risk of renal cell carcinoma development, to describe the evidence available to date about the link obesity-outcome and to evaluate the mechanisms to explain this apparently paradoxical relationship.

Key Words

- ▶ renal cell carcinoma
- ▶ obesity
- ▶ obesity paradox
- ▶ tyrosine kinase inhibitors
- ▶ immune checkpoint inhibitors

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Introduction

Renal cell carcinoma (RCC) is the 9th most common cancer in men and the 14th most common cancer in women worldwide (Znaor *et al.* 2015). It accounts for about 4% of all new cancer cases and it is the most lethal of the common urological cancers with a 5-year relative survival of 75.2% (<https://seer.cancer.gov/statfacts/html/kidrp.html> November 2020). Surgery is the mainstay of treatment for localized or locally advanced RCC (<https://uroweb.org/guideline/renal-cell-carcinoma/#7> November 2020). Therapy landscape of metastatic disease has evolved dramatically over the past 15 years (Gong *et al.* 2016). Since 2005, multiple new drugs have been approved including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). Consequently, the overall survival (OS) of patients with metastatic RCC (mRCC) has increased from 1 year during the cytokine era to approximately

2.5–3 years in the TKIs and immunotherapy era (Gong *et al.* 2016). Metastatic RCC therapeutic standard is further changing following the results of recent studies showing the superiority of immunotherapy combinations (nivolumab+ipilimumab) and immunotherapy plus TKIs combinations (pembrolizumab+axitinib, avelumab+axitinib, nivolumab+cabozantinib and lenvatinib+pembrolizumab) compared to TKIs monotherapy in the first line (Motzer *et al.* 2018, 2019, Rini *et al.* 2019, Choueiri *et al.* 2021, Motzer *et al.* 2021). Although major advances have been made in understanding the molecular basis of RCC carcinogenesis, the therapeutic choice is still based on the clinical features of patients. Two risk models, the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC),

are commonly used to predict prognosis and guide therapeutic choice (Motzer *et al.* 2000, Heng *et al.* 2009). These risk models include clinical and laboratory factors: MSKCC model includes hemoglobin, performance status, time from diagnosis to systemic treatment, calcium and LDH levels while IMDC model includes the first MSKCC four criteria plus neutrophil and platelet count. These models identify three risk categories characterized by different prognosis: favorable (0 risk factors), intermediate (1–2 risk factors) and poor (>2 risk factors).

RCC etiology is still largely unknown. Carcinogenic agents according to International Agency for Research on Cancer (IARC) are tobacco smoking, trichloroethylene, X-radiation and gamma-radiation (Cho *et al.* 2011). Risk factors for RCC also include hypertension, a family history of RCC and genetic conditions such as von Hippel–Lindau disease, hereditary papillary renal cell carcinoma, hereditary leiomyomatosis and Birt–Hogg–Dube syndrome (Cho *et al.* 2011). Overweight, especially obesity, is a well-established, modifiable risk factor for the development of several types of cancer in both women and men, including RCC (Bergström *et al.* 2001, Cho *et al.* 2011, Davoodi *et al.* 2013). In 2016, IARC showed that the absence of excess body fat reduces the risk of most cancers including RCC (Lauby-Secretan *et al.* 2016).

Although obesity represents a strong risk factor for RCC development, several studies have shown that it is associated with a better prognosis than patients with normal weight. The aim of this review is to summarize the evidence currently available regarding the association between obesity and RCC trying to explain what is defined as the obesity paradox: why obesity, which increases the risk of developing RCC, is associated with better outcomes?

Obesity paradox

In recent years there has been a growing interest in the so-called 'obesity paradox'. Despite the known association between obesity and the onset of some chronic diseases, multiple studies reported that obesity confers better survival. The obesity paradox was first described in 1999 in overweight and patients with obesity undergoing hemodialysis and has subsequently been found in patients with hemodynamic and metabolic disorders such as heart failure, coronary heart disease, atrial fibrillation, hypertension and diabetes (Fleischmann *et al.* 1999, Uretsky *et al.* 2007, Carnethon *et al.* 2012, Sharma *et al.* 2015, Liu *et al.* 2020). Several theories have been

proposed to explain this paradox. These diseases should be diagnosed earlier in patients with obesity than in normal-weight patients, therefore, they could have an earlier use of treatments (Uretsky *et al.* 2007, Oreopoulos *et al.* 2008). Lower BMI values are associated to a negative survival status as sarcopenia and cachexia (Romero-Corral *et al.* 2006, Oreopoulos *et al.* 2008, Sharma *et al.* 2015). In addition, patients with obesity have some cardiovascular protective factors: lower levels of brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NTproBNP), reduced activation of sympathetic nervous system and renin–angiotensin system (RAA) (Oreopoulos *et al.* 2008). Furthermore, the adipocytes produce the receptor for tumor necrosis factor- α (TNF α) which neutralizes cardiotoxic effects of TNF α (negative inotropic effect and arrhythmogenic factor) (Uretsky *et al.* 2007, Oreopoulos *et al.* 2008). The abundance of adipose tissue could eventually counteract the negative effects of catabolic state in patients with chronic renal failure or heart failure, thus improving their prognosis (Oreopoulos *et al.* 2008).

The obesity paradox has also been investigated in different cancer settings. Greenlee *et al.* suggest that the association between BMI and cancer survival is not consistent across all cancer types (Greenlee *et al.* 2017). One of the cancers in which the obesity paradox has been extensively studied is RCC. In RCC, obesity represents a validated risk factor, but at the same time, it seems to be a positive prognostic factor. Studies evaluating the obesity paradox in RCC used several parameters to define the obesity state. The most used parameter is BMI, defined as weight divided by the square of the body height. BMI is universally expressed in units of kg/m², resulting from mass in kilograms and height in meters. Overweight is defined as a BMI of 25 to 29.9 kg/m² (23–25 kg/m² in Asian populations) while obesity is defined as a BMI of 30 kg/m² or greater (25 kg/m² or greater in Asian populations) (<https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi>; accessed November 2020). Other parameters investigated are s.c. fat area (SFA) and visceral fat area (VFA) measured at the level of the umbilicus using standard CT scans (Tokunaga *et al.* 1983). Body fat tissue is traditionally distributed in two compartments: s.c. and visceral adipose tissue. Subcutaneous adipose tissue is the fat tissue between the skin and muscle, whereas visceral adipose tissue is allocated within the main cavities of the body, primarily in the abdominal cavity (Mittal 2019). BMI, VFA and SFA are different and not always concordant parameters in defining obesity. BMI is a convenient

measure but could not indicate the differences among body fat, muscle and bone mass, consequently, skeletal muscle and adipose tissue areas vary widely in patients with the same BMI (Antoun *et al.* 2014). In addition, BMI also fails to display the distribution of fat (s.c. and visceral) among individuals. Moreover, VFA and SFA could be a more sensitive parameter to estimate nutritional status than BMI (Dai *et al.* 2020).

Obesity as a risk factor for RCC

It has been estimated that approximately 25% of RCC could be attributed to overweight and obesity (Scelo & Larose 2018); obesity confers a 1.5–2.5 relative risk increase in developing RCC (Calle & Kaaks 2004). A meta-analysis including 17 epidemiological studies estimated that there is 24% increase in the risk of developing RCC in men and 34% in women for each 5-point increase in BMI (Renehan *et al.* 2008). The mechanisms that link excess weight and cancer risk are not fully understood. White adipose tissue is a complex cellular system including different cells in addition to adipocytes, such as adipose stromal cells, B and T lymphocytes, macrophages, neutrophils, dendritic cells and mast cells. These cells produce proactive substances which are involved in the regulation of signaling pathways promoting carcinogenesis and leading to an increase in cell proliferation, survival, and angiogenesis (Aurilio *et al.* 2019). Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes, which lead to elevated blood levels of insulin-like growth factor-1 (IGF1) and blood insulin. These hormones cause the activation of the insulin receptors (INSR) and IGF1 receptors (IGF1R) triggering transduction pathways such PI3K/AKT, mTOR/cyclin D1, mTOR/HIF1A/VEGF and Ras which able to promote proliferation, angiogenesis and reduce apoptosis (Calle & Kaaks 2004, Hursting & Dunlap 2012, Stone *et al.* 2018, Aurilio *et al.* 2019). Moreover, patients with obesity have high levels of the hormone leptin, a potent stimulator of cell proliferation and tumor growth by involving MAPK, Jak/Stat, and PI3K/AKT pathways (Hursting & Dunlap 2012, Stone *et al.* 2018, Aurilio *et al.* 2019). On the other hand, adiponectin, whose concentrations are significantly lower in individuals with obesity compared to normal-weight subjects, through its ADIPOR1 and ADIPOR2 receptors, has an anti-TOR effect, thus inhibiting the angiogenesis process (Gao *et al.* 2015, Stone *et al.* 2018, Aurilio *et al.* 2019). Furthermore, patients with obesity exhibit high levels of ceruloplasmin that is involved in angiogenesis through interaction with its SLC31A1 receptor that induces VEGF

production (Stone *et al.* 2018, Aurilio *et al.* 2019). Obesity is associated with chronic inflammation favoring tumor initiation and progression, largely through the generation of pro-inflammatory cytokines, in particular TNF α and IL6. These trigger the production of cyclooxygenase 2, which in turn produces prostaglandin E2, favoring cancer progression. TNF α has anti-apoptotic potential through the stimulation of nuclear factor κ B (NF κ B). The complex IL6/IL6 receptor has an anti-apoptotic and proliferative mechanism through its action via the Janus kinase 2 (Jak 2) signaling pathway. In addition, IL6 induces the PI3K/AKT pathway, which results in the enhancement of cancer cell proliferation and anti-apoptotic effects (Hursting & Dunlap 2012, Stone *et al.* 2018, Aurilio *et al.* 2019).

Obesity as a prognostic factor for RCC

Several studies show that obesity is linked to better outcomes compared to normal weight both in non-metastatic (nmRCC) and mRCC patients. In a large Korean cohort study of 1543 patients with nmRCC, Choi *et al.* found that patients with a BMI ≥ 25 had a 53% lower risk of dying from RCC compared to patients with a BMI < 25 . The authors also performed a meta-analysis of 20 studies assessing the link between BMI and outcome in patients with nmRCC and further confirmed that having an increased BMI is associated with better results (41% lower risk of death from RCC in patients with a high BMI than in patients with a normal BMI) (Choi *et al.* 2013). This meta-analysis also showed that patients with obesity had better overall survival (HR 0.57 (0.43–0.76)) and recurrence-free survival (RFS) (HR 0.49 (0.30–0.81)) compared to non-obese patients. Instead, there are conflicting results regarding the relationship between SFA/VFA and outcome in patients with nmRCC. Mano *et al.* showed that SFA and VFA were not associated with OS in 201 patients with nmRCC (HR 0.72 (0.5–1.05), $P = 0.091$ and HR 0.82 (0.49–1.36), $P = 0.0446$, respectively) while Naya *et al.* found that increased VFA in 117 patients was an independent prognostic factor of better survival ($P = 0.0257$) (Naya *et al.* 2010, Mano *et al.* 2014). In Kaneko's study, VFA was an independent predictor of better RFS in 285 patients with localized RCC ($P = 0.037$) (Kaneko *et al.* 2015) (Table 1).

Several retrospective studies examined the prognostic role of obesity in patients with mRCC undergoing systemic therapy including both TKIs and immunotherapy. Albiges and collaborators found that a BMI > 25 may be a prognostic factor of better survival in two cohorts of patients ($n = 6632$) who received TKIs, both in first- and second-line settings (HR 0.84 (0.73–0.95)

Table 1 Obesity biomarkers in non metastatic renal cell carcinoma.

First author (year)	Trial design	Sample size	Obesity biomarkers	Gender	Ethnicity/race	Histology	Fuhrman grade	Results
Choi (2012)	R	1543	BMI	Female 29.4% Male 70.6%	Asian	Clear cell 84.7% Non clear cell 15.3%	G1-2 48.3% G3-4 51.7%	OS: HR 0.45 (0.29–0.68), $P < 0.001$; CSS: HR 0.47 (0.29–0.77), $P < 0.001$.
Choi (2012)	Meta-analysis	16,089	BMI	NA	NA	NA	NA	OS: HR 0.57 (0.43–0.76); CSS: HR 0.59 (0.48–0.74); RFS: HR 0.49 (0.30–0.81).
Mano (2014)	R	201	SFA and VFA	Female 25% Male 75%	White 90.5% Other 9.5%	Clear cell 100%	G1-2 42.3% G3-4 57.7%	No interference in OS; SFA: HR 0.72 (0.5–1.05), $P = 0.091$; VFA: HR 0.82 (0.49–1.36), $P = 0.0446$
Naya (2010)	R	117	VFA	Male 100%	Asian	Clear cell 100%	G1-2 79.5% G3-4 20.5%	Improved OS, $P = 0.0257$
Kaneko (2015)	R	285	VFA	Female 19.6% Male 80.5%	Asian	Clear cell 84.6% Non clear cell 15.4%	G1-2 90.5% G3-4 9.5%	Improved RFS, $P = 0.037$

BMI, body mass index; CSS, cancer-specific survival; NA, not available; OS, overall survival; R, retrospective; RFS, recurrence free survival; SFA, subcutaneous fat area; VFA, visceral fat area.

and 0.83 (0.74–0.93) in the two cohorts, respectively) (Albiges *et al.* 2016). In Choueiri's study, obesity is an independent factor for better OS in 475 patients who received sunitinib or sorafenib (median OS 32.5 vs 20.6 months, $P = 0.0001$) (Choueiri *et al.* 2010). In a recent study, Sanchez *et al.* investigated the association between patient survival and transcriptomic profiles of the primary tumor and peritumoral adipose tissue. They analyzed 478 patients with a BMI > 30 from three independent clinical cohorts of patients with RCC: COMPARZ trial ($n = 256$), The Cancer Genome Atlas (TCGA, $n = 93$) and MSK immunotherapy ($n = 129$). OS was significantly longer in patients with obesity than in those with normal weight treated with sunitinib or pazopanib in COMPARZ (adjusted HR 0.68 (0.48–0.96)) and TCGA (adjusted HR 0.41 (0.22–0.75)) cohorts even after adjustment for IMDC criteria (Sanchez *et al.* 2020). Bergerot *et al.* evaluated the link between overweight outcomes in 353 patients treated with TKIs or ICIs. Among patients treated with TKI with BMI < 25 ($n = 72$), median OS was 24 months (20.7–27.2) vs 36 months (18.6–53.3) among patients with BMI > 25 ($n = 157$) ($P = 0.02$) (Bergerot *et al.* 2019). Instead in Steffens' study, BMI was not significantly associated with PFS ($P = 0.63$) or OS ($P = 0.61$) in 116 patients treated with

TKIs while VFA and SFA were associated with better PFS ($P = 0.005$ $P = 0.04$) and OS ($P = 0.04$ $P = 0.01$). (Steffens *et al.* 2011). Mizuno *et al.* failed to show any association between BMI and PFS ($P = 0.2887$) or OS ($P = 0.4476$) in 114 patients treated with TKIs. However, in this study, a high VFA was found to be a predictive factor for better PFS ($P = 0.0070$) and OS ($P = 0.0001$) (Mizuno *et al.* 2017). Gu *et al.* found that the radiologic measurement of VFA and SFA was independently associated with OS in 124 patients treated with TKIs (HR 0.981, $P = 0.002$ and HR 0.987, $P = 0.048$, respectively) (Gu *et al.* 2015). These results are directly in contrast to those published by Ladoire who described that, in 64 patients treated with first-line antiangiogenic agents, a high SFA and VFA are predictive biomarkers for shorter PFS ($P = 0.048$ and $P = 0.0009$, respectively) and OS ($P = 0.0203$ and $P = 0.0003$, respectively) (Ladoire *et al.* 2011). The association between BMI and outcomes was also evaluated in a prospective study; Goebell *et al.* showed a significant and independent correlation of a BMI < 24 with shorter OS (HR= 1.94 (1.48–2.54)) in 606 mRCC patients treated with systemic therapies (in particular TKIs) (Goebell *et al.* 2018).

The obesity-outcomes link was also assessed in patients with mRCC treated with immunotherapy. In this regard,

a non-peer-reviewed abstract by Lalani *et al.* showed that in 147 patients treated with immunotherapy alone or in combination with TKIs, a BMI > 25 is associated with OS improvement ($P=0.016$) while only a non-significant trend was found for PFS. Interestingly, patients who presented a BMI reduction during immunotherapy from >25 to <25 had shorter OS than patients with no BMI changes ($HR=2.25$ (0.94–5.35)) (Lalani *et al.* 2019). In a study of 90 mRCC patients treated with ICIs, Labadie *et al.* evaluated the correlation between a series of clinical variables and the response to immunotherapy treatment. In patients with clinical benefit from ICIs ($n=52$) increased BMI ($P=0.007$) and overweight BMI status ($P=0.03$) correlated with improved PFS and OS, respectively (Labadie *et al.* 2019). De Giorgi found that a BMI < 25 is significantly associated with worse OS ($HR=1.59$ (1.10–2.30), $P=0.01$) in 313 patients treated with Nivolumab progressing after prior antiangiogenic therapy. Furthermore, in this study, the authors demonstrated that patients with BMI < 25 and a high immune inflammation index (a combination of neutrophils, platelets and lymphocytes) had the worst prognosis ($HR=3.37$ (2.29–4.95), $P<0.0001$) (De Giorgi *et al.* 2019). Sanchez *et al.* showed that the inverse association between BMI and OS was not significant after adjustment for IMDC risk score in the MSK immunotherapy cohort (adjusted $HR=0.72$ (0.40–1.30)) (Sanchez *et al.* 2020). Similarly, in the subgroup of patients in the Bergerot study who had received immunotherapy ($n=42$), a non-statistically significant difference in OS was found in favor of patients who had a BMI < 25 compared to those who had a BMI > 25 (mOS 23.6 vs 19.9 months, $P=0.26$) (Bergerot *et al.* 2019). The obesity paradox in ICIs-treated mRCC patients was not demonstrated in the study by Boi *et al.* ($n=72$) in which patients with obesity had lower PFS ($HR=0.54$ (0.31–0.95), $P=0.0322$) and OS ($HR=0.48$ (0.24–0.96), $P=0.0371$) than non-obese patients (Boi *et al.* 2020). The obesity-outcomes relationship in patients treated with immunotherapy has also been evaluated in other types of cancers; Xu *et al.* performed a meta-analysis to evaluate the overweight impact on survival in 4090 patients with different cancer (mainly melanoma and non-small cell lung cancer) treated with ICIs. It was found that BMI > 25 improved OS ($HR=0.72$ (0.51–1.02); $P=0.06$) and PFS ($HR=0.67$ (0.48–0.95); $P=0.02$). OS improvement was independent of cancer type except for RCC: three studies (424 patients in total) reported the relationship between high BMI and survival of patients with mRCC with contradictory results (Xu *et al.* 2019) (Table 2). To date, no study has evaluated the role of VFA and SFA in patients with mRCC who received immunotherapy.

The mechanism by which obesity improves the survival of patients with nmRCC and mRCC is not well understood. Patients with higher BMI may adequately preserve their fat and muscle mass, thus allowing a better nutritional status and potential survival advantage delaying the onset of cachexia (Choi *et al.* 2013). Another possible explanation is that tumors arising in nmRCC patients with obesity may be more indolent than those in normal-weight patients; patients with obesity have favorable clinical and pathologic conditions at diagnosis when compared with normal-weight patients (lower stage, lower Fuhrman grade, smaller tumor size and absence of symptoms and distant metastasis). Although patients with obesity are characterized by a higher rate of tumor growth, they may have more indolent tumors probably because they may be diagnosed at earlier stages as they are at a higher likelihood of being screened for other diseases (Choi *et al.* 2013). However, Hakimi *et al.* showed that BMI is inversely associated with advanced stage, regardless of earlier detection during assessments for other comorbidities (hypertension, hypercholesterolemia or diabetes). In this study the association between BMI and better outcomes was attenuated and became non-significant when controlling for stage and grade (Hakimi *et al.* 2013); instead in Choi's study, the association between obesity and better prognosis remained highly significant despite the adjustment for classic risk factors (stage, grade, tumor size and presence of symptoms) (Choi *et al.* 2013). An alternative explanation for the obesity paradox may be a different gene expression involving fatty acid metabolism genes. *FASN* (fatty acid synthase) is a gene that regulates *de novo* biosynthesis of fatty acids, an essential process for tumor growth. *FASN* is downregulated in patients with obesity and higher *FASN* expression is associated with worse survival (median 15 vs 36.8 months; $P=0.002$) (Horiguchi *et al.* 2008a, Hakimi *et al.* 2013, Albiges *et al.* 2016). An upregulation of *FASN* gives cancer cells a survival advantage, making it a potential metabolic oncogene (Menendez & Lupu 2007). In pre-clinical models, it has been shown that the pharmacological inhibition of *FASN* is able to induce a significant reduction of renal tumor cell growth *in vitro* (Horiguchi *et al.* 2008b). Lastly, obese and normal-weight patients could have different transcriptomic profiles. Sanchez *et al.* showed that tumors of patients with obesity have a different molecular profile comparing with those of normal-weight patients. The molecular profile of obese tumors is characterized by the upregulation of genes associated with hypoxia, angiogenesis and epithelial-mesenchymal transition (Sanchez *et al.* 2020).

Table 2 Obesity biomarkers and renal cell carcinoma response to medical therapies.

First author (Year)	Trial design	Sample size	Drug class	Obesity biomarkers	Gender	Ethnicity/race	Histology	Risk group	Outcome
Albiges (2016)	R	6632	TKIs	BMI	M 72% F 28%	White 69% Asian 19.5% Other 14.5%	CC 87.5% nCC 12.5%	F 15% I 45% P 25% U 15% NA	OS: cohort 1: 25.6 vs 17.1 months HR 0.84 (0.73–0.95); OS: cohort 2: 23.4 vs 15.9 months HR 0.83 (0.74–0.93). Improved OS, 32.5 vs 20.6 months, $P = 0.0001$. Improved OS, HR 0.68 (0.48–0.96).
Choueri (2019)	R	475	TKIs	BMI	NA	NA	NA	NA	Improved OS, HR 0.68 (0.48–0.96).
Sanchez COMPARZ cohort (2020)	R	256	TKIs	BMI	M 75.2% F 24.8%	NA	CC 100%	F 27% I 60.5% P 8.5% U 4% NA	Improved OS, HR 0.68 (0.48–0.96).
Sanchez TCGA cohort (2020)	R	93	TKIs	BMI	M 65.1% F 34.9%	NA	CC 100%	NA	Improved OS, HR 0.41 (0.22–0.75).
Bergerot (2019)	R	353	TKIs	BMI	M 72.5% F 27.5%	White 72.5% Black 3.2% Hispanic 14.6% Asian 9.7%	CC 79.7% nCC 20.3%	F 22.4% I 64.8% P 12.8%	Improved OS: 36 vs 24 months, $P = 0.02$.
Steffens (2011)	R	116	TKIs	BMI, VFA and SFA	M 68.1% F 31.9%	NA	CC 84.5% nCC 15.5%	NA	No interference by BMI: PFS $P = 0.63$; OS $P = 0.61$. Improved PFS ($P = 0.005$, $P = 0.04$) and OS ($P = 0.04$, $P = 0.01$) by VFA and SFA, respectively.
Mizuno (2017)	R	114	TKIs	BMI and VFA	M 82.5% F 17.5%	Asian 100%	CC 91.2% nCC 18.8%	F 27.2% I 53.5% P 19.3%	No interference by BMI: PFS $P = 0.2887$; OS $P = 0.4476$. Improved PFS ($P = 0.0070$) and OS ($P = 0.0001$) by VFA.
Gu (2015)	R	124	TKIs	VFA and SFA	M 64.5% F 35.5%	Asian 100%	NA	F 29.1% I 66.1% L 4.8% NA	Improved OS: VFA: HR 0.981, $P = 0.002$; SFA: HR 0.987, $P = 0.048$.
Ladoire (2011)	R	64	TKIs	VFA and SFA	M 64.6% F 35.4%	NA	CC 100%	NA	Shorter PFS ($P = 0.0009$ and $P = 0.048$) and OS ($P = 0.0003$ and $P = 0.0203$) by VFA and SFA, respectively.
Goebell (2018)	P	606	TKIs	BMI	M 70.3% F 29.7%	NA	CC 72.8% nCC 20.3% U 6.9%	F 32.8% I 45.9% L 8.9% U 12.4% I 60%	Improved OS, HR = 1.94 (1.48–2.54).
Lalani (2019)	R	147	TKIs+ ICIs	BMI	M 76% F 24%	NA	CC 85% nCC 15% CC 100%	NA	Improved OS, $P = 0.016$.
Labadie (2019)	R	90	ICIs	BMI	M 72.2% F 27.8%	Caucasian 65% African American 9% Hispanic 6% Asian 3% Unknown 17%	CC 100%	F 20% I 65% P 6% U 9%	Improved PFS ($P = 0.007$) and OS ($P = 0.03$).

De Giorgi (2019)	R	313	ICIs	BMI	M 75% F 25%	White 100%	CC 89.5% nCC 8.9% U 1.6% CC 100%	F 19% I 69.8% P 11.2% F 17.9% I 65.3% P 16.8% F 16.7% I 83.3% P 0%	Improved OS, low BMI vs high BMI: HR = 1.50 (1.05–2.15), P = 0.02 No interference in OS, HR = 0.72 (0.40–1.30). No interference in OS: 23.6 vs 19.9, P = 0.26.
Sanchez MSK immunotherapy cohort (2020)	R	203	ICIs	BMI	M 74% F 26%	NA			
Bergerot (2019)	R	42	ICIs	BMI	M 66.7% F 33.3%	White 71.4% Black 2.4% Hispanic 9.5% Asian 16.7%	CC 76.2% nCC 23.8%		
Boi (2020)	R	72	ICIs	BMI	M 73.6% F 26.4%	White 88.9% Others 11.1%	CC 84.7% nCC 15.3%	NA	Lower PFS: HR 0.54 (0.31–0.95), P = 0.0322 lower OS: HR 0.48 (0.24–0.96), P = 0.0371.
Xu (2019)	R	424	ICIs	BMI	NA	NA	NA	NA	No interference in OS: HR 0.58, (0.28–1.23), P = 0.16.

BMI, body mass index; CC, clear cell; F, favorable; I, intermediate; ICIs, immune checkpoint inhibitors; NA, not available; nCC, non-clear cell; OS, overall survival; P, poor; P, prospective; PFS, progression free survival; R, retrospective; SFA, subcutaneous fat area; TKIs, tyrosine kinase inhibitors; U, unknown; VFA, visceral fat area.

Visceral adiposity may create regions of hypoxia, which promotes angiogenesis and tumor microenvironment alterations regulating RCC proliferation. The upregulation of angiogenesis in RCC might explain the increased susceptibility of these tumors to TKIs while it is not clear how these results explain the better outcomes of patients treated with ICIs (Gan & Heng 2020). No differences were observed in the overall immune infiltration or tumor mutational burden (TMB) in the primary tumors between obese and normal-weight patients (Sanchez *et al.* 2020). Even in COMPARZ cohort, there was a lower expression of immune checkpoint molecules, as PDL1 (programmed death ligand 1) in obese patients (Sanchez *et al.* 2020).

These results are in contrast with Wang's study that explored connections between obesity, leptin pathway and PD1 (programmed cell death protein 1) expression on T cells in a pre-clinical model of melanoma and found that obesity increases T-cell aging resulting in a higher PD1 expression and dysfunction which could be driven, at least in part, by leptin signaling. The PD1-mediated T cell dysfunction in obesity could explain better outcomes for patients with obesity treated with ICIs (Wang *et al.* 2019). However, these results were not confirmed by Khojandi *et al.* that found no associations between BMI, leptin levels and PD1 expression on CD8+ tumor-infiltrating lymphocytes in a mixed cohort of melanoma and breast cancer patients (Khojandi *et al.* 2021).

Sanchez *et al.* also found that in the peritumoral fat of patients with obesity there was a greater infiltration of immune cells and a greater level of hypoxia (Sanchez *et al.* 2020). Peritumoral adipose tissue might act as a reservoir of immune cells that increases antitumor immune response in the presence of ICIs (Gan & Heng 2020).

Discussion

Obesity enhances the risk of developing RCC and at the same time appears to be a factor that increases the survival of both nmRCC and mRCC patients regardless of the treatments performed. This phenomenon is called 'obesity paradox', a phenomenon that has also been demonstrated in other chronic diseases where obesity is a risk factor. The mechanisms that could explain this paradoxical relationship are the presence of a better nutritional status, more indolent tumors, different gene expression and molecular profile of patients with obesity compared to normal-weight patients.

Multiple studies showed that obesity is a prognostic factor in nmRCC. Patients with a high BMI had better OS, RFS, and cancer-specific survival than patients with a

low BMI. However, these studies have crucial limitations. All the trials, except one, are retrospective. All the studies described have evaluated outcomes between patients with high BMI vs patients with normal and low BMI. Since sarcopenia and cachexia have been described as possible mechanisms that could explain the obesity paradox, it would be useful to know whether the relationship between obesity and better outcomes is confirmed by excluding patients with a low BMI. The studies that analyzed the link between BMI and outcomes in patients with RCC have another important limitation which is represented by the BMI cutpoint used to define the patient as obese; in fact, in some studies the patients were defined as obese with a BMI > 25 rather than >30.

Moreover, using BMI as a surrogate marker for adiposity has limitations due to its imprecise measure of body composition. In particular, BMI might fail to identify sarcopenic obesity, a condition of concomitant high-fat body mass and low muscle mass, which represents a worse prognostic factor for cancer patients. Compared to BMI, radiological detection of VFA or SFA might be more accurate in the definition of body composition. We have conflicting data about the association between VFA and SFA with outcomes in nmRCC patients. In particular, in one study, there was no correlation between VFA and SFA with OS while two other studies showed better OS and RFS in patients with high VFA.

The role of obesity as a prognostic factor in mRCC is still an open and intriguing question. BMI appears to be associated with better OS in TKIs-treated patients while its role in immunotherapy-treated patients is less defined. VFA and SFA also appear to be positive prognostic factors in terms of PFS and OS in patients treated with TKIs, while no studies have ever evaluated them in patients treated with ICIs. Another open question is whether weight changes during therapy can influence prognosis or treatment effectiveness. To date, only Lalani *et al.* found that BMI reductions are associated with worse outcomes in patients treated with immunotherapy (Lalani *et al.* 2019). Therefore, although the available data seem to show an association between obesity and outcomes in RCC, the crucial limitations described point to a more complex relationship.

The lack of validated predictive factors of treatment response which able to guide oncological decision-making is still an unsolved and challenging issue in mRCC. Currently, treatment decision in patients with mRCC is based on the clinical and biochemical criteria of MSKCC and IMDC. These prognostic scores were developed in an era where nephrectomy and cytokines were the only treatment options. The MSKCC and IMDC criteria have

been validated in patients treated with TKIs (Tanaka *et al.* 2016), nonetheless, whether the same prognostic factors are still relevant for patients treated with immunotherapy remain unclear. Patients treated with ICI may require specific risk stratification given the unique mechanism of action of immunotherapy. Martini *et al.* elaborated a new risk scoring system in a retrospective analysis of 100 patients. This model includes monocyte-to-lymphocyte ratio (MLR), number and sites of metastases and BMI. It identifies poor-risk patients (BMI $\leq$ 24, metastases > 2 with liver metastases, and MLR > 0.93) and good-risk patients (BMI > 24, MLR < 0.93, and metastases < 2); in poor-risk patients, both OS ($P = 0.002$) and PFS ($P = 0.03$) were significantly shorter than in good-risk patients, suggesting that the variables used are promising factors for predicting survival (Martini *et al.* 2020). However, prospective studies are needed to validate obesity as a factor to be taken into consideration in therapeutic choice.

Conclusions

Obesity is one of the main risk factors for the development of RCC. At the same time, several retrospective studies have shown that obesity appears to be a factor that positively influences the prognosis of patients with RCC. Actually, the available data about the predictive role of obesity are to be considered as a hypothesis generator. A challenge for the next future will be the planning of prospective studies which able to define the role of adipose tissue assessment as a prognostic factor in order to study its possible inclusion in the current prognostic models.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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