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

# Renal cell carcinoma (RCC): fatter is better? A review on the prognostic role of obesity in patients with RCC.


## ABSTRACT

Obesity represents a well-known risk factor for renal cell carcinoma (RCC) development. Several studies evaluated the relationship between obesity and outcome in patients with non-metastatic and metastatic RCC using different parameters such as body mass index (BMI), visceral fat area (VFA) and subcutaneous fat area (SFA). These studies suggest that obesity is associated with a better prognosis in RCC patients. This phenomenon called obesity paradox 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 analyse the mechanisms by which obesity increases the risk of RCC development, to describe evidence available to date about the link obesity-outcome and to evaluate the mechanisms to explain this paradoxical relationship.


## INTRODUCTION

Renal cell carcinoma (RCC) is the 9th most common cancer in men and the 14th most common cancer in women worldwide [1]. It accounts for about 4% of all new cancer cases [2] and it is the most lethal of the common urological cancers [3] with a 5-year relative survival of 75.2% [4]. Surgery is the mainstay of treatment for localized or locally advanced RCC [31]. Therapy landscape of metastatic disease has evolved dramatically over the past fifteen years [27]. Prior to 2005, the backbone of therapy were interleukin-2 (IL-2) and interferon-a (IFN-a) [32, 33]. Since 2005, multiple new drugs have been approved including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). TKIs (sunitinib, pazopanib, cabozantinib, axitinib, sorafenib, lenvatinib, and tivozanib) target the vascular endothelial growth factor receptor (VEGFR). ICIs target immunocheckpoints programmed death-1 (PD-1; nivolumab and pembrolizumab), its ligand (PD-L1; atezolizumab) or cytotoxic T lymphocyte antigen 4 (CTLA-4; ipilimumab) [34]. Consequently metastatic RCC (mRCC) overall survival (OS) has increased from 1 year during the cytokine era to approximately 2.5-3 years in the TKIs and immunotherapy era [27]. Metastatic RCC therapeutic standard is further changing following the results of recent studies showing the superiority of immunotherapics combinations[25] (nivolumab + ipilimumab) and immunotherapy plus TKIs combinations [16, 24, 79] (pembrolizumab + axitinib, avelumab + axitinib and nivolumab + cabozantinib) compared to TKIs monotherapy in first line. Although major advances have been made in understanding the molecular basis of RCC carcinogenesis, therapeutic choice is still based on clinical features of patients [34]. Two risk models, the Memorial Sloan Kettering Cancer Center (MSKCC) [33] and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)[12], are commonly used to predict prognosis and to guide therapeutic choice. 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 low (>2 risk factors).

RCC etiology is still largely unknown [26]. Carcinogenic agents according to International Agency for Research on Cancer (IARC) are: tobacco smoking [6], trichloroethylene, X-radiation and gamma-radiation [17]. Risk factors for RCC include also hypertension [6, 18], a family history of RCC [19] and genetic conditions such as von Hippel-Lindau disease [20], hereditary papillary renal cell carcinoma [21], hereditary leiomyomatosis [22] and Birt-Hogg-Dube syndrome [23]. Overweight, especially obesity, is a well-established, modifiable risk factor for development of several types of cancer in both women and men, including RCC [6, 7].

Although obesity represents a strong risk factor for RCC development, several studies have shown that it is associated with better prognosis than patients with normal weight. The aim of this review is to summarize evidence currently available regarding the association between obesity and RCC trying to explain what is defined as the obesity paradox: why obesity, which increases RCC risk, 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 a greater survival[14]. The obesity paradox was first described in 1999 in overweight and obese patients undergoing hemodialysis [37] and has subsequently been found in patients with hemodynamic and metabolic disorders such as heart failure [57, 60], coronary heart disease [48, 49, 61, 62], atrial fibrillation [35], hypertension [61] and diabetes [63]. Several theories have been proposed to explain this paradox. These diseases would be diagnosed earlier in obese patients than in normal weight patients, therefore they have an earlier use of treatments [60, 61]. Lower body mass index (BMI) values are associated to negative survival status as sarcopenia and cachexia.[60, 62, 64]. In addition obese patients have some cardiovascular protective factors: lower levels of brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-proBNP), reduced activation of sympathetic nervous system and renin–angiotensin system (RAA) system [60]. Furthermore, the adipocytes produce the receptor for tumor necrosis factor alpha (TNF-α) which neutralizes cardiotoxic effects of TNF-α (negative inotropic effect and arrhythmogenic factor) [60, 61]. The abundance of adipose tissue could eventually counteract negative effects of catabolic state of patients with chronic renal failure or hearth failure, thus improving their prognosis [60].

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 [67]. 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 seems to be a positive prognostic factor. Studies evaluating the obesity paradox in RCC used several parameters to define 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 metres [10, 11]. 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) [10]. Other parameters investigated are subcutaneous fat area (SFA) and visceral fat area (VFA) measured at the level of the umbilicus using standard CT scans [13]. Body fat tissue is traditionally distributed in two compartments: subcutaneous and visceral adipose tissue [8]. 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 [5]. 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 [66]. In addition, BMI also fails to display the distribution of fat (subcutaneous and visceral) among individuals. Moreover VFA and SFA could be a more sensitive parameter to estimate nutritional status than BMI [56].

### Obesity as a risk factor for RCC

It has been estimated that about 30-40% of RCC could be attributed to overweight and obesity [7, 9]; obesity confers a 1.5-2.5 relative risk increase in developing RCC [72]. A meta-analysis including 17 epidemiological studies estimated that there is a 24% increase in the risk of developing RCC in men and 34% in women for each 5-point increase in BMI [15]. 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 involved in the regulation of signalling pathways promoting carcinogenesis and leading to an increase in cell proliferation, survival, and angiogenesis [34]. 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 (IGF-1) and blood insulin. These hormones cause activation of the insulin receptors (INSR) and IGF-1 receptors (IGF-1R) triggering transduction pathways such PI3K/AKT, mTOR/cyclin D1, mTOR/HIF1A/VEGF and Ras able to promote proliferation, angiogenesis and to reduce apoptosis [34, 40, 72, 73]. Moreover, obese patients 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 [34, 40, 73]. On the other hand, adiponectin, whose concentrations are significantly lower in obese individuals compared to normal weight subjects, through its ADIPOR1 and ADIPOR2 receptors, has an anti-TOR effect, thus inhibiting the angiogenesis process [34, 40]. Furthermore, obese patients exhibit high levels of ceruloplasmin that is involved in angiogenesis through interaction with its SLC31A1 receptor that induces VEGF production[34, 40, 41]. Obesity is associated with chronic inflammation favouring tumor initiation and progression, largely through the generation of pro-inflammatory cytokines, in particular TNF-α and IL-6 [34, 40, 73]. The latters trigger the production of cyclooxygenase 2, which in turn produces prostaglandin E2, favouring cancer progression. TNF-α has anti-apoptotic potential through the stimulation of nuclear factor-kb (NF-kb). The complex IL-6/IL-6 receptor have anti-apoptotic and proliferative mechanism through its action via Janus kinase 2 (Jak 2) signaling pathway. In addition IL-6 induces the PI3K/AKT pathway, which results in the enhancement of cancer cell proliferation and anti-apoptotic effects [34, 40] (Figure 1).

**Obesity as a prognostic factor for RCC**

Several studies show that obesity is linked to a better outcome 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 obese patients than normal weight patients) [43]. Instead, there are conflicting results regarding the relationship between SFA/VFA and outcome in patients with nmRCC: Mano et al. [28] 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 in 117 patients that increased VFA was an independent prognostic factor of better survival (p=0.0257) [69] In Kaneko's study VFA was an independent predictor of better recurrence free survival in 285 patients with localized RCC (p=0.037) [47].

Several retrospective studies examined the prognostic role of obesity in patients with mRCC undergoing systemic therapy including both TKIs and immunotherapy. Albiges and collaborators[38] found that a high BMI 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) and 0.83 (0.74-0.93) in the two cohorts respectively]. In Choueiri's study [46] 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). In a recent study, Sanchez et al. investigated the association between patient survival and trascriptomic profiles of primary tumour and peritumoral adipose tissue [53]. They analyzed 478 patients with a BMI>30 kg/m² 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 [53]. Instead in Steffens' study [44] BMI was not significantly associated with PFS (p=0.63) or OS (p=0.61) in 116 patients treated with TKIs. 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 [45]. 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) in patients treated with TKIs. Gu et al. found that 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) [70]. These results are directly in contrast to those published by Ladoire [39] 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). The association between BMI and outcomes was also evaluated in a prospective study: Goebell et al. showed a significant and independent correlation of a low BMI with shorter OS [HR= 1.94 (1.48-2.54)] in 606 mRCC patients treated with systemic therapies (in particular TKIs) [68].

The relationship between obesity and outcomes in patients treated with antiangiogenetic drugs has also been evaluated in other types of tumors (non-small cell lung cancer, colorectal cancer and ovarian cancer) with discordant results. [36, 74-77].

The obesity-outcomes link was also assessed in patients with mRCC treated with immunotherapy. In this regard, Lalani et al. showed in 147 patients treated with immunotherapy alone or in combination with TKIs that a high BMI 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)] [30]. De Giorgi found that a low BMI is significantly associated with worse OS [HR=1.50 (1.05–2.15), p=0.02) in 313 patients treated with Nivolumab progressing after prior antiangiogenic therapy [29]. Sanchez et al. show that the inverse association of BMI with OS was not significant after adjustment for IMDC risk score in the MSK immunotherapy cohort [adjusted HR=0.72 (0.40–1.30)]. The obesity-outcomes relationship in patients treated with immunotherapy has also been evaluated in other types of cancers: Xu et al. [55] performed a meta-analysis to evaluate obesity impact on survival in 4090 patients with different cancer (mainly melanoma and non-small cell lung cancer) treated with ICIs. It was found that high BMI 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 (Table 1). To date, no study has evaluated the role VFA and SFA in patients with mRCC who received immunotherapy.

The mechanism by which obesity improves survival of patients with mRCC is not well understood. Patients with higher BMI may adequately preserve their fat and muscle mass, thus allowing better nutritional status and potential survival advantage delaying the onset of cachexia[43]. Another possible explanation is that tumors arising in obese patients may be more indolent than those in normal-weight patients: obese patients 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). In fact, obese patients may be diagnosed at earlier stages probably because they are at a higher likelihood of being screened for other diseases [43]. However Hakimi et al showed that BMI is inversely associated with advanced stage, regardless of earlier detection during assessments for other comorbidity (hypertension, hypercolesterolemia or diabetes) [42]. In this study the association between BMI and better outcomes was attenuated and became non significant when controlling for stage and grade; instead in Choi's study [43] 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). An alternative explanation for the obesity paradox may be a different gene expression involving fatty acid metabolism genes. FASN (fatty acid syntetase) is a gene that regulates de novo biosynthesis of fatty acids, an essential process for tumor growth. FASN is downregulated in obese patients and higher FASN expression is associated with worse survival (15 vs 36.8 month; p=0.002) [38, 42, 50]. An upregulation of FASN gives cancer cells a survival advantage, making it a potential metabolic oncogene [51]. In preclinical models it has been shown that the pharmacological inhibition of FASN is able to induce a significant reduction of renal tumor cells growth in vitro [52]. Lastly obese and normal weight patients could have different transcriptomic

profiles. Sanchez et al. [53] showed that tumors of obese patients have a different molecular profile comparing those of normal weight patients. The molecular profile of obese tumors is characterized by upregulation of genes associated with hypoxia, angiogenesis and epithelial-mesenchymal transition. Visceral adiposity may create regions of hypoxia, which promotes angiogenesis and tumour microenvironment alterations regulating RCC proliferation. The upregulation of angiogenesis in RCC might explain the increased susceptibility of these tumors to TKIs [65]. No differences were observed in the overall immune infiltration or tumour mutational burden in the primary tumors between obese and normal weight patients. Even in COMPARZ cohort there was a lower expression of immune checkpoint molecules, as PD-L1 in obese patient tumors [53]. In contrast Wang demonstrated in tumor models that obesity causes the aging of T cells with consequent higher expression of PD-L1. This phenomenon regulated by the leptin pathway makes obese patients more sensitive to immunotherapy [54]. Sanchez et al. also found that in peritumoral fat of obese patients there was a greater infiltration of immune cells and a greater level of hypoxia. Peritumoural adipose tissue might act as a reservoir of immune cells that increases antitumour immune response in the presence of ICIs [65].

## DISCUSSION

Obesity enhances the risk of developing RCC and at the same time appears to be a factor that increases 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 obese compared to normal weight patients.

Multiple studies showed that obesity is a prognostic factor in nmRCC. However these studies have crucial limitations. All the trials, except one, are retrospective. We do not have significant data about the role of VFA and SFA in this setting. Moreover using BMI as a surrogate marker of 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 patient. Compared to BMI, radiologically detection of VFA or SFA might be more accurate in the definition of body composition.

The role of obesity as prognostic factor in mRCC is still an open and intriguing question. BMI appears to be an independent prognostic factor of response to TKIs while its role in immunotherapy-treated patients is less defined. Furthermore, whether weight changes during therapy are able to influence prognosis or treatment effectiveness is unclear. To date only Lalani et al. found that BMI reductions are associated with worse outcome in patients treated with immunotherapy[30].

The lack of validated predictive factors of treatment response able to guide oncologists decision making is still an unsolved and challenging issue in mRCC. Currently, treatment decision in patients with mRCC is based on 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 [58], nonetheless, whether the same prognostic factors are still relevant for patients treated with immunotherapy remains 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-lymphocite ratio (MLR), number and sites of metastases and BMI [59]. It identifies poor-risk patients (BMI≤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 [59]. 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 through the release by the adipose tissue of various cytokines and growth factors promoting carcinogenesis. 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. A challenge for the next future will be the planning of prospective studies able to define the role of adipose tissue assessment as prognostic factor in order to study its possible inclusion in the current prognostic models.