

Body Mass Index and Survival in a Prospective Randomized Trial of Localized High-Risk Renal Cell Carcinoma

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Abstract

Background: The relationship between adiposity and renal cell carcinoma is poorly understood. Prior studies have suggested body mass index (BMI) may be associated with indolent disease.

Methods: We reviewed the clinicopathologic records of 845 patients across 14 countries who were enrolled in a prospective, placebo-controlled study of adjuvant girentuximab treatment for high-risk renal cell carcinoma. Clinical features analyzed included age, gender, race, BMI, and performance status. BMI was stratified into <25 kg/m², 25.0–29.9 kg/m², 30.0–34.9 kg/m², and ≥35 kg/m². We examined the association of BMI with stage and survival using logistic and Cox regression analyses, respectively.

Results: 845 patients were included for analysis. The majority (72%) were overweight/obese. There was an inverse relationship between BMI and lymph node involvement ($P = 0.04$). Obesity

was associated with improved disease-free and overall survival (log rank <0.01 for both). When compared with normal weight subjects, those with a BMI 30–34.9 [HR 0.50; 95% confidence interval (CI) 0.31–0.81] and BMI ≥35 (HR 0.24; 95% CI 0.09–0.60) had significantly improved overall survival. A trend towards improved disease-free survival was found among subjects with BMI 30–34.9 (HR 0.77; 95% CI 0.56–1.05) and ≥35 (HR 0.74; 95% CI, 0.48–1.15).

Conclusions: In a prospective cohort of nephrectomized patients with high-risk disease, obesity is associated with lower risk of lymphatic spread and improved overall survival.

Impact: This is the first study utilizing data from a prospective randomized trial reporting an association between obesity and improved overall survival for patients with clear cell renal cell carcinoma. *Cancer Epidemiol Biomarkers Prev*; 25(9); 1326–32. ©2016 AACR.

Introduction

The relationship between adiposity and renal cell carcinoma (RCC) is poorly understood. Virtually all epidemiologic studies, including case-control and cohort studies from Asia, Europe, and the United States have identified obesity or high relative weight as a risk factor for the development of RCC (1), making obesity one of the few well-established risk factors for RCC. Various putative biological mechanisms have been hypothesized to explain the relationship between increased adiposity and RCC carcinogenesis, including chronic tissue hypoxia, altered hormonal milieu within adipose tissue, and immune dysfunction (2, 3). Indeed, natural and synthetic estrogens are known to induce renal neoplasms in Syrian hamsters with an incidence approaching 100% (4). Some have estimated almost 30% of RCC may be attributable to increased adiposity (5).

The rising prevalence of obesity in the United States over the past 4 decades (6, 7) has largely been paralleled by increases in the incidence of predominantly small, asymptomatic low-stage RCC (8), resulting in an overall downward stage migration. Similar parallel increases in obesity and low-stage RCC have been observed in countries with relatively low rates of body mass index (BMI), such as Japan and South Korea (9–14). While much of this increase likely results from the detection of incidental, small, asymptomatic tumors by imaging studies performed for unrelated reasons, some have questioned whether other factors may be contributing to the rise of RCC. However, despite the downward stage migration in RCC and seemingly appropriate increases in treatment, attendant decreases in advanced stage disease or mortality from RCC have not been realized (8, 15). Attempts to elucidate the relationship between obesity and mortality from RCC have had both conflicting and paradoxical results. Both single institution retrospective series (16–18) and large meta-analyses (19) have concluded that despite the accepted association between adiposity and RCC carcinogenesis, adiposity is also an independent predictor for improved survival from RCC. This so-called "obesity paradox" was not supported by other investigations, which concluded obesity is not an independent prognostic factor after controlling for stage and grade (20, 21). Definitive conclusions have been limited by the nature of the above studies, the majority of which are single-institution series with data collected in retrospective fashion, and as such, at present the relationship between adiposity and survival from RCC remains unclear.

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To our knowledge, no studies to date have evaluated the relationship between adiposity and RCC survival in prospectively collected data, the reliability of which may exceed that of retrospectively collected data (22). Our objective was to examine the relationship between adiposity, measured as BMI, and pathologic and survival outcomes of patients with ccRCC in a large prospective clinical trial of patients with ccRCC.

Methods

Study design

The ARISER Trial (NCT00087022) was a prospective, randomized, international, placebo-controlled trial comparing the efficacy and safety of adjuvant girentuximab versus placebo in patients with clinically localized, completely resected clear cell RCC (ccRCC) at high risk of recurrence. Girentuximab is a chimeric mAb specific for carbonic anhydrase IX, which is ubiquitously expressed in ccRCC and minimally expressed in normal tissues. Patients were eligible for inclusion in the ARISER trial if they had undergone partial or radical nephrectomy for ccRCC and were deemed to be at high risk for cancer recurrence by meeting one of the following high-risk pathologic criteria, based on the 6th edition UICC 2002 TNM staging: (1) pT3/T4 Nx/N0/M0, (2) pTany N+/M0, or (3) pT1b/T2 Nx/N0/M0 and high-grade. All pathologic specimens were centrally reviewed for assessment of tumor typing (i.e. confirmation of the clear cell histology, as well as grade and stage). Pathology for node-positive patients (risk

group 2) was reviewed centrally to confirm lymph node metastasis. Eligible patients underwent baseline assessment no less than 3 weeks prior to randomization, at which time clinical data including age, gender, race, Eastern Cooperative Oncology Group (ECOG) performance status, height in meters, weight in kilograms, were collected and recorded in case report forms. Randomization took place not more than 12 weeks from the date of nephrectomy. Patients were randomized to drug or placebo arm and were followed for disease recurrence with CT imaging every three months for the first two years, every 6 months for the next two years, and annually thereafter until final analysis. A copy of the protocol and proposed informed consent form were reviewed and approved by the relevant Institutional Review Board or Independent Ethics Committee prior to the enrolment of the first patient at each participating site. The study sponsor and investigators were to abide by the principles of the International Conference on Harmonization Guideline for Good Clinical Practice, the latest version of the Declaration of Helsinki, as well as any local regulations.

Patient cohort

The study took place at 142 centers in 14 countries on three continents from 2004 to 2008. In total, 864 patients were accrued and randomized to two treatment arms. Of these, 19 patients were excluded from our analysis because of incomplete data regarding BMI, grade, or ECOG performance status, resulting in a final patient cohort of 845 patients.

Table 1. Bivariable analysis stratified by BMI category

BMI category (kg/m ²)	<25	25–29.9	30–34.9	≥35	Total	P
Age group						0.34
<50	51 (22)	71 (19.5)	29 (17.7)	17 (20.2)	168 (19.9)	
50–59	79 (34.1)	137 (37.5)	64 (39)	38 (45.2)	318 (37.6)	
60–69	61 (26.3)	113 (31)	52 (31.7)	21 (25)	247 (29.2)	
≥70	41 (17.7)	44 (12.1)	19 (11.6)	8 (9.5)	112 (13.3)	
Age	58 (51–66)	58 (51–65)	58 (52–64)	58 (51–63)		0.80
Sex						0.018
Female	75 (32.3)	106 (29)	66 (40.2)	36 (42.9)	283 (33.5)	
Male	157 (67.7)	259 (71)	98 (59.8)	48 (57.1)	562 (66.5)	
Race						0.48
Caucasian	221 (95.3)	342 (93.7)	154 (93.9)	76 (90.5)	793 (93.8)	
Other	11 (4.7)	23 (6.3)	10 (6.1)	8 (9.5)	52 (6.2)	
Treatment						0.71
Placebo	113 (48.7)	189 (51.8)	81 (49.4)	38 (45.2)	421 (49.8)	
Girentuximab	119 (51.3)	176 (48.2)	83 (50.6)	46 (54.8)	424 (50.2)	
ECOG ^a						0.21
0	193 (83.2)	323 (88.5)	139 (84.8)	69 (82.1)	724 (85.7)	
1	39 (16.8)	42 (11.5)	25 (15.2)	15 (17.9)	121 (14.3)	
Continent						<0.01
North America	41 (17.7)	76 (20.8)	51 (31.1)	53 (63.1)	221 (26.2)	
South America	13 (5.6)	29 (7.9)	13 (7.9)	1 (1.2)	56 (6.6)	
Europe	178 (76.7)	260 (71.2)	100 (61)	30 (35.7)	568 (67.2)	
T Stage						0.51
T1	13 (5.6)	22(6)	10 (6.1)	8 (9.5)	53 (6.3)	
T2	24 (10.3)	32 (8.8)	15 (9.1)	12 (14.3)	83 (9.8)	
T3	192 (82.8)	298 (81.6)	133 (81.1)	63 (75)	686 (81.2)	
T4	3 (1.3)	13 (3.6)	6 (3.7)	1 (1.2)	23 (2.7)	
Nuclear grade						0.53
G1/G2	74 (31.9)	129 (35.3)	62 (37.8)	33 (39.3)	298 (35.3)	
G3/G4	158 (68.1)	236 (64.7)	102 (62.2)	51 (60.7)	547 (64.7)	
N stage						0.04
N0/NX	207 (89.2)	337 (92.3)	156 (95.1)	82 (97.6)	782 (92.5)	
N1/N2	25 (10.8)	28 (7.7)	8 (4.9)	2 (2.4)	63 (7.5)	
Total	232 (100)	365 (100)	164 (100)	84 (100)	845 (100)	

NOTE: Continuous variables displayed as median (IQR).

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Multivariable logistic regression model for prediction of lymph node involvement

	OR (95% CI)	P
Age group		
<50	1.00 (referent)	***
50–59	0.41 (0.2–0.8)	0.01
60–69	0.72 (0.36–1.4)	0.33
≥70	0.31 (0.11–0.87)	0.03
Gender		
Female	1.00 (referent)	***
Male	0.81 (0.46–1.42)	0.47
Race/ethnicity		
Other	1.00 (referent)	***
White	4.4 (0.57–33.88)	0.16
BMI (kg/m ²)		
<25	1.00 (referent)	***
25.0–29.9	0.69 (0.38–1.24)	0.21
≥30	0.34 (0.15–0.76)	0.01
ECOG Performance status		
0	1.00 (referent)	***
1	0.79 (0.34–1.81)	0.57
Continent		
North America	1.00 (referent)	***
South America	1.15 (0.34–3.83)	0.82
Europe	1.2 (0.61–2.39)	0.6
T Stage		
T1	1.00 (referent)	***
T2	0.62 (0.22–1.77)	0.38
T3	0.33 (0.14–0.78)	0.01
T4	0.5 (0.09–2.69)	0.42
Nuclear grade		
Low	1.00 (referent)	***
High	1.16 (0.63–2.14)	0.63

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Statistical analysis

BMI was calculated as weight in kilograms divided by height in meters squared, and stratified into the following groups: <25,

25–29.9, 30–34.5, ≥35. Descriptive statistics were calculated for the study cohort. We evaluated the association between clinicopathologic variables using bivariable analysis. Differences between groups were tested using student's *t* and χ^2 tests for continuous and categorical variables, respectively. We then explored associations between independent predictor variables and the outcome of lymph node involvement using multivariable logistic regression analysis. Disease-free survival was calculated from the date of randomization to the date of documented relapse; patients with no documented relapse were censored at the date of their last evaluation on study. Relapse was defined as signs of metastatic disease or local recurrence as confirmed by CT, death (excluding deaths unrelated to the disease), or start of new antitumor therapy. Overall survival was calculated from the date of randomization to the date of documented death; patients with no documented death were censored at the date of their last evaluation on study (the last date the patient was known to be alive). Kaplan–Meier survival analysis was used to estimate disease-free and overall survival and tests of equality were quantified using the log-rank test. HRs for disease-free survival and overall survival were generated using multivariable Cox regression analysis. All statistical tests were two-tailed, with the probability of type 1 error set at 0.05. Statistical analysis was performed using STATA 12.1.

Results

We identified 845 patients with complete clinical, pathologic, and follow-up data for inclusion in our analysis. The cohort was 67% male, 94% Caucasian, 86% ECOG status 0, 67% European, with a median age of 58 [interquartile range (IQR) = 51–65]. Pathologic stage T3/T4 tumors made up 84% of the cohort, and 65% of tumors were high grade. Median BMI was

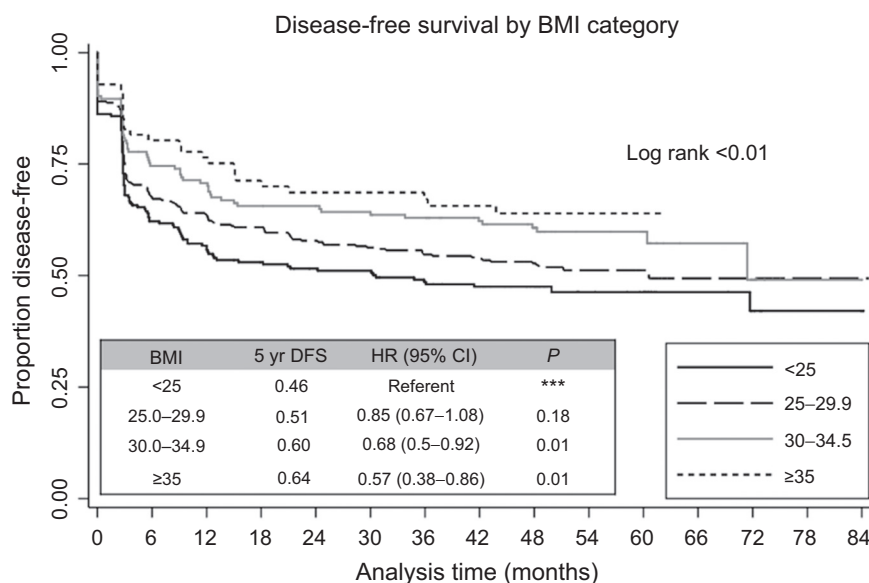


Figure 1. Kaplan–Meier estimates of disease-free survival by BMI category.

Number at risk	<25	25–29.9	30–34.5	≥35
0	232	365	164	84
6	137	236	117	63
12	123	219	110	59
18	111	203	101	55
24	105	191	100	50
30	103	183	97	46
36	95	174	94	44
42	88	167	86	42
48	79	140	77	33
54	36	71	38	16
60	33	58	32	13
66	12	12	8	0
72	8	10	5	0
78	3	2	1	0
84	2	2	1	0

27.4 (24.7–30.8) kg/m² (Table 1). Median follow-up for the entire cohort was 54 months (IQR = 43–61), during which time 381 patients (45%) experienced disease recurrence and 178 patients (21%) died. The median time period between nephrectomy and baseline BMI measurement was 57 days (IQR = 43–75).

There was no significant difference in BMI distribution between T-stages (*P* = 0.51; Table 1). The proportion of patients with lymph node involvement progressively decreased with each increase in BMI category: 11% in those with BMI <25, 8% in those with BMI 25–29.9, 5% in those with BMI 30–34.5, and 2% in those with BMI ≥35. This finding was consistent when using varying cut-off points for BMI. In multivariable logistic regression analysis, as BMI increased, the rate of lymph node metastasis decreased (Table 2). When compared with men with a normal BMI, those with a BMI of ≥30 [OR 0.34; 95% confidence interval (CI), 0.15–0.76] had a significantly lower odds of lymphatic involvement.

Kaplan–Meier analysis demonstrated that with each increase in BMI category there was progressively prolongation and a statistically significant difference in both disease-free and overall survival (log rank <0.01 for both, Figs. 1 and 2). Multivariable Cox proportional hazard models were used to generate HRs for disease-free survival and overall survival across categories of BMI. Covariates for both models included age, gender, race, ECOG performance status, Continent (Europe, North America, South America), T-stage, N-stage, and nuclear grade. When compared with patients with a normal BMI, there was a nonsignificant trend toward improved disease-free survival in patients with a BMI of 30–34.9 (HR 0.77; 95% CI, 0.56–1.05) and BMI ≥35 (HR 0.74; 95% CI, 0.48–1.15; Table 3). When compared with patients with a normal BMI, a BMI of 30–34.9 (HR 0.50; 95% CI, 0.31–0.81), and BMI ≥35 (HR 0.24; 95% CI,

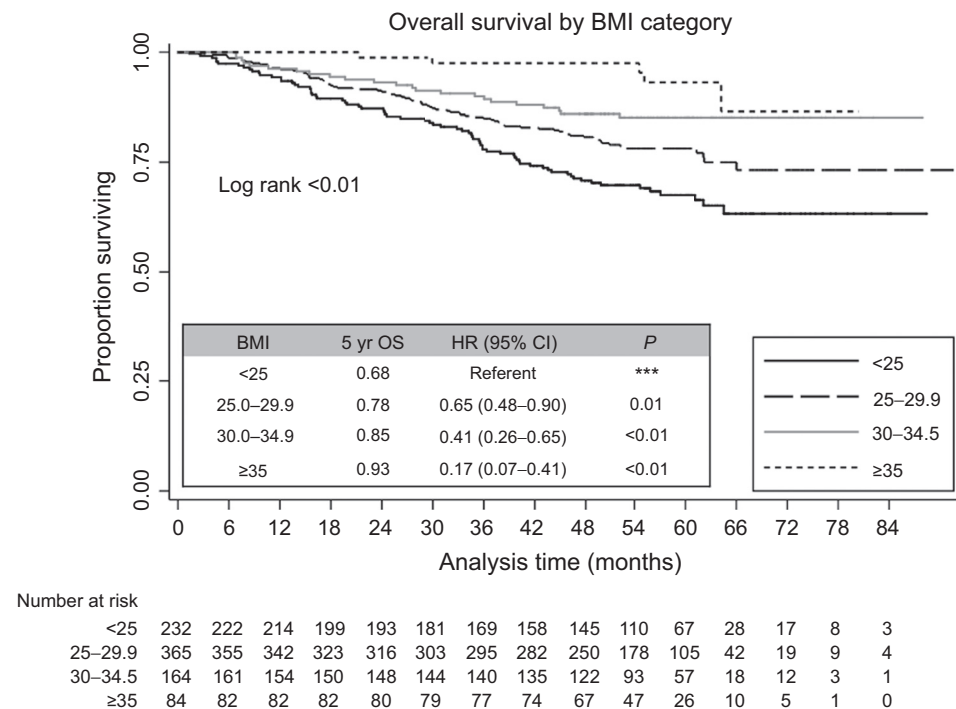
0.09–0.60) were both associated with improved overall survival (Table 3).

Discussion

We utilized data from a large prospective international phase III randomized clinical trial of patients with high-risk ccRCC to investigate the relationship between BMI and lymph node metastasis, disease-free survival, and overall survival. We observed that as BMI increased, the rate of lymph node metastasis decreased, a finding that was significant despite controlling for patient and tumor characteristics. Next, we observed an association between increased BMI and improved disease-free and overall survival. Using multivariable models, patients who were obese (30–34.9) or morbidly obese (BMI ≥35) had a statistically significant overall survival advantage and enjoyed a trend towards improved disease-free survival.

Our findings support the concept of an obesity paradox in ccRCC, however, at this time, the biological mechanisms underlying this observation are not known. One potential explanation for the paradox is that RCC developing in the obese may represent a biologically distinct and less aggressive form of the disease. There is an increasing appreciation of the genomic heterogeneity within the clear cell histologic subtype, and distinct molecular subtypes of ccRCC which demonstrate divergent survival patterns have been described (23, 24). Hakami and colleagues observed that fatty acid synthase, a gene associated with poor RCC outcomes when upregulated, appeared downregulated in tumors from obese patients. This serves as a potential mechanism to explain improved survival in this population (20, 25). Various other putative biochemical pathways linking obesity to cancer progression are the subjects of active research (26).

Figure 2. Kaplan–Meier estimates of overall survival by BMI category.



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Table 3. Multivariable COX regression analysis of disease-free and overall survival

	Disease-free survival		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P
Age group				
<50	1.00 (referent)	***	1.00 (referent)	***
50–59	1.27 (0.93–1.74)	0.14	1.21 (0.74–1.97)	0.45
60–69	1.89 (1.38–2.60)	<0.01	1.99 (1.24–3.21)	<0.01
≥70	2.23 (1.54–3.22)	<0.01	2.70 (1.62–4.50)	<0.01
Gender				
Female	1.00 (referent)	***	1.00 (referent)	***
Male	1.00 (0.80–1.24)	0.97	0.96 (0.69–1.32)	0.79
Race/ethnicity				
Other	1.00 (referent)	***	1.00 (referent)	***
White	0.87 (0.55–1.38)	0.57	1.01 (0.49–2.11)	0.97
BMI (kg/m ²)				
<25	1.00 (referent)	***	1.00 (referent)	***
25.0–29.9	0.91 (0.72–1.16)	0.46	0.73 (0.53–1.01)	0.06
30.0–34.9	0.77 (0.56–1.05)	0.09	0.50 (0.31–0.81)	<0.01
≥35	0.74 (0.48–1.15)	0.18	0.24 (0.09–0.60)	<0.01
ECOG Performance status				
0	1.00 (referent)	***	1.00 (referent)	***
1	1.20 (0.91–1.58)	0.19	1.18 (0.79–1.78)	0.42
Continent				
North America	1.00 (referent)	***	1.00 (referent)	***
South America	0.99 (0.62–1.59)	0.98	1.18 (0.62–2.24)	0.62
Europe	1.18 (0.91–1.52)	0.20	1.07 (0.73–1.55)	0.73
T Stage				
T1	1.00 (referent)	***	1.00 (referent)	***
T2	2.95 (1.53–5.69)	<0.01	1.28 (0.54–3.05)	0.57
T3	3.23 (1.80–5.79)	<0.01	1.86 (0.90–3.84)	0.09
T4	4.91 (2.21–10.92)	<0.01	1.09 (0.29–4.14)	0.90
N Stage				
Nx/NO	1.00 (referent)	***	1.00 (referent)	***
N+	3.23 (2.37–4.40)	<0.01	3.84 (2.60–5.68)	<0.01
Nuclear grade				
Low	1.00 (referent)	***	1.00 (referent)	***
High	1.98 (1.56–2.52)	<0.01	2.12 (1.48–3.05)	<0.01

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

There is conflicting evidence as to whether improved survival in the obese can be accounted for by tumor stage and grade alone. Hakami and colleagues found that BMI was associated with lower risk of cancer-specific death and overall death; however, the association was attenuated and became nonsignificant when controlling for stage and grade. The authors concluded that the improved outcomes in obese patients were attributable to lower grade and stage tumors in this population. Other retrospective studies have similarly failed to find BMI independently prognostic of overall survival when controlling for stage (27–29). We did not find an association between BMI and T-stage in our analysis; however, our study cohort consisted predominantly of patients with pT3/pT4 disease (84%) and as such there may have been insufficient variability in stage to detect an association. We did, however, find that increases in BMI were associated with a lower risk of lymphatic involvement, supporting the concept that tumors forming in an obesogenic environment may harbor less aggressive biology, even among those with high risk of recurrence. In other words, our finding that BMI was positively associated with improved overall survival even when controlling for T-stage, N-stage, and grade, suggests that the effect of obesity is not completely accounted for in the stage and grade of tumors.

One alternative explanation for the obesity paradox may relate to the role that disease–host as well as treatment–host interactions play in modulating overall disease course. Body adiposity is known to be associated with a state of chronic

systemic inflammation, with persistently elevated levels of proinflammatory cytokines including C-reactive protein (CRP), tumor necrosis factor (TNF), and IL6 and IL18, among others (30). Given the propensity of RCC to respond to immunotherapeutic treatment approaches (31, 32), the question is raised of whether these chronically elevated cytokine levels exert some form of antitumor effect. This hypothesis, however, appears unlikely given the absence of an obesity paradox among other obesity-related cancers, such as breast and colorectal carcinomas (33). An alternative explanation is that BMI may be a reflection of physiologic host reserve and overall wellness, which may confer a survival advantage, particularly in diseases associated with wasting, such as cancer. This hypothesis is supported by studies evaluating the relationship between the skeletal muscle compartment and survival. Studies of both localized and metastatic RCC have demonstrated that sarcopenia, or decreased skeletal muscle mass (34), as well as decreased skeletal muscle density (35) independently predicts worse cancer-specific and overall survival. While this may reflect greater host reserve in a disease known to cause wasting, the known propensity of the targeted agents used in the metastatic setting to exacerbate muscle wasting (36, 37), potentially leading to dose-limiting toxicities in those with pre-existing muscle wasting may also contribute to this phenomenon. Interestingly, obesity and sarcopenia are not mutually exclusive, and within each strata of BMI there is a wide range of

skeletal muscle mass, including obese patients with cachectic levels of skeletal muscle mass (35, 38). Various other image-based metrics of body composition have been evaluated, including visceral adipose tissue, subcutaneous adipose tissue, and what is clear is that the relationship between body composition, both within adipose and muscular compartments, and cancer-specific outcomes is complex and somewhat poorly understood at this time (39).

Our findings should be considered in light of the increasing appreciation that many incidentally diagnosed small renal masses (<4cm) may display an indolent natural history if left untreated. The concept of the indolent small renal mass is supported by multiple epidemiologic observations, including the failure of mortality rates to decrease in the face of downward stage migration and seemingly appropriate treatment of these masses (15), along with the relative stability in incidence of more advanced stage disease (8). These observations suggest the possibility that many of these masses, if left untreated, would not be destined to cause clinically significant disease. This has raised the question of potential overtreatment of these small, incidentally detected kidney tumors (40). These considerations have resulted in the relatively infrequent but increasing use of active surveillance as a management strategy for small renal masses (41, 42). Active surveillance is particularly relevant for patients in whom there is significant perioperative risk, such as the elderly or those with severe comorbidities, or in those in whom treatment may be complex or high risk, such as in the obese patient. Given the high prevalence of obesity, coupled with the fact that the majority of newly diagnosed renal tumors are <4 cm (43) urologists are now frequently faced with the dilemma of managing an obese patient with a renal mass of unclear malignant potential. Our study suggests that in obese patients, irrespective of the underlying mechanism, renal masses may be less aggressive than those of their leaner counterparts, and that active surveillance of these masses may be oncologically sound. This, combined with the recognition of increased risks inherent in operating on the obese (44, 45), may shift the risk-benefit ratio away from intervention.

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Conclusion

Using data from large international prospective clinical trial of surgically treated patients with high-risk ccRCC, we found that increasing BMI was associated with a lower risk of lymph node metastasis and a decreased risk of death. These findings add to the growing number of studies demonstrating a seemingly paradoxical relationship between BMI and survival in patients with ccRCC. Whether these observations relate specifically to BMI, or are rather a reflection of differences in body composition remains unknown. Molecular characterization of ccRCC and studies of tumor-host interactions in patients with different body composition will be required to understand this relationship.

Disclosure of Potential Conflicts of Interest

P. Bevan is a director and a consultant/advisory board member at Wilex AG. A.S. Belldgrun is a consultant for Wilex AG. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: N.M. Donin, A. Pantuck, P. Bevan, A.S. Belldgrun, K. Chamie

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