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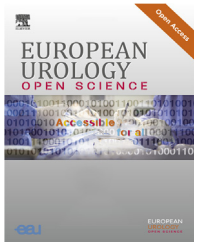

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Kidney Cancer

The Detrimental Effect of Metabolic Syndrome on Long-term Renal Function in Patients Undergoing Elective Partial Nephrectomy for Small Renal Masses

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Abstract

Background and objective: Metabolic syndrome (MetS) is a clinical condition associated with higher rates of overall and cardiovascular mortality. There is scarce evidence regarding the impact of MetS on surgical and functional outcomes for patients undergoing partial nephrectomy (PN) for clinically localized small renal masses (SRMs).

Methods: We analyzed data from a prospectively maintained institutional database for 690 patients with cT1a renal cancer undergoing PN between 2000 and 2023 at a tertiary referral center. MetS was defined according to international guidelines. Cumulative incidence curves were used to estimate the 5-yr risk of stage IIIB–V chronic kidney disease (CKD) stage and other-cause mortality (OCM). Multivariable regression models were used to analyze the impact of MetS on the risk of complications, acute kidney injury (AKI), stage IIIB–V CKD, and OCM.

Key findings and limitations: Overall, 10% of the PN cohort had MetS. The MetS group was older (median age 70 yr, interquartile range [IQR] 65–74 vs 61 yr, IQR 50–69; $p < 0.001$) and had worse preoperative kidney function (median estimated glomerular filtration rate 65 [IQR 62–81] vs 88 [IQR 69–98] ml/min/1.73 m^2; $p < 0.001$) than the group without MetS. The MetS group had higher incidence of complications (odds ratio [OR] 1.81, 95% confidence interval [CI] 1.05–3.08; $p = 0.03$) and postoperative AKI (OR 3.17, 95% CI 1.54–6.41; $p = 0.001$). The 5-yr risk of stage IIIB–V CKD (45% vs 7.2%; hazard ratio [HR] 2.34, 95% CI 1.27–4.30; $p = 0.006$) and OCM (14% vs 3.5%; HR 3.00, 95% CI 1.06–8.55; $p = 0.039$) were also

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higher in the MetS group. The main limitations are the extended accrual time and unmeasured confounders that could potentially affect outcomes.
Conclusions and clinical implications: Patients with MetS had worse postoperative, functional, and survival outcomes after SRM surgery in comparison to patients without MetS. Multidisciplinary care could help in reducing the preoperative metabolic burden in these patients. Further research should explore if alternative approaches (eg, surveillance or focal therapy) could minimize postoperative comorbidities and protect long-term renal function in this population.
Patient summary: Patients with a condition called metabolic syndrome who have part of their kidney removed for small kidney tumors are at higher risk of complications and long-term kidney issues. Patient care from a multidisciplinary team could help in reducing the metabolic burden before surgery. Further research is needed to explore if less invasive treatment options could reduce these risks.

1. Introduction

Metabolic syndrome (MetS) is a prevalent clinical condition that affects 25% of the world population [1]. MetS is characterized by the presence of at least three of the following characteristics: insulin resistance (fasting glucose ≥110 mg/dl); atherogenic dyslipidemia (high-density lipoprotein cholesterol [HDL-C] <40 mg/dl for men, <50 mg/dl for women); hypertriglyceridemia (triglycerides ≥150 mg/dl); large waist circumference (≥102 cm for men, ≥88 cm for women); and hypertension (≥130/85 mm Hg) [2,3]. This clinical syndrome has been associated with unfavorable surgical outcomes in several malignancies [4–6] and is a significant risk factor for long-term medical renal impairment [7–9]. However, there is a lack of evidence regarding the impact of MetS on clinically relevant perioperative and oncological outcomes for patients undergoing renal surgery (medical and surgical renal impairment). Specifically, few data are available on morbidity, mortality, and functional outcomes after partial nephrectomy (PN) for small renal masses (SRMs) in patients with MetS [10,11].

Current guidelines suggest active surveillance or a percutaneous procedure such as thermal ablation for comorbid or frail patients with clinically localized cT1 renal masses [12–14]. Thus, we hypothesized that MetS might predispose patients to worse perioperative and postoperative outcomes after PN.

Given these premises, our aim was to assess the impact of MetS on morbidity, mortality, and functional outcomes for patients undergoing PN for clinically localized SRMs, as these individuals might have been suitable candidates for conservative approaches.

2. Patients and methods

2.1. Study population

After institutional board approval (GO/URC/ER/mm protocol no. 79/DG), we collected data from a prospectively maintained database comprising 4019 patients who underwent renal surgery between 1987 and 2023. We included patients with histologically confirmed renal cell carcinoma, cT1a disease (clinical size ≤4 cm), and a preoperative estimated glomerular filtration rate (eGFR) of ≥60 ml/min/1.73 m^2 who underwent PN performed by an experienced surgeon (≥30 surgeries overall) at our center between 2000 and 2023. Patients with a solitary kidney, hereditary cancer, or missing data for the outcomes of interest were excluded (n = 147).

2.2. Definition of variables

MetS was defined according to established international guidelines as the presence of at least three of the following characteristics: (1) hypertension (≥130/85 mm Hg); (2) large waist circumference (≥102 cm for men, ≥88 cm for women); (3) insulin resistance (fasting glucose ≥110 mg/dl); (4) atherogenic dyslipidemia (HDL-C <40 mg/dl for men, <50 mg/dl for women); and (5) hypertriglyceridemia (triglycerides ≥150 mg/dl) [2,3]. Waist circumference was calculated according to body mass index, gender, and age using a previously described model [15]. Complications were categorized as any adverse event occurring during the hospital stay. Major complications were defined as Clavien-Dindo grade ≥3 [16]. Renal function was assessed as eGFR according to the Chronic Kidney Disease (CKD) Epidemiology Collaboration formula. Acute kidney injury (AKI) was defined according to the Risk-Injury-Failure-Loss-End-stage (RIFLE) criteria [17]. Stage IIIB–V CKD was defined as eGFR <45 ml/min/1.73 m^2 (Kidney Disease-Improving Global Outcomes categories) at the first single measurement below this threshold after surgery [18]. Other-cause mortality (OCM) was defined as death from any cause other than kidney cancer.

2.3. Statistical analyses

We conducted statistical analyses in accordance with established guidelines [19]. Results for continuous variables are reported as the median and interquartile range (IQR). For categorical variables, differences in proportions were evaluated using a χ^2 test. For continuous variables, differences in the distribution of ranks across groups were evaluated using the Wilcoxon rank-sum test.

Multivariable regression analysis (MVA) was used to predict the association of MetS with the study endpoints among several clinically relevant features. We used logistic MVA to assess the association of MetS with the occurrence of any complications and AKI. Cumulative incidence curves were plotted to estimate the 5-yr risk of stage IIIB–V, using death from any cause as a competing event. Similarly, the 5-yr OCM rate was estimated using death from cancer as a competing event. These analyses were stratified according to the presence or absence of MetS. Cox regression MVA was performed to investigate the association of MetS with long-term stage IIIB–V CKD and OCM. In these analyses, competing events were censored at the time of their occurrence. The same models were used to assess the effect of different numbers of MetS characteristics. Finally, we performed linear regression analysis to investigate the association between preoperative eGFR and MetS.

All statistical analyses were conducted using R version 5.4 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). All tests were two-sided at a level of significance set at $p < 0.05$.

3. Results

3.1. Characteristics of the study population

Overall, 71 patients (10%) with MetS were identified. The MetS group was older (median age 70 yr [IQR 65–74] vs 61 yr [IQR 50–69]; $p < 0.001$] and had worse preoperative renal function [median eGFR 65 [IQR 56–83] vs 88 [IQR 69–98] ml/min/1.73 m^2; $p < 0.001$) in comparison to the group without MetS. Baseline characteristics of the study population are listed in Table 1.

3.2. Intraoperative and postoperative surgical outcomes

Median operative time was longer for the MetS group (163 min) than for the group without MetS (154 min; $p = 0.038$). However, median length of stay and median blood loss were similar between the groups, as reported in Table 2.

The MetS group had a higher rate of overall complications but a similar rate of major complications (Clavien-Dindo grade ≥3) in comparison to the group without MetS.

Table 1 – Baseline characteristics of 690 patients who underwent partial nephrectomy for organ-confined T1a small renal masses from 2000 to 2023 at a tertiary referral center, stratified according to MetS status

Parameter	No MetS	MetS	*p* value [a]
Patients, *n* (%)	619 (100)	71 (100)	
Median age, yr (IQR)	61 (50–69)	70 (65–74)	**<0.001**
Male, *n* (%)	419 (68)	56 (79)	0.073
Charlson comorbidity index ≥2, *n* (%)	144 (23)	42 (59)	**<0.001**
Previous abdominal surgery, *n* (%)	337 (54)	42 (59)	0.5
Median clinical tumor size, cm (IQR)	3 (2.3–3.5)	3 (2–3.7)	>0.9
Median p-eGFR, ml/min/1.73 m^2 (IQR)	88 (69–98)	65 (62–81)	**<0.001**
Surgical approach, *n* (%)			0.3
Open	427 (69)	54 (76)	
Robotic	192 (31)	17 (24)	

IQR = interquartile range; MetS = metabolic syndrome; p-eGFR = preoperative estimated glomerular filtration rate.
[a] Wilcoxon rank-sum test or Pearson's χ^2 test. Bold values indicate statistical significance ($p < 0.05$).

Table 2 – Complication and perioperative data for 690 patients who underwent partial nephrectomy for organ-confined T1a small renal masses from 2000 to 2023 at a tertiary referral center, stratified according to MetS status

Parameter	No MetS	MetS	*p* value [a]
Patients, *n* (%)	619 (100)	71 (100)	
Median intraoperative blood loss, ml (IQR)	250 (100–600)	350 (100–600)	0.3
Median operating time, min (IQR)	154 (120–192)	163 (141–201)	**0.038**
Median length of stay, d (IQR)	6 (5–7)	6 (5–7.5)	0.7
At least one complication of any grade, *n* (%)	194 (31)	31 (44)	**0.036**
Major complication (Clavien Dindo grade ≥3), *n* (%)	33 (5.3)	5 (7)	0.7
Type of complication, *n* (%)			0.2
Bleeding/anemia/hematoma	54 (8.7)	9 (13)	
Fever	48 (7.8)	4 (5.6)	
Intestinal occlusion	1 (0.2)	0 (0)	
Urine leak	16 (2.6)	2 (2.8)	
Wound infection	2 (0.3)	0 (0)	
Other	73 (12)	16 (23)	
Acute kidney injury, *n* (%) [b]	96 (15)	19 (27)	**0.025**

IQR = interquartile range; MetS = metabolic syndrome.
[a] Wilcoxon rank-sum test or Pearson's χ^2 test. Bold values indicate statistical significance ($p < 0.05$).
[b] According to the RIFLE criteria.

Table 3 – Multivariable regression analysis results for prediction of overall complications, acute kidney injury, long-term stage IIIB–V chronic kidney disease, and other-cause mortality

Outcome predicted and variable	OR (95% CI)	*p* value [a]
Overall complications		
Metabolic syndrome (yes vs no)	1.81 (1.05–3.08)	**0.030**
Age (per 10 yr increment)	0.91 (0.79–1.05)	0.2
Charlson comorbidity index ≥2 (vs 0–1)	1.06 (0.71–1.58)	0.8
Clinical tumor size (per 1 cm increment)	1.26 (1.02–1.57)	**0.031**
Previous abdominal surgery (yes vs no)	1.18 (0.84–1.65)	0.3
Open surgery (vs robot-assisted)	0.70 (0.49–1.00)	0.052
Operative time (per 60 min increment)	1.23 (1.05–1.43)	**0.009**
Acute kidney injury		
Metabolic syndrome (yes vs no)	3.17 (1.54–6.41)	**0.001**
Age (per 10 yr increment)	1.14 (0.87–1.50)	0.3
Charlson comorbidity index ≥2 (vs 0–1)	0.51 (0.28–0.89)	**0.022**
Clinical tumor size (per 1 cm increment)	1.44 (1.08–1.93)	**0.015**
Preoperative eGFR (per 10 ml/min/1.73 m^2 increment)	1.20 (1.02–1.43)	**0.034**
Open surgery (vs robot-assisted)	1.77 (0.99–3.30)	0.061
Intraoperative blood loss (per 100 ml increment))	1.05 (1.02–1.10)	**0.006**
Operative time (per 60 min increment)	1.21 (0.99–1.47)	0.063
	HR (95% CI)	***p* value** [a]
Long-term stage IIIB–V chronic kidney disease		
Metabolic syndrome (yes vs no)	2.34 (1.27–4.30)	**0.006**
Age (per 10 yr increment)	1.76 (1.26–2.44)	**<0.001**
Charlson comorbidity index ≥2 (vs 0–1)	1.09 (0.64–1.83)	0.8
Preoperative eGFR (per 10 ml/min/1.73 m^2 increment)	0.68 (0.58–0.79)	**<0.001**
Acute kidney injury (yes vs no)	1.87 (1.07–3.27)	**0.029**
Clinical tumor size (per 1 cm increment)	1.11 (0.79–1.55)	0.6
Other-cause mortality		
Metabolic syndrome (yes vs no)	3.00 (1.06–8.55)	**0.039**
Age (per 10 yr increment)	2.26 (1.38–3.70)	**0.001**

CI = confidence interval; HR = hazard ratio; OR = odds ratio.
[a] Bold values indicate statistical significance ($p < 0.05$).

Specifically, the incidence of at least one complication was 31% in the MetS group and 44% in the group without MetS (odds ratio [OR] 1.81, 95% confidence interval [CI] 1.05–3.08; $p = 0.030$; Table 3) The rate of major complications was low for both groups (<7%).

Common complications in the MetS group included bleeding/hematoma/anemia ($n = 9$, 13%), fever ($n = 4$, 5.6%), and urine leaks ($n = 2$, 2.8%; Table 2).

3.3. *Postoperative functional outcomes*

Overall, the postoperative AKI rate was higher in the MetS group than in the group without MetS (27% vs 15%; OR 3.17, 95% CI 1.54–6.41; $p = 0.001$; Table 3).

The median functional follow-up for patients who did not experience any event was 57 mo (IQR 29–89). At 5 yr the risk of stage IIIB–V CKD was higher in the MetS group than in the group without MetS (45% vs 7.2%), which was confirmed by MVA (hazard ratio [HR] 2.34, 95% CI 1.27–4.30; $p = 0.006$; Fig. 1 and Table 3). Interestingly, linear regression analysis revealed that MetS was also a predictor for lower preoperative eGFR after adjusting for age and Charlson comorbidity index ($\beta = -7.1$, 95% CI −11 to −3.5; $p < 0.001$; Supplementary Table 1).

3.4. *Survival outcomes*

Median follow-up for patients who did not experience any event was 61 mo (IQR 31–94). At 5 yr, the risk of OCM was higher for patients with MetS than for those without MetS (14% vs 3.5%), which was confirmed by MVA (HR 3.00, 95% CI 1.06–8.55; $p = 0.039$; Fig. 2 and Table 3).

3.5. *Sensitivity analysis*

In the MetS group, 34 patients (48%) had three, 25 (35%) had four, and 12 (17%) had five of the clinical MetS characteristics. In comparison to patients without MetS, patients with four or five of the MetS characteristics had a higher risk of complications, AKI, stage IIIB–V CKD, and OCM. For patients with three MetS characteristics, the risks of complications and OCM were similar to those for the group without MetS, but their risk of postoperative short-term and long-term renal impairment was higher (Supplementary Table 2).

4. Discussion

MetS is a prevalent medical condition that affects a substantial proportion of the population [1]. Previous studies demonstrated greater morbidity and worse long-term survival outcomes for patients with MetS undergoing surgery for different primary tumors and non-oncological indications [4–6,20–23]. We analyzed for the first time the impact of MetS on perioperative, functional, and oncological outcomes in a large cohort of patients treated with PN for SRMs. In this setting, current guidelines suggest offering conservative approaches to comorbid and frail patients [12]. More specifically, the risk of SRM overtreatment is substantial, particularly in comorbid and frail patients who have a higher competing risk of death from other causes rather than from cancer. A systematic review by Cheung and Finelli [24] revealed that the rate of conversion from active surveillance to active treatment is low (4–26%) for SMR cases. Another systematic review by Quirós Rivero

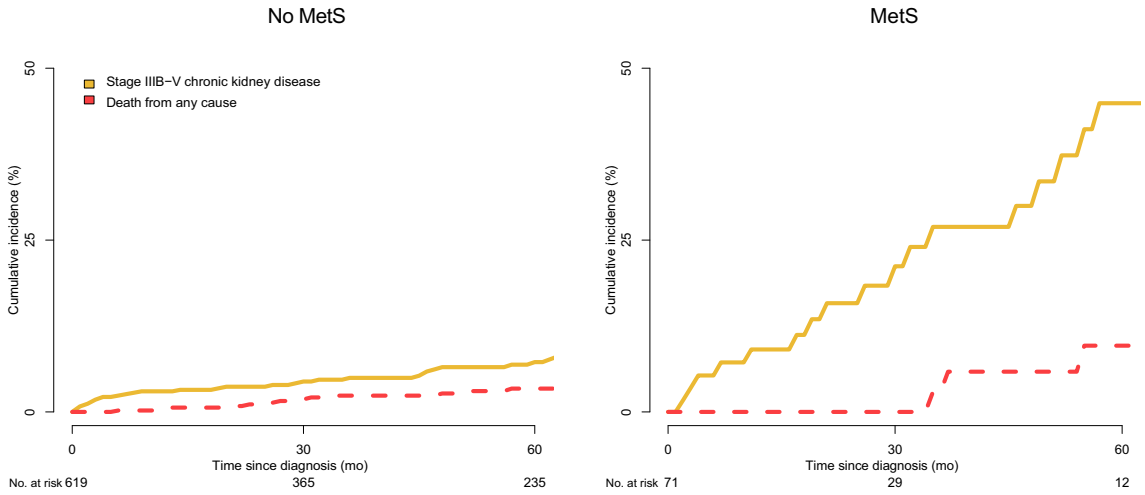

Fig. 1 – Cumulative incidence of stage IIIB–V chronic kidney disease for patients with and without metabolic syndrome (MetS), using death from any cause as a competing event.

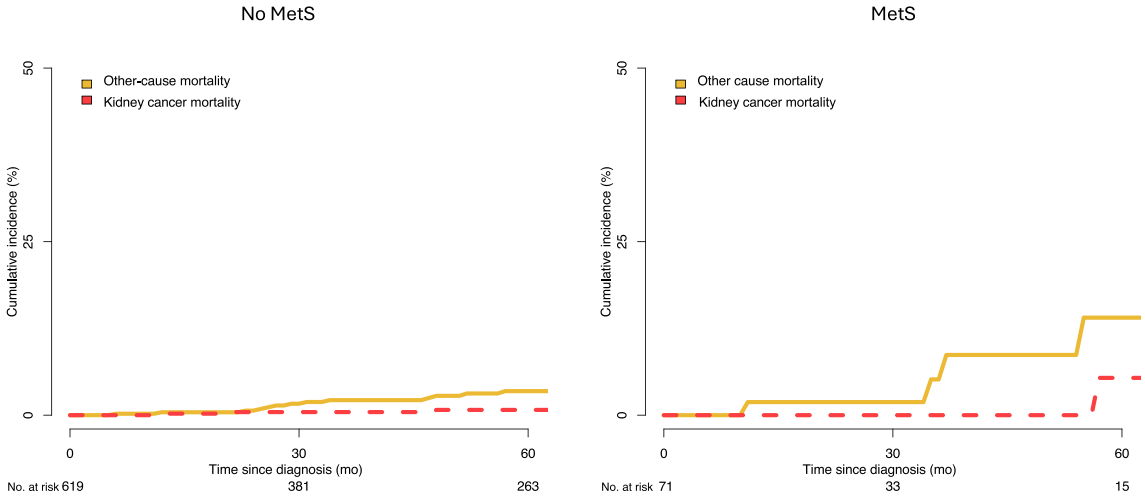

Fig. 2 – Cumulative incidence of death from other causes and death from kidney cancer for patients with and without metabolic syndrome (MetS).

et al [25] showed that in comparison to PN, conservative techniques such as thermal ablation results in lower rates of complications and eGFR decline, with similar rates of local recurrence and metastasis. However, T1a renal cancers (SRMs as defined in our study) seem to benefit the most from conservative treatment [26]. Thus, we hypothesized that evaluation of patients with MetS may help in identifying individuals at risk of unfavorable functional outcomes who might benefit from multidisciplinary care and could be candidates for alternative strategies.

Our study has several clinical implications. First, our analyses demonstrated a higher rate of postoperative complications for MetS patients (44% vs 31%). This finding was corroborated by MVA, which revealed MetS as an independent predictor after adjusting for patient and tumor characteristics. In a study using Nationwide Inpatient Sample data, the incidence of MetS in a cohort of 25 875 patients undergoing PN was 11%, is in line with the rate in our cohort (10%). The study identified 1.77-fold higher risk of postoperative complications for individuals with MetS in comparison to those without MetS ($p < 0.001$) [10]. In contrast to our analyses, the authors could not adjust their findings for clinical size and tumor T stage. Moreover, our results are consistent with previous studies addressing the effect of MetS in patients undergoing surgery in other clinical settings. For instance, Tee et al [5] observed 2.6-fold higher risk of postoperative comorbidity ($p < 0.001$) in a cohort of 1070 patients with MetS undergoing elective partial pancreatectomy in comparison to a group without MetS. Similar results were reported by Akinyemiju et al [23] for a cohort of 311 491 patients registered in the Healthcare Cost and Utilization Project undergoing surgery for prostate, breast, or colorectal cancer. The authors found that in comparison to patients without MetS, the risk of postoperative complications was higher for patients with MetS treated for prostate cancer (1.22-fold) or breast cancer (1.20-fold).

Second, we demonstrated correlation between MetS and both short-term and long-term impairment of renal

function. Specifically, MetS patients had a higher risk of postoperative AKI (27% vs. 15%; p = 0.025) and MVA confirmed that MetS was an independent predictor of AKI. Moreover, the risk of long-term stage IIIB–V CKD was 3.4-fold higher for MetS patients than for patients without MetS. While previous studies showed worse long-term renal function after radical nephrectomy for patients with MetS, to our knowledge this is the first study to address long-term functional outcomes after PN [11]. Previous evidence demonstrated a higher risk of AKI for patients with impaired preoperative kidney function [27,28]. We observed the same finding in our study for patients with MetS. It is of note that patients with MetS are at higher risk of long-term impairment of renal function due to chronic vascular damage [28]. Most of these patients have a large waist circumference, which is strongly related to visceral obesity [1–3,15]. Adipose tissue is a significant source of systematic inflammation, and the interaction between macrophages and adipocytes contributes to the development of insulin resistance, a known cause of vascular injury [9,29,30]. Consequently, we highlight the critical importance of meticulous follow-up for MetS patients after surgery, even after several years. Collaborative efforts involving health care professionals that include nutritionists and nephrologists are essential to mitigate deterioration of renal function [31].

Third, we observed higher OCM risk for patients with MetS, in agreement with many studies demonstrating a higher risk of cardiovascular events and therefore of cardiovascular-related death for MetS patients. For instance, a systematic review and meta-analysis by Mottillo et al [32] revealed higher incidence of cardiovascular disease (2.35-fold), all-cause mortality (1.58-fold), myocardial infarction (1.99-fold), and stroke (2.77-fold) for patients with MetS than for individuals without MetS. Given the very low risk of dying from renal cancer for cases with organ-confined SRMs [33–35], our findings are even more important in this patient setting.

Taken together, these results support our hypothesis that MetS patients have worse survival and functional outcomes after PN than patients without MetS. MetS patients represent one of the most crucial subgroups for which an accurate multidisciplinary evaluation might affect clinical decisions and perioperative management and could ultimately improve long-term functional and survival endpoints. In our main analysis, we considered the MetS group as a homogeneous entity. However, a sensitivity analysis according to the number of risk factors revealed that the presence of three MetS risk factors did not have a significant impact on the rate of complications or mortality from other causes, while the effect on renal function persisted in reference to patients without MetS. This indicates that each patient should be evaluated carefully on a case-by-case basis before surgery, particularly those with a higher metabolic burden.

There are several unknown confounders that might play a role in renal function after PN that we could not account for, and our findings have to be interpreted in this context. In addition, MetS definitions have been heterogeneous over time, so our results might not be applicable when definitions different from ours are used. We recommend following current international guideline definitions for proper selection of MetS patients in the preoperative setting.

Despite its strengths, our study is not devoid of limitations. First, the inclusion of data over an extended period may introduce selection bias and could have influenced the results, considering the improvements in patient care over the years. Second, we could not assess if any patients without MetS at surgery developed MetS and its sequelae during follow-up. Third, patients were selected from a tertiary high-volume referral center. Therefore, our results may not be applicable to other populations treated in smaller centers. Despite assessing the incremental effect of different clinical factors involved in the definition of MetS, we could not adjust for the severity of each factor in determining the adverse outcomes. Of note, our study is retrospective, although data were collected prospectively. As a consequence, our results may be subject to limitations such as bias from confounding by indication.

5. Conclusions

Patients with MetS had worse postoperative, functional, and survival outcomes after SRM surgery in comparison to patients without MetS. Multidisciplinary care could help in reducing the preoperative metabolic burden for patients with MetS. Further research should explore if alternative approaches (eg, surveillance or focal therapy) could minimize postoperative comorbidities and protect long-term renal function in these patients.

Author contributions: Giuseppe Rosiello had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rosiello, Capitanio, Scilipoti.
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Analysis and interpretation of data: Rosiello, Scilipoti.
Drafting of the manuscript: Rosiello, Scilipoti.
Critical revision of the manuscript for important intellectual content: Capitanio, Larcher, Montorsi, Briganti, Salonia, Bertini, Mottrie, Karakiewicz, Tian, Bettiga, Trevisani.
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Appendix A. Supplementary material

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