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Sex-based Disparities in Metastatic Renal Cell Carcinoma: Real-World Data from Meet-URO33 Study.

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Background

Sex-related biological differences may affect cancer immunity and outcomes with immune checkpoint inhibitors (ICIs) in patients with metastatic renal cell carcinoma (mRCC).
This sub-analysis aimed to explore sex-based differences in a real-world cohort of patients with mRCC treated with first-line systemic therapy within the Meet-URO 33 (REGAL) study.

Material and Methods

The Meet-URO 33 study is a multicentre ambispective registry collecting real-world data on patients with mRCC.
Clinical-pathological features, haematological parameters, toxicities, and outcomes were compared by sex and age (< 50 vs ≥ 50 years).

	N	Females	Males	p-value
Grade 3–4 toxicities	411	123/349 (35.2%)	288/1031 (27.9%)	0.012
Diarrhoea	41	12/401 (3.0%)	29/1159 (2.5%)	0.589
Hypothyroidism	24	7/401 (1.7%)	17/1159 (1.5%)	0.645
Hypertension	33	9/401 (2.2%)	24/1159 (2.1%)	0.841
Treatment interruption	265	70/342 (20.5%)	195/1009 (19.3%)	0.637
High dose steroid use	192	62/344 (18.0%)	130/1006 (12.9%)	0.025
TKI interruption	32	10/45 (22.2%)	22/143 (15.4%)	0.362
ICI interruption	222	55/286 (19.2%)	167/843 (19.8%)	0.864

Table 2. Summary of toxicities, steroid administration and treatment interruptions among female and male patients.

Results

Among 1560 patients, 401 were females and 1159 were males. Females presented with lower BMI (≤ 25 kg/m², 52% *vs* 43%, *p* = 0.008) and lower median NLR (2.8 vs 3.1, *p* = 0.005), and had **worse baseline characteristics**, such as liver metastases (18% *vs* 11%, *p* = 0.002) and sarcomatoid variant (20.3% *vs* 14.5%, *p* = 0.025), **Table 1**.
Grade 3–4 adverse events (AEs) were more frequent in females (35% *vs* 28%, *p* = 0.012), but no sex-related differences emerged in the pattern of AEs and discontinuation rates, **Table 2**. No significant differences were observed in PFS (14.8 *vs* 17.6 months) and OS (39.3 *vs* 39.7 months), **Fig 1**.
Females < 50 years experienced a shorter PFS (8.5 *vs* 19.6 months, HR 2.02, *p* = 0.009), **Fig 2**.
In multivariable Cox complete-case analyses, sex was not independently associated with either PFS (HR 1.21, 95% CI: 0.97–1.51, p = 0.099) or OS (HR 1.16, 95% CI: 0.87–1.55, p = 0.307), and sensitivity analysis based on multiple imputation produced consistent results.

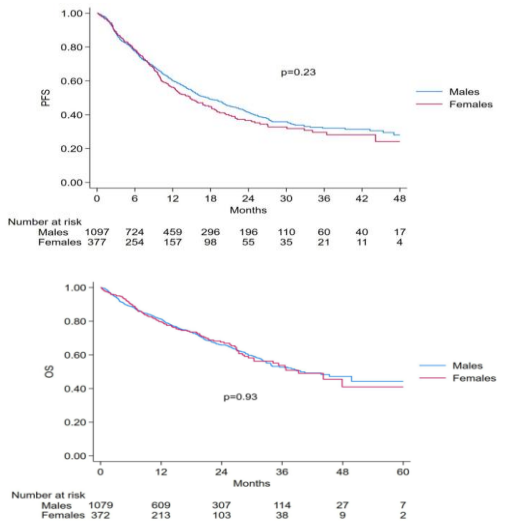

Fig. 1 Progression Free Survival and Overall Survival for first-line treatment in female and male patients.

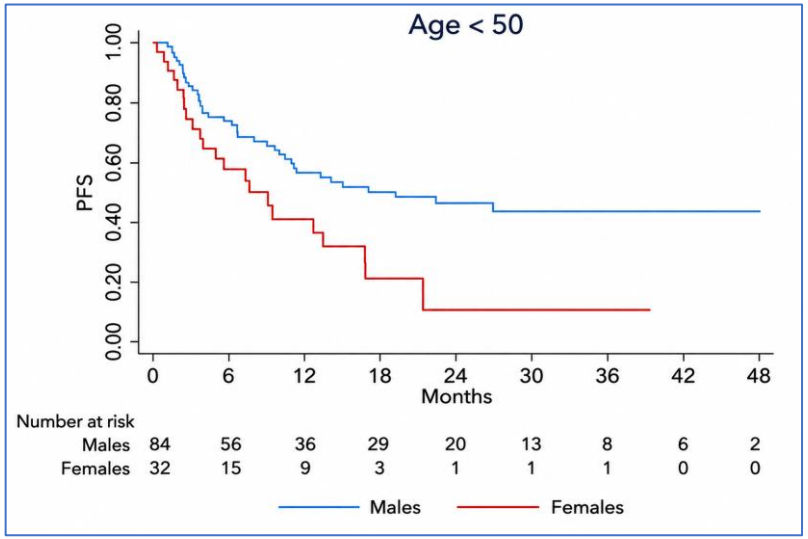

Fig. 2 Progression-free survival for first-line treatment in female and male patients **aged < 50 years**.

Variable	Category	N	Females (N = 401)	Males (N = 1159)	p-value
Age, median (IQR)		1560	66.7 (59.3–74.1)	65.8 (58.1–73.5)	0.14
NLR, median (IQR)		1275	2.8 (2.0–4.1)	3.1 (2.1–4.7)	0.005
BMI	≤ 25 kg/m²	660	194/377 (51.5%)	466/1073 (43.4%)	0.008
	> 25 kg/m²	790	183/377 (48.5%)	607/1073 (56.6%)	
IMDC	Favourable	308	80/398 (20.1%)	228/1153 (19.8%)	0.66
	Intermediate	876	221/398 (55.5%)	655/1153 (56.8%)	
	Poor	312	87/398 (21.9%)	225/1153 (19.5%)	
	Not assessable	55	10/398 (2.5%)	45/1153 (3.9%)	
Meet-URO score	0–3	581	161/322 (50.0%)	420/933 (45.0%)	0.30
	4–8	580	139/322 (43.2%)	441/933 (47.3%)	
	9	94	22/322 (6.8%)	72/933 (7.7%)	
Histology	Clear cell	1305	346/397 (87.2%)	959/1149 (83.5%)	0.036
	Chromophobe	27	11/397 (2.8%)	16/1149 (1.4%)	
	Undifferentiated	57	8/397 (2.0%)	49/1149 (4.3%)	
	Papillary	95	18/397 (4.5%)	77/1149 (6.7%)	
	Other	62	14/397 (3.5%)	48/1149 (4.2%)	
Nephrectomy	No	646	163/401 (40.7%)	483/1159 (41.7%)	0.72
	Yes	914	238/401 (59.4%)	676/1159 (58.3%)	
ECOG PS	0	980	247/399 (61.9%)	733/1157 (63.4%)	0.20
	1	451	118/399 (29.6%)	333/1157 (28.8%)	
	2	111	27/399 (6.8%)	84/1157 (7.3%)	
	3–4	14	7/399 (1.8%)	7/1157 (0.6%)	
Sarcomatoid variant	Present	170	56/276 (20.3%)	114/785 (14.5%)	0.025
	Absent	891	220/276 (79.7%)	671/785 (85.5%)	
Metastases at diagnosis	No	887	216/389 (55.5%)	671/1140 (58.9%)	0.26
	Yes	642	173/389 (44.5%)	469/1140 (41.1%)	
Number of metastatic sites	1	683	172/381 (45.1%)	511/1103 (46.3%)	0.63
	2	461	114/381 (29.9%)	347/1103 (31.5%)	
	3	221	59/381 (15.5%)	162/1103 (14.7%)	
	≥4	119	36/381 (9.5%)	83/1103 (7.5%)	
Metastatic site	Lung	1560	229/401 (57.1%)	659/1159 (56.9%)	
	Nodes	1560	152/401 (37.9%)	500/1159 (43.1%)	
	Liver	1560	72/401 (18.0%)	134/1159 (11.6%)	0.002
	Bone	1560	109/401 (27.2%)	349/1159 (30.1%)	
	Adrenal glands	1560	57/401 (14.2%)	159/1159 (13.7%)	
	Brain	1560	24/401 (6.0%)	56/1159 (4.8%)	
	Pancreas	1560	48/401 (12.0%)	81/1159 (7.0%)	0.003
	Thyroid	1560	4/401 (1.0%)	5/1159 (0.4%)	0.25

Table 1. Baseline clinical characteristics among female and male subgroups.

Conclusion

Female patients with mRCC presented with more adverse baseline features and experienced higher severe toxicity rates, although PFS and OS were comparable to male patients. However, **multivariable analyses demonstrate that sex does not have an independent prognostic value.** Subgroup analysis in female patients aged < 50 years showed worse PFS, suggesting a potential hormonal influence warranting further investigation. Stronger female representation and translational research are needed to guide sex-tailored strategies in advanced RCC.