EAU23

MILAN, ITALY

10-13 March 2023

Cutting-edge Science at
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Characterization of Patients with Metastatic Renal Cell Carcinoma Undergoing Deferred, Upfront, or No Cytoreductive Nephrectomy in the Era of Combination Immunotherapy: Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

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European Association of Urology

Conflict of Interest Disclosure

I have no potential conflict of interest to report

CN in the era of cytokines

- Cytoreductive nephrectomy (CN) became the standard of care in the era of cytokine therapy
- Prospective, randomized clinical trials demonstrated an overall survival benefit

CN in the era of VEGF

- The role of the CN became less clear with the emergence of VEGF targeted therapies (VEGF-TT) due to conflicting evidence from prospective and retrospective studies
- CARMENA suggested that sunitinib alone was non-inferior to sunitinib plus CN
- A post-hoc sub-group analysis demonstrated longer OS in the subgroup of patients with only 1 IMDC prognostic risk factor or IMDC intermediate patients with lung metastases only

Timing of CN

- The SURTIME trial compared upfront CN (uCN) to deferred (dCN) and found that the deferred approach resulted in more patients receiving therapy with sunitinib and a longer OS
- These findings are supported by large, retrospective studies

CN in the new IO era

- Contemporary Immuno-oncology (IO) combination therapies consisting of ipilimumab plus nivolumab (IPI NIVO) or a combination of IO plus VEGF-TT (IO-VEGF) have resulted in a paradigm shift in the treatment of mRCC
- The role of the CN must be evaluated in the light of the contemporary systemic therapies

Objectives

- To evaluate characteristics and clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) receiving immuno-oncology (IO)-based combination therapy according to CN status.

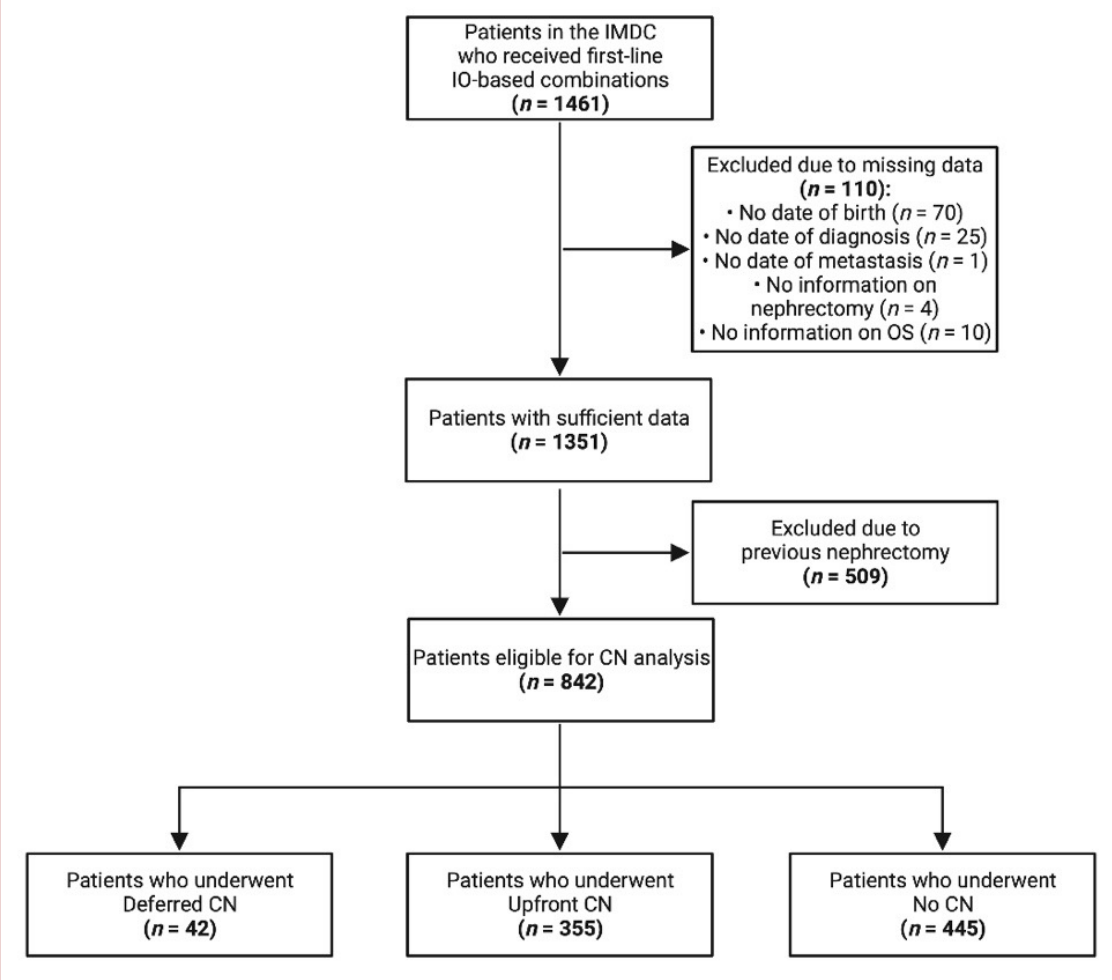
  - Upfront CN (uCN)= CN within 3 months prior to documentation of metastatic disease or at anytime after documentation of metastatic disease but before systemic therapy was initiated
  - Deferred CN (dCN)= CN after systemic therapy was initiated

Patient Selection

- Consecutive patient data was collected from the IMDC, which includes 40 institutions worldwide
- Patients were included if:
  - Diagnosed with de novo mRCC or had not previously undergone nephrectomy for localized RCC
  - Received first-line IOIO* of IO-VEGF✦ combinations

*IPI NIVO

✦ Pembrolizumab/axitinib, avelumab/axitinib, nivolumab/cabozantinib, pembrolizumab/lenvatinib, or atezolizumab/bevacizumab



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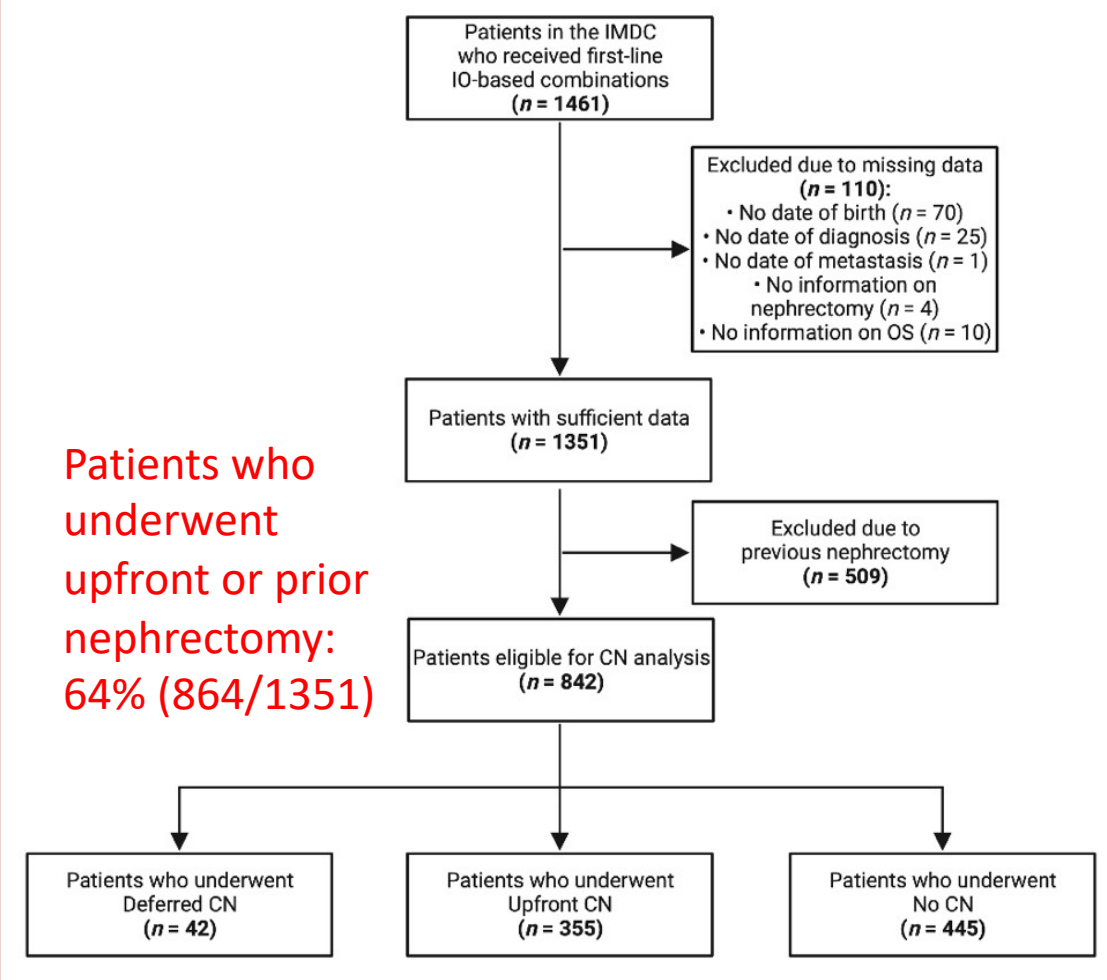


Patients who underwent upfront or prior nephrectomy: 64% (864/1351)

Baseline Characteristics

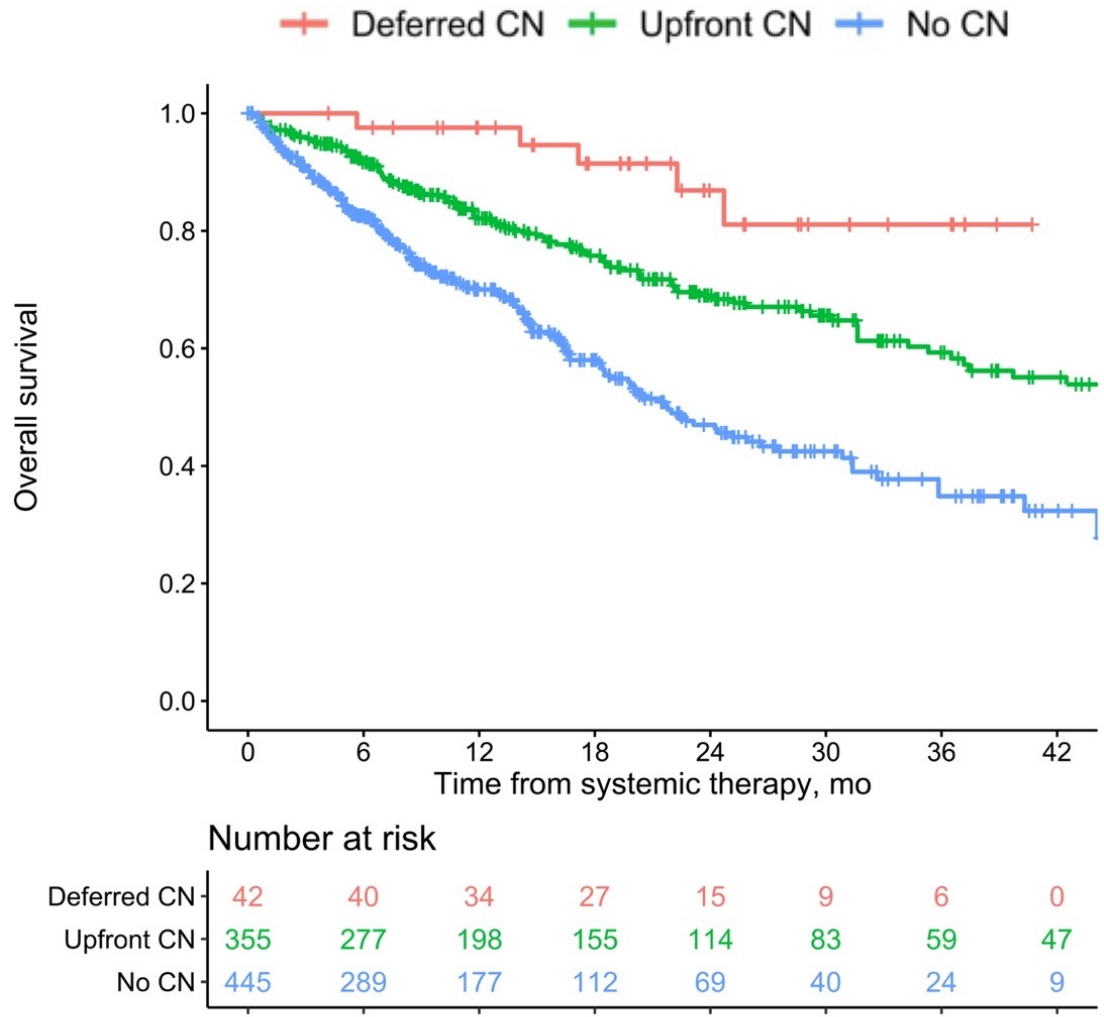
Variable	Deferred CN (n = 42)	Upfront CN (n = 355)	No CN (n = 445)	p[a]
Median age, yr (IQR)	61.1 (51.3–66.6)	61.0 (53.4–67.3)	63.2 (56.2–70.5)	< 0.001
Male, n (%)	30/42 (71.4%)	265/355 (74.6%)	316/445 (71.0%)	0.519
Non-clear cell histology, n (%)	12/38 (31.6%)	54/298 (18.1%)	39/306 (12.7%)	0.008
Sarcomatoid dedifferentiation, n (%)	6/32 (18.8%)	98/283 (34.6%)	51/271 (18.8%)	< 0.001
Brain, bone, or liver metastases, n (%)	15/40 (37.5%)	144/342 (42.1%)	263/432 (60.9%)	< 0.001
Multiple sites of metastases, n (%)	28/36 (77.8%)	270/331 (81.6%)	353/403 (87.6%)	0.034
KPS < 80%, n (%)	5/38 (13.2%)	39/332 (11.7%)	86/411 (20.9%)	0.003
IMDC prognostic category, n (%)				< 0.001
Favourable	0/35 (0.0%)	26/318 (8.2%)	8/392 (2.0%)	
Intermediate	21/35 (60.0%)	202/318 (63.5%)	185/392 (47.2%)	
Poor	14/35 (40.0%)	90/318 (28.3%)	199/392 (50.8%)	
First-line regimen, n (%)				< 0.001 [b]
Nivolumab/Ipilimumab	31/42 (73.8%)	221/355 (62.3%)	341/445 (76.6%)	
Pembrolizumab/Axitinib	8/42 (19.0%)	47/355 (13.2%)	64/445 (14.4%)	
Avelumab/Axitinib	0/42 (0%)	27/355 (7.6%)	4/445 (0.9%)	
Nivolumab/Cabozantinib	0/42 (0%)	9/355 (2.5%)	8/445 (1.8%)	
Pembrolizumab/Lenvatinib	0/42 (0%)	8/355 (2.3%)	5/445 (1.1%)	
Atezolizumab/Bevacizumab	3/42 (7.1%)	43/355 (12.1%)	23/445 (5.2%)	

[a]Fisher's exact tests for categorical variables and Mann–Whitney U tests for continuous variables
[b]IO/IO (Nivolumab/Ipilimumab) vs IO/VEGF (all the rest)

Best overall response

Best overall response, n (%)	Deferred CN (n = 42)	Upfront CN (n = 355)	No CN (n = 445)
Objective response	20/38 (52.6%)	152/310 (49.0%)	114/365 (31.2%)
Complete response	4/38 (10.5%)	16/310 (5.2%)	4/365 (1.1%)
Partial response	16/38 (42.1%)	136/310 (43.9%)	110/365 (30.1%)
Stable disease	14/38 (36.8%)	95/310 (30.6%)	144/365 (39.5%)
Progressive disease	4/38 (10.5%)	63/310 (20.3%)	107/365 (29.3%)

Overall survival



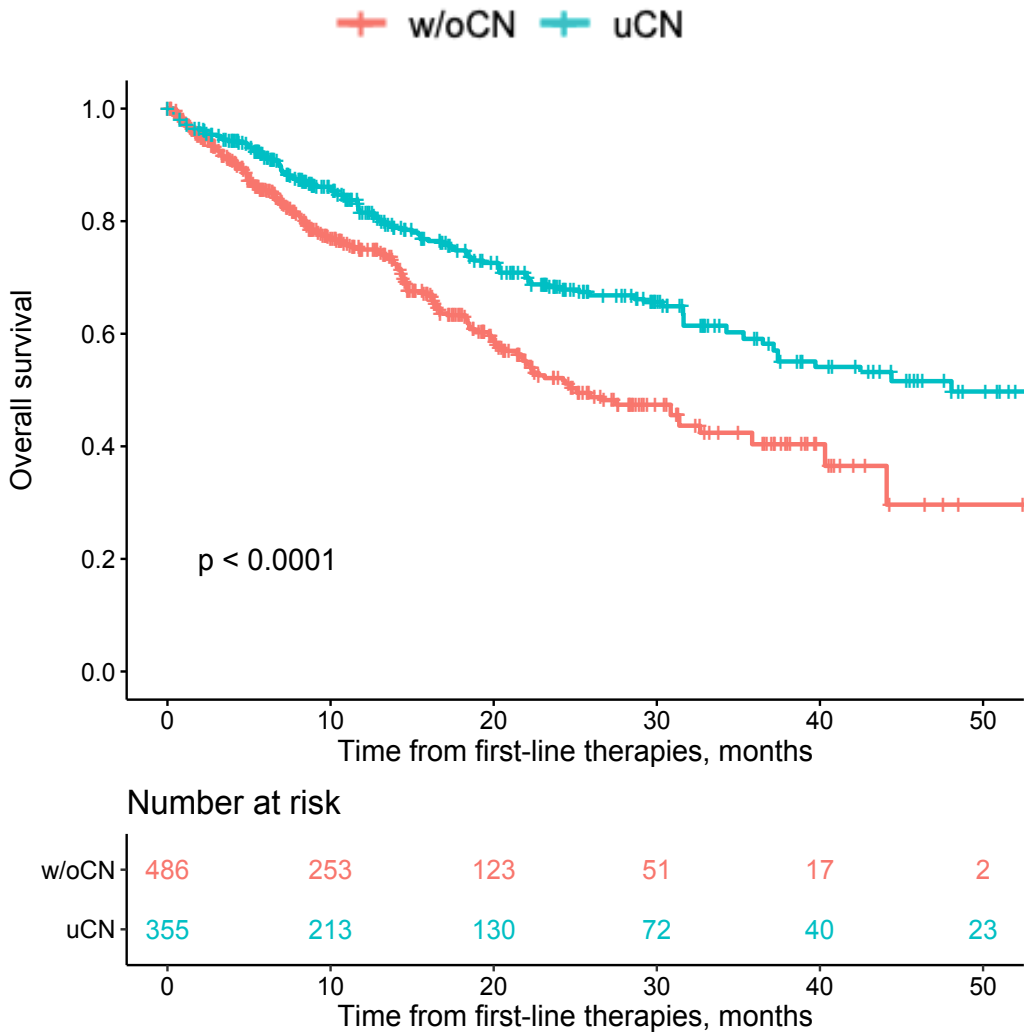
Median OS

dCN NR (95% CI NR–NR)

uCN 53.5 months (95% CI 37.2–NR)

No CN 21.8 months (95% CI 18.5–26.6)

Overall survival



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Multivariable analyses

Variable	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Age (as a continuous variable)	1.02 (0.01–1.04)	< 0.001	1.02 (1.00–1.04)	0.013
Female (vs male)	1.23 (0.95–1.59)	0.119	1.24 (0.86–1.78)	0.253
Non-clear cell histology (yes vs no)	1.51 (1.06–2.17)	0.024	1.52 (0.96–2.41)	0.077
Sarcomatoid dedifferentiation (yes vs no)	1.39 (1.02–1.90)	0.036	1.59 (1.06–2.38)	0.024
Brain, bone, or liver metastases (yes vs no)	1.70 (1.34–2.17)	< 0.001	1.50 (1.07–2.12)	0.020
Multiple sites of metastases (yes vs no)	1.78 (1.18–2.70)	0.006	1.46 (0.87–2.45)	0.154
KPS (< 80% vs ≥ 80%)	2.41 (1.83–3.19)	< 0.001	1.82 (1.20–2.75)	0.005
IMDC (poor vs favourable/intermediate)	2.36 (1.85–3.02)	< 0.001	1.47 (1.01–2.12)	0.042
First-line regimen (IO/IO vs IO/VEGF)	1.05 (0.82–1.35)	0.700	0.70 (0.50–0.96)	0.027
CN status (as a time-varying covariate)	**0.52 (0.41–0.67)**	**< 0.001**	**0.57 (0.40–0.81)**	**0.002**

Sensitivity analysis

Variable	Pre-IPTW Mean			Post-IPTW Mean		
	Upfront CN	No CN	SMD	Upfront CN	No CN	SMD
Age	60.1	63.3	0.304	61.9	61.9	0.007
Sex			0.082			0.009
Male	0.746	0.710		0.719	0.723	
Female	0.254	0.290		0.281	0.277	
Non-clear cell histology			0.386			0.009
Yes	0.152	0.088		0.125	0.126	
No	0.687	0.600		0.616	0.619	
Unknown	0.161	0.312		0.258	0.254	
Sarcomatoid dedifferentiation			0.521			0.017
Yes	0.276	0.115		0.178	0.182	
No	0.521	0.494		0.502	0.504	
Unknown	0.203	0.391		0.320	0.313	
Brain, bone, or liver metastases			0.378			0.007
Yes	0.406	0.591		0.523	0.525	
No	0.558	0.380		0.445	0.443	
Unknown	0.037	0.029		0.031	0.032	
Multiple sites of metastases			0.188			0.039
Yes	0.761	0.793		0.779	0.795	
No	0.172	0.112		0.138	0.126	
Unknown	0.068	0.094		0.083	0.079	
KPS			0.246			0.025
< 80%	0.825	0.730		0.780	0.770	
≥ 80%	0.110	0.193		0.154	0.158	
Unknown	0.065	0.076		0.066	0.071	
IMDC prognostic category			0.446			0.003
Favourable/Intermediate	0.642	0.434		0.520	0.519	
Poor	0.254	0.447		0.361	0.362	
Unknown	0.104	0.119		0.119	0.119	
First-line regimen			0.316			0.026
IO/IO	0.623	0.766		0.710	0.698	
IO/VEGF	0.377	0.234		0.290	0.302	

HR for uCN v no CN

0.65 (95% CI 0.49-0.88; p = 0.005)

Strengths and limitations

- Strengths
  - Large, multicentre, patient cohort
  - Inclusion of a consecutive series of patients outside of a clinical trial protocol also increases the generalizability of our findings to real-world patients with mRCC encountered in clinical practice
- Limitations
  - Retrospective analysis
  - Treatment selection bias
  - Immortal time bias in deferred CN population

Conclusions

- Fewer patients with mRCC are undergoing nephrectomy in the IO era compared to previous (64% vs 90%)
- Patient selection has become more discerning to identify the patients that will truly benefit from CN
- This presentation provides benchmark survival outcomes for patients with deferred, upfront, or no CN
- Future prospective, randomized clinical trials are needed to further clarify appropriate patient selection criteria and timing for CN (upfront vs. deferred)