



Kidney involvement in Erdheim-Chester disease: a multicenter cohort study on 195 patients

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Azienda
Ospedaliero Universitaria





- Renal and ureteral involvement is common (approximately **60-70%**) in ECD patients
- It usually presents as “retroperitoneal fibrosis” involving the peri-renal (**hairy kidneys**), peri-ureteral and periaortic space
- It is frequently **asymptomatic** and therefore overlooked
- It can cause varying degrees of acute or **chronic kidney failure** (up to 38%), secondary to obstructive uropathy and vascular peduncle involvement
- Other renal complications (*e.g.*, renal artery stenosis) are uncommon

Feature	(n = 47)
Median age, y (IQR)	57 (49, 68)
Median follow-up, y (IQR)	3.0 (1.8, 7.3)
Sex, n (%)	
Male	31 (66%)
Female	16 (34%)
Presenting symptom, n (%)	
Urologic	4 (9%)
Nonurologic	43 (9%)
Pathologic diagnosis by biopsy, n (%)	38 (81%)
Cross-sectional imaging (CT/MRI), n (%)	35 (74%)
Urologic involvement, n (%)	37 (79%)
Retroperitoneal involvement, n (%)	
Any	28 (60%)
Perinephric soft tissue inflammation	24 (51%)
Hydronephrosis, unilateral or bilateral	10 (21%)
Renal atrophy, unilateral or bilateral	15 (32%)
Other	6 (13%)
CKD, n (%)	18 (38%)
Hypertension, n (%)	18 (38%)
LUTS, n (%)	
Any	21 (45%)
Storage symptoms	11 (53%)
Voiding symptoms	8 (38%)
Stent irritation	4 (19%)
Urologic surgery, n (%)	
Any	13 (28%)
Ureteral stent placement	5 (11%)
Open retroperitoneal, renal biopsy	3 (6%)
Other	5 (11%)



- **Obstructive uropathy** is thought to be the major cause of renal failure in ECD patients, but its optimal management is unclear
- Anecdotal reports of ECD patients that develop kidney failure requiring hemodialysis or kidney transplant
- The true **prevalence of CKD or kidney failure** in ECD is **unknown**
- No data on the **response to treatment** at kidney level
- Unknown **predictors of long-term kidney outcome**

Aims of the study



- To describe the different **patterns of kidney involvement** in ECD
- To assess the **frequency and severity of renal and ureteral involvement** in ECD at diagnosis and during follow up
- To investigate the impact of **ureteral decompressive procedures** on renal outcome
- To analyze the **response to medical treatment** at kidney level
- To identify **predictors of CKD or poor kidney outcome**

Methods and study population



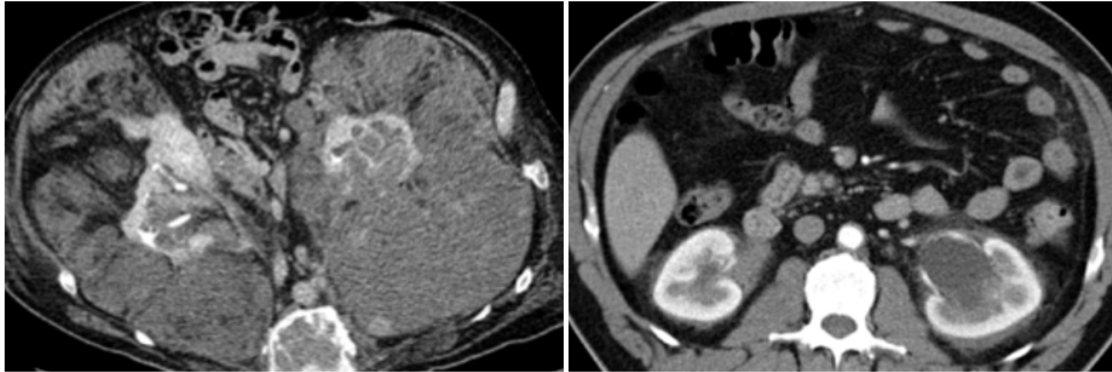
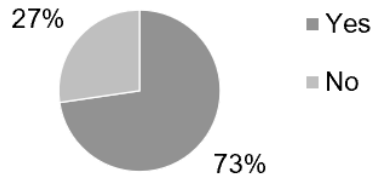
	n=195
Female gender, n (%)	55 (28)
Age at onset, mean (SD) – years	52.0 (15.4)
Age at diagnosis, mean (SD) – years	56.5 (14.3)
Comorbidities, n (%)	
Obesity	34 (17)
Hypertension	81 (42)
Hypercholesterolaemia	49 (25)
Diabetes mellitus	50 (26)
Coronary artery disease	47 (24)
Main organ involvement, n (%)	
Retroperitoneum	147 (75)
CNS	69 (35)
Bone	166 (85)
Large vessels	123 (63)
Heart	97 (50)
Lung	68 (35)
Skin	73 (37)
Facial - orbits	83 (43)
Hypothalamic - pituitary	66 (34)
Testis	8 (4)
<i>BRAF</i> status, n (%)	
V600E	119 (61)
WT	57 (29)
Unknown	19 (10)
Associated Histiocytoses, n (%)	
LCH	30 (15)
RDD	3 (2)
Renal function	
sCreatinine, median (IQR) - mg/dL	0.92 (0.78-1.2)
eGFR, median (IQR)- mL/min/1.73m ²	83 (59-99)
eGFR > 90 mL/min/1.73m ² , n (%)	73 (37)
eGFR > 60 ≤ 90 mL/min/1.73m ² , n (%)	72 (37)
eGFR < 60 mL/min/1.73m ² , n (%)	50 (26)

- **195** consecutive patients followed between 2000 and 2021 at 4 referral centers in France, Italy and Israel
- Histology-confirmed ECD diagnosis
- Median follow-up: **43 months** (IQR 54)
- Abdominal CT or MRI scans available for review
- Clinical data collected at baseline, 1-2-5 years, and last follow-up
- Renal function evaluated as eGFR (calculated using the CKD-EPI formula)
- Medical treatment and urologic procedures according to local practice (no established therapeutic algorithm)

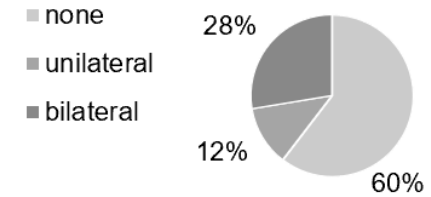
Results – Phenotypes of retroperitoneal involvement



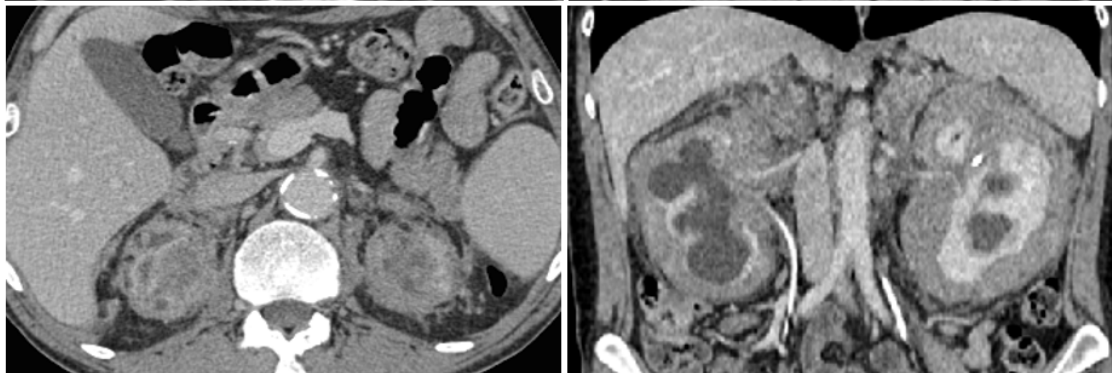
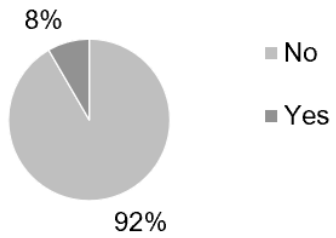
Perirenal involvement



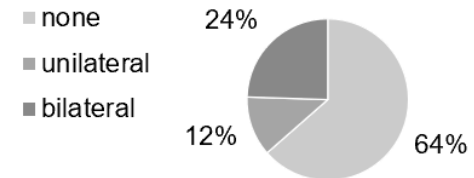
Periureteral involvement



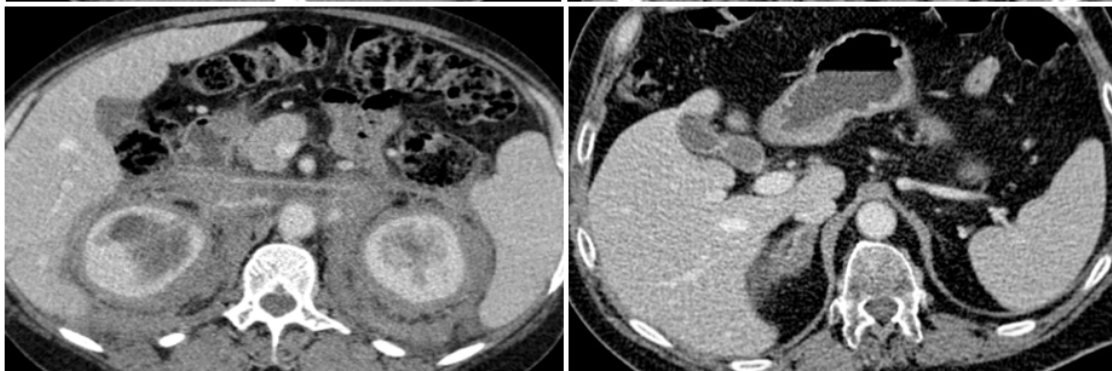
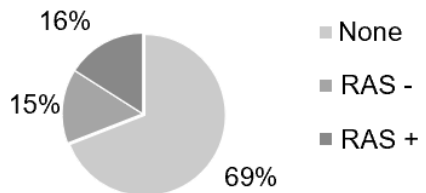
Kidney atrophy



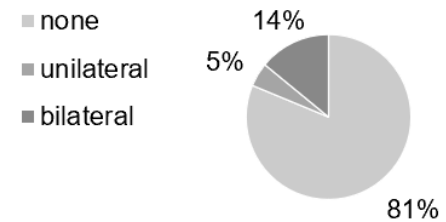
Hydronephrosis



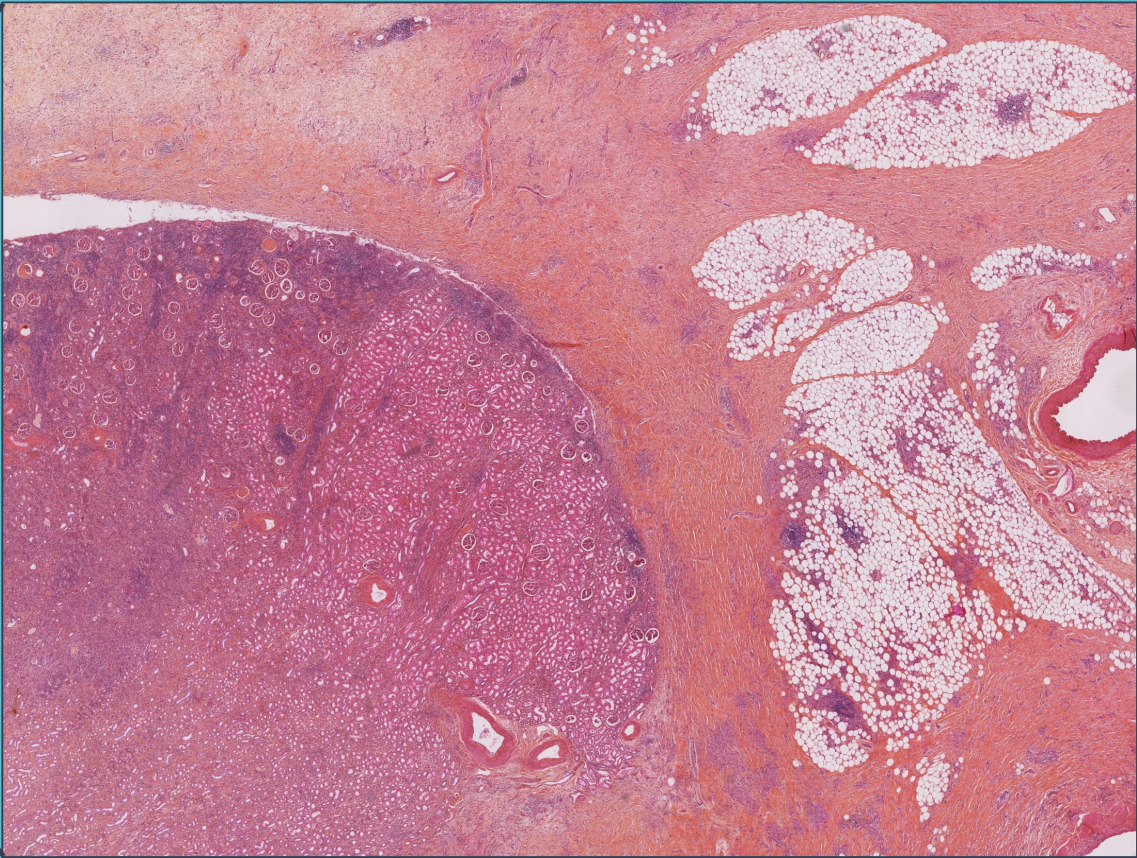
Vascular involvement



Adrenal involvement



Results – *Histology*



Results – Patients with and without RP involvement



	Peri-renal n=142	No peri-renal n=53	p value
Female gender, n (%)	32 (23)	23 (43)	0.004
Age, mean (SD)	54.2 (15.1)	46.2 (14.8)	0.001
Comorbidities, n (%)			
Hypertension	69 (49)	12 (23)	0.001
Diabetes	40 (28)	10 (19)	0.19
Obesity	26 (18)	8 (15)	0.60
Hyperlipidaemia	39 (27)	10 (19)	0.22
Coronary artery disease	44 (31)	3 (6)	<0.001
Organ involvement, n (%)			
CNS	46 (33)	23 (43)	0.15
Bone	124 (87)	42 (79)	0.16
Large vessels	101 (71)	22 (42)	<0.001
Heart	82 (58)	15 (28)	<0.001
Lung	51 (36)	17 (32)	0.62
Skin	49 (35)	24 (45)	0.17
Facial - orbits	66 (46)	17 (32)	0.07
Hypothalamic - pituitary	45 (32)	21 (40)	0.30
Testis	7 (5)	1 (2)	0.69
<i>BRAF</i> ^{V600E} , n (%) (out of the cases with known status)	95 (67)	24 (45)	0.006
Associated LCH, n (%)	22 (16)	8 (15)	0.95
Renal function			
sCreatinine, median (IQR) - mg/dL	1.00 (0.80-1.34)	0.84 (0.69-0.93)	<0.001
eGFR, median (IQR) - mL/min/1.73m ²	74 (53-93)	98 (84-112)	<0.001
eGFR >90 mL/min/1.73m ² , n (%)	41 (29)	32 (60)	<0.001
eGFR ≥60 ≤90 mL/min/1.73m ² , n (%)	55 (39)	17 (32)	0.39
eGFR < 60 mL/min/1.73m ² , n (%)	46 (32)	4 (8)	<0.001

Baseline differences in terms of:

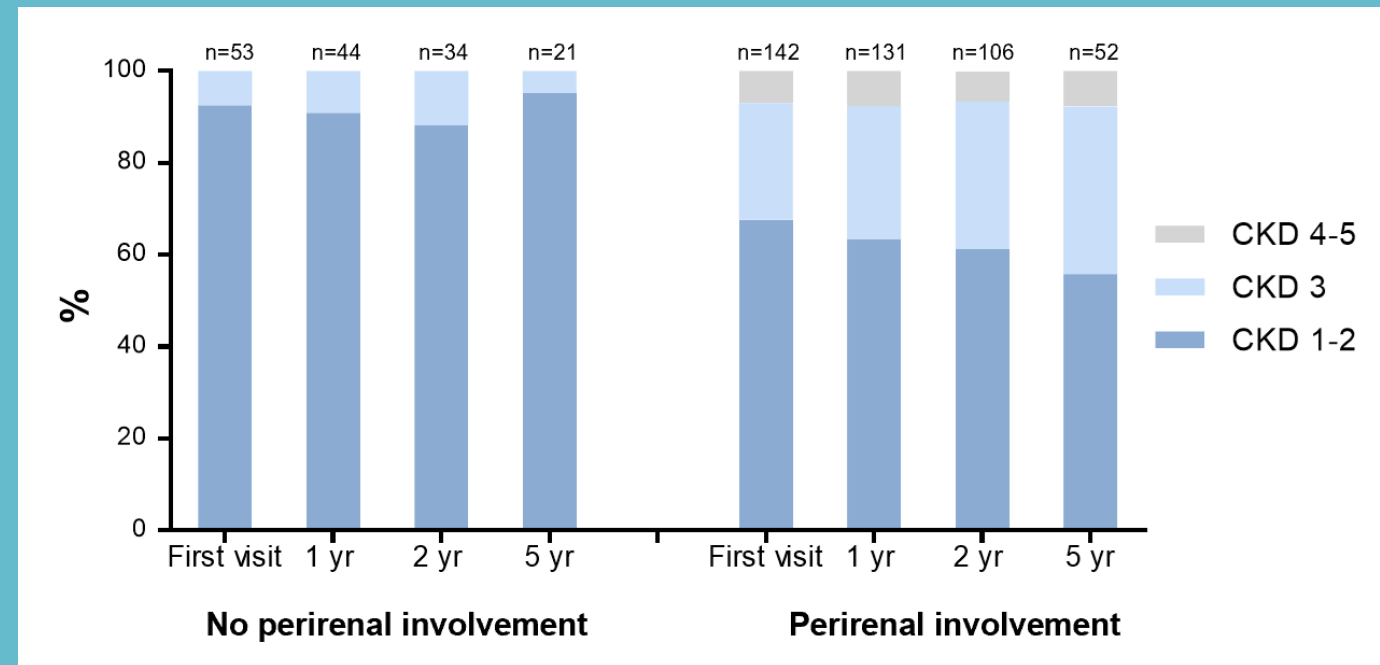
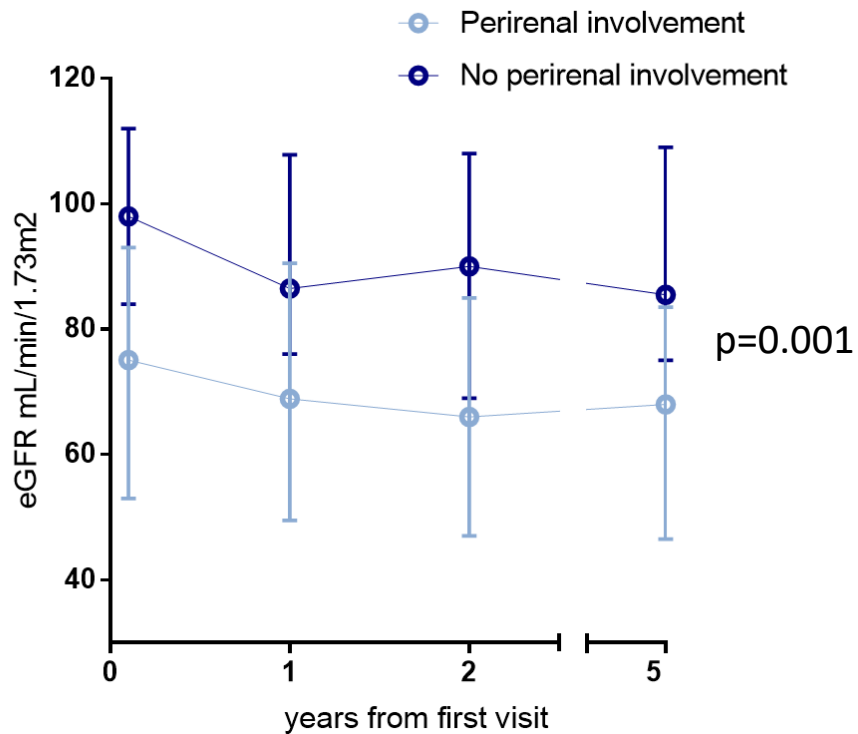
- Sex
- Age
- Comorbidities
- Organ involvement
- *BRAF*^{V600E} mutation
- Renal function

Results – eGFR and CKD stages at different time points



Median eGFR during the follow-up remained lower in patients with perirenal involvement

No significant difference in progression of kidney function loss ($p=0.8$)





Patients receiving **BRAFi** or **mTORi** had more frequently **radiologic** ($p=0.02$) and **metabolic** ($p=0.001$) **improvement** of perirenal infiltration, compared with patients receiving conventional therapies

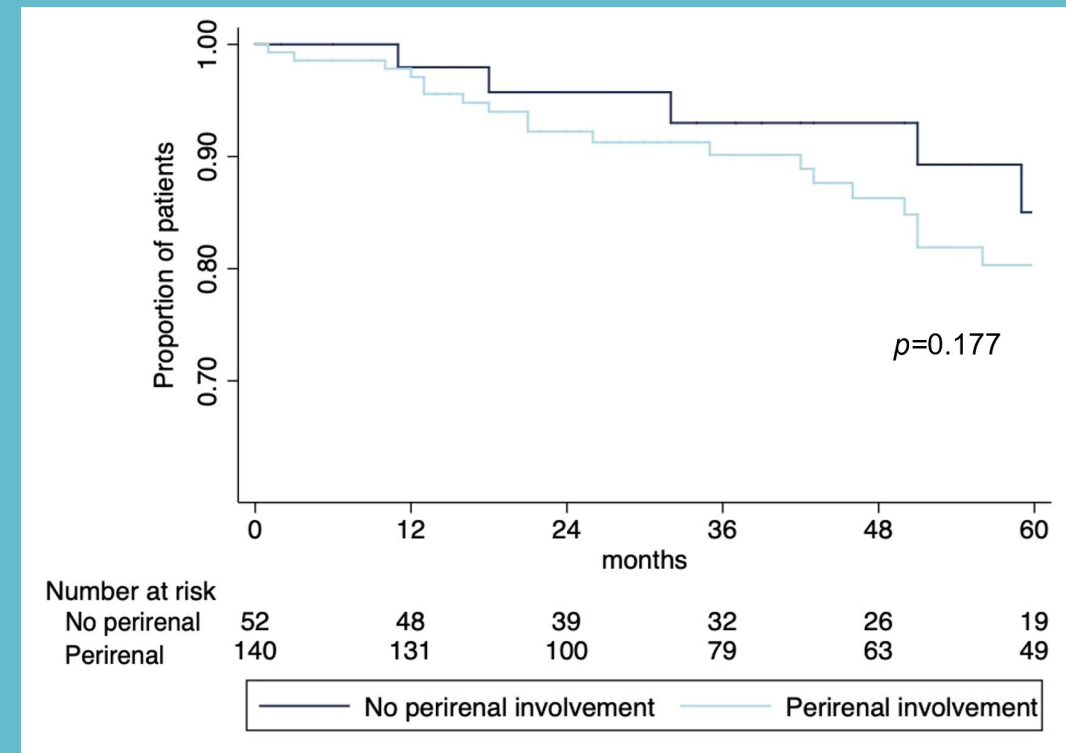
First-line therapy	eGFR change at 1 year			CT/MRI response of peri-renal infiltration at 1 year **	PET-CT response of peri-renal infiltration at 1 year ***
	<i>Worsening</i> < - 25%	<i>Stable</i> >-25% < 25%	<i>Improvement</i> > 25%		
BRAFi (31 pts), n (%)	7 (23)	21 (67)	3 (10)	8 (26)	7/13 (54)
IFNa (110 pts), n (%)	14 (13)	86 (78)	10 (9)	13 (13)	13/50 (26)
mTORi (13 pts), n (%)	1 (8)	11 (84)	1 (8)	3 (23)	5/6 (83)
Others* (41 pts), n (%)	5 (12)	34 (85)	2 (5)	4 (10)	1/11 (9)
Ureteral stenting (28 pts), n (%)	7 (25)	17 (61)	4 (14)	NA	NA



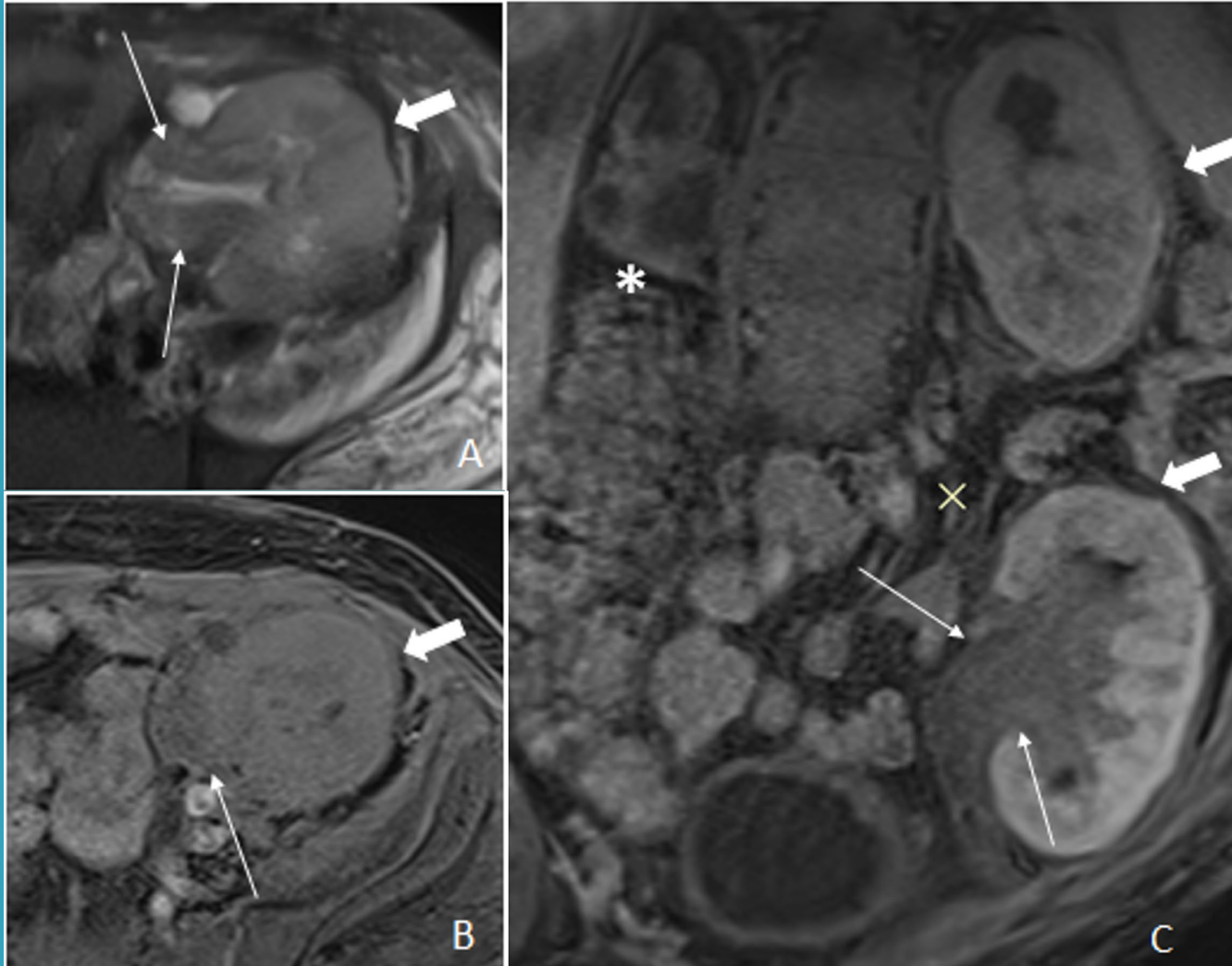
- Eight patients (4%) progressed to kidney failure and five (2.5%) were started on haemodialysis
- 35 patients (18%) died during follow-up

Median time between diagnosis and death of 46 months (IQR 46)

No difference in mortality or kidney failure between patients with and without perirenal involvement



Results – *ECD recurrence on kidney graft*



End-stage cardiac failure + kidney failure



Combined heart and kidney transplant



histology

Cardiac and renal involvement of ECD



After 6 months, **ECD recurrence** around the **transplanted kidney**

Results – Unadjusted predictors of kidney outcome



	Risk of CKD 4-5 or eGFR decrease >25%		Risk of ESKD or death	
	Crude OR (95% CI)	p value	Crude HR (95% CI)	p value
Sex female	0.81 (0.38 – 1.75)	0.592	1.30 (0.64 – 2.66)	0.468
Age at onset >50y	2.94 (1.35 – 6.37)	0.006	3.36 (1.58 – 7.16)	0.002
Comorbidities				
Hypertension	2.09 (1.06 – 4.14)	0.034	1.98 (1.03 – 3.78)	0.039
Diabetes	3.81 (1.86 – 7.80)	<0.001	1.43 (0.71 – 2.90)	0.319
Obesity	1.29 (0.55 – 3.03)	0.556	1.12 (0.47 – 2.71)	0.796
Hypercholesterolemia	1.94 (0.94 – 4.01)	0.074	0.75 (0.33 – 1.70)	0.487
CAD	4.23 (2.09 – 8.94)	<0.001	1.62 (0.83 – 3.14)	0.158
Smoking	1.64 (0.81 – 3.30)	0.169	1.02 (0.51 – 2.05)	0.947
Involved sites				
> 4 sites involved	2.23 (1.08 – 4.59)	0.029	1.28 (0.64 – 2.55)	0.481
Retroperitoneum	3.11 (1.15 – 8.41)	0.026	1.49 (0.65 – 3.40)	0.343
Peri-renal	2.86 (1.13 – 7.24)	0.026	1.75 (0.77 – 3.99)	0.183
Kidney atrophy	3.51 (1.26 – 9.73)	0.016	1.08 (0.38 – 3.06)	0.885
Ureteral involvement	1.20 (0.61 – 2.35)	0.604	0.94 (0.35 – 1.39)	0.300
Hydronephrosis	1.90 (0.96 – 3.76)	0.063	0.75 (0.37 – 1.51)	0.415
Vascular peduncle	1.95 (0.98 – 3.92)	0.059	0.91 (0.46 – 1.81)	0.784
CNS	0.81 (0.40 – 1.67)	0.574	1.06 (0.44 – 2.06)	0.867
Large vessels	2.37 (1.09 – 5.15)	0.029	1.18 (0.58 – 2.38)	0.652
Heart	1.44 (0.73 – 2.84)	0.287	1.16 (0.60 – 2.21)	0.660
Lung	1.40 (0.70 – 2.79)	0.341	1.26 (0.66 – 2.42)	0.484
Skin/subcutaneous	0.64 (0.31 – 1.31)	0.221	0.95 (0.49 – 1.84)	0.871
Bone	1.98 (0.65 – 6.04)	0.228	2.05 (0.63 – 6.70)	0.232
Facial/orbit	1.66 (0.85 – 3.26)	0.141	0.99 (0.52 – 1.89)	0.979
Hypothalamic/pituitary	1.31 (0.65 – 2.63)	0.446	0.64 (0.31 – 1.31)	0.222
Associated LCH	1.59 (0.67 – 3.78)	0.292	1.01 (0.44 – 2.30)	0.988
BRAF ^{V600E} mutation	2.06 (0.94 – 4.52)	0.071	2.44 (1.10 – 5.41)	0.028
Renal function at baseline				
eGFR - mL/min/1.73m ²	0.98 (0.97 – 0.99)	0.030	0.99 (0.98 – 0.99)	0.035
sCreatinine - mg/dL	1.73 (1.04 – 2.87)	0.034	1.28 (0.76 – 2.16)	0.345
CKD 3-5	1.97 (0.95 – 4.05)	0.067	1.90 (0.96 – 3.75)	0.065
1 st line treatment				
Targeted (BRAFi/MEKi/mTORi)	0.79 (0.34 – 1.87)	0.599	2.14 (0.84 – 5.44)	0.110
IFNa, others*	1.04 (0.48 – 2.26)	0.912	0.33 (0.14 – 0.78)	0.012
Ureteral decompression procedures	1.81 (0.86 – 3.81)	0.121	0.90 (0.43 – 1.92)	0.795

3 unadjusted predictors of both CKD 4-5/eGFR decrease >25% and kidney failure/death at last visit:

- Age at onset >50y
- Hypertension
- Low eGFR at baseline

Results – *Multivariable analysis*



	Risk of CKD 4-5 or eGFR decrease >25%	
	OR (95% CI)	p value
Age >50y	2.26 (0.96 – 5.33)	0.060
CV risk factors*	3.51 (1.47 – 8.38)	0.005
Perirenal involvement	1.30 (0.45 – 3.75)	0.617
eGFR at baseline	0.99 (0.98 – 1.01)	0.695
<i>BRAF</i> ^{V600E}	1.77 (0.77 – 4.08)	0.174

	Risk of ESKD or death	
	HR (95% CI)	p value
Age >50y	3.30 (1.42 – 7.22)	0.005
CV risk factors*	1.69 (0.80 – 3.59)	0.170
IFNa / non targeted treatments	0.33 (0.12 – 0.90)	0.029
eGFR at baseline	0.99 (0.98 – 1.01)	0.570
<i>BRAF</i> ^{V600E}	2.01 (0.90 – 4.52)	0.090

Conclusions



- High frequency of retroperitoneal involvement (**73%**), higher than in previous studies (58-65%)
- **32% of CKD 3-5 at diagnosis** in patients with retroperitoneal involvement (vs. 8% in patients without) but no difference in the median loss of eGFR during follow-up
- Kidney disease **already established at diagnosis** → kidney function does not recover after ureteral stenting
- Retroperitoneal involvement **not significantly associated with lower survival** as previously reported (Cohen-Aubart F, et al. *Am J Hematol.* 2018)



- **Targeted treatments** reduce **size** and **metabolism** of the retroperitoneal infiltrate, but **do not improve kidney function** at one year (long-term data not available)
- Putative effect of **BRAFi-induced tubular toxicity** (Jhaveri KD, et al. *JAMA Oncol.* 2015)
- **Conventional therapies** associated with **reduced risk of kidney failure or death** (do we use conventional therapies in patients with a less severe phenotype?)
- **Cardiovascular risk factors** → **kidney function worsening**
- **Age at onset >50y** → **kidney failure or death**



- Perirenal infiltration in ECD is associated with **worse renal function at diagnosis** but not with a faster progression of kidney damage over time



Prompt diagnosis and early treatment

- **Cardiovascular risk factors** and **age** are **independent predictors** of kidney outcome



Prevention and treatment of cardiovascular risk factors

Acknowledgments



Meyer Children's Hospital, Firenze

Augusto Vaglio
Valerio Maniscalco
Elena Gelain
Annamaria Buccoliero
Elena Sieni

Hôpital Pitié-Salpêtrière, Paris

Julien Haroche
Fleur Cohen-Aubart
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Hassan Izzedine
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Alessandra Bettiol

Weizmann Institute of Science, Rehovot

Roei D. Mazor

University Hospital, Parma

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ECD Global Alliance

Kathy Brewer