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## Background

- Immunotherapy (IO) combination (IO-IO or IO-VEGF TKI), has improved outcomes for patients with metastatic RCC (mRCC)<sup>1,2,3</sup>
- The role and timing of cytoreductive nephrectomy (CN) for mRCC are unclear; a recent analysis showed pathologic outcomes for CN<sup>4</sup>

## Methods

- Single-center, retrospective analysis of mRCC patients undergoing cytoreductive nephrectomy between 4/2016 and 10/2022 (n=51)
- Patients were divided into two cohorts according to treatment approach: upfront surgery (mRCC-Nx-Tx) vs. surgery after IO-VEGF based treatments (mRCC-Tx-Nx). Median follow up was 21 months.

**Primary Endpoint:** Pathologic tumor size reduction and downstaging  
**Secondary Endpoints:** PFS and OS

## Results

- Median age was 62 (range 36-86) years, with majority male and Caucasian (**Table 1**).
- 84.3% (n=43) patients were treatment-naïve when starting IO therapy

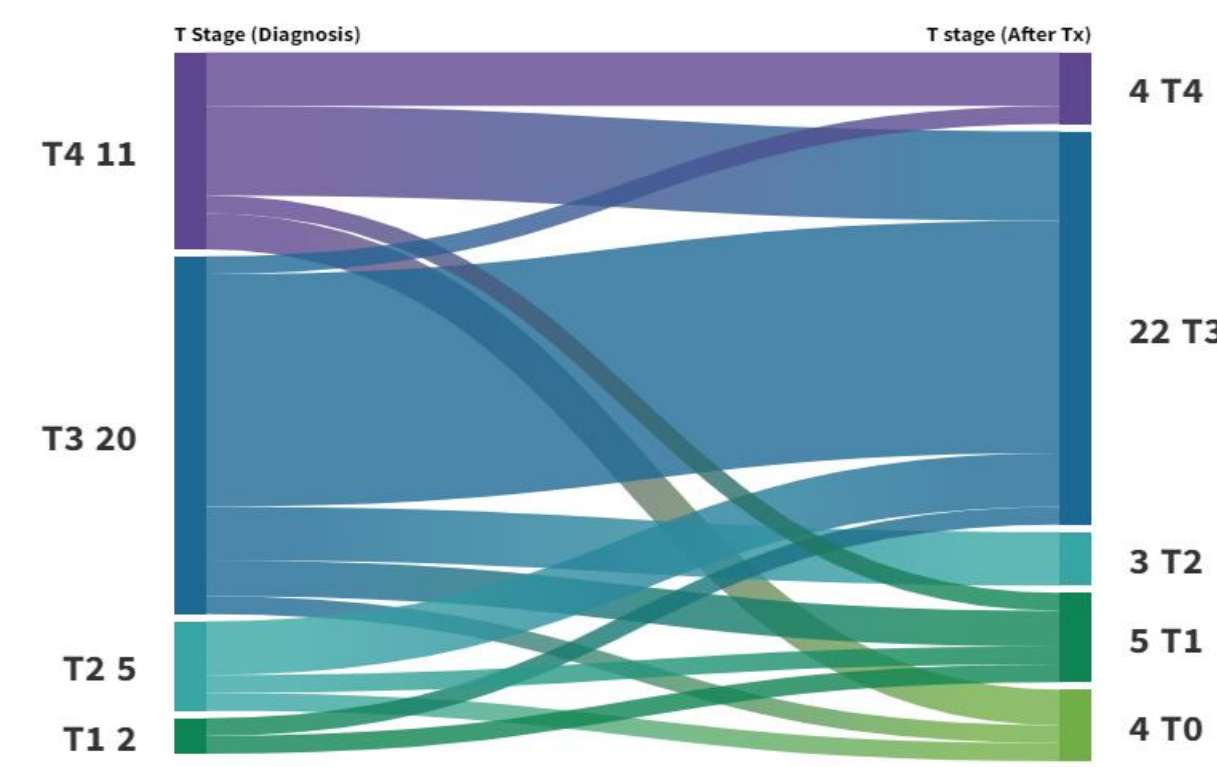
Table 1. Patient Characteristics

	mRCC-Nx-Tx	mRCC-Tx-Nx
<b>Age (Mean)</b>	59.62	62.53
<b>Sex</b>		
Female	3 (23.1%)	9 (23.7%)
Male	10 (76.9%)	29 (76.3%)
<b>Race</b>		
Caucasian	12 (92.3%)	31 (81.6%)
African American	1 (7.7%)	2 (5.3%)
Hispanic	0 (0%)	5 (13.2%)
<b>Tumor histology</b>		
Clear cell	10 (76.9%)	34 (89.5%)
Papillary	2 (15.4%)	1 (2.6%)
Other	1 (7.7%)	3 (7.9%)
<b>Treatment</b>		
Ipilimumab/nivolumab	8 (61.5%)	24 (63.2%)
Pembrolizumab/axitinib	0 (0%)	6 (15.8%)
Pembrolizumab/lenvatinib	1 (7.7%)	4 (10.5%)
IO monotherapy*	4 (30.8%)	4 (10.5%)
- Nivolumab	1	4
- Pembrolizumab	3	0
<b>Tumor Necrosis</b>		
Yes	7 (53.8%)	28 (76.3%)
No	6 (46.2%)	9 (23.7%)
Percentage (Mean ± SD)	6.9% ± 9.25%	28.4% ± 30.55%

\* 2 of 8 patients treated with IO monotherapy pembrolizumab as front-line

- Pathologic T downstaging occurred in 42% (n=16) of patients, 11% (n=4) of whom had pT0 disease (**Figure 1**)

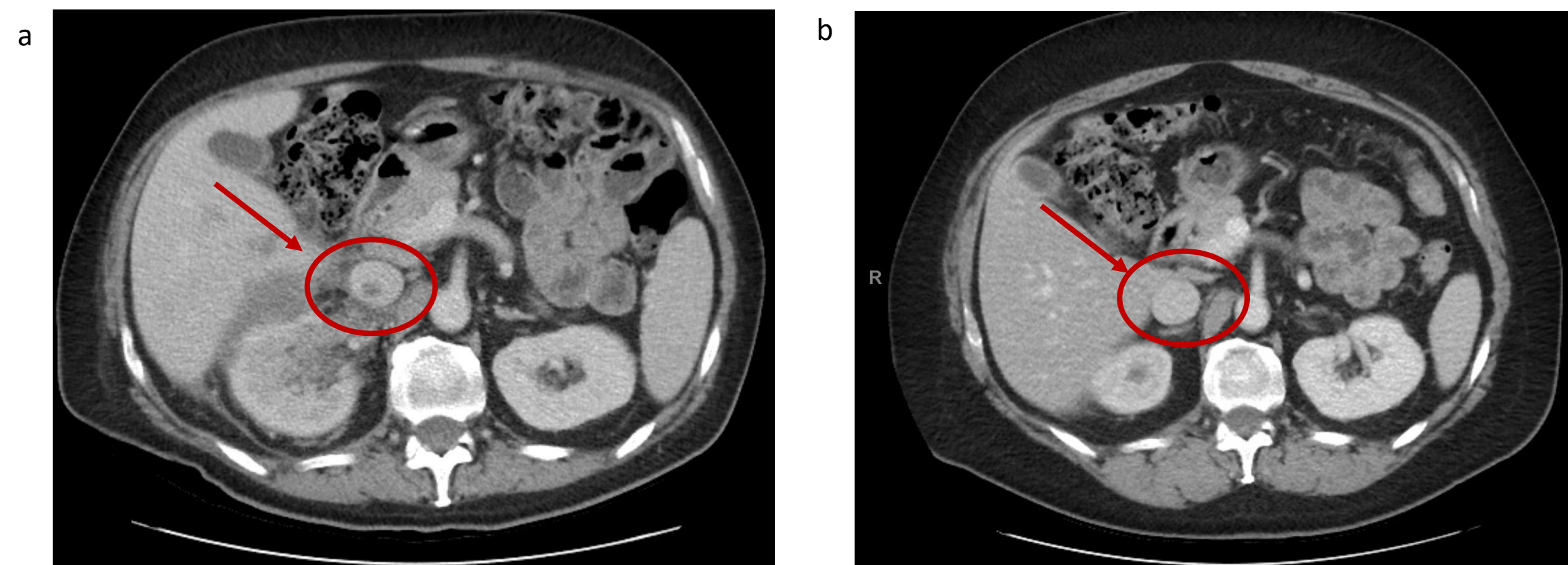
Figure 1. Pathological T Staging changes



Decreasing the extent of the IVC thrombus and pathological downstaging with perioperative IO-based therapies improves complexity of nephrectomy

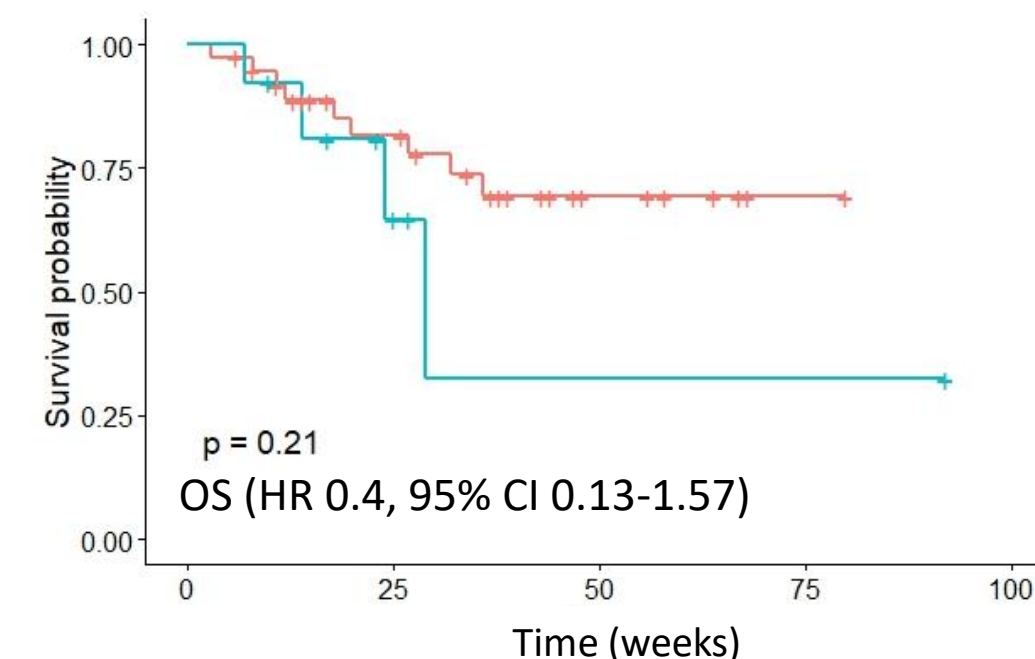
- Thrombus downstaging occurred in 13% (n=6), all with either PR or CR in metastases. (**Figure 2**)

Figure 2. Example CT imaging from patient with Level II IVC thrombus at diagnosis (a) and full thrombus resolution after IO-based treatment (b).

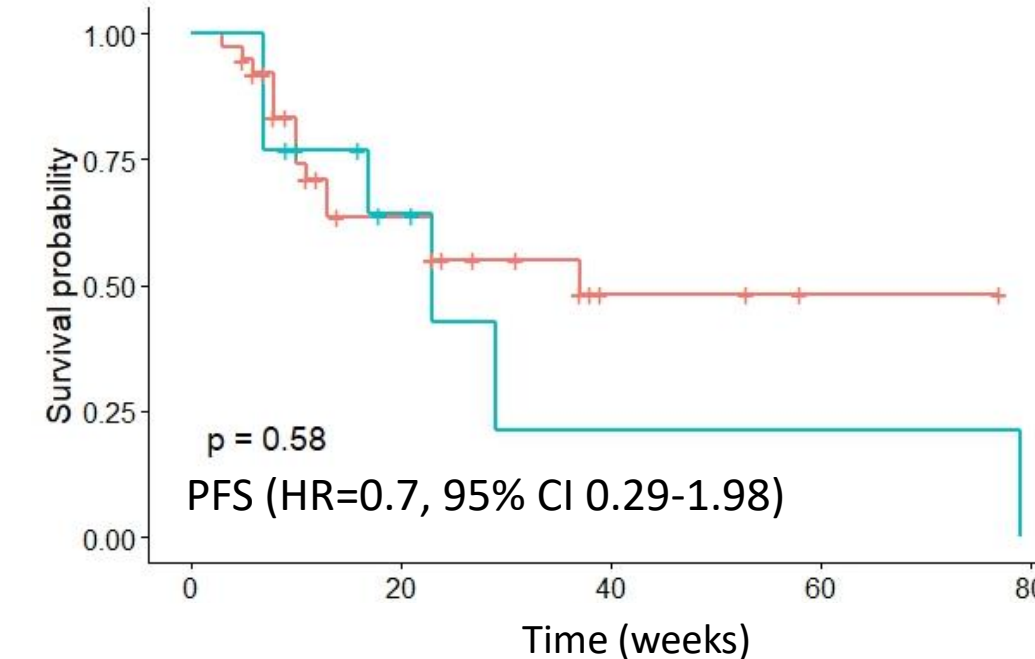


- Two patients with synchronous bilateral renal masses underwent staged radical nephrectomy and nephron-sparing partial nephrectomy after neoadjuvant treatment.

PFS and OS were not statistically significant, though trended better for patients treated with neoadjuvant therapy



	mRCC-IO-Nx	mRCC-IO-Nx	mRCC-Nx-IO	mRCC-Nx-IO
At Risk	38	23	7	1
Events	0	6	9	9



	mRCC-IO-Nx	mRCC-IO-Nx	mRCC-Nx-IO	mRCC-Nx-IO
At Risk	38	15	3	1
Events	0	12	15	15

Table 2. Pre- and Post-Neoadjuvant Disease Characteristics (mRCC-Tx-Nx)

	Pre-Treatment	Post-Treatment	P-Value
<b>Tumor size</b>			
Median tumor size (25-75%)	10 cm (7-13)	7.5 cm (5.4-10.4)	P < 0.05
<b>T Stage</b>	<b>Clinical T stage</b>	<b>Pathological T stage</b>	
T0	0 (0%)	4 (10.5%)	P < 0.05
T1	2 (5.3%)	5 (13.2%)	
T2	5 (13.2%)	3 (7.9%)	
T3	20 (52.6%)	22 (57.9%)	
T4	11 (28.9%)	4 (10.5%)	
<b>Thrombus Level</b>			
0	5 (13.2%)	2 (5.3%)	P < 0.05
1	5 (13.2%)	4 (10.5%)	
2	5 (13.2%)	3 (7.9%)	
3	1 (2.6%)	3 (7.9%)	
4	2 (5.3%)	2 (5.3%)	
No thrombus	20 (52.6%)	24 (63.2%)	
<b>N Stage</b>	<b>Clinical N stage</b>	<b>Pathological N stage</b>	
N0	23 (60.5%)	27 (71.1%)	P=0.374
N1	15 (39.5%)	5 (13.2%)	
Nx		6 (15.8%)	
<b>Clinical M Stage</b>			
M0		19 (50%)*	P < 0.001
M1	38 (100%)	18 (47.4%)	
Unknown		1 (2.6%)	

\*After primary tumor resection, patients with CR in metastatic lesions were evaluated as M0.

## Conclusions & Future Directions

- Neoadjuvant IO-VEGF based treatment resulted in reductions in tumor size and pathologic necrosis at the time of nephrectomy
- Effective IO-VEGF based therapies administered prior to nephrectomy have promising potential in disease control
- Patients with T stage progression after IO-based treatment received an average of 3.3 cycles, while those with T-stage downstaging had an average of 7.3 cycles, possibly from IO-resistant disease needing surgery earlier than those with early disease control.
- Patients with IVC thrombus downgrading had improved systemic disease control.
- Randomized trials are ongoing to investigate the timing and outcomes of cytoreductive nephrectomy for patients with mRCC.

### References:

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