Optimal timing?

Which systemic therapy to combine with TKI / ICI ?

OS benefit

CYTOREDUCTIVE NEPHRECTOMY

Role of IMDC/MSKCC risk scores

Metastatic burden

Kidney Cancer

Upfront Versus Deferred Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma: A Systematic Review and Individual Patient Data Meta-analysis

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- Upfront CN (uCN)– CN performed at any point prior to ST initiation

- Deferred CN (dCN) – CN performed at any point after systemic therapy ST initiation

- Mechanism :-
  - ICI - Enhanced T-cell priming through exposure to a higher tumor antigen load.
  - TKI - Directly reducing the tumor load prior to surgery, similar to neo-adjuvant chemotherapy in other solid tumours.

- Benefits:-
  - Additional prognostic information on basis of response to ST .
  - Rapid progression on ST → Poor prognosis and poor candidates for CN.
  - Minimizes treatment delay.
  - Ensures atleast ST for all.

Study selection and Data extraction

- **Post screening and assessment for eligibility – 12 studies (2 RCT and 10 retrospective cohorts)**
- **Total of 3323 (2610 uCN and 713 dCN) patients.**

Table 1 – Summary of the included studies

Study	Type	Location	Dates	uCN	dCN	ST	Time to dCN	OS definition
Bex et al (2019) [9]	RCT	The Netherlands, Canada, Belgium, UK	July 2010–March 2016	50	49	TKI	16 wk	Randomization
Bhindi et al (2020) [27]	Retrospective cohort	Canada, USA, Belgium, Denmark, Germany, Greece, Italy, South Korea, Singapore, Japan, New Zealand, Australia	2006–2018	805	85	TKI	8.4 ± 5.9 wk	Treatment initiation
de Bruijn et al (2020) [28]	Retrospective cohort	The Netherlands, Germany, Austria, UK	2006–2016	149	189	TKI	NA	Diagnosis
Dragomir et al (2022) [29]	Retrospective cohort	Canada	January 2011–April 2020	383	73	Both	7.6 ± 4.5 wk	Index date
Ghatalia et al (2022) [30]	Retrospective cohort	USA	2011–2020	605	142	Both	NA	Treatment initiation
Gross et al (2023) [31]	Retrospective cohort	USA	2000–2020	202	30	Both	12.5 ± 13.5 wk	Diagnosis
Hatakeyama et al (2021) [32]	Retrospective cohort	Japan	January 2008–November 2019	107	39	TKI	NA	Treatment initiation
Kapoor et al (2019) [33]	Retrospective cohort	Canada	2009–2016	32	22	TKI	NA	Diagnosis
Shen et al (2023) [34]	RCT	China	2018–2020	42	42	ICI	NA	Surgery
Singla et al (2020) [35]	Retrospective cohort	USA	2015–2016	197	24	ICI	19.2 ± 7.8 wk	NA
Stroup et al (2013) [36]	Retrospective cohort	USA	May 2005–August 2009	17	11	TKI	12 wk	NA
Yoshino et al (2022) [37]	Retrospective cohort	Japan	September 2016–July 2021	21	7	ICI	10.4 mo	Treatment initiation

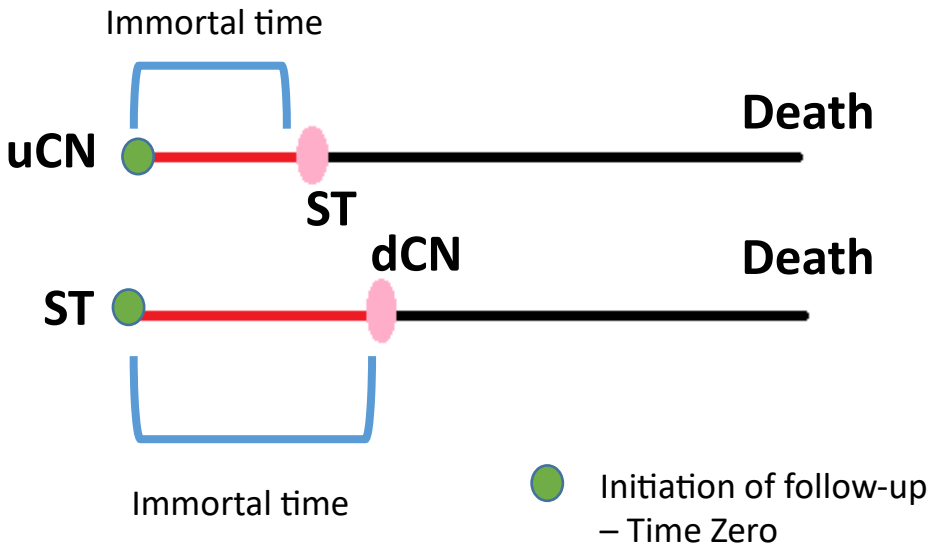
dCN = deferred cytoreductive nephrectomy; ICI = immune checkpoint inhibitor; NA = not available; OS = overall survival; RCT = randomized controlled trial; ST = systemic therapy; TKI = tyrosine kinase inhibitor; uCN = upfront cytoreductive nephrectomy.

IPD – individual participant data

- Use of **Individual participant data IPD** –
  - Extract and synthesize the raw, participant-level data from a set of relevant studies – followed by one or two stage analysis.
  - Advantages:-
    - Gives more freedom - to investigate individual-level interactions, such as treatment-effect modifiers.
    - Lesser bias
    - Avoids reliance on published results

Immortal time bias

- In retrospective cohort based data –immortal time bias– time interval between start of follow-up and the intervention.
- Magnitude of this bias is disproportionate between the two cohorts, as the average time interval from upfront ST to dCN is significantly longer than the interval of uCN to subsequent ST.
- Immortal time bias inherently favored dCN over uCN, potentially leading to invalid conclusions.



Analytic approaches to mitigate immortal time bias

Mitigate the effect of immortal time bias by performing two pre - specified landmark analyses in this meta ananlysis

- 6-mo landmark as our primary analysis, represent in the typical timeframe within which most patients will receive both CN and ST, irrespective of their order
- 12-mo landmark as an exploratory analysis that would include potential outliers as it is less common for dCN to occur after 12 mo from the initiation of ST
- Landmark analyses limit the study population to only patients surviving past the pre-specified landmark

dCN - older ,more likely-multiple metastatic sites ,more likely to receive pazopanib or sunitinib over nivolumab/ipilimumab

Variable		Upfront CN (n = 2610)	Deferred CN (n = 713)	p value
Mean age (yr)		60.9 (10.5)	62.4 (10.1)	0.002
Gender				
	Male	1315/1805 (72.9)	448/617 (72.6)	
	Female	490/1805 (27.1)	169/617 (27.4)	0.91
Histology				
	Clear cell	1460/1566 (93.2)	375/393 (95.4)	
	Non–clear cell	106/1566 (6.8)	18/393 (4.6)	0.11
IMDC risk score				
	Favorable	12/1043 (1.2)	1/256 (0.4)	
	Intermediate	600/1043 (57.5)	140/256 (56.9)	
	Poor	431/1043 (41.3)	105/256 (42.7)	0.55
MSKCC risk score				
	Favorable	0/199 (0.0)	0/234 (0.0)	
	Intermediate	169/199 (84.9)	202/234 (86.0)	
	Poor	30/199 (15.1)	32/234 (14.0)	0.94
Karnofsky performance status				
	<80	19/160 (11.9)	14/68 (20.6)	
	>80	140/160 (88.1)	54/68 (79.4)	0.09
Number of metastatic sites				
	1	316/603 (52.4)	110/318 (34.6)	
	>2	287/603 (47.6)	208/318 (65.4)	<0.001
Location of metastases				
	CNS	36/926 (3.9)	6/208 (2.9)	0.49
	Bone	255/964 (26.5)	67/222 (30.2)	0.26
	Liver	96/1007 (9.5)	26/264 (9.8)	0.88
	Lung	610/944 (64.6)	136/215 (63.3)	0.71
	Lymph nodes	284/884 (32.1)	66/192 (34.4)	0.55
Systemic therapy				
	Sunitinib	1467/2179 (67.3)	344/637 (54.0)	<0.001
	Pazopanib	266/2179 (12.2)	157/637 (24.6)	<0.001
	Nivolumab/ipilimumab	152/2211 (6.9)	27/659 (4.1)	0.01

CN = cytoreductive nephrectomy; CNS = central nervous system; IMDC = International Metastatic RCC Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma.
Values in parentheses denote percentages for categorical variables and standard deviations for continuous variables.

dCN associated with superior survival outcomes

Analysis	Outcome measure	Value	95% CI	*p* value
One-stage meta-analysis	Hazard ratio	0.75	0.67–0.84	<0.001
One-stage meta-analysis (6-mo landmark)	Hazard ratio	0.74	0.65–0.84	<0.001
One-stage meta-analysis (12-mo landmark)	Hazard ratio	0.78	0.68–0.91	<0.001
Two-stage meta-analysis	Hazard ratio	0.69	0.58–0.84	<0.001
1-yr RMST	Life expectancy difference (mo)	0.31	0.01–0.52	0.005
1-yr RMST	Life expectancy ratio	1.03	1.01–1.05	0.004
3-yr RMST	Life expectancy difference (mo)	3.24	2.21–4.27	<0.001
3-yr RMST	Life expectancy ratio	1.13	1.09–1.18	<0.001
5-yr RMST	Life expectancy difference (mo)	5.15	3.23–7.08	<0.001
5-yr RMST	Life expectancy ratio	1.16	1.10–1.22	<0.001
TKI only (6-mo landmark)	Hazard ratio	0.53	0.63–0.75	<0.001
ICI only (6-mo landmark)	Hazard ratio	0.49	0.27–0.86	0.01
Intermediate IMDC/MSKCC risk only (6-mo landmark)	Hazard ratio	0.73	0.55–0.97	0.03

Subgroup analyses

CI = confidence interval; ICI = immune checkpoint inhibitor; IMDC = International Metastatic RCC Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma; RMST = restricted mean survival time; TKI = tyrosine kinase inhibitor.

dCN associated with superior OS compared with uCN

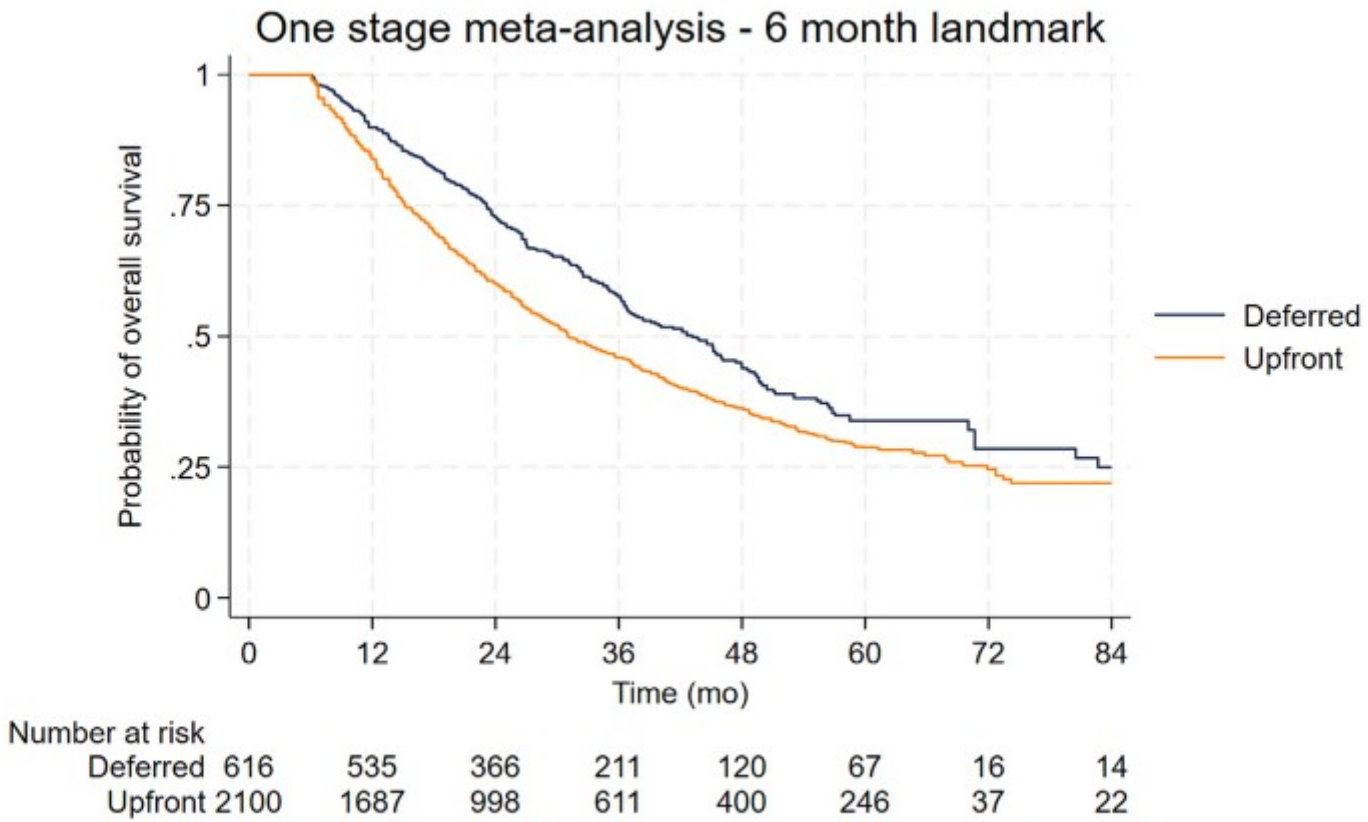


Fig. 2 – Kaplan-Meier survival curve of overall survival derived from one-stage meta-analysis of reconstructed individual patient data using a 6-mo landmark to account for immortal time bias.

Limitations

- High risk of bias in included studies limiting the validity of their data.
- Majority received TKIs as ST, which is no longer considered the standard of care for mRCC.
- Not adjusted confounders in regression models due to limited access to patient datasets and IPD were limited to unadjusted survival.
- Sample size limited due to data availability.
- Studies included used varying starting points to define OS, and therefore any delays in initiating treatment had a negative impact when the date of diagnosis was used as the index instead of the date of treatment initiation.

Conclusions

- In patients with mRCC undergoing CN, dCN is associated with superior OS compared with uCN, regardless of the type of ST used.
- Results need to be validated by well designed RCTs as well as real-world observational studies that appropriately address confounding and immortal time bias in their design.

Thank you