

Role of Surgery in Advanced and Metastatic Renal Cell Carcinoma

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Financial and Other Disclosures

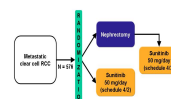
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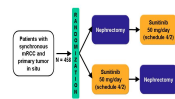
CARMENA investigated the role of CN SURTIME the sequence of CN

CARMENA Phase III Study of Sunitinib Only Vs. Nephrectomy Followed by Sunitinib



Primary objective: Is sunitinib alone non-inferior to nephrectomy plus sunitinib in terms of OS?
Major secondary objectives: clear cut primary metastatic and EDOG performance S1

SURTIME, a EORTC-GU 30073 Phase II Study Investigating the Sequence of Nephrectomy and Sunitinib

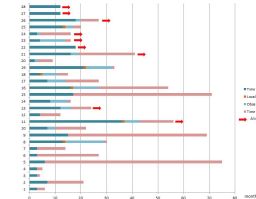


Primary end point: PFS
Secondary end points: OS, association with prognostic gene and cancer expression profiles



SURTIME and CARMENA included patients who require sunitinib

Time to targeted therapy in patients with low-volume but non-resectable metastatic disease after CN



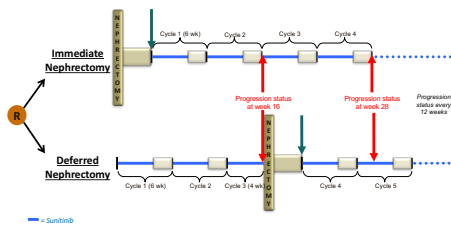
N=28 from an institutional database of 202 primary mRCC patients

Median time to TT 14 months

Bex et al., GU ASCO, J Clin Oncol 34, 2016 (suppl 26), abstr 604



Study design



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The future of cancer therapy

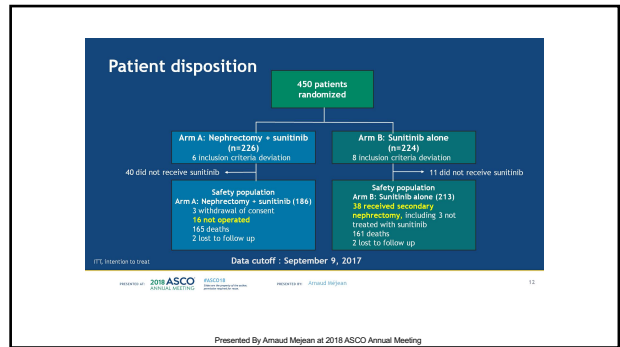
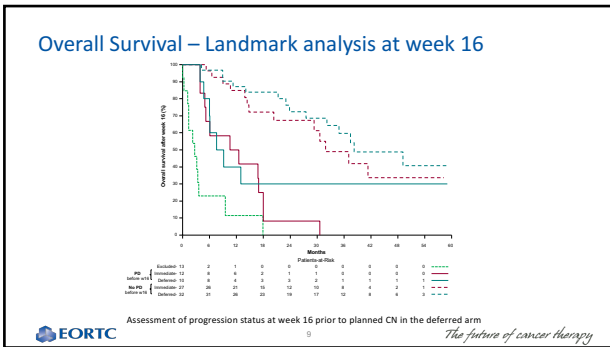
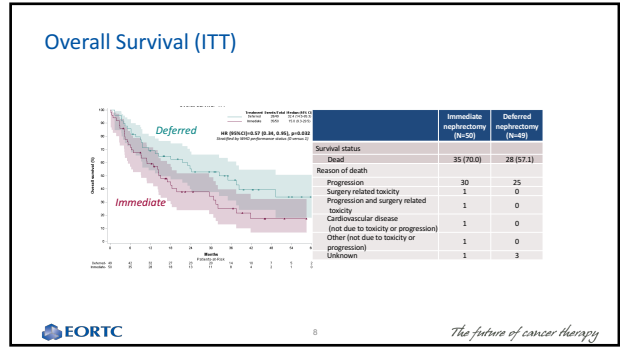
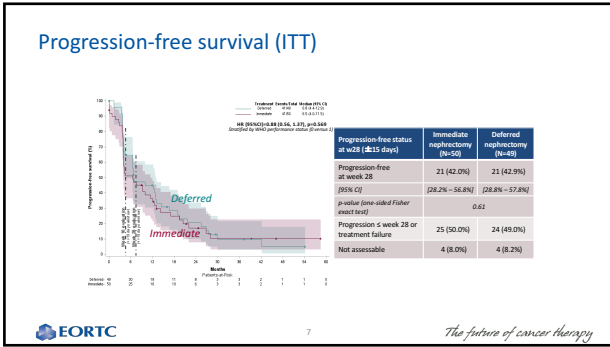
Baseline characteristics

	Immediate nephrectomy (n=20)	Deferred nephrectomy (n=8)
Median age (years)	60	58
Performance status (WHO)		
- WHO 0	36 (72.0%)	31 (63.3%)
- WHO 1	14 (28.0%)	18 (36.7%)
Male	41 (82.0%)	39 (79.6%)
MSKCC intermediate risk	43 (86.0%)	44 (89.8%)
≥ 2 measurable metastatic sites	43 (86.0%)	46 (93.9%)
Mean (SD) primary tumor size (mm)	93.1 (37.8)	96.8 (31.3)



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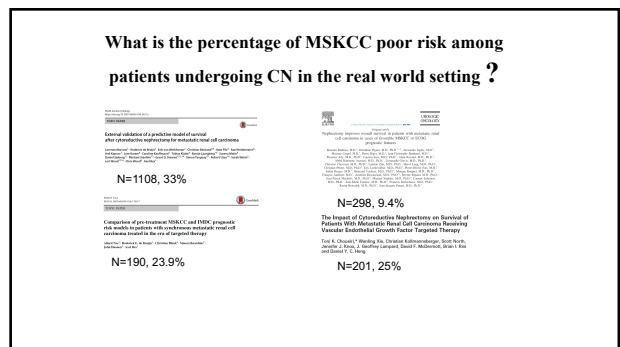
The future of cancer therapy



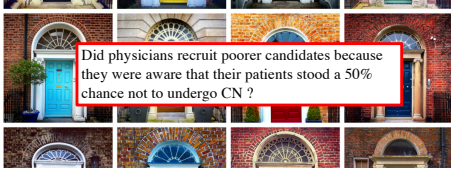
Patient characteristics (1)

Characteristic	Arm A: Nephrectomy + sunitinib (N = 226)	Arm B: Sunitinib alone (N = 224)
Median age (range), years	63 (33-84)	62 (30-87)
Male sex, n (%)	169 (75)	167 (75)
MSKCC score, n (%)		
Intermediate	125 (56)	131 (59)
Poor	100 (44)	93 (41)
Missing		
ECOG PS, n (%)		
0	130 (57)	122 (54)
1	96 (42)	102 (45)

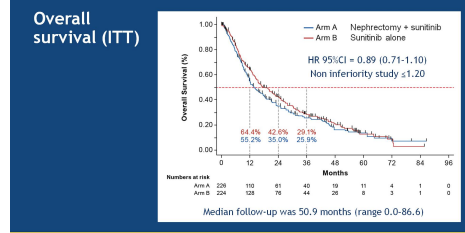
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Was there selection at the 'front door' ?



Did physicians recruit poorer candidates because they were aware that their patients stood a 50% chance not to undergo CN ?



Presented By Arnaud Mejean at 2018 ASCO Annual Meeting

Overall survival (ITT)

Median OS, months (95% CI)	Arm A: Nephrectomy + Sunitinib (n = 226)	Arm B: Sunitinib alone (n = 224)	HR (95% CI)
Overall	13.9 (11.8-18.3)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
MSKCC Intermediate risk	19.0 (12.0-28.0)	23.4 (17.0-32.0)	0.92 (0.6-1.24)
MSKCC poor risk	10.2 (9.0-14.0)	13.3 (9.0-17.0)	0.86 (0.62-1.17)

Non inferiority study ≤ 1.20

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Overall survival by patient population

Population	Arm A (Nephrectomy + sunitinib)			Arm B (Sunitinib)			HR (95% CI), stratified by MSKCC risk group
	n	Events, n (%)	Median (95% CI), months	n	Events, n (%)	Median (95% CI), months	
ITT	226	165 (73)	13.9 (11.8-18.3)	224	161 (72)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
PP1*	205	149 (73)	14.5 (11.9-20.2)	206	143 (69)	20.5 (15.6-25.2)	0.87 (0.69-1.11)
PP2*	176	122 (64)	18.3 (13.7-23.2)	206	143 (69)	20.5 (15.6-25.2)	0.98 (0.77-1.25)

*The PP1 analysis included only patients who had nephrectomy in Arm A, and patients who receive sunitinib in Arm B. The PP2 analysis included only patients who had nephrectomy and received sunitinib after nephrectomy in Arm A, and patients who receive sunitinib in Arm B. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MSKCC, Memorial Sloan-Kettering Cancer Center; PP, post protocol.

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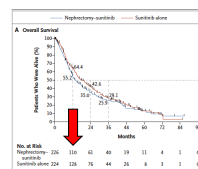
Secondary nephrectomy in Arm B (sunitinib alone)

- 38 patients required secondary nephrectomy
 - For emergency treatment of the primary tumor
 - For CR or near CR in metastatic sites (> 6 months)
- Median 11.1 months (range 0.7-85.4) from randomisation to surgery
- 31.3% of patients with secondary nephrectomy restarted sunitinib

	Arm B: Sunitinib alone (N = 224)
Secondary nephrectomy, n (%)	
No	185 (83.0)
Yes	38 (17.0)
Missing	1
Emergency	
Yes	7 (18.9)
No	30 (81.1)
Missing	1

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A different perspective on the 17% CN rate



The median time to secondary nephrectomy was 11.1 months

At +/- 12 months 128 patients in the sunitinib-alone arm are still alive

Subtract 41% poor risk patients = 76 intermediate at this point in time

50% of those alive had a secondary CN

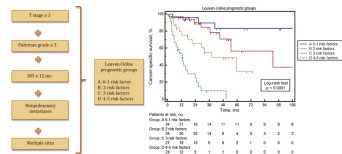
Updated EAU guidelines for cytoreductive nephrectomy in patients with synchronous metastatic clear-cell RCC

Recommendation - 1	Strength
Do not perform CN in MSKCC poor risk patients.	Strong
Recommendation - 2	Strength
Do not perform immediate CN in MSKCC intermediate risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Recommendation - 3	Strength
Start sunitinib without CN in MSKCC intermediate risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Recommendation - 4	Strength
Discuss delayed CN in MSKCC intermediate risk patients under VEGFR-TKI therapy who derive long term sustained benefit and/or minimal residual metastatic burden.	Weak

Bex et al., Eur Urol. 2018 Aug 31. doi: 10.1016/j.eururo.2018.08.008.



Leuven-Undine metastasectomy score



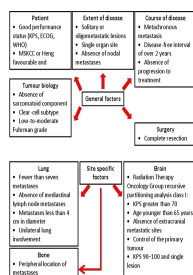
More contemporary than the Leibovich metastasectomy score developed from 727 metastasectomies in the period 1970-2000

Tosco et al. Eur Urol 4:646-652, 2012
Leibovich et al., J Urol 174(5), 2005



How to select patients for metastasectomy ?

- Multiple factors are associated with a favorable outcome



An oncological 'uncertainty principle'



$$\Delta x \Delta p \geq \frac{h}{4\pi}$$

Δx = Uncertainty of Position
 Δp = Uncertainty of Momentum



We can know the *position* of the metastasis but the *momentum* of metastatic progression is uncertain



Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial

Rini et al., N Engl J Med. 2016 Oct 20; 375(16):1525-1532. doi: 10.1056/NEJMoa1601525.

- Median time to progression 9.4 months (95% CI 7.4-13.4)
- 47% of RECIST progressing patients continued surveillance
- Time to targeted therapy was 14.9 months (95% CI 10.0-25.0)

Surveillance for 3 months may help to select rapidly progressing patients

Characteristic	No. of patients	%
Age (years)	21 (50.0)	100.0
Median	64	30.0
Range	47-74	
Sex	21 (50.0)	100.0
Male	19 (90.5)	
Female	2 (9.5)	
WHO performance grade	21 (50.0)	100.0
0	19 (90.5)	
1	2 (9.5)	
MSKCC risk	21 (50.0)	100.0
Intermediate	12 (57.1)	
Poor	9 (42.9)	
Time to progression (months)	21 (50.0)	100.0
Median	9.4	
95% CI	7.4-13.4	
Time to targeted therapy (months)	21 (50.0)	100.0
Median	14.9	
95% CI	10.0-25.0	
Time to death (months)	21 (50.0)	100.0
Median	14.9	
95% CI	10.0-25.0	
Time to death or progression (months)	21 (50.0)	100.0
Median	9.4	
95% CI	7.4-13.4	
Time to death or progression or death (months)	21 (50.0)	100.0
Median	9.4	
95% CI	7.4-13.4	

Rini et al., Lancet Oncol 2016



Finally, open questions remain

- Should CN be performed at a later stage in all patients except those who progress (SURTIME) or only when necessary (CARMENA)?
- First-line therapy with nivolumab plus ipilimumab will replace sunitinib for intermediate and poor risk patients.
- Will we need new studies or treat patients with primary metastatic RCC with the tumour in place followed by resection when necessary ?

