



RCC oligometastatico: la necessità di un approccio multidisciplinare

Nefrectomia citoreduttiva: il punto di vista dell'oncologo

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Cytoreductive Nephrectomy (CN)

- La CN **prolunga la sopravvivenza** dei pazienti?
- È importante il **timing** della CN (prima o dopo l'inizio di target therapy)?
- È corretto **selezionare i candidati** per la CN?

CN – “INF Era”

SWOG 8949 – EORTC 30947

KEY ELIGIBILITY CRITERIA:

- Metastatic RCC
- Presence of primary tumor technically resectable

Stratification Factors:

- ECOG PS (0 or 1)
- Site of metastases (lung only vs other)
- Disease measurability

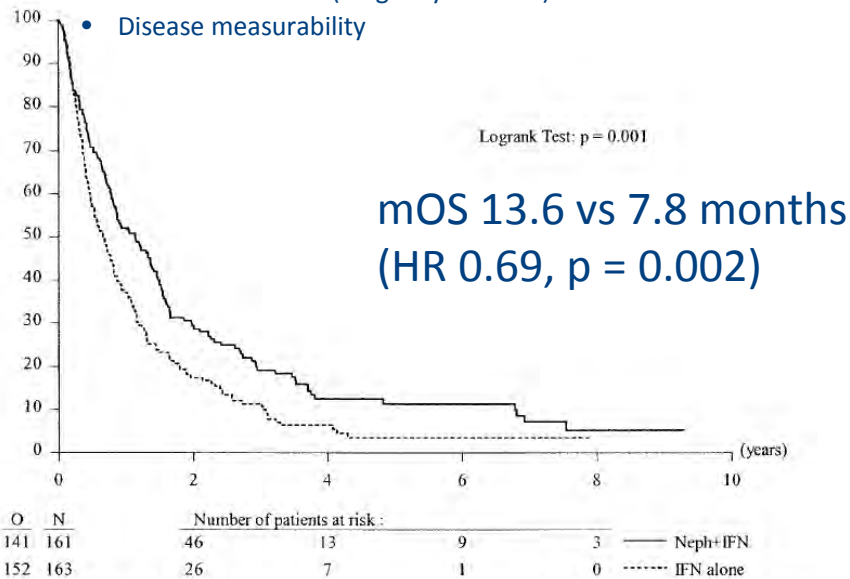
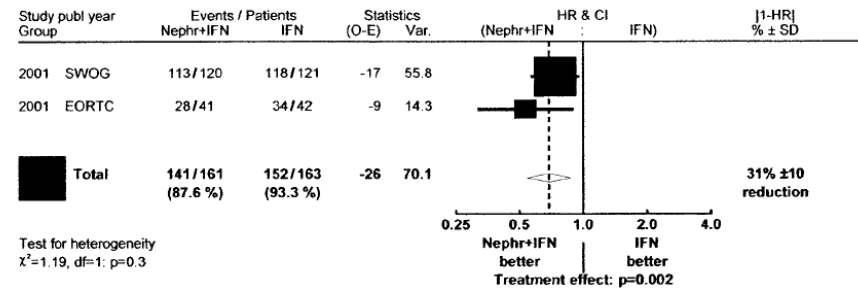
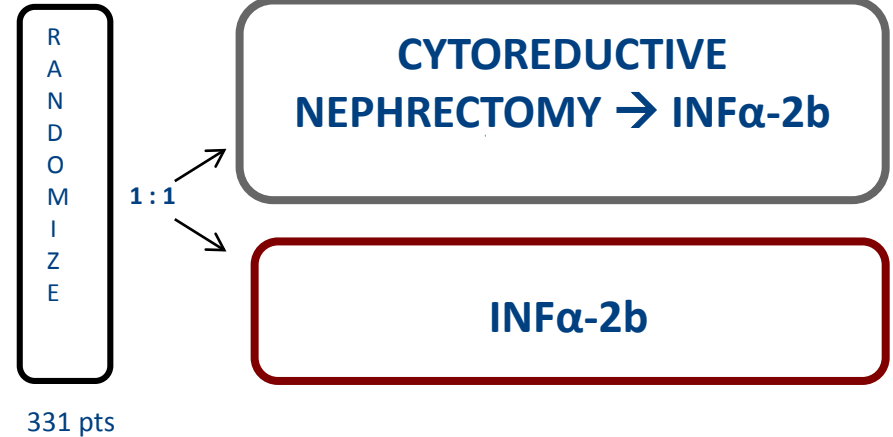


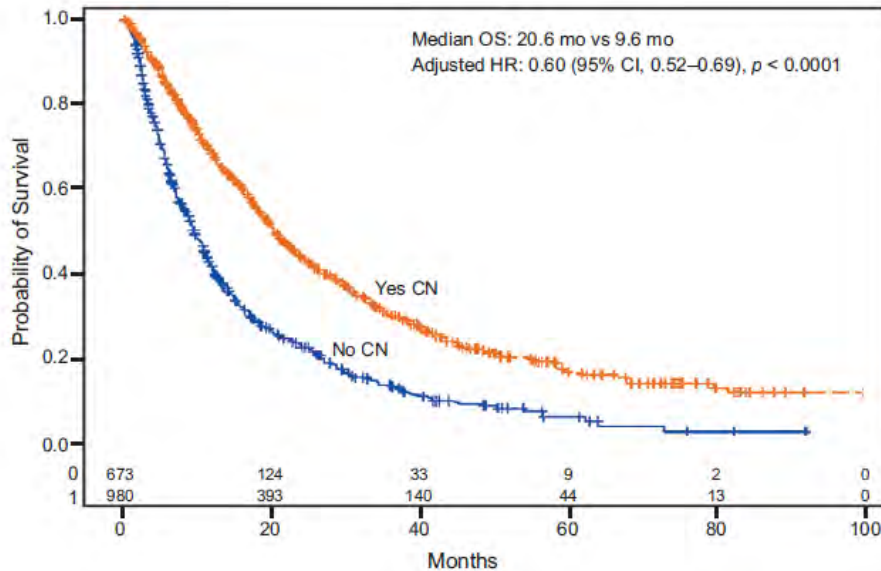
FIG. 1. Duration of survival in combined SWOG and EORTC trials. O, observation. N, nephrectomy



- Cytoreductive nephrectomy **improves significantly overall survival** in patients with metastatic renal cancer treated **with interferon immunotherapy**, independent of patient PS, the site of metastases and the presence of measurable disease.

CN – “Targeted Agents Era”

Retrospective data from patients with synchronous mRCC (n=1658) from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) were used to compare 982 mRCC patients who had a CN with 676 mRCC patients who did not.



- CN is beneficial in synchronous mRCC patients treated with targeted therapy
- Patients with 4 or more of the IMDC prognostic criteria did not benefit from CN
- Patients estimated to survive <12 months may receive marginal benefit from CN

Table 4 – Overall survival differences in those with and without cytoreductive nephrectomy by number of International Metastatic Renal Cell Carcinoma Database Consortium criteria met

No. of IMDC criteria met	No CN OS, mo (n)	CN OS, mo (n)	p value
0	92% of patients (65/71) had CN, insufficient number to compare		
1	22.5 (n = 72)	30.4 (n = 178)	0.002
2	10.2 (n = 143)	20.2 (n = 253)	<0.001
3	10.0 (n = 113)	15.9 (n = 106)	<0.001
4	5.4 (n = 103)	6.0 (n = 67)	0.166
5	3.6 (n = 36)	2.8 (n = 14)	0.504
6	25% of patients (3/12) had CN, insufficient number to compare		

Overall, 1168 of 1658 subjects (70%) had complete information about prognostic factors, nephrectomy, and outcomes and were used in this complete case analysis; the rest were excluded. Shaded rows indicate patient groups that may not benefit from cytoreductive nephrectomy. CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.

CN – “Targeted Agents Era”



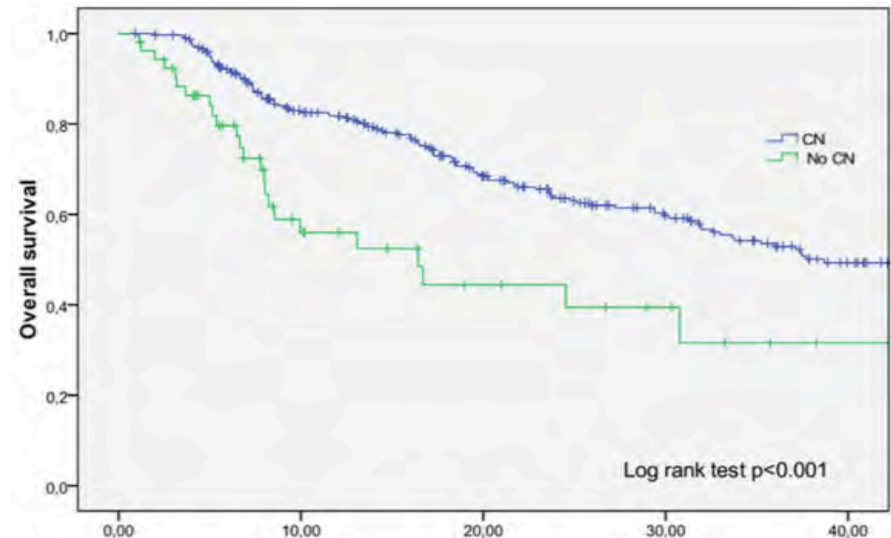
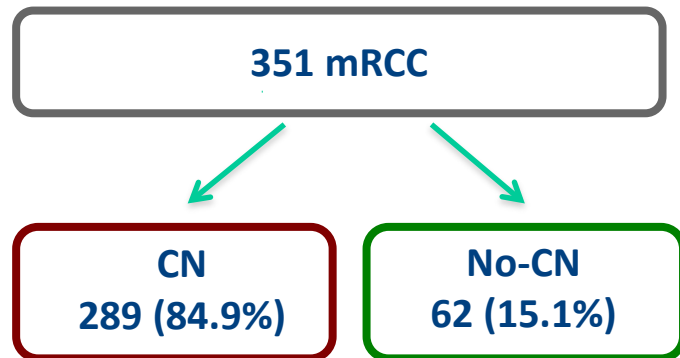
Urologic Oncology: Seminars and Original Investigations 33 (2015) 339.e9–339.e15

UROLOGIC
ONCOLOGY

Original article

Nephrectomy improves overall survival in patients with metastatic renal cell carcinoma in cases of favorable MSKCC or ECOG prognostic features

Romain Mathieu, M.D.^a, Géraldine Pignot, M.D., Ph.D.^{b,*1}, Alexandre Ingles, M.D.^b



- CN improves OS in patients with mRCC.
- However, this effect does not seem to be significant for the patients in ECOG PS groups of 2 to 3 or poor MSKCC prognostic group.

CN - Targeted Agents Era

- Is the **timing of CN** important (before or after targeted therapy)?

Prospective clinical trials

SURTIME - NCT01099423

Untreated mRCC patients with primary in place

R
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1:1

CN → SUNITINIB

SUNITINIB (3 mo)
→ CN →
SUNITINIB

CARMENA - NCT00930033

Untreated mRCC patients with primary in place

R
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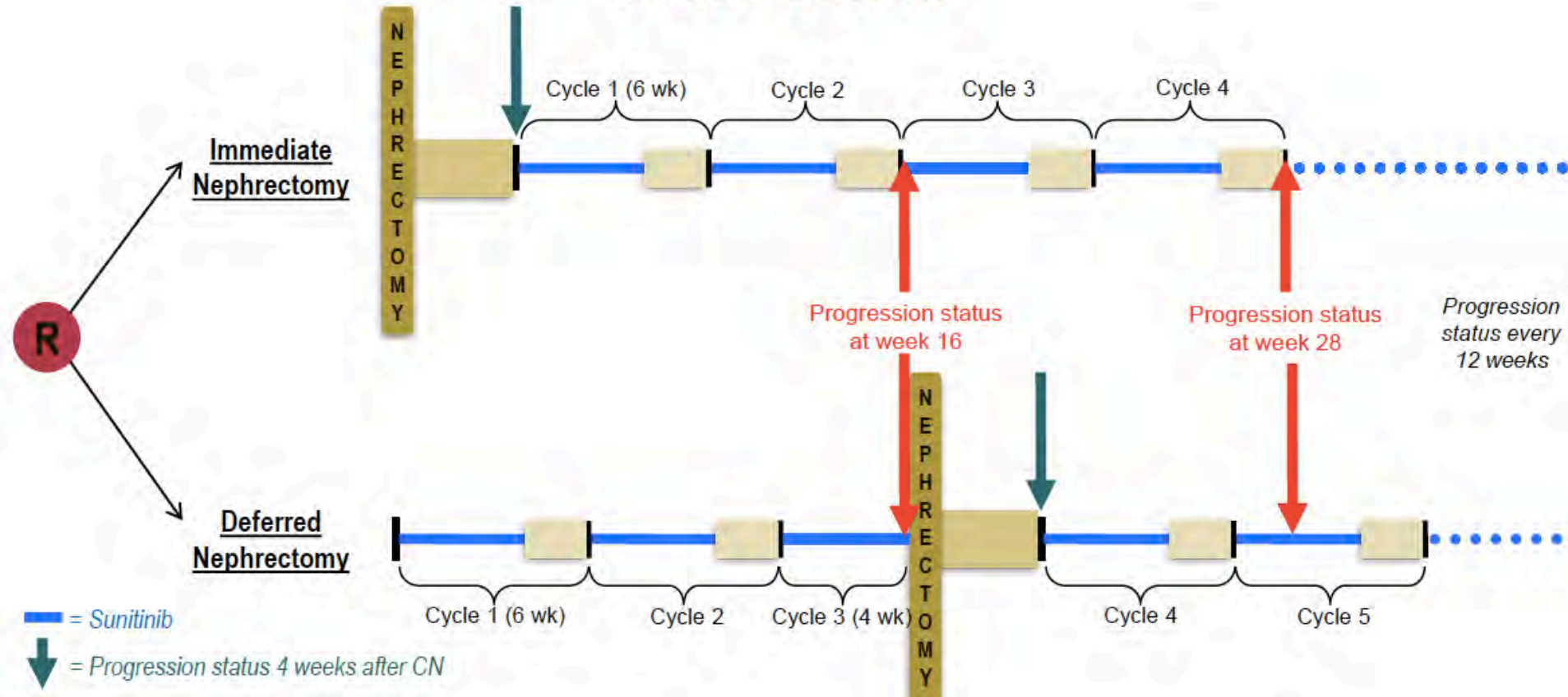
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CN → SUNITINIB

SUNITINIB

CN – SURTIME STUDY

STUDY DESIGN



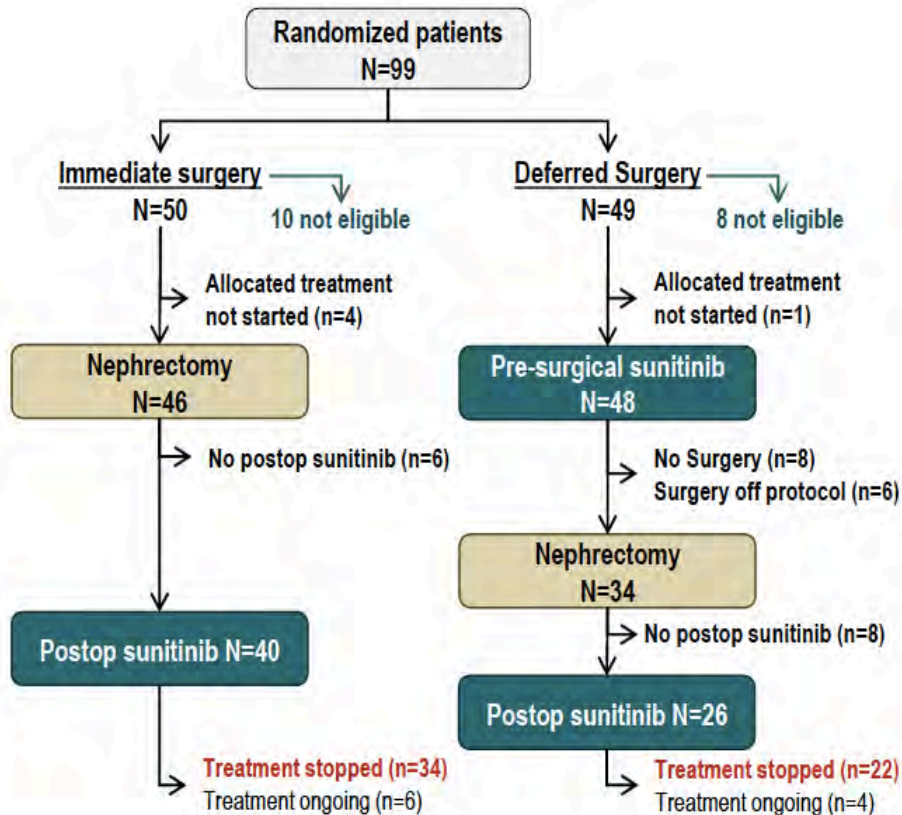
CN – SURTIME STUDY

OBJECTIVE / ENDPOINTS / SAMPLE SIZE (2)

- Due to **poor accrual (64 patients after 3 years recruitment)**, a revised statistical design had been submitted before the end of accrual to the Independent Data Monitoring Committee (IDMC) and approved the following changes:
- **Primary endpoint:** Progression-free rate (PFR) at 28 weeks, using RECIST v1.1
- **Sample size:** Based on the PFR at 7 months (28 weeks) in the sunitinib arm in the pivotal trial comparing sunitinib and interferon-alpha, in which 90% of the patients had a nephrectomy¹, a PFR at 28 weeks of 70% was assumed for the immediate arm in trial 30073. To show an increase in the PFR at 28 weeks from 70% in the immediate arm to 90% in the deferred arm (H0: no difference versus H1: increase of 20% in the PFR), based on a one sided Fisher Exact test at 5% with 80% power in the intention-to-treat population, **98 patients were needed**.

¹Motzer et al., N Engl J Med 2007; 356: 115-124.

CN – SURTIME STUDY



	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
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%)	43 (87.7%)
≥ 2 measurable metastatic sites	43 (86.0%)	46 (93.9%)
Mean (SD) primary tumor size (mm)	93.1 (37.8)	96.8 (31.3)

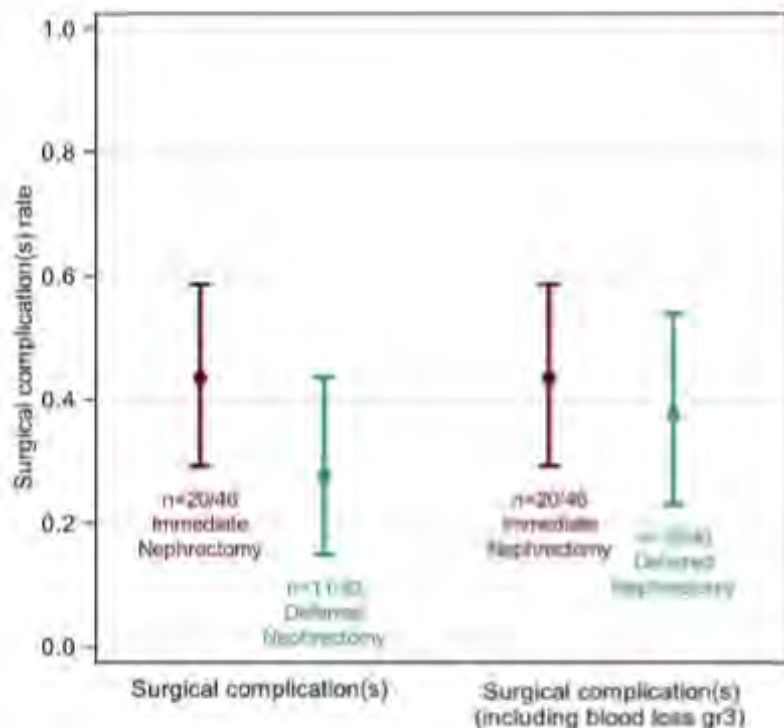
CN – SURTIME STUDY

TREATMENT RECEIVED

	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
No treatment	4 (2 early PD, 1 patient decision, 1 acute pneumonia)	1 (1 ineligible)
Pre-surgical sunitinib:	-	48
- Early stop of sunitinib (≤ 2 cycles)		8 (4 PD, 1 death, 1 toxicity)
- Treatment with 90% to 110% relative dose intensity		34 (70.8%)
- Progression prior to planned surgery		14 (29.1%)
No surgery	-	8 (7 PD, 1 death before surgery)
Surgery	46	34 (+ 6 off-protocol)
- Confirmed RECIST disease progression 4 weeks after surgery	9 (19.6%)	8 (23.5%)
No postoperative sunitinib	6 (1 decrease ejection fraction, 2 deaths, 1 PD, 1 non-surgical morbidity, 1 investigator decision)	8 (3 sunitinib toxicity, 1 ineligible, 1 death, 1 surgical morbidity, 2 investigator decision)
Postoperative sunitinib	40	26

CN – SURTIME STUDY

SAFETY (2) - SURGICAL ADVERSE EVENTS



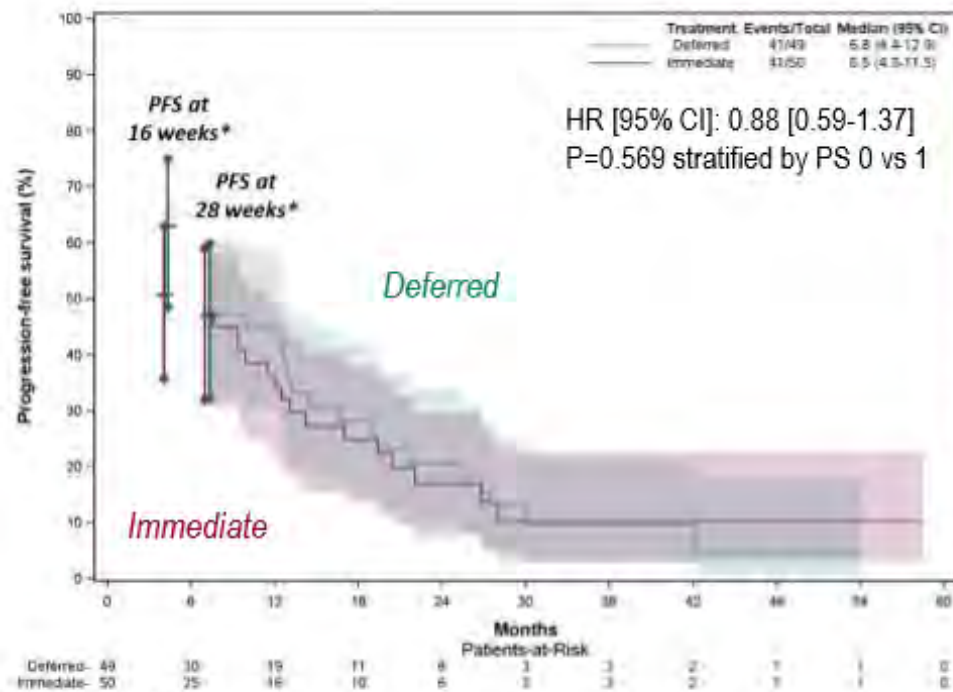
	Immediate nephrectomy	Deferred nephrectomy [‡]
Type of surgical complication:		
- In-hospital mortality	2*	1
- Number of patients with prolongation of hospitalization (>20days) and/or readmission (within 30 days after surgery)	6	3
- Number of patients (events) with intraoperative complication (including vascular and organ damage [#] and blood-loss grade 3)	14 (23)	9 (11)
• Grade ≥3	8 (11)	6 (6)
• Grade 5	1 (1)	-
- Number of patients with postoperative adverse events within 30 days after surgery [#]		
• Grade ≥3	7	7
• Grade 5	1	1

[‡]median days after sunitinib 4.5 (range 1.0-63.0), *1 death during surgery;

[#]grade 3 or more according to CTCAE, version 4.0 and judged by physicians as likely related to surgery

CN – SURTIME STUDY

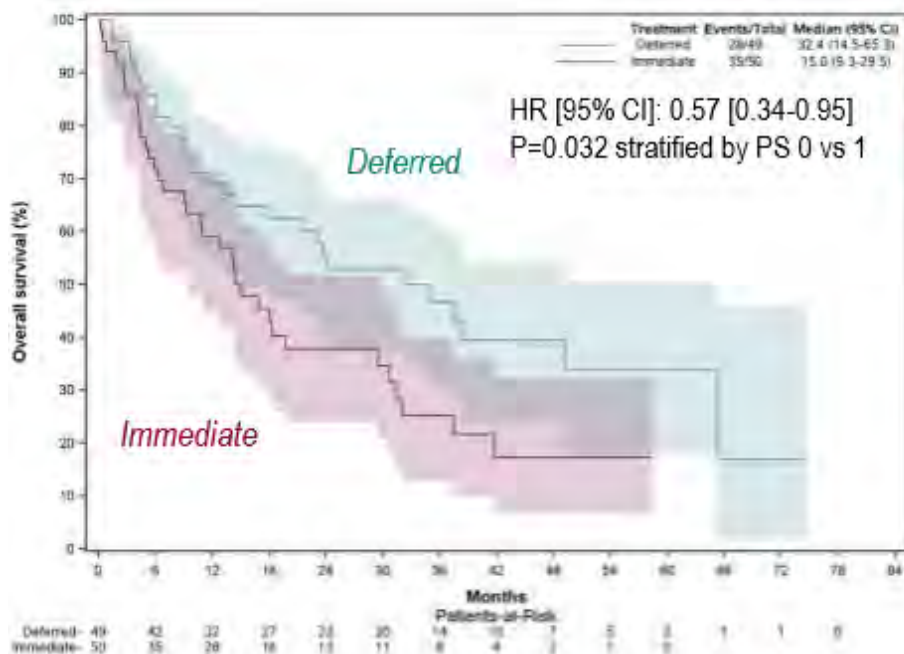
PROGRESSION-FREE SURVIVAL - INTENTION TO TREAT -



Progression-free status at w 28 (±15 days)	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Progression-free at week 28	21 (42.0%)	21 (42.9%)
[95% CI]	[28.2% – 56.8%]	[28.8% – 57.8%]
p-value (Fisher exact test)	>0.99	
Progression before or at week 28, or treatment failure	25 (50.0%)	24 (49.0%)
Not assessable	4 (8.0%)	4 (8.2%)

CN – SURTIME STUDY

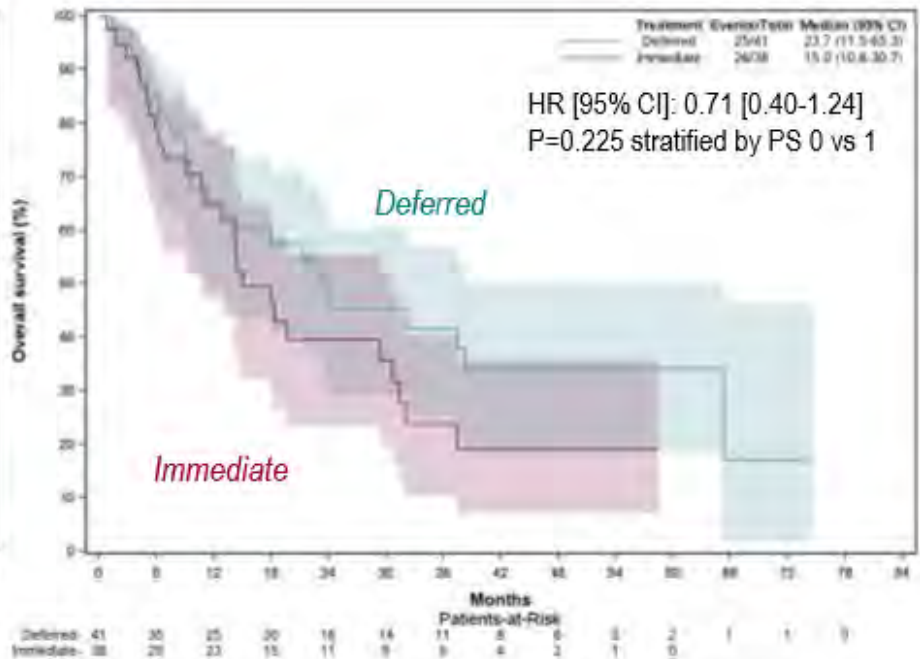
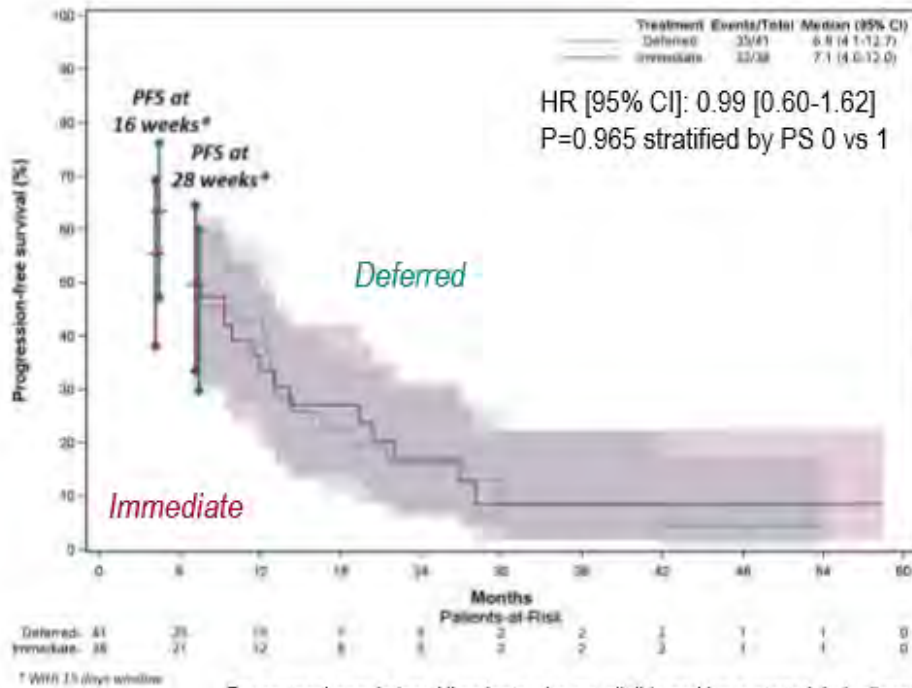
OVERALL SURVIVAL - INTENTION TO TREAT-



	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Survival status		
Dead	35 (70.0)	28 (57.1)
Reason of death		
Progression	30	25
Surgery related toxicity	1	0
Progression and surgery related toxicity	1	0
Cardiovascular disease (not due to toxicity or progression)	1	0
Other (not due to toxicity or progression)	1	0
Unknown	1	3

CN – SURTIME STUDY

PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL - PER PROTOCOL -



Per protocol population: All patients who are eligible and have started their allocated treatment (excluding 18 ineligible patients and 5 who did not proceed to allocated treatment).

CN – SURTIME STUDY



CONCLUSIONS

- The trial accrued poorly and therefore results are mainly exploratory.
- The sequence of CN and sunitinib did not affect the PFR at 28 weeks.
- With hindsight, PFS as primary endpoint has shortcomings due to frequent treatment breaks.
- The sample size precludes definitive conclusions from other endpoints, although an OS signal was seen for deferred CN.
- The survival in the deferred arm is comparable to data reported from previous single-arm phase II studies of presurgical sunitinib or pazopanib¹⁻³.
- The deferred CN approach appears to select out patients with inherent resistance to systemic therapy. This confirms previous findings from single-arm phase II studies¹⁻³.
- The deferred CN approach initiates therapy quickly, does not lead to inability to perform CN and surgery appears safe after sunitinib.

¹Powles et al., JAMA Oncol 2016, 10:1303-130, ²Powles et al., Eur Urol 2011, 60:448-5 ; ³Bex et al., Urology 2011, 78:832-7

CN – “Targeted Agents Era”

- Could we do a better job at selecting CN candidates?

Comprehensive Characterization of the Perioperative Morbidity of Cytoreductive Nephrectomy

Table 3 – Univariable and multivariable analyses of clinicopathologic features significantly associated with 30-d complications (n = 294)

Feature	Univariable		Multivariable model 1 ^a		Multivariable model 2 ^b	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at surgery (yr)	1.14 (0.81–1.59) ^c	0.46				
Male gender	0.97 (0.46–2.04)	0.93				
ECOG PS	1.35 (0.86–2.13) ^d	0.20				
Charlson score	1.15 (0.84–1.56) ^d	0.39				
Body mass index (kg/m ² ; n = 267)	1.01 (0.95–1.08) ^d	0.81				
Symptoms at presentation	2.78 (1.04–7.42)	0.04				
Smoking history (n = 292)						
None	1.0 (reference)					
Current	0.66 (0.20–2.17)	0.48				
Former	1.98 (0.89–4.41)	0.10				
Preoperative hemoglobin <LLN	1.06 (0.51–2.17)	0.88				
Preoperative calcium >ULN (n = 224)	1.39 (0.51–3.76)	0.52				
Preoperative platelets >ULN (n = 170)	0.84 (0.23–3.08)	0.79				
RETT (n = 280)	3.42 (1.63–7.17)	0.001	3.02 (1.42–6.45)	0.004		
Presurgical systemic therapy (any vs none)	0.73 (0.16–3.24)	0.67				
Two or more organs with metastases	2.09 (1.03–4.26)	0.04				
Liver metastasis	5.20 (2.24–12.05)	<0.001	3.73 (1.53–9.09)	0.004	3.37 (1.28–8.86)	0.014
Lung metastasis	0.95 (0.46–1.97)	0.89				
Laparoscopic approach (vs open)	0.92 (0.20–4.19)	0.91				
Performance of RPLND	1.76 (0.81–3.82)	0.15				
Concurrent metastasectomy	1.49 (0.72–3.08)	0.28				
Concurrent liver metastasectomy	2.91 (0.87–9.70)	0.08				
Complete concurrent metastasectomy	1.21 (0.57–2.56)	0.62				
Tumor size (cm; n = 291)	1.08 (0.99–1.18) ^d	0.08				
Tumor stage (n = 292)			NA	NA		
pT1	1.0 (reference)					
pT2	2.08 (0.22–19.58)	0.52				
pT3	3.93 (0.51–30.27)	0.19				
pT4	5.65 (0.61–52.00)	0.13				
Node stage			NA	NA		
pNX	1.0 (reference)					
pN0	1.10 (0.44–2.76)	0.83				
pN1	2.92 (1.23–6.92)	0.02				
Nuclear grade 4 (vs 1–3)	5.80 (2.66–12.65)	<0.001	NA	NA	5.67 (2.41–13.32)	<0.001
Coagulative tumor necrosis	3.10 (1.06–9.08)	0.04	NA	NA		
Sarcomatoid differentiation	3.35 (1.58–7.10)	0.002	NA	NA		
Intraoperative transfusion, # units (n = 292)	1.15 (1.08–1.23) ^d	<0.001	NA	NA	1.14 (1.07–1.22) ^d	<0.001
≥13 lymph nodes removed (n = 168)	1.79 (0.74–4.36)	0.20	NA	NA		

- Only 5% Clavien grade □3 complications
- 61% of CN patients did not receive timely ST (within 60 d)
- Delay ST was surgery-related in only 11%
- Liver metastases, intraoperative transfusion, and pN1 disease were independently associated with perioperative morbidity

Cytoreductive Nephrectomy (CN) - Conclusioni

- La CN **prolunga la sopravvivenza** dei pazienti?

Few, nonprospective and nonrandomized studies available

- È importante il **timing** della CN (prima o dopo l'inizio di target therapy)?
 - ✓ **Probabilmente no, ma sono necessarie ulteriori conferme**
 - ✓ Utile per evitare CN nei pazienti primary refractory
- È corretto **selezionare i candidati** per la CN?

NO

- **≥ 4 IMDC prognostic factors**
- **Estimated survival time <12 months**
- **ECOG PS ≥ 2**
- **Poor MSKCC score**
- **Brain metastases (NCCN guidelines), Liver metastases**