

RCC CASES

ESMO Asia

20 DEC 2015 Shingapore

Yoshihiko TOMITA MD
Niigata Univ., JAPAN



RCC Case Discussion

- Session Objective:
 - Obtain opinions from the panel of experts on controversial areas in RCC management.

SURGERY

nephrectomy

metastasectomy

SYSTEMIC Therapy

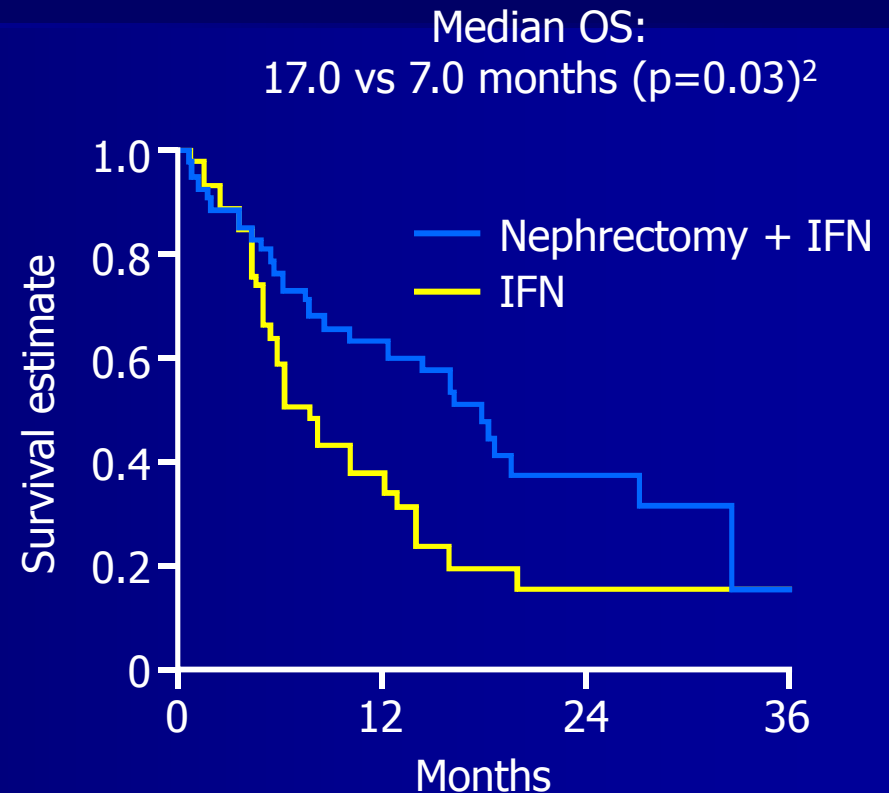
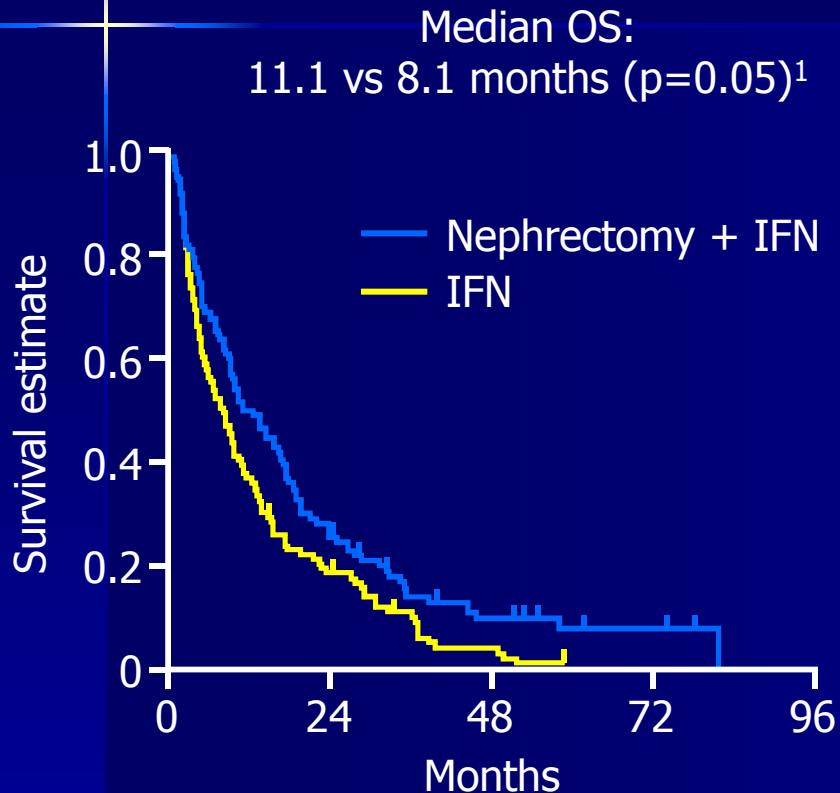
Is cytoreductive nephrectomy justified in M1 cases?

In cytokine era

Yes

Very much so in patients with good
PS

Nephrectomy in metastatic patients



1. Flanigan, et al. NEJM 2001; 2. Mickisch, et al. Lancet 2001

Is **cytoreductive nephrectomy** justified in M1 cases?

In targeted therapy era

UNKNOWN

**No high level
evidence**

**Metastasectomy improve
prognosis.**

But it is not true in all cases.

RCC

real cases

- NO information was given to the panelists.

CASE 1

metastasectomy

Age 74, male

- 2007/8/13 Rt. Radical Nx
- Patho: clear cell carcinoma, G1>>2>>3, pT1b, INFa, v-
- 2008 MARCH, 6M after surgery, liver met +, solitary
- MSKCC Risk ; intermediate risk
 - PS0, Hb12.4, cCa9.2, LDH144, met6M

CT

2009/3/3



Option

- 1. Liver segmentectomy
- 2. Systemic therapy
- 3. Others

Age 74, male

- 2008/3/17 sorafenib 800mg/day start
- AE: HT G2
- 2008/4/15 ileus, sorafenib stop
- Liver met \Rightarrow slight shrinkage,
NO new legion

CT

2009/3/3



2009/4/21



Option

- 1. Liver segmentectomy
- 2. Continue systemic therapy
- 3. Others

Age 74, male

- 2009/5/20 liver S7 subsegmentectomy
 - Op. Time 254min. EBL 507ml
- Pathology: clear cell carcinoma G2, surgical margin-negative
- ⇒ Active surveillance

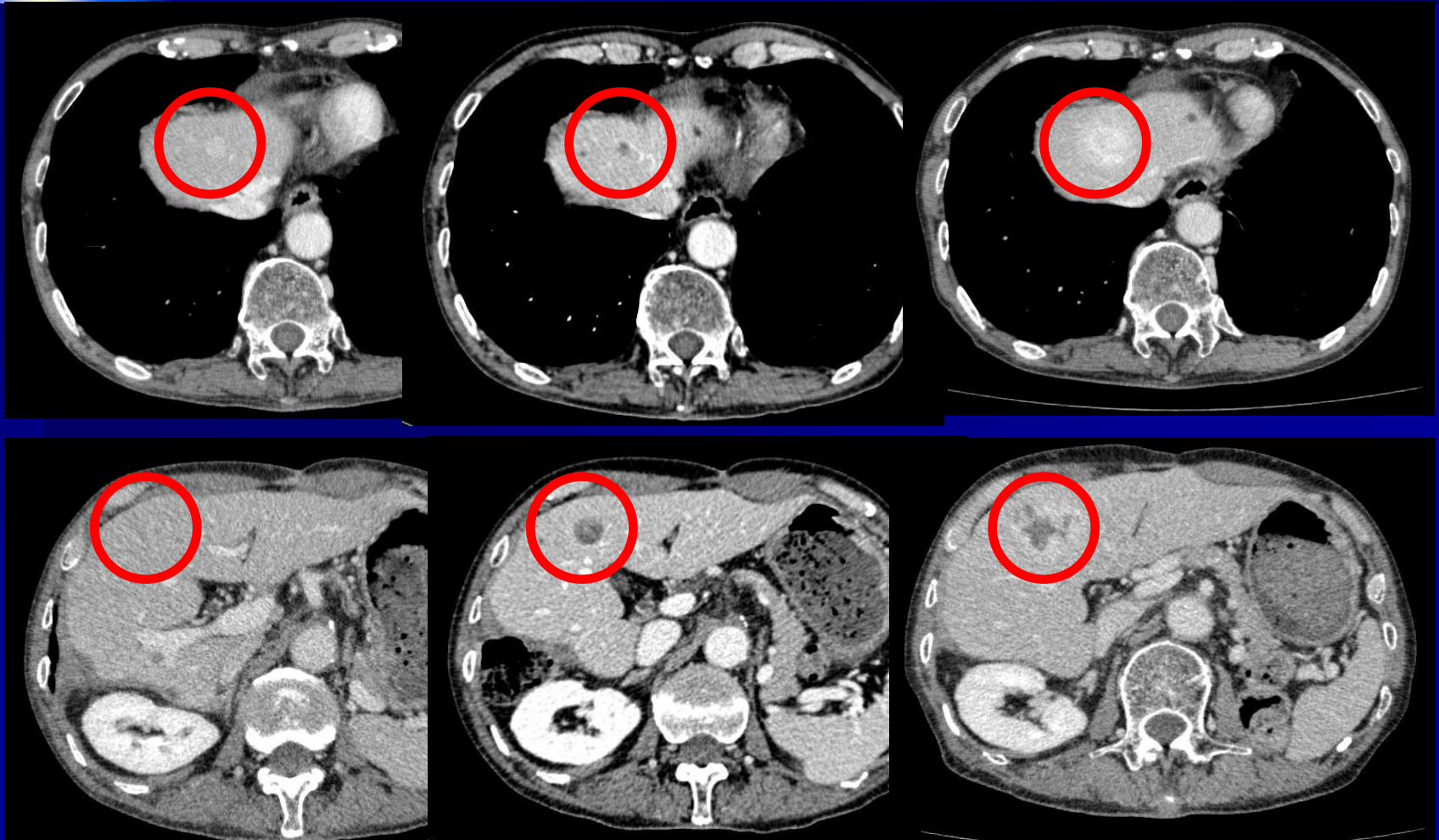
Age 74, male

- 2009/7/8 liver met+, multiple(2
legions) susp.
- 2009/8/18 sunitinib 50mg/day start
- Day15 stop, AE: hyponatremia G3
- 9/31 sunitinib 37.5mg/day re-start
- AE: fatigue G3
- 2010/1/8 sunitinib 25mg/day
- 2010/3/29 CT ⇒ PD ⇒ BSC

CT

2009/7/8(SU start) 2009/9/15

2010/3/22(PD)



Age 74, male

- Died at MAY 2010 ...
26 months after Dx of mets.
- Intermediate risk

Metastasectomy and Targeted therapy

- **This case might be a very unhappy case, but...**
 - We may be very careful for applying metastasectomy in targeted therapy era.

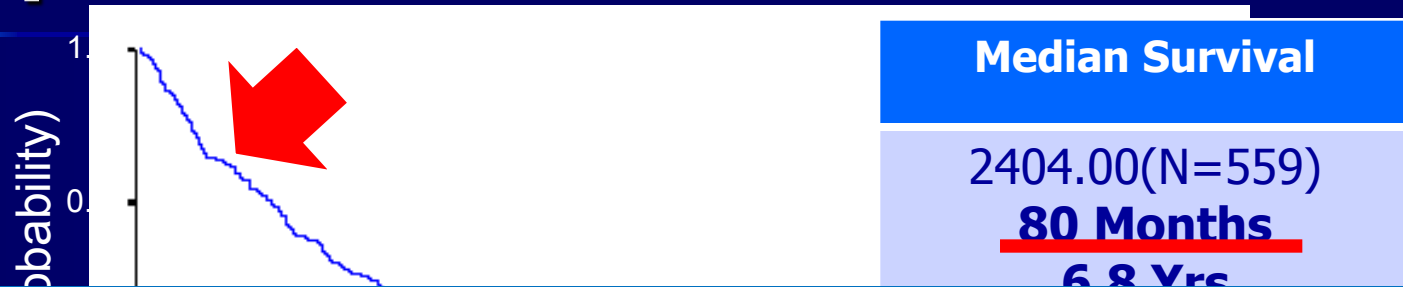
Oncology

Prognostic Factors of Patients With Metastatic Renal Cell Carcinoma With Removed Metastases: A Multicenter Study of 556 Patients

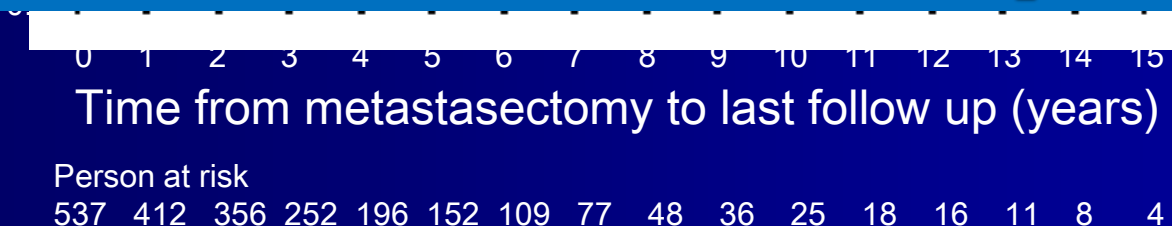
Sei Naito, Hidefumi Kinoshita, Tsunenori Kondo, Nobuo Shinohara, Takashi Kasahara, Kazutaka Saito, Tatsuya Takayama, Naoya Masumori, Wataru Takahashi, Masayuki Takahashi, Toshiro Terachi, Seiichiro Ozono, Seiji Naito, and Yoshihiko Tomita

UROLOGY 82: 846–851, 2013.

Prognosis of the patients with Metastasectomy in 559 pts. In Japan



<Question>
What is clinical factors for
early death after
metastasectomy?



Multivariate analysis(Death)

Variable Label	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
T \geq 3	-0.01853	0.23233	0.0064	0.9364	0.982	0.623	1.548
<1 Year							90
Grade3							23
Liver							91
LN							90
BONE							33
Brain							71
Incomplete							95
Resection							10
ECOG PS							
Anemia	0.19348	0.23423	0.6823	0.4088	1.213	0.767	1.920
ALP > 360	-0.65551	0.34670	3.5748	0.0587	0.519	0.263	1.024
cCa >10	0.16673	0.39920	0.1744	0.6762	1.181	0.540	2.584
CRP > 1.0mg/dl	1.04486	0.25060	17.3842	<.0001	2.843	1.740	4.646

Poor Prognostic Factors;

- ✓ **Brain mets**
- ✓ **Incomplete resection**
- ✓ **ECOG PS \geq 1**
- ✓ **CRP > 1.0mg/ml**

CASE 2

nephrectomy

Age 59, male

- Jan. 2009.
 - Gross hematuria and rt. flank pain
- rt. Renal tumor and liver tumors were pointed out in a private clinic and referred.

Age 59, male

■ CT scan

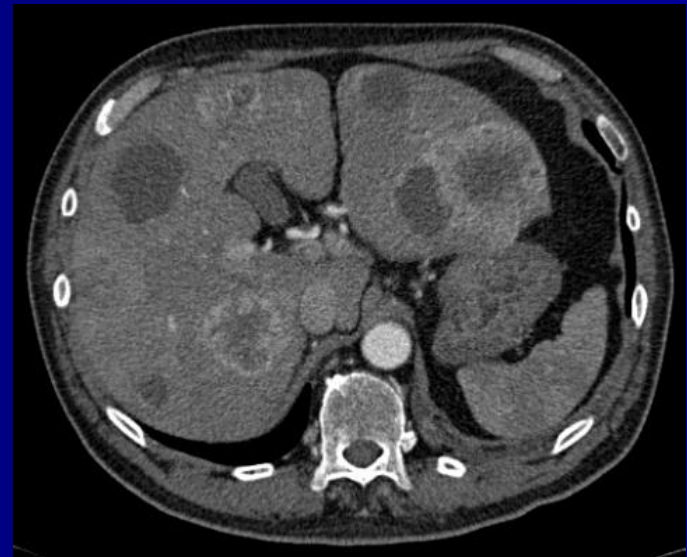
- Rt. Renal tumor
- Multiple liver mets
- Multiple lung mets
- Retroperitoneal LN mets
- Ipsilateral adrenal mets

Clinical stage cT4N1M1

MSKCC criteria poor risk group

Abdominal CT scan

2009/1/30 (Base line)



cT4N1M1

Option

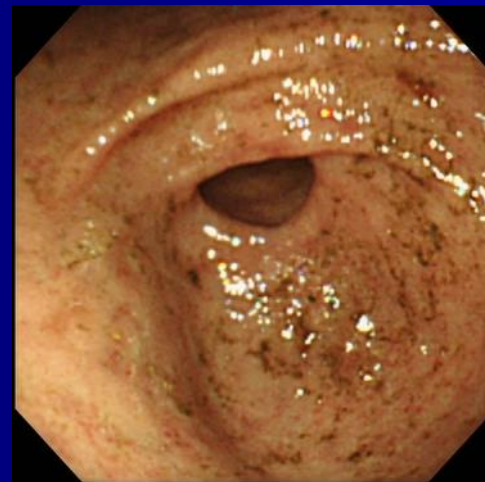
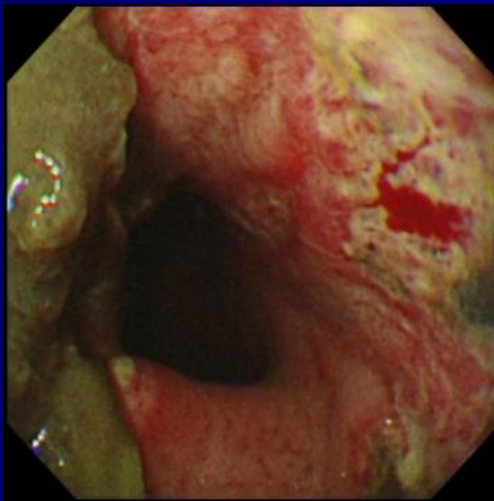
- 1. Immediate nephrectomy
- 2. Presurgical systemic therapy

Option

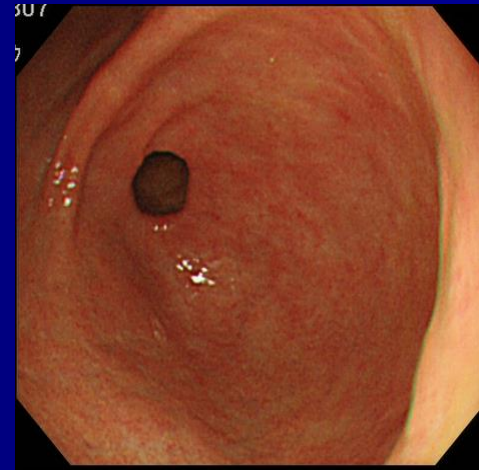
Systemic therapy. Which Drug?

- 1. sunitinib
- 2. sorafenib
- 3. pazopanib
- 4. everolimus
- 5. temsirolimus
- (6. axitinib)

- Feb 2009 **sunitinib** 50mg/day
- Sunitinib Course 1 Day 17 (C1D17)
 - Severe abdominal pain



- Seven days after interruption of sunitinib



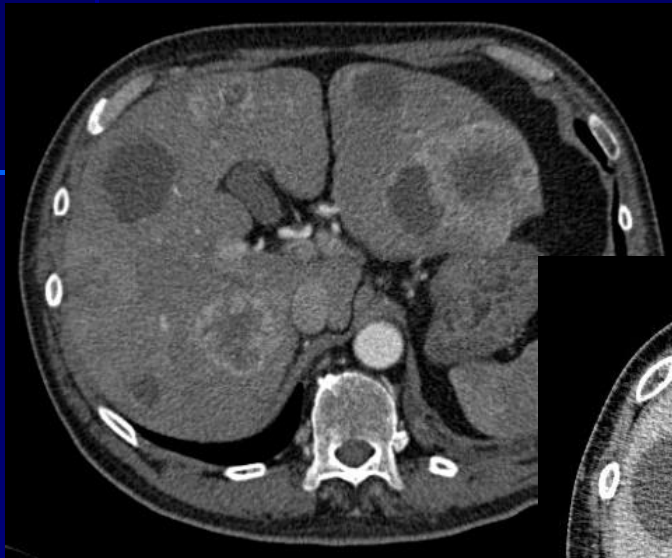
Option

Systemic therapy.

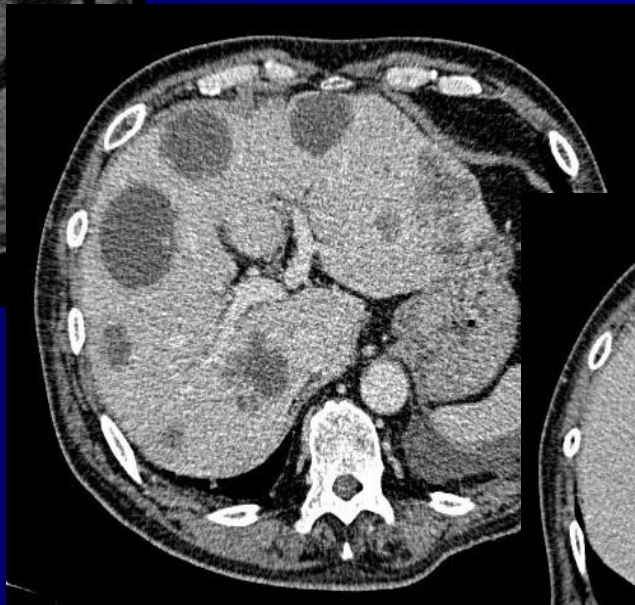
- 1. continue sunitinib
- 2. convert to
 - ✓ a. axitinib
 - ✓ b. sorafenib
 - ✓ c. pazopanib
 - ✓ d. everolimus
 - ✓ e. temsirolimus

- Mar 2009 re-started sunitinib (37.5mg q.d)
- No grade ≥ 3 AE

CT scan **LIVER 1**



2009/1/30 (Base line)

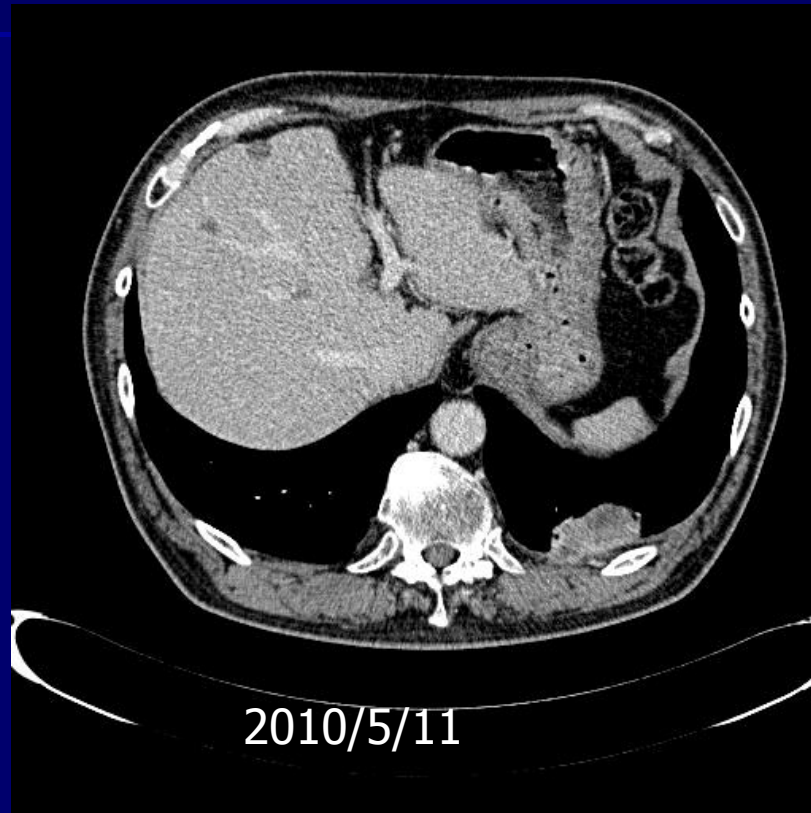


2009/3/9 (C1-D28)
Sunitinib 17/28 dose



2009/7/9 (After 4 courses)

CT scan **LIVER 2**

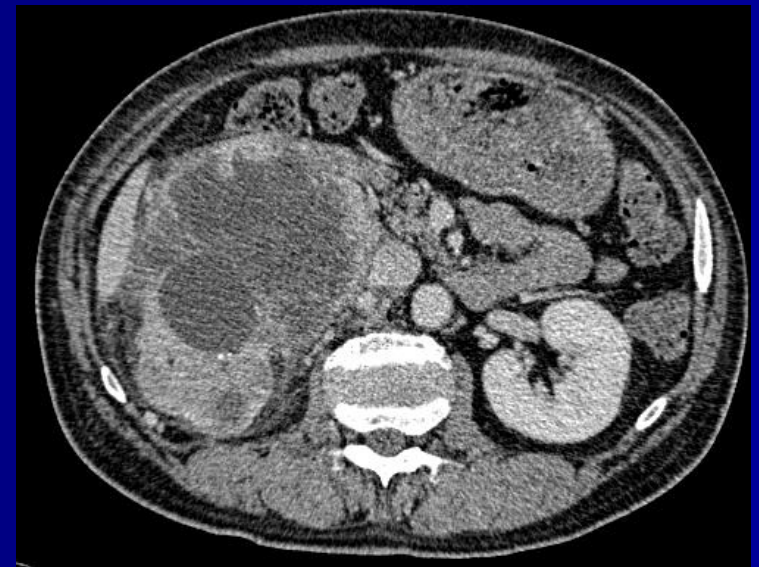


(After 11 courses)

CT scan **KIDNEY 1**

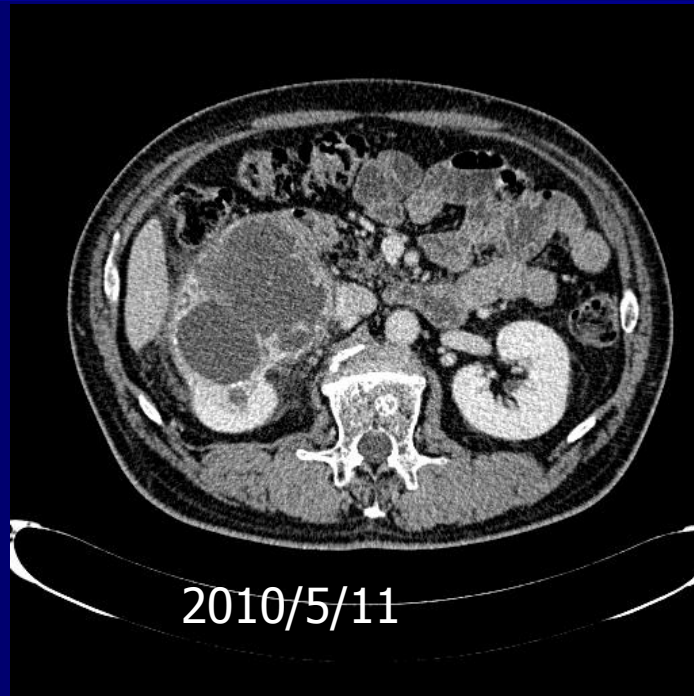


2009/1/30 (Base line)



2009/7/9 (After 4 courses)

CT scan **KIDNEY 2**

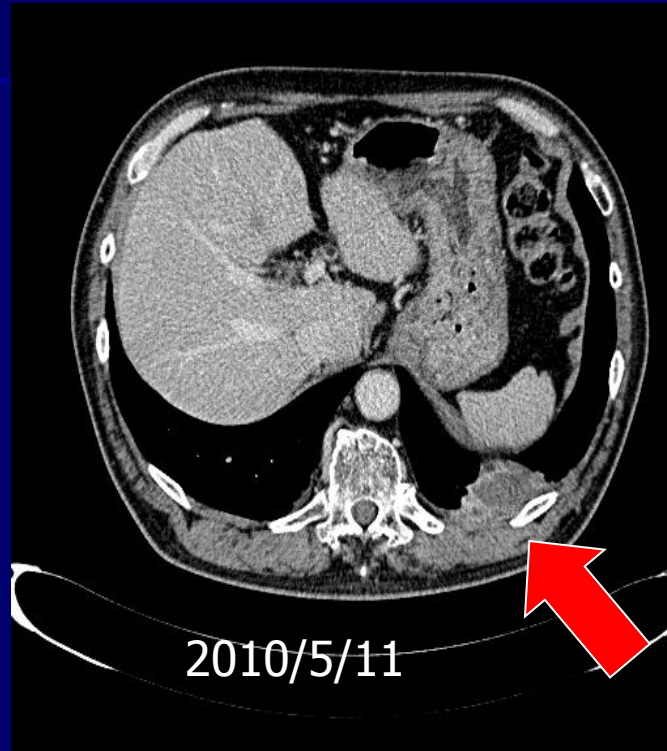


(After 11 courses)

Option

- 1. Nephrectomy
- 2. Continue systemic therapy

Abdominal - Chest CT scan



(After 11 courses)

Age 59, male

- After the conversions to sorafenib, and re-challenge with sunitinib.
- **NC to PD.**
- Died at JULY 2012 ... **42** months after Dx.
- Categorized in Poor risk group (Far advanced case)

CASE 3

nephrectomy 2

Case notes

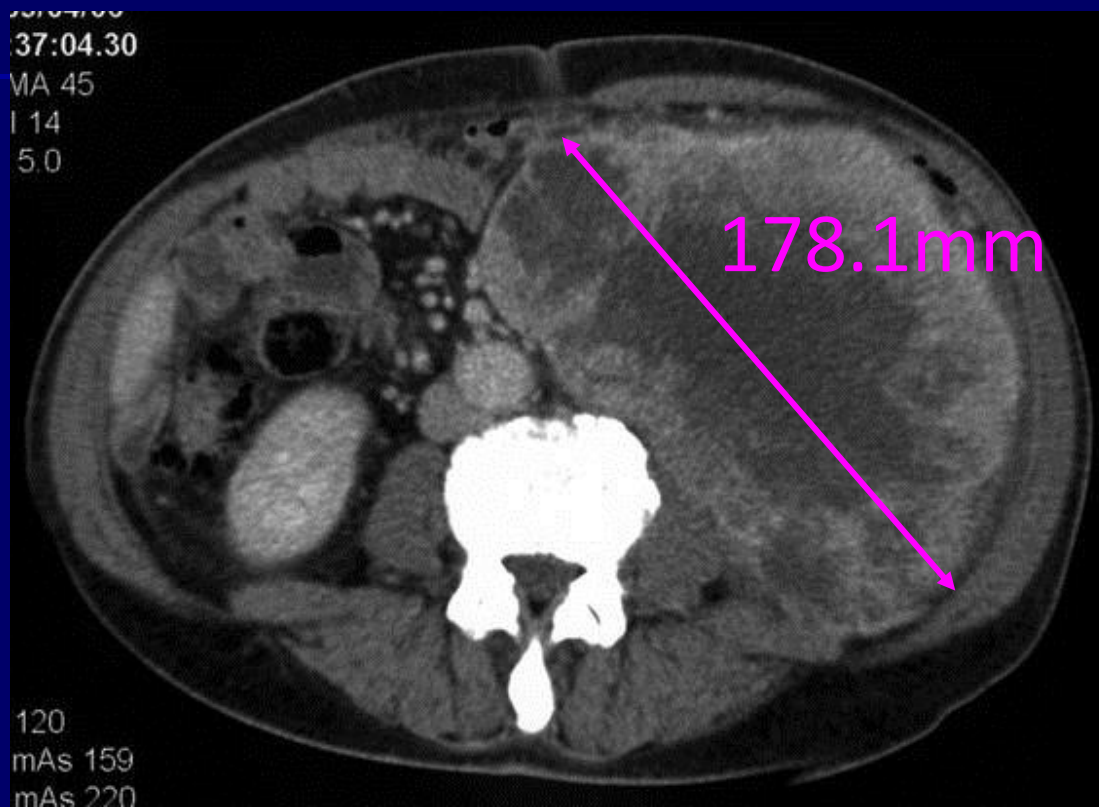
- Age 72 years
- MPH Receiving treatment for hypertension. (well controlled)

Case notes (cont.)

- Jan. 2009 complained urinary frequency and visited a clinic.
- Abdominal ultrasound showed lt.RCC, and he was referred to Yamagata Univ. Hospital.
- PS=0, Hb 8.9, corrected serum Ca 11.7, LDH 151

CT scan

cT3aN0M0



23 MAR 2009

Option

- 1. Immediate nephrectomy
- 2. Systemic therapy

Option

Systemic therapy. Which Drug?

- 1. sunitinib
- 2. sorafenib
- 3. everolimus
- 4. temsirolimus
- (5. axitinib)

Case notes (cont.)

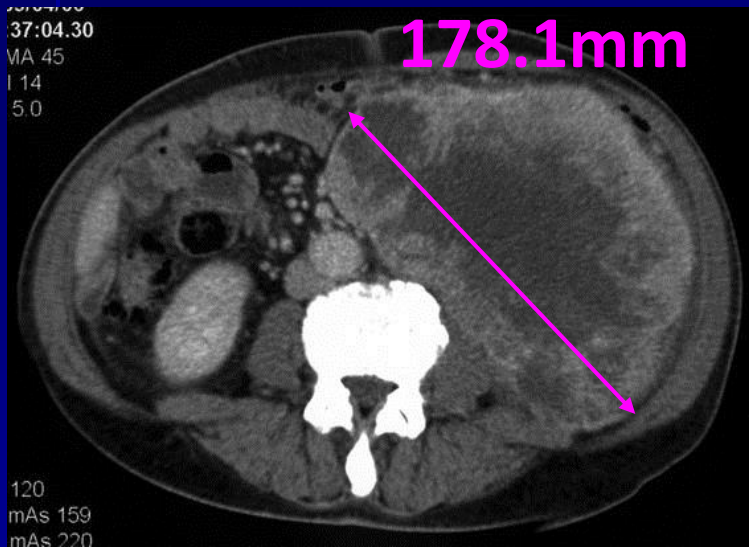
- 08APR 2009 **sunitinib** 50mg qd started.
- At day 16, weakness grade 3, tipped over, appearance of paroxysmal atrial fibrillation. Stopped sunitinib.
- At day 40, anemia grade 3. Transfusion.

Case notes (cont.)

- 26 MAY 2009 sunitinib second cycle of sunitinib @ 37.5mg qd started.
- At day 25, thrombocytopenia grade 3, Stopped sunitinib.
- 13 JUL 2009 sunitinib 3rd cycle started @ 25mg qd. Well tolerated.
- CT at the end of 3rd cycle: **PD**

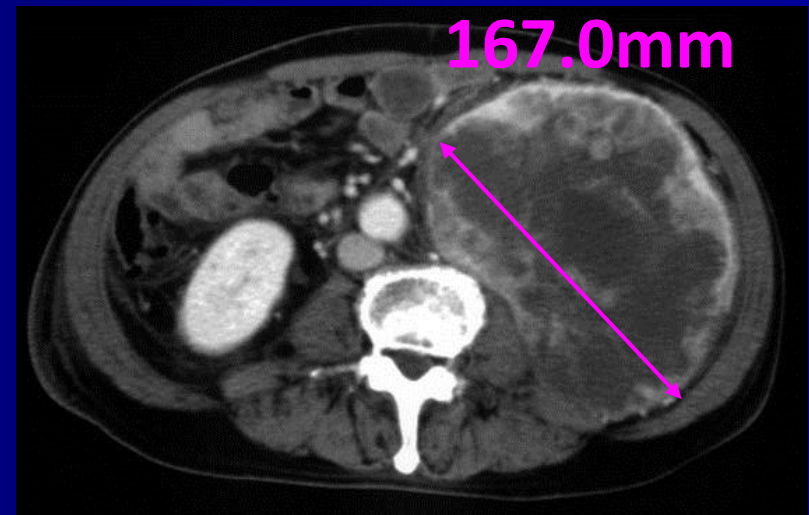
CT scan KIDNEY

Base line



23 MAR 2009

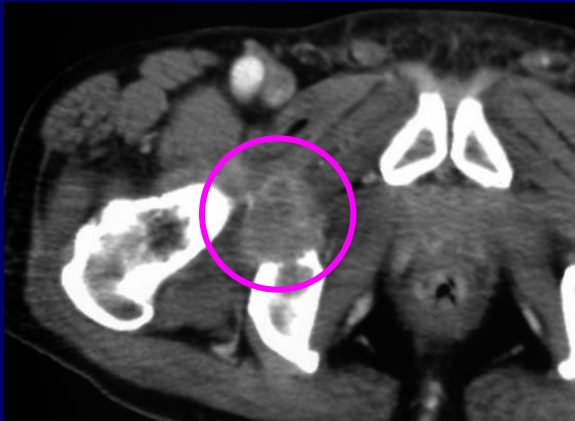
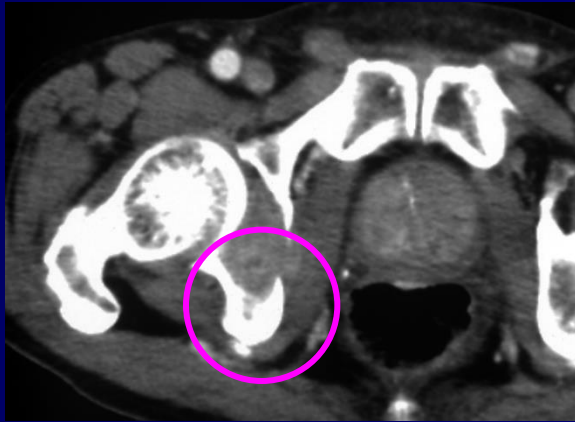
After 3 courses
sunitinib



13 AUG 2009

CT scan Pelvis and L5

new lesion; bone mets.



13 AUG 2009

Option

- 1. Nephrectomy
- 2. Continue systemic therapy

Case notes (cont.)

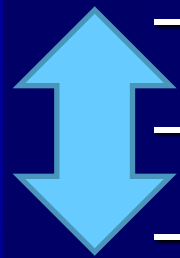
- 07 SEP 2009 lt. radical nephrectomy
op. time 370min. Blood loss 2169g
- Clear Cell Ca., Fuhrman grade 2, pT3a
- N(-) 0/4
- Vast majority of the tumor...necrosis.
- Atelectasis, pneumonia after the surgery... recovered

Case notes (cont.)

- 06-29 OCT 2009. Radiation to pelvic bone.
- 11 NOV 2009. sorafenib 400mg bid.
- CT scan after 2 courses (8wks) of sorafenib ... **PD**
- Qiuted sorafenib at 27 MAY 2010.
- Died at JULY 2010... 15 months after Dx.

My anecdotes say...

■ CASE 1



– Difference of response to Targeted drugs, poor risk

■ CASE 2

- M0 disease, (intermediate risk)
- With nephrectomy
- Survive 15 months after Dx.

Effect of targeted drugs on primary RCC

Neoadjuvant setting

Sunitinib

Neoadjuvant Tx **sunitinib** **efficacy**

Sunitinib 2(3)courses

- ✓ 50-85% cases show tumor shrinkage
- ✓ But decrease of size up to 20%
- ✓ Practical benefit approximate 25% of cases.

Neoadjuvant Tx **sunitinib** **safety**

Sunitinib 2(3)courses

- ✓ Be careful for wound healing.
- ✓ Wound dehiscence ... up to 20%
- ✓ Prominent tissue fibrosis may be happened.
- ✓ Interval 2-3 days.

Axitinib

Terminal half-life in compounds for RCC

Compound	Terminal half-life (hr)
Axitinib	4.8~5.9 hr
Sunitinib	sunitinib 49.5 hr N-desethyl metabolite (active metabolite) 75.3 hr
Sorafenib	25.5 hr
Pazopanib	37.8~42.5 hr
Temsirolimus	temsirolimus 13.5~14.8 hr sirolimus (active metabolite) 59.2~67.0 hr
Everolimus	approximately 30 hr
Bevacizumab	11.7~13.4 day

Source: Japanese package insert in each compound (everolimus, US package insert)

Axitinib as neoadjuvant setting

- N=24 case prospective non-randomized phase II.
- Patients with locally advanced (clinical stage T2-T3b N0 M0) biopsy-proven clear cell RCC.
- **Axitinib** 5mg qd for 12 wks. Last dose 36hrs prior to surgery.

Patient Characteristics

Table 1 – Baseline patient characteristics

	<i>n</i>	%
No. of patients	24	100
Median age, yr (range)	60 (42–83)	
Gender		
Male	19	79.2
Female	5	21.8
ECOG performance status		
0	19	79.2
1	5	21.8
Clinical stage		
T3a	24	100
Clear cell RCC (biopsy)	24	100

ECOG = Eastern Cooperative Oncology Group; RCC = renal cell carcinoma.

Karam et al., Eur. Urol. 2014

- 22/24 achieved 12 wks,
1–7 wks, 1–11wks.
- AEs during axitinib Tx
 - Hypertension .. most common
79.2% (grade3 41.7%)
 - Acute Kidney Injury (grade3)
 - AST/ALT↑ (grade3) and Plts↓ (grade3)

Table 3 – Surgical and pathologic characteristics

	<i>n</i>	%
No. of patients	24	100
Nephrectomy		
Radical	19	79.2
Partial	5	21.8
Surgery		
Open	19	79.2
Laparoscopic	5	21.8
Median operative time, min (range)	87 (56–128)	
Median blood loss, ml (range)	225 (25–3500)	
Pathologic T stage		
T1a	3	12.5
T1b	1	4.2
T2b	1	4.2
T3a	18	75.0
T4	1	4.2
Fuhrman grade		
2	11	45.8
3	11	45.8
4	2	8.3
Pathologic N stage		
N0	12	50
Nx	12	50
N1	0	0
Median no. of lymph nodes removed (range)	8.5 (1–23)	

Karam et al., Eur. Urol., 2014

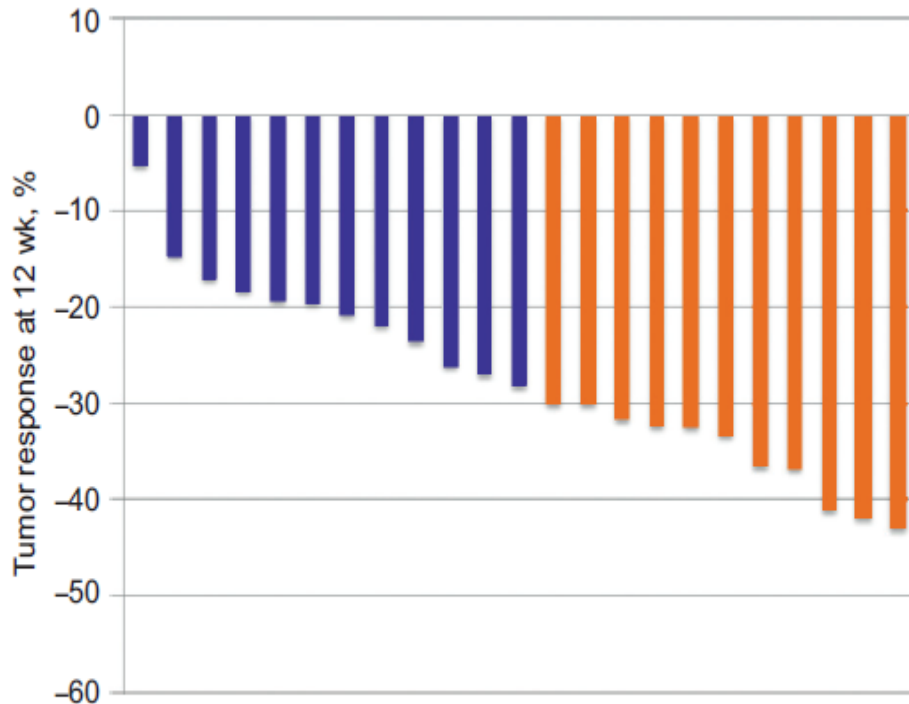


Fig. 3 – Waterfall plot of tumor response in percentages at 12 wk of treatment. Orange indicates partial response, and blue indicates stable disease per Response Evaluation Criteria in Solid Tumors.

**Median reduction
Of primary
...28.3%**

11 PRs

Neoadjuvant Tx **sunitinib** **efficacy**

Sunitinib 2(3)courses

- ✓ 50-85% cases show tumor shrinkage
- ✓ But decrease of size up to 20%
- ✓ Practical benefit approximate

2. **Axitinib**

- ✓ Decrease of size...30%?
- ✓ Practical benefit...40%?

Neoadjuvant Tx **sunitinib** **safety**

Sunitinib 2(3)courses

- ✓ Be careful for wound healing.
- ✓ Wound dehiscence ... up to 20%
- ✓ Prominent tissue fibrosis may be

✓ I

Axitinib

- ✓ Post-surg. Bleeding?
- ✓ Chylous ascites?

Tentative consensus

■ In Case with metastasis

- Do systemic therapy first.
- BUT consider surgery when...???

■ Without metastasis

- Immediate nephrectomy.
- BUT consider systemic therapy when...???

Tentative consensus

■ In Case with metastasis

- Do systemic therapy first.
- BUT consider surgery when...???

Small tumor volume, Good PS

■ Without metastasis

- Immediate nephrectomy.
- BUT consider systemic therapy when...???

Presence of poor risk factors

CONCEPT

'Moratorium' observational systemic therapy

If cancer control can be achieved by systemic Tx, surgery may be considered.

DURATION app. 3 months?

OTHER IMPORTANT LINES

- Progression of non-renal lesion may be irrelevantly occur.
- Preservation of remnant renal function in affected kidney might be beneficial for feasibility of targeted therapy.

NEEDS robust data

- For appropriate strategy based on evidence, we need to identify;

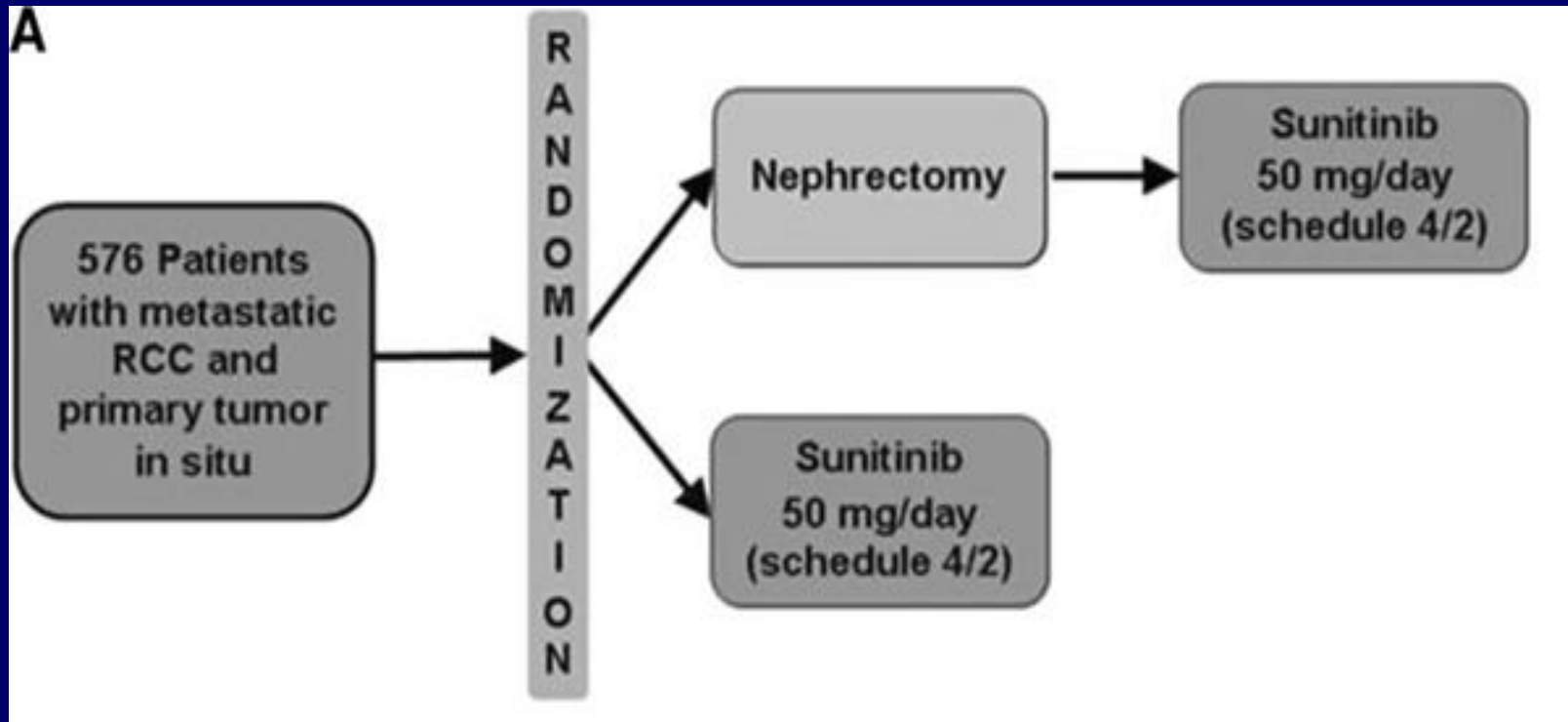
Clinical factors

NEEDS collaboration

Back up

Ongoing RCT-1

CARMENA (00930033)



Ongoing RCT-1

SURTIME (01099423)

