



Cytoreductive Nephrectomy for metastatic Renal Cell Carcinoma

contra

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Cytoreductive Nephrectomy for metastatic RCC randomized trials

Trial	No. patients	Median survival (months)		
		IFN alone	Surgery + IFN	P
SWOG 8949	241	8.6	11.1	0.05
EORTC 30957	85	7	17	0.03
Combined analysis	331	7.8	13.6	0.002

Cytoreductive Nephrectomy for metastatic RCC inclusion criteria

- Metastatic RCC
- WHO 0-1 performance status
- Resectable primary tumor
- No serious comorbidities
- Will be treated with interferon- α

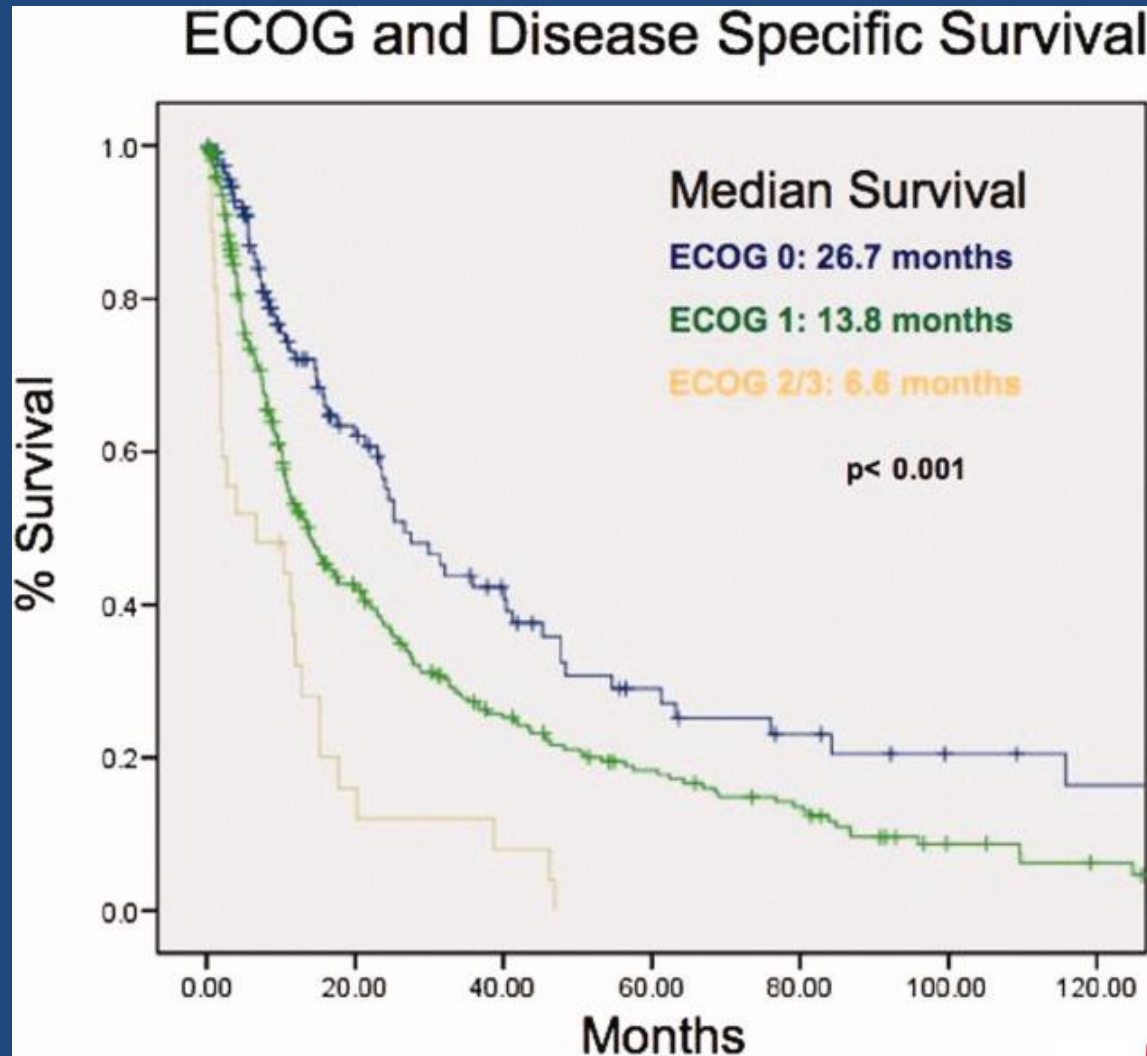
Cytoreductive Nephrectomy for metastatic RCC mortality

- EORTC/SWOG trials peri-operative mortality was only 1% and 20% surgical complications in a selected population
- Nephrectomy series of MD Anderson
 - patients younger than 75: 4 of 380 (1%) died
 - patients older than 75: 5 of 24 (21%) died !
 - older patients had more comorbidity (hypertension, cardiovascular disease and diabetes), longer operations and more blood loss Kader et al. J. Urol. (2007)
- **Elderly patients have significantly increased risk for peri-operative mortality!**

Cytoreductive Nephrectomy for metastatic RCC in case of poor performance?

- Randomized trial of SWOG and EORTC included only patients with WHO 0-1 performance status
- Most retrospective studies exclude patients with WHO 2-3 performance status

Cytoreductive Nephrectomy for metastatic RCC poor performance is associated with shorter survival



Shuch et al. Cancer (2008)

Cytoreductive Nephrectomy for metastatic RCC not for patients with non-clear cell histology

- Most of the data is based on patients with clear cell histology
- MD Anderson reported results after CN in patients with papillary (39%), chromophobe (5%), collecting duct (9%) and 47% unclassified(47%) having a worse survival (9 months) compared to clear cell RCC (21 months)
Kassouf et al. J. Urol. (2007)
- Motzer showed in a smaller series similar results (JCO 2002)
- Shuch et al. showed that patients (n=62) with sarcomatoid histology undergoing CRN have a poor prognosis (4.9 months)
J. Urol. (2009)

Cytoreductive Nephrectomy for metastatic RCC patients fail to receive systemic therapy

- Kutikov et al. showed in a retrospective study that nearly 1/3 of the patients (n=141) undergoing CN never received post-operative treatment
- Most important reasons for receiving no medical therapy was peri-operative death (19%), rapid progression of disease (30%), patient refusal (23%) and decision for surveillance (21%)
- Poor performance, higher tumor grade, sarcomatoid features and visceral (liver) metastases were associated with shorter overall survival after surgery

Cytoreductive Nephrectomy for metastatic RCC mechanism?

- induction of spontaneous remission
- reduction of tumor burden
- removal of paraneoplastic cytokines
- reversal of immunosuppressive environment of RCC
- primary tumor rarely responds to immunotherapy
- removal of pro-angiogenic factors (e.g. VEGF)

Cytoreductive Nephrectomy for metastatic RCC induction of spontaneous remission?

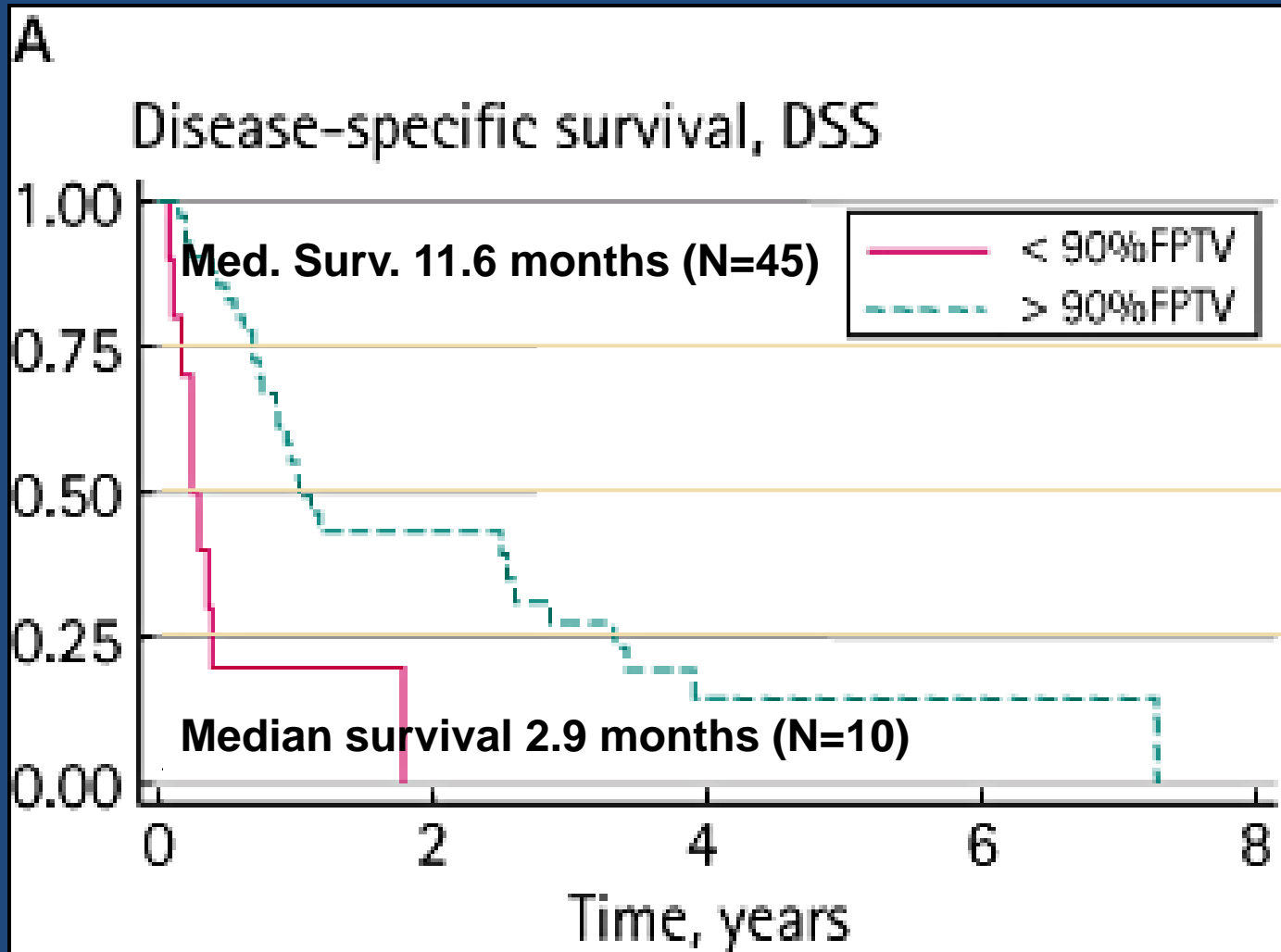
- Induction of spontaneous remission is rarely seen (< 1%, 4% in case of only lung metastases)
- Only in good-prognosis patients

Cytoreductive Nephrectomy for metastatic RCC reduction of tumor load?

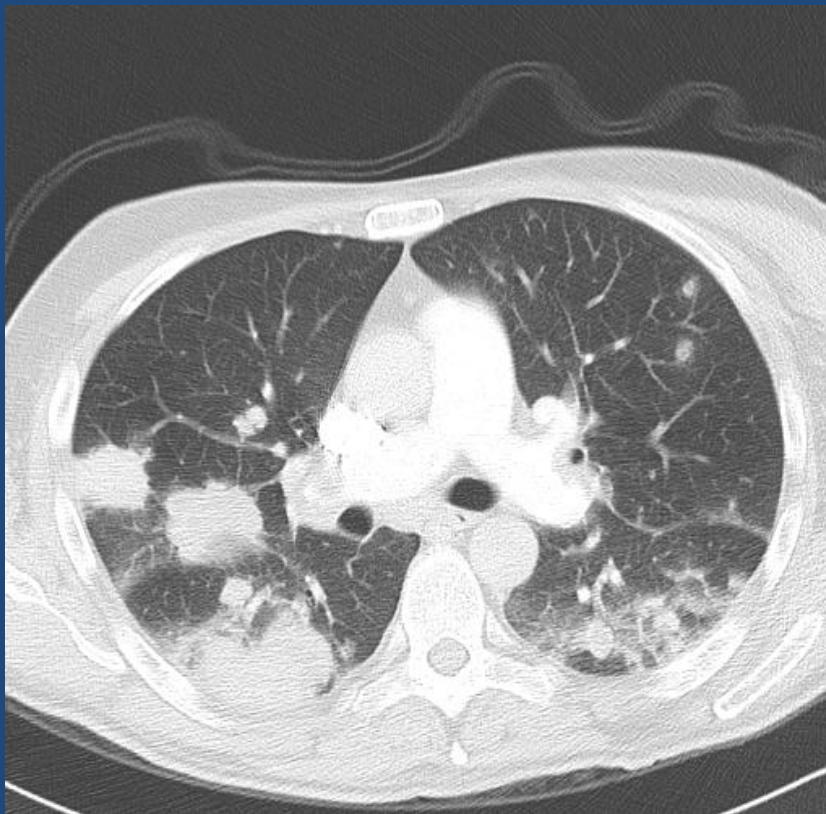
- Improvement of performance status
- Removal of paraneoplastic cytokines
- Resection of a high percentage of tumor volume (FPTV)*
is associated with improved survival

* Fractional percentage of tumor volume (FPTV) removed:
the volume of disease removed at the time of cytoreductive
nephrectomy, including metastases

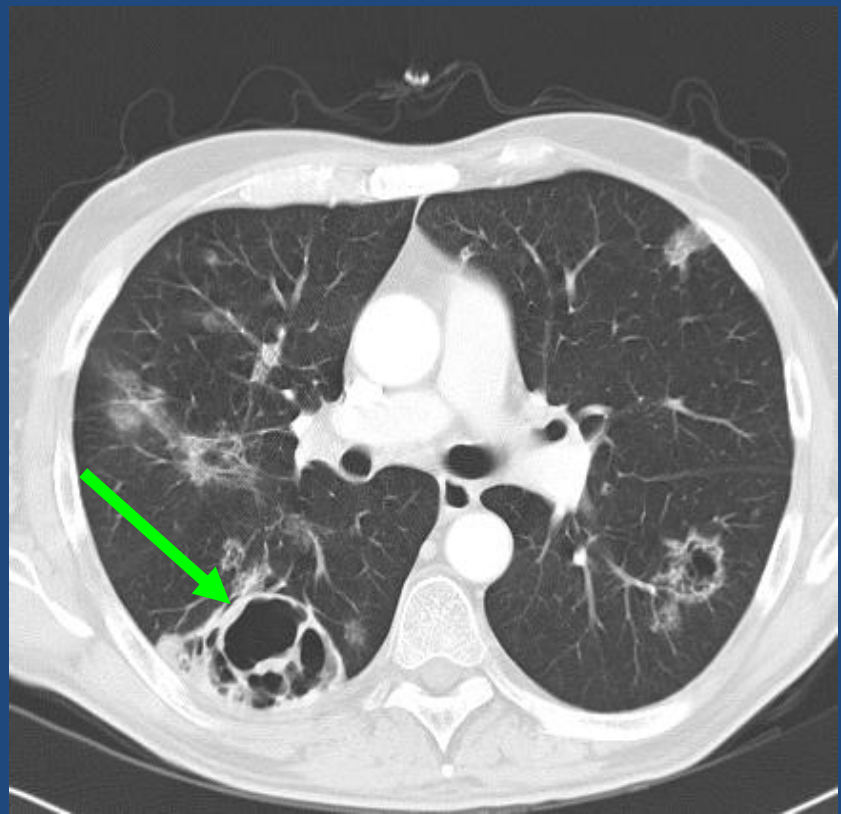
Cytoreductive Nephrectomy for metastatic RCC high FPTV predicts survival



Sunitinib reduces tumor load in RCC patients



At baseline



At first evaluation

Sunitinib reduces tumor load in RCC patients

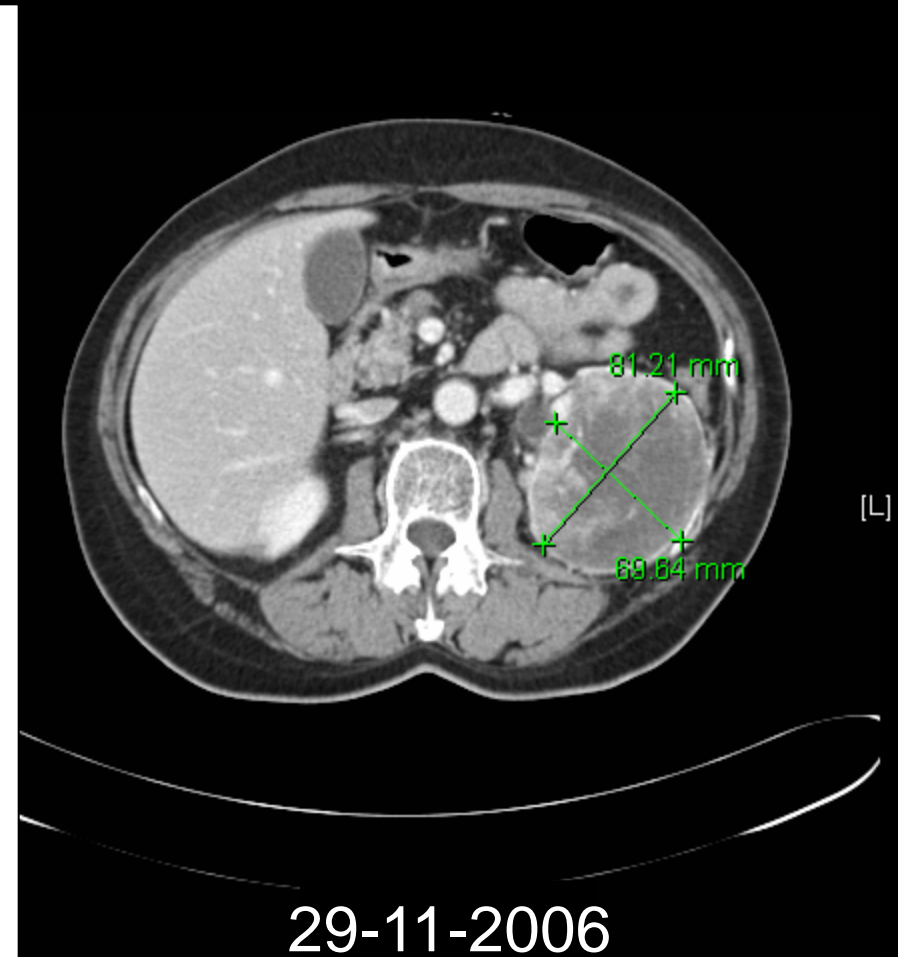
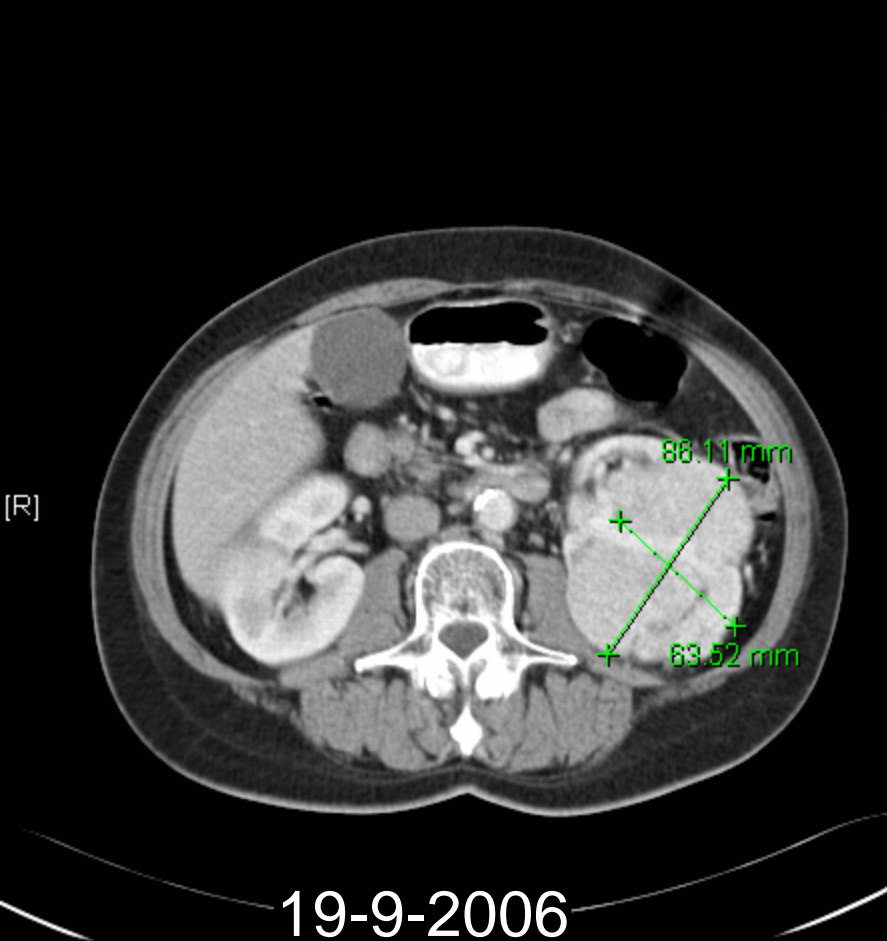
	<u>Choi criteria</u>	<u>RECIST</u>
	<u>First evaluation*</u>	<u>Best response</u>
	n (%)	n (%)
PR	36 (65)	17 (31)
SD	6 (11)	28 (51)
SD ≥ 12 weeks	n.a.	24 (44)
PD	13 (24)	10 (18)

* *First evaluation was done after a median of 2 months*

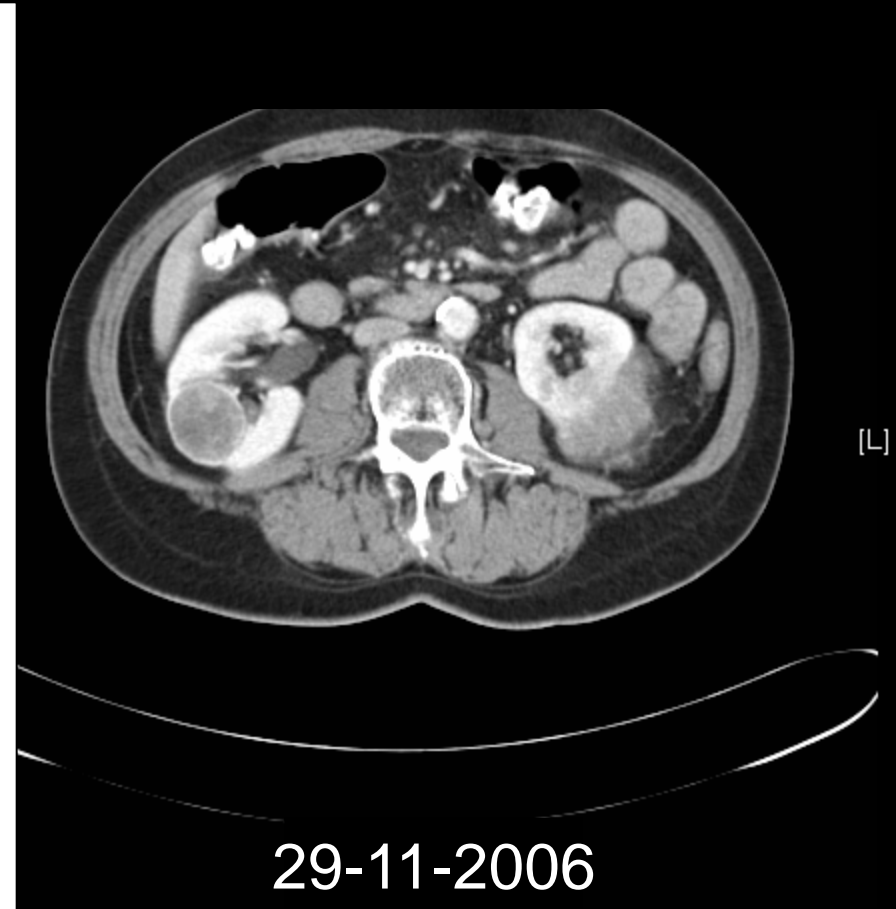
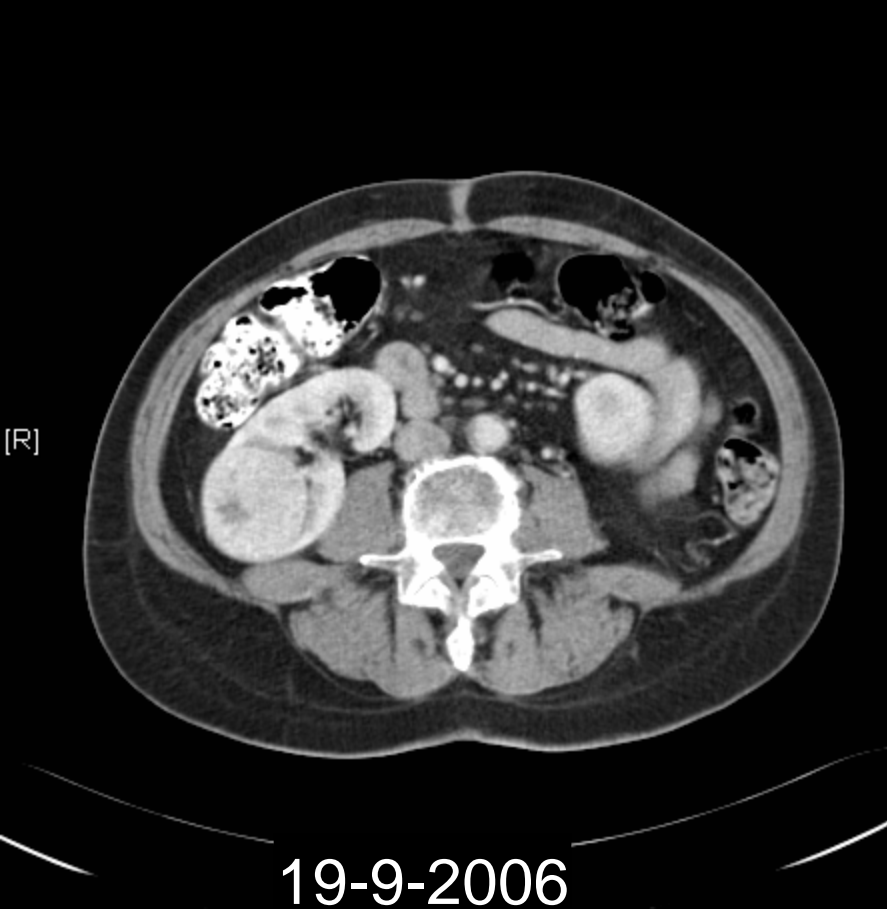
Cytoreductive Nephrectomy for metastatic RCC reversal immune suppression?

- reversal of immunosuppressive environment of RCC
 - increased production of VEGF, TGF- β , gangliosides, prostaglandines, IL-10 by tumor cells
 - decreased expression of activation markers on dendritic cells in tumor and circulation
 - supported by pre-clinical studies (tumor models)
- primary tumor rarely responds to immunotherapy
- phase III trials show improved survival after CN, but no higher response rate
- **No well controlled prospective studies have been performed to prove this immunological concept**

Sunitinib can induce a response in the primary tumor



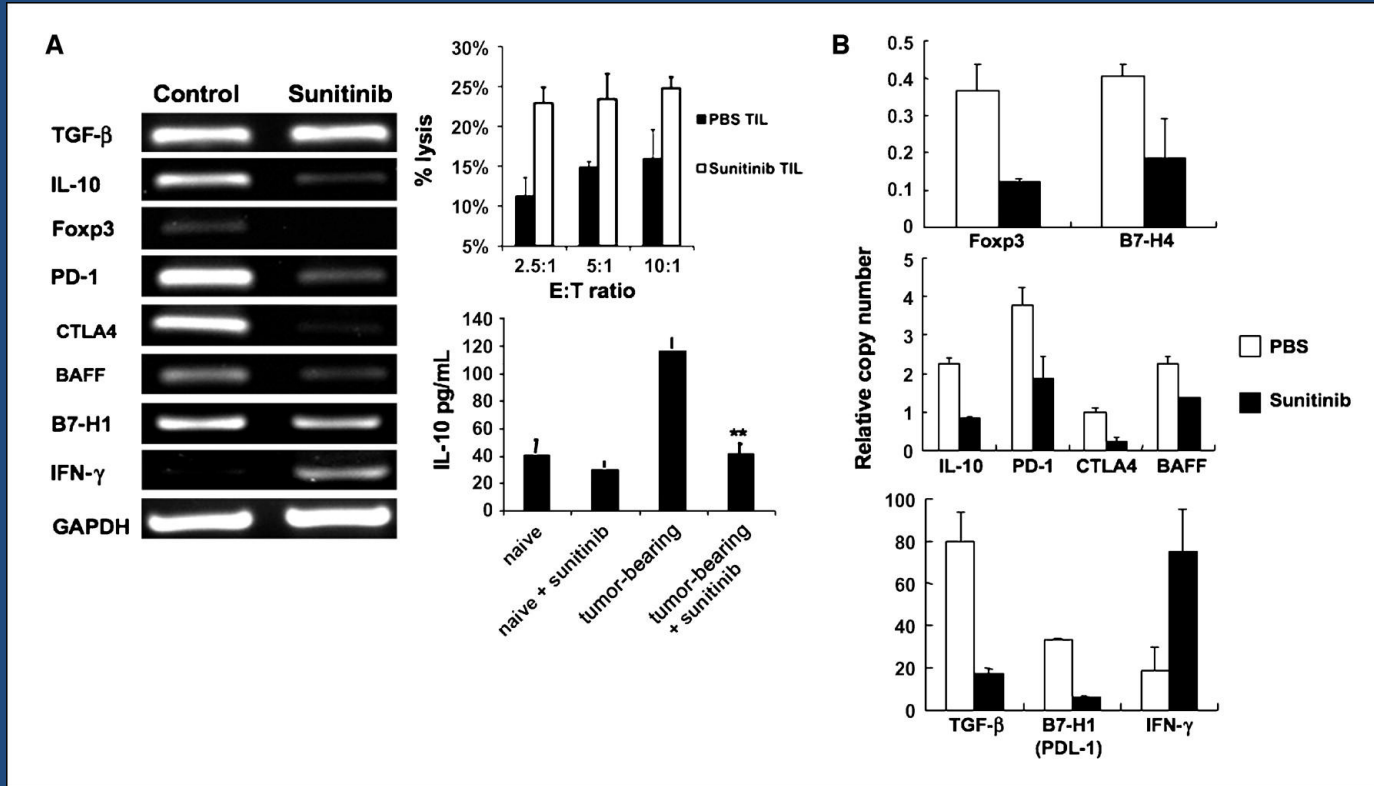
Sunitinib can induce a response in the primary tumor



Sunitinib can induce a response in the primary tumor

Pt no.	Diameter baseline (cm)	Volume				
		Tumor baseline (cm ³)	Tumor Δ (%)	Necrosis* baseline (cm ³)	Necrosis* Δ (%)	Solid Δ (%)
1	13	695	-64	131	-43	-68
2	7	138	-51	61	-13	-81
3	6	131	-24	14	195	-50
4	13	536	-27	189	39	-63
5	7	189	-18	28	109	-40
6a †	11	773	-58	124	34	-75
6b	5	49	-60	3	359	-87
7	7	133	-31	51	7	-54
8	8	227	12	4	-14	13
9	15	1715	-46	642	29	-90
10	8	281	-38	208	-43	-24
11	10	439	53	271	39	77
12	9	293	-30	45	129	-59
13	6	116	-37	22	5	-47
14	6	158	-42	22	245	-88
15	7	174	14	28	53	7
16	16	1651	-25	228	158	-54
17	5	57	8	16	163	-52

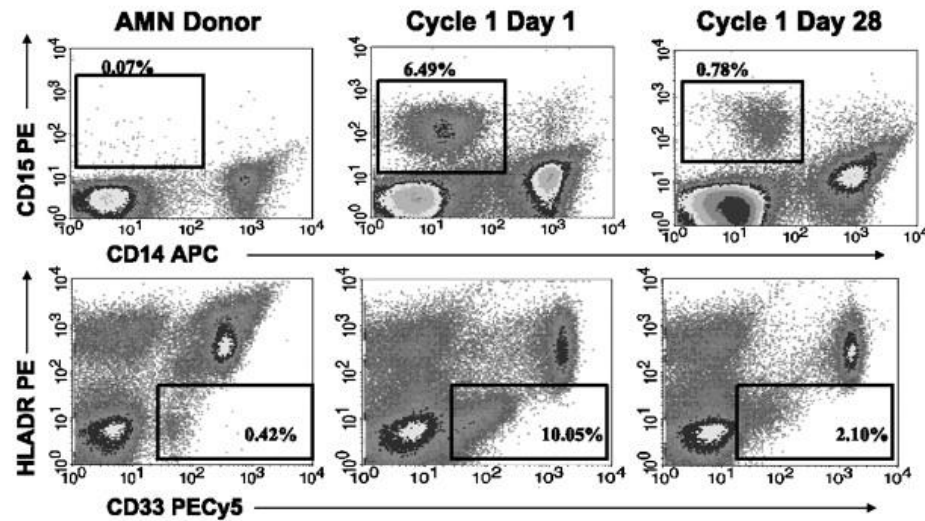
Sunitinib can reverse immune suppression of tumor microenvironment



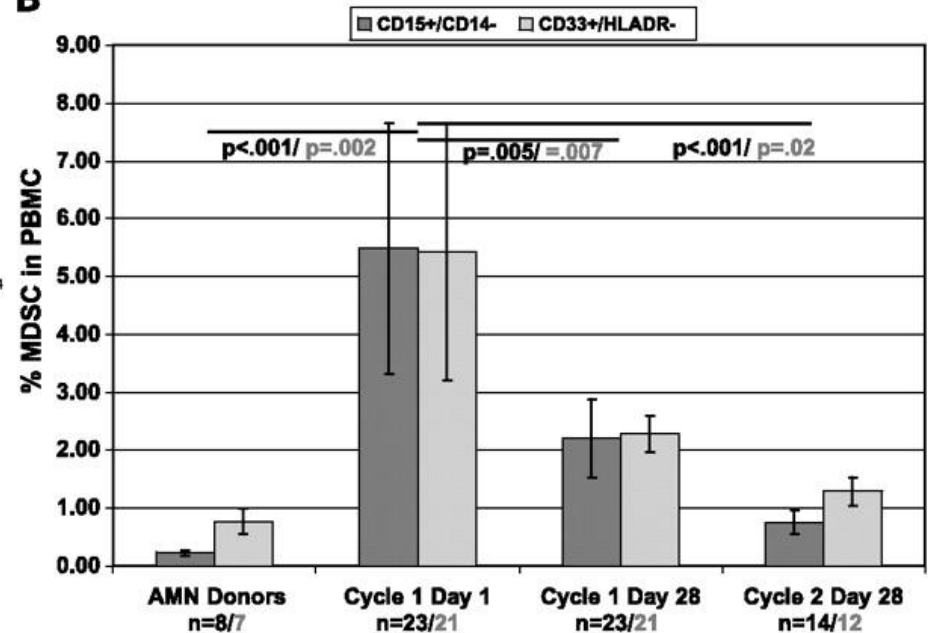
Ozao-Choy, J. et al. Cancer Res 2009;69:2514-2522

Elevated myeloid-derived suppressor cells in mRCC patients decline in response to sunitinib

A



B



Sunitinib improves immune status of RCC patients

After one cycle of treatment of RCC patients

- Reduction of myeloid-derived suppressor cells
- An increase in the percentage of IFN- γ -producing T cells
- A decreased percentage of Treg cells

Finke et al. Clin. Canc. Res. (2008)

After one cycle of treatment of RCC patients

- An increase to high levels of myeloid DC (MDC) subset frequencies relative to other myeloid subsets was observed
- the observed high CD1c/BDCA-1(+) MDC frequencies were predictive for tumor regression and improved progression-free survival

Van Cruijssen et al. Clin Canc.Res. (2008)

Cytoreductive nephrectomy in the sunitinib era arguments pro??

- 80% of the patients treated with sunitinib had a nephrectomy
- 90% of the patients had a color TV



Should all patients treated with sunitinib have
a nephrectomy and a color TV???

Cytoreductive Nephrectomy for metastatic RCC is not indicated for patients

- with serious comorbidities
- with WHO 2/3/4 performance status
- older than 75 years
- with non-clear cell histology
- to induce a complete remission
- who will not be treated with IFN- α
- with rapidly progressive disease
- who will be treated with sunitinib
 - # to decrease tumor load
 - # because primary tumor will not respond
 - # to reverse immune suppressive status of patients
 - # and is not participating in a clinical trial (EORTC30073)

Cytoreductive Nephrectomy for metastatic RCC



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