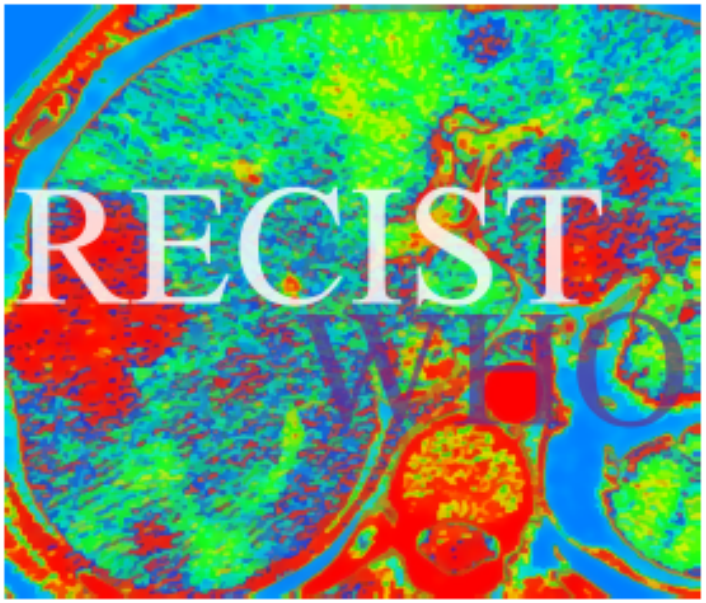
Thesis for doctoral degree (Ph.D.)
2012

Computed Tomography Based Assessment of Treatment Response in Solid Tumors



Chikako Suzuki

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Focus on RECIST

- How to say that cancer medicine is effective?
  → Response rate (RR), Progression-free survival (PFS), Overall survival (OS)
- How to define response, progress/regress in standardized way in clinical trial?
- We need a common protocol & language
- That's **RECIST** etc…
  →Response Evaluation Criteria In Solid Tumors

- Therasse P, Arbuck SG, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer. *J Natl Cancer Inst. 2000 Feb 2;92(3):205-16.*
- Eisenhauer EA, Therasse P, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer. 2009 Jan;45(2):228-47.*

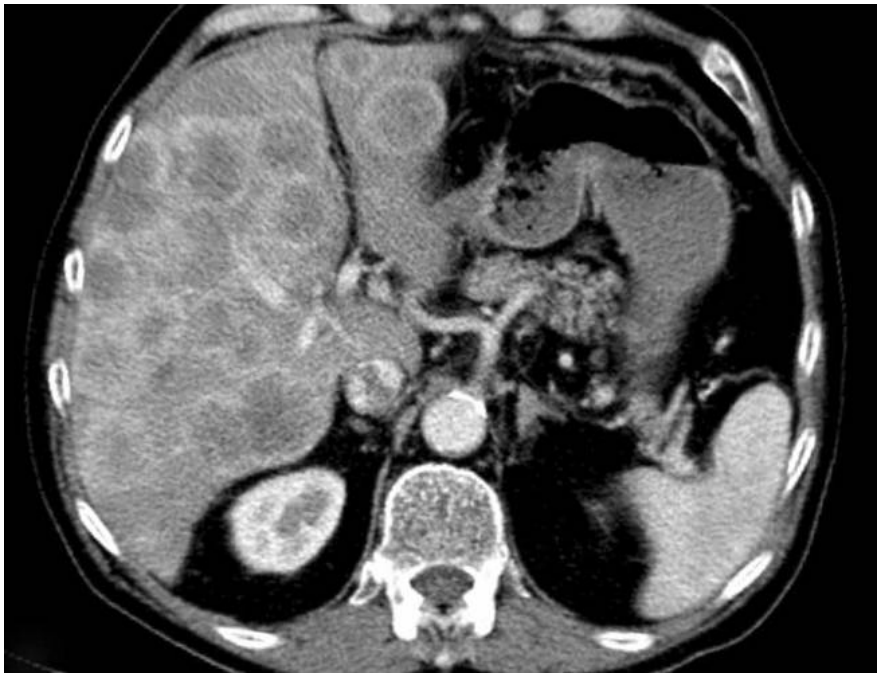
4 steps to evaluate response, RECIST

1. **Selection** of target lesions
   a. Maximum 5 in the same organ, maximum 10 in total (RECIST)
   b. Maximum 2 in the same organ, maximum 5 in total (RECIST 1.1.)
2. **Measurement**
   a. 2D = largest x perpendicular diameter (WHO)
   b. 1D longest diameter (RECIST, RECIST 1.1)
   c. 1D short axis for LN (RECIST 1.1)
3. **Identification** of new lesions and/or progression of non-target lesions
4. **Categorization** on the basis of criteria

Progressive disease=PD	Partial response=PR
Stable disease=SD	Complete response=CR

Repeat step 2-4, until PD

Select and Measure Target Lesion(s) !



- 5 radiologists
- Select up to 5 lesions, then measure the longest diameter

Select and Measure Target Lesion(s)!

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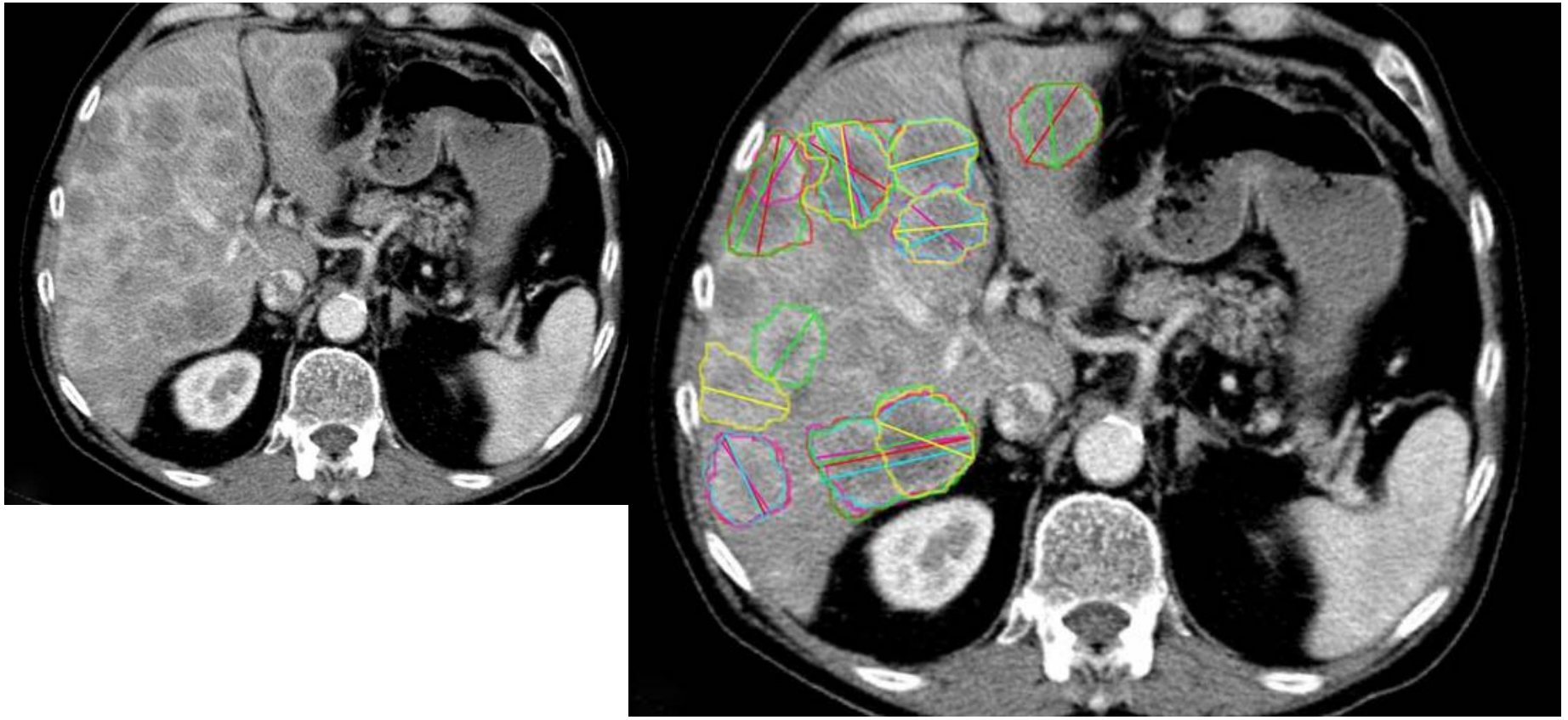
Answer



Each color corresponds with each radiologist

4 steps to evaluate response, RECIST

1. **Selection** of ta
   a. Maximum 5 i n total (RECIST)
   b. Maximum 2 i total (RECIST 1.1.)
2. **Measurement**
   a. 2D = largest
   b. 1D longest diameter (RECIST, RECIST 1.1)
3. lesions
4. **Categorization**

Prog rtial response=PR
Stable disease=SD Complete response=CR

Repeat step 2-4, until PD

Consistency?
Repeatability?
Objectivity?

To test Accuracy, Reliability

Study I & II

Study I

The British Journal of Radiology

The minimum number of target lesions that need to be measured to be representative of the total number of target lesions (according to RECIST)

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ABSTRACT. Response evaluation criteria in solid tumors (RECIST) were introduced as a means to classify tumour response with no definition of the minimum number of lesions. This study was conducted in order to evaluate discrepancies between full assessments based on either all target lesions or fewer lesions. RECIST evaluation was performed on separate occasions based on between one and seven of the target lesions, with simultaneous assessment of non-target lesions. 99 patients were included. 38 patients demonstrated progressive disease, 61% of which was as a result of the appearance of new lesions or unequivocal progress in non-target lesions. 32 patients showed stable disease, with 8 having results that differed when 1–3 target lesions were measured. 22 cases were considered as having partial regression, with only 1 case differing when performing 1–3 target lesion assessments. Seven cases demonstrated complete response. The number of discordant cases increased gradually from measuring three lesions to one target lesion. The average number of available target lesions among those with discrepancies was 7.1, which was significantly higher than those demonstrating concordance (4.1 lesions; $p<0.05$). In conclusion, measuring fewer than four target lesions might cause discrepancies when more than five target lesions are present.

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DOI: 10.1259/bjr/72829563

- Focus on the No. of target lesion(s)
- How many target lesions can be reduced without changing Pt's response category?

Darkeh, M. H. et al, *Br J Radiol* **82**, 681-686(2009)

Results from Study I

- Reduce the no. of lesion one by one
  → compare to the original result obtained by full assessment
- Discordance rate in response increased from 7.5% to 15.1% as the target lesion number for assessment was decreased from 3 to 1L(Table).

Type of assessment	1L	2L	3L	4L, 5L, 6L, 7L
Number of ''mistakes'' (discordant cases) when all 99 patients are considered	8	6	4	0
Percentage of discordant cases in all 99 cases	8%	6%	4%	0%
Percentage of discordant cases in patients with ⩾5 lesions (53 cases)	15.1%	11.3%	7.5%	0%

Conclusion of Study I

- Measuring fewer than 4 lesions is a potential source of error in response evaluation when more than 5 target lesions are present.

Study II

Acta Oncologica, 2010; 49: 509–514

informa
healthcare

ORIGINAL ARTICLE

Interobserver and intraobserver variability in the response evaluation of cancer therapy according to RECIST and WHO-criteria

CHIKAKO SUZUKI[1], MICHAEL R. TORKZAD[2], HANS JACOBSSON[1], GUNNAR ÅSTRÖM[3], ANDERS SUNDIN[1], THOMAS HATSCHEK[4], HIROFUMI FUJII[5] & LENNART BLOMQVIST[1]

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Abstract

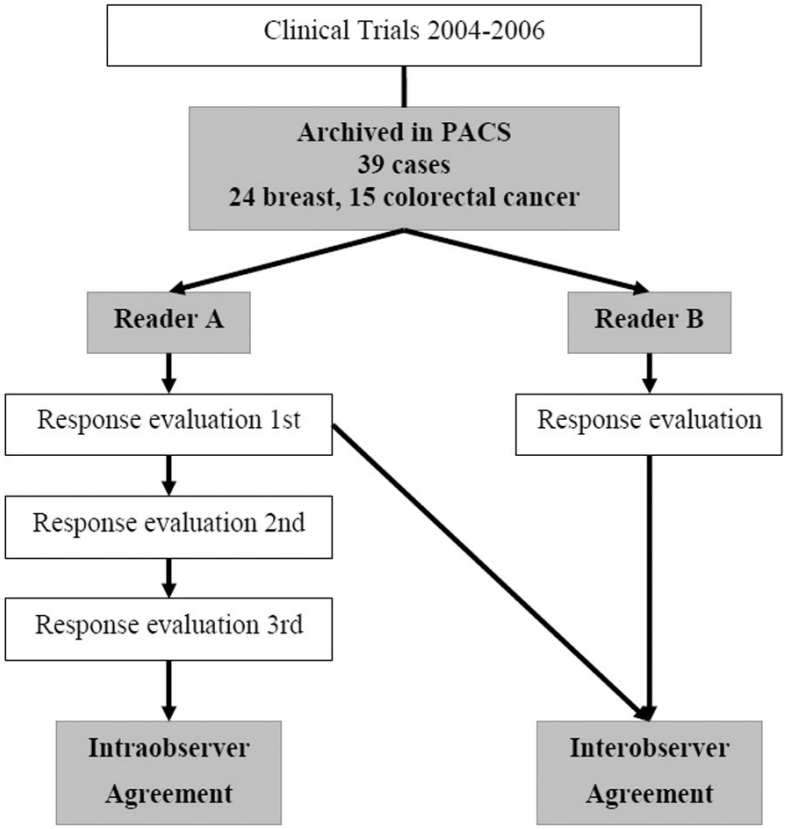
Background. Response Evaluation Criteria In Solid Tumors (RECIST) and WHO-criteria are used to evaluate treatment effects in clinical trials. The purpose of this study was to examine interobserver and intraobserver variations in radiological response assessment using these criteria. *Material and methods.* Thirty-nine patients were eligible. Each patient's series of CT images were reviewed. Each patient was classified into one of four categories according RECIST and WHO-criteria. To examine interobserver variation, response classifications were independently obtained by two radiologists. One radiologist repeated the procedure on two additional different occasions to examine intraobserver variation. Kappa statistics was applied to examine agreement. *Results.* Interobserver variation using RECIST and WHO-criteria were 0.53 (95% CI 0.33–0.72) and 0.60 (0.39–0.80), respectively. Response rates (RR) according to RECIST obtained by reader A and reader B were 33% and 21%, respectively. RR according to WHO-criteria obtained by reader A and reader B were 33% and 23% respectively. Intraobserver variation using RECIST and WHO-criteria ranged between 0.76–0.96 and 0.86–0.91, respectively. *Conclusion.* Radiological tumor response evaluation according to RECIST and WHO-criteria are subject to considerable inter- and intraobserver variability. Efforts are necessary to reduce inconsistencies from current response evaluation criteria.

- What is the extent of inter- and intra-observer variation in RECIST and WHO-criteria based tumor response evaluation?
- What are the sources for these variations?

Suzuki, C. *et al. Acta Oncol* **49**, 509-514, (2010).

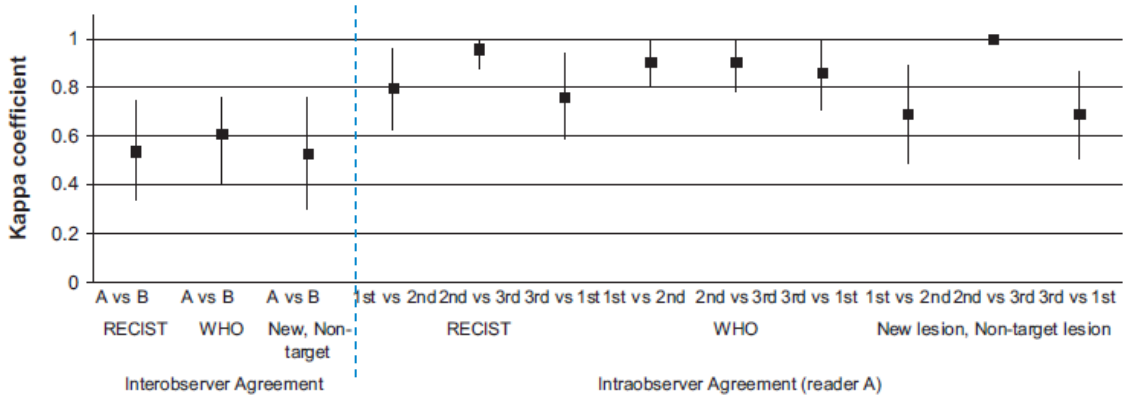
Patients and Methods of Study II

- 2 board certified radiologists re-evaluated 39 patient's CTs
- Response evaluation was performed according to RECIST and WHO-criteria
- One radiologist repeated the procedure on two additional occasions
- *Kappa* analysis



Results from Study II

- Inter-observer agreement (A vs B) < Intra-observer agreement (A 1st -3rd)
- Possible sources for inconsistency
  - → different radiologists performing the evaluations
  - → difference in selection of target lesions
  - → difference in measurement of target lesions
  - → difference in detecting new lesions/ progression of non-target lesions



95% CI upper	0.75	0.76	0.76	0.96	1	0.94	1	1	1	0.89	1	0.87
95% CI lower	0.34	0.41	0.3	0.63	0.88	0.59	0.8	0.78	0.71	0.49	1	0.51
Kappa coefficient	0.54	0.61	0.53	0.8	0.96	0.76	0.91	0.91	0.86	0.69	1	0.69

Figure 5. Non-weighted kappa coefficient value and corresponding 95% confidence interval (CI) for agreement.

Conclusion of Study II

- RECIST and WHO-criteria are subject to considerable inter- and intra-observer variability.

  → tumor response of the same patient's may be evaluated differently by different clinicians (50% probability)

Go beyond RECIST!

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Are there any better way for response evaluation?

Key : Quick & efficient read-out, correlate with OS/PFS

Focus on the 1st change/response

↓

Study III for colorectal cancer
Study IV for breast cancer

Definition of 1st change (the initial change/response)

- 1st change = [(1st sum) – (baseline sum)] / baseline sum (%)
  (week 8)
  (1st sum = sum of target lesion size at the 1st evaluation)
  (baseline sum = sum of target lesion size at the baseline evaluation)
- no change = 0
- disappearance of metastatic lesions = -100%
- appearance of new lesion, progression of non-target lesion = 100%

Study III

original article

Annals of Oncology
doi:10.1093/annonc/mdr350

The initial change in tumor size predicts response and survival in patients with metastatic colorectal cancer treated with combination chemotherapy

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Background: To determine whether the change in tumor diameters at the first follow-up computed tomography (CT) examination after baseline examination (first change) correlates with outcome in patients with metastatic colorectal cancer (mCRC) treated with combination chemotherapy.

Patients and methods: The first change was analyzed in a multicenter randomized phase III trial (Nordic VI, *N* = 567) comparing first-line irinotecan with either bolus or infused 5-fluorouracil. Cox proportional hazards multiple regression model and Kaplan–Meier survival analyses after correction for guarantee-time bias were carried out to evaluate correlations between first change, objective response according to RECIST 1.0, progression-free survival (PFS), and overall survival (OS).

Results: The hazard ratios for PFS and OS decreased along with first change. A decrease between 10% and <30%, albeit RECIST does not regard this as a partial response, was a positive prognostic factor for PFS and OS. Patients who had new lesions or unequivocal progression of nonmeasurable lesions had a worse prognosis than those with only an increase in size of >20%.

Conclusions: The change in tumor size at the first follow-up CT is strongly prognostic for PFS and OS in mCRC.

Key words: imaging, metastatic colorectal cancer, response evaluation, survival

- Does 1st change correlate with OS in metastatic colorectal cancer (mCRC)?
- Nordic VI (n=567)
  - → metastatic colorectal cancer
  - → Phase III

Suzuki, C. *et al. Ann Oncol* **23**, 948-954, (2012).

Results from Study III

Relationship between 1st change and OS

- 1st change correlate with OS

  → different cut-off values compared to RECIST's definition

  → increase >=20% was not significantly associated with impaired OS

  → decrease >10% predicted improved OS

  → Appearance of new lesion or progression of non-target lesion was the most negative prognostic factor

Cox regression analysis

Covariate (first change)	*n*	*P*	HR	95% CI	OR
Continuous[a]	506 (327)	<0.001	2.01	1.75–2.31	–
Categorized					
New, nontarget	33 (29)	<0.001	3.77	2.08–6.83	PD
Increase (%)					
≥20	26 (22)	0.611	1.18	0.63–2.20	
≥10 to <20	15 (10)	0.722	1.15	0.53–2.49	
>0 to <10	25 (18)	–	1	–	
0 to decrease <10%	104 (69)	0.310	0.76	0.45–1.28	SD
Decrease (%)					
≥10 to <20	95 (57)	0.031	0.56	0.33–0.95	
≥20 to <30	57 (31)	0.002	0.39	0.22–0.70	
≥30 to <40	68 (47)	0.046	0.57	0.33–0.99	PR
≥40 to<50	40 (25)	0.010	0.45	0.24–0.82	
≥50	43 (19)	<0.001	0.25	0.13–0.49	

Number in parentheses indicates the number of deaths. New, nontarget: appearance of new lesion or progression of nontarget lesion.

[a]First change as a continuous valuable. Patients with new lesions or progression in nontarget lesion at the first follow-up study converted into an increase of 1.0.

CI, confidence interval; HR, hazard ratio; OR, objective response if based upon the first change only; PD, progressive disease; PR, partial response; SD, stable disease.

Study IV

Med Oncol (2013) 30:415
DOI 10.1007/s12032-012-0415-5

ORIGINAL PAPER

Impact of the first tumor response at eight weeks on overall survival in metastatic breast cancer patients treated with first-line combination chemotherapy

Chikako Suzuki · Lennart Blomqvist · Thomas Hatschek · Lena Carlsson · Zakaria Einbeigi · Barbro Linderholm · Birgitta Lindh · Niklas Loman · Martin Malmberg · Samuel Rotstein · Martin Söderberg · Marie Sundqvist · Thomas M. Walz · Gunnar Åström · Hirofumi Fujii · Hans Jacobsson · Bengt Glimelius

Received: 10 July 2012 / Accepted: 11 November 2012

Abstract The aim of this was to determine whether the change of size observed at the first response evaluation after initiation of first-line combination chemotherapy correlates with overall survival (OS) in patients with metastatic breast cancer (MBC). The change in size of tumors derived from measurements according to Response Evaluation Criteria In Solid Tumors (RECIST) at the first evaluation on computed tomography (CT) was obtained from a multicenter, randomized phase III trial ("TEX trial," $n = 287$) comparing treatment with a combination of epirubicin and paclitaxel alone or with capecitabine (TEX). Cox regression and Kaplan–Meier analyses were performed to evaluate the correlations between the first change in tumor size, response according to RECIST and OS. Data from CT evaluations of 233 patients were available. Appearance of new lesions or progression of non-target lesions (new/non-target) indicated short OS by univariable regression analysis (HR 3.76, 95 % CI 1.90–7.42, $p < 0.001$). A decrease by >30 % at this early time point was prognostic favorable (HR 0.69, 95 % CI 0.49–0.98, $p = 0.04$) and not significantly less than the best overall response according to RECIST. After adjustment for previous adjuvant treatment and the treatment given within the frame of the randomized trial, OS was still significantly shorter in patients with new/non-target lesions after a median 8 weeks of treatment (HR 4.41, 95 % CI 2.74–7.11, $p < 0.001$). Disease progression at the first evaluation correlates with OS in patients with MBC treated with first-line combination chemotherapy. The main reason for early disease progression was the appearance of new lesions or progression of non-target lesions. These patients had poor OS even though more lines of treatment were available. Thus, these factors should be focused on in the response evaluations besides tumor size changes.

- Does 1st change correlate with OS in metastatic breast cancer (MBC)?
- TEX (n=287)
  - → metastatic breast cancer
  - → Phase III, 1st line treatment

Suzuki, C. *et al. Med Oncol* **30**, 415, (2013).

Results from Study IV

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Table 2 Univariable Cox regression analyses on overall survival (OS) in 233 patients with 158 events

	No. (censored)	HR	95 % CI	*p* value
Change of size at the first response evaluation				
New/non-target[a]	23 (1)	3.76	1.90–7.42	<0.001
Increase <20 %	23 (7)	0.86	0.42–1.76	0.68
No change–decrease 10 %	20 (5)	1	–	–
Decrease >10–20 %	36 (10)	0.94	0.49–1.77	0.84
Decrease >20–30 %	39 (12)	0.95	0.50–1.80	0.87
Decrease >30–40 %	35 (16)	0.69	0.35–1.37	0.29
Decrease >40–50 %	27 (13)	0.48	0.23–1.00	0.05
Decrease >50 %	30 (11)	0.79	0.40–1.56	0.49
New/non-target (a)	23 (1)	4.00	2.46–6.53	<0.001
Decrease ≤30 %–Increase <20 %	118 (34)	1	–	–
Decrease >30 %	92 (40)	0.69	0.49–0.98	0.04
Best overall response				
PD	23 (1)	3.49	2.09–5.84	<0.001
SD	72 (21)	1	–	–
PR	127 (48)	0.66	0.46–0.94	0.02
CR	11 (5)	0.43	0.18–1.01	0.053
Non-responder versus responder		1.97	1.43–2.71	<0.001
PD versus disease control (SD + PR + CR)		4.66	2.90–7.47	< 0.001

[a] New/non-target: appearance of new lesion or progression of non-target lesion

- **New/non-target indicated significantly short OS**

Conclusion of Study III & IV

- 1st change in tumor size correlates with OS
  → *"shrink more, survive longer"*
  → *not categorical but rather continuous way* Why categorize?
- Comparison of cytotoxic treatments can be achieved by 1st change approach than waiting for best response using RECIST Why follow-up?
- Appearance of new lesions or progression of non-target lesions indicated short OS
  → poor prognosis even though there were more lines of treatment

1st Change method might reduce time, the number of Pts, inconsistency and budget required for clinical trial

Why it matters?

The Price Tag on Progress, Chemotherapy for Colorectal Cancer

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Table. Estimated Drug Costs for Eight Weeks of Treatment for Metastatic Colorectal Cancer.

Regimen	Drugs and Schedule of Administration	Drug Costs*
		$
Regimens containing fluorouracil		
Mayo Clinic	Monthly bolus of fluorouracil plus leucovorin	63
Roswell Park	Weekly bolus of fluorouracil plus leucovorin	304
LV5FU2	Biweekly fluorouracil plus leucovorin in a 48-hr infusion	263
Regimens containing irinotecan or oxaliplatin		
Irinotecan alone	Weekly bolus	9,497
IFL	Weekly bolus of fluorouracil plus irinotecan	9,539
FOLFIRI	LV5FU2 with biweekly irinotecan	9,381
FOLFOX	LV5FU2 with biweekly oxaliplatin	11,889
Regimens containing bevacizumab or cetuximab		
FOLFIRI with bevacizumab	FOLFIRI with fortnightly bevacizumab	21,399
FOLFOX with bevacizumab	FOLFOX with biweekly bevacizumab	21,033
Irinotecan with cetuximab	Weekly irinotecan plus cetuximab	30,790
FOLFIRI with cetuximab	FOLFIRI and weekly cetuximab	30,675

* Costs represent 95 percent of the average wholesale price in May 2004.

Survival
without Chemo Tx: 8Mo

+ FU: 12Mo
$100 /8w initial tx

+ FU+IRI+OX: 21Mo
$10,000

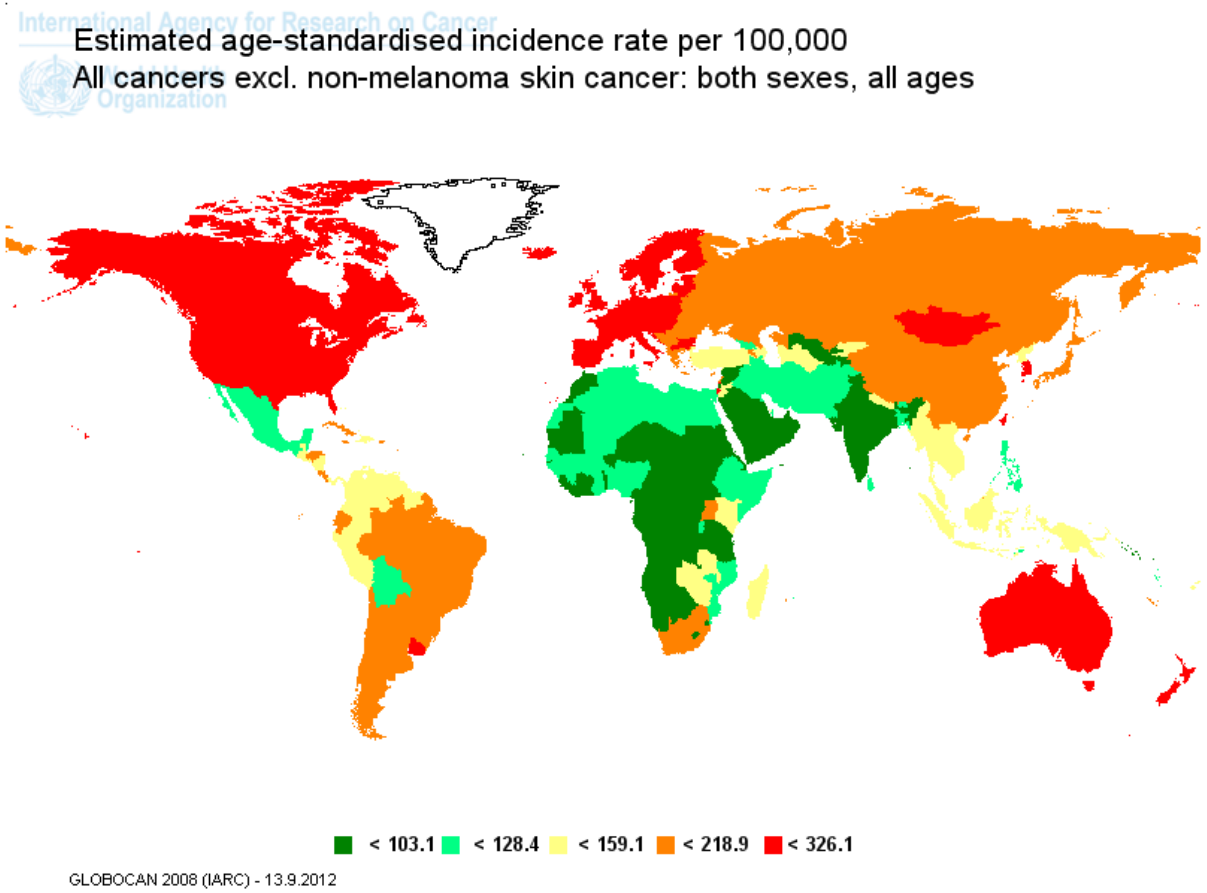
+ FU+IRI+OX+mab:
beyond 21Mo (2,3 Mo)
$30,000

$1.2 bil. for 56,000 pats in USA

- drug prices are **"astronomical"**
- the drug costs threaten to overwhelm our ability to pay for health care

(Shrag NEJM 2004;351, p317-)

Cancer Population Explosion



12 million new cancer cases, 7 million deaths in 2008,
can be doubled by 2020
can be triple by 2030: 26 million new cases, 17 million deaths

(GLOBOCAN, IARC, WHO)

Future Perspective

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1st Change

Why it matters?

to confront increase of drug cost & number of cancer patient

Publications

1. Darkeh MH, Suzuki C, Torkzad MR. The minimum number of target lesions that need to be measured to be representative of the total number of target lesions (according to RECIST). *Br J Radiol.* 2009 Aug;82(980):681-6.

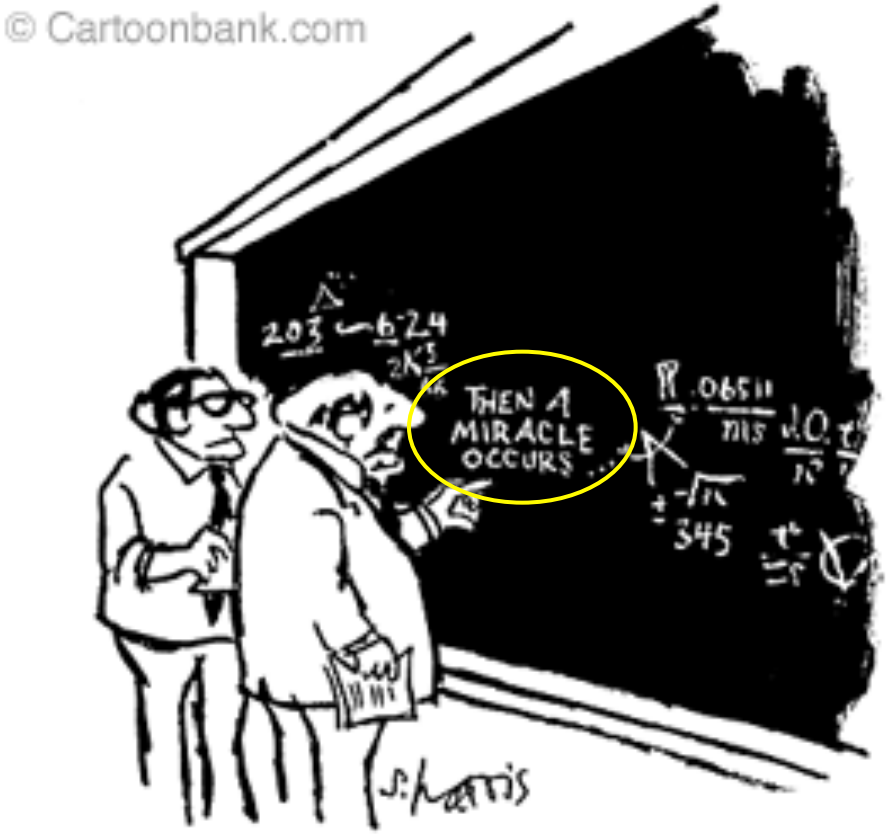
2. Suzuki C, Torkzad MR, Jacobsson H, Astrom G, Sundin A, Hatschek T, et al. Interobserver and intraobserver variability in the response evaluation of cancer therapy according to RECIST and WHO-criteria. *Acta Oncol.* 2010 May;49(4):509-14.

3. Suzuki C, Blomqvist L, Sundin A, Jacobsson H, Bystrom P, Berglund A, et al. The initial change in tumor size predicts response and survival in patients with metastatic colorectal cancer treated with combination chemotherapy. *Ann Oncol.* 2012 Apr;23(4):948-54.

4. Suzuki C, Blomqvist L, Hatschek T, Carlsson L, Einbeigi Z, Linderholm B, et al. Impact of the first tumor response at eight weeks on overall survival in metastatic breast cancer patients treated with first-line combination chemotherapy. *Med Oncol.* 2013 Mar;30(1):415.

- *Suzuki C, Jacobsson H, Hatschek T, Torkzad MR, Boden K, Eriksson-Alm Y, et al. Radiologic measurements of tumor response to treatment: practical approaches and limitations. Radiographics. 2008 Mar-Apr;28(2):329-44.*

Thank you for your attention!



"I think you should be more explicit here in step two."