Clinical Research in Rare Cancers

Understanding endpoints & patient reported outcomes

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Aknowledgments

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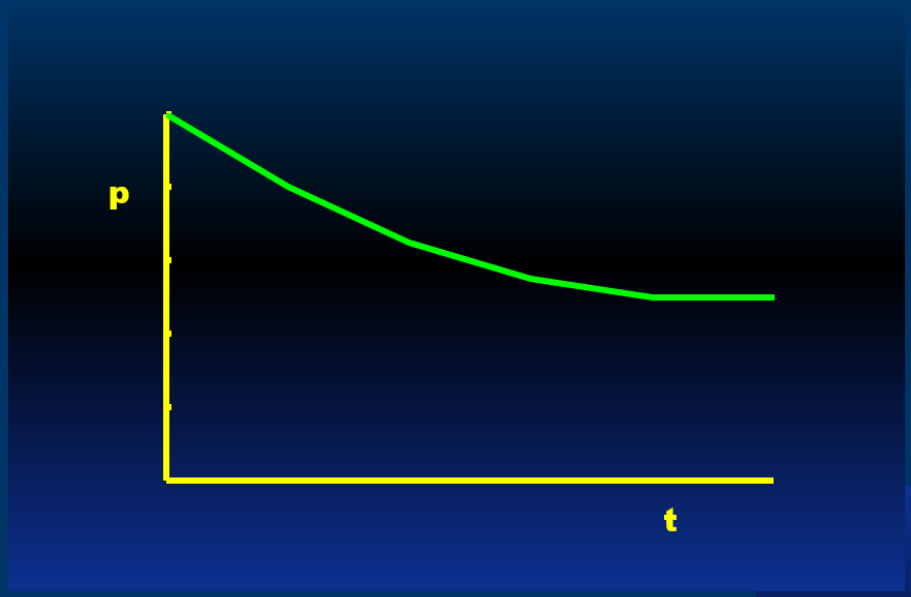
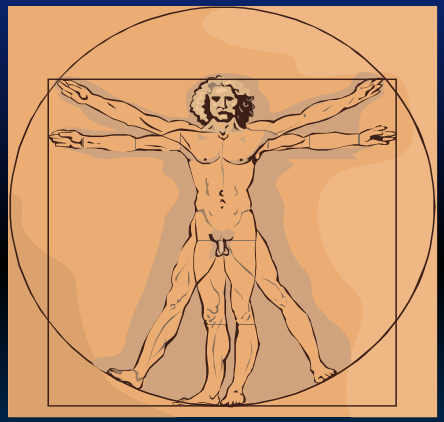
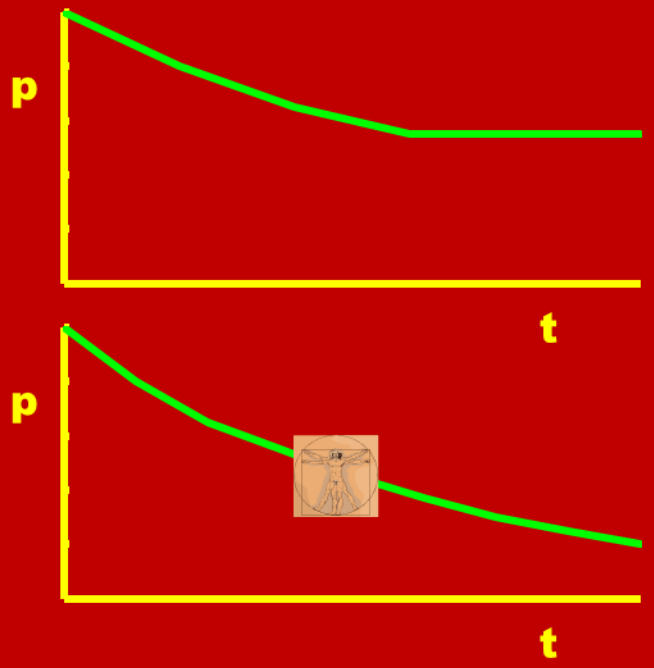
Survival and Quality of life

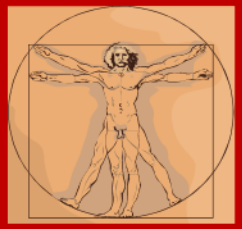




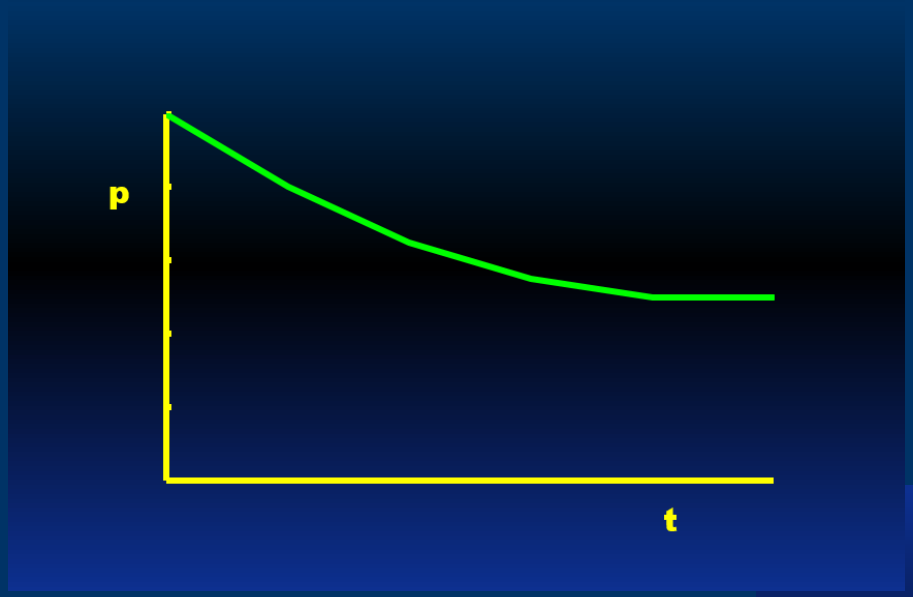
Cancer treatment: goals

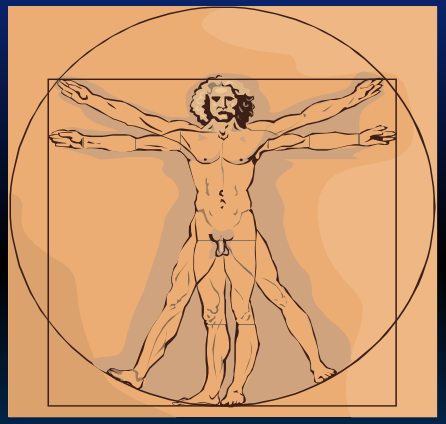
- cure
- control
- palliation





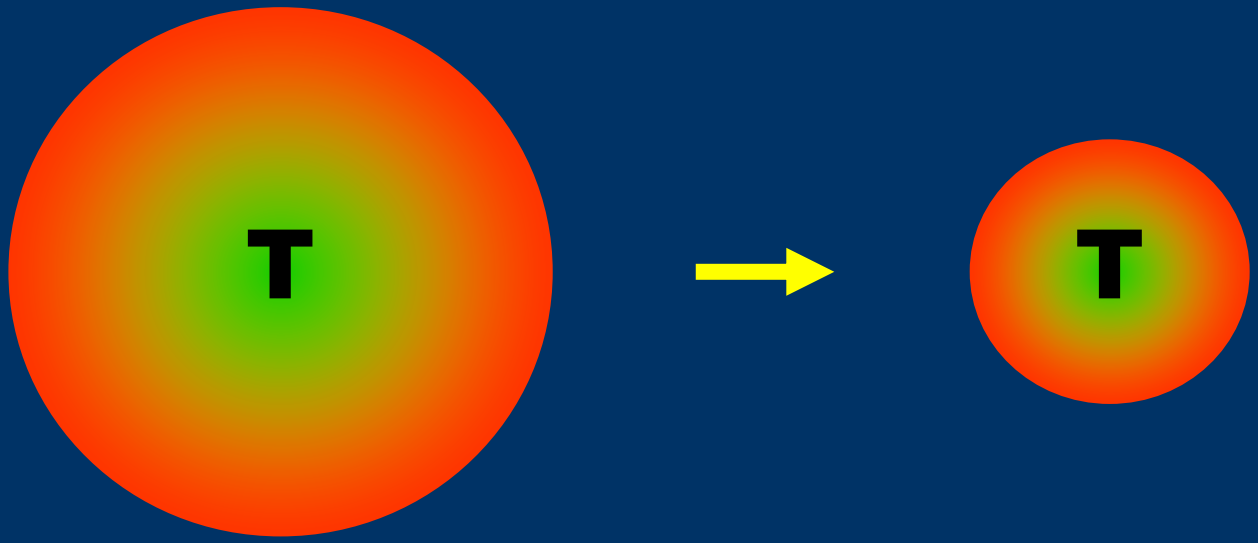
Phase 3 trials





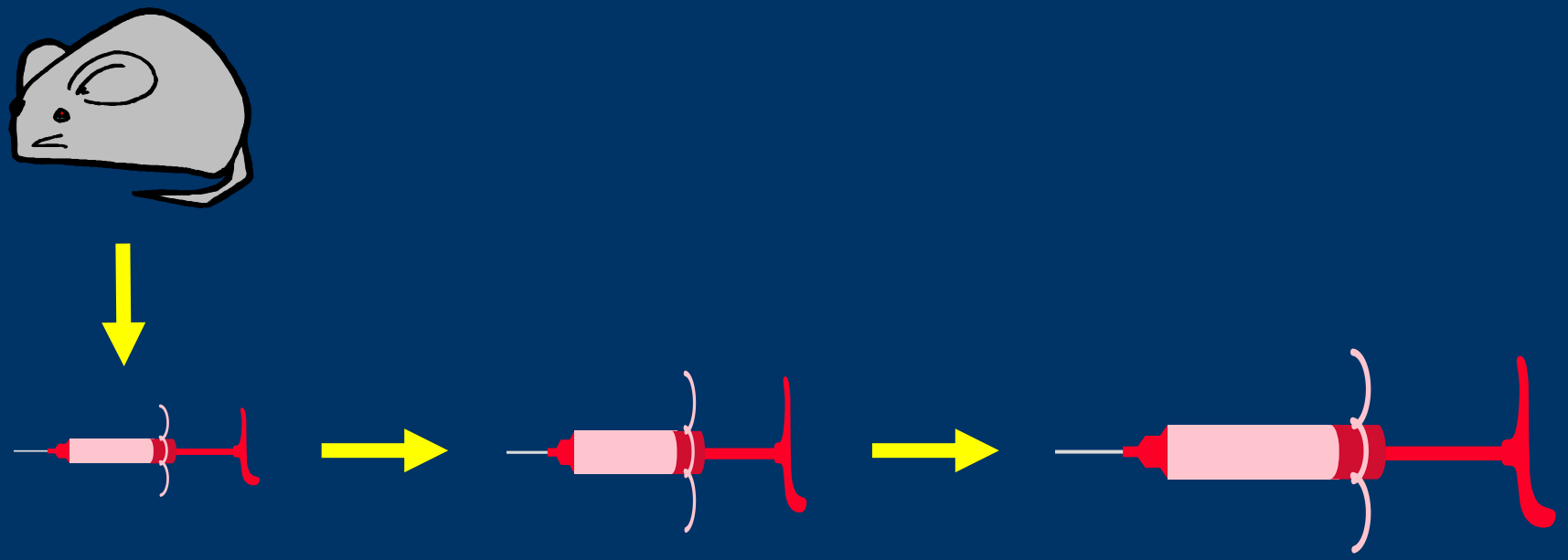
practice changing

Phase 2 studies



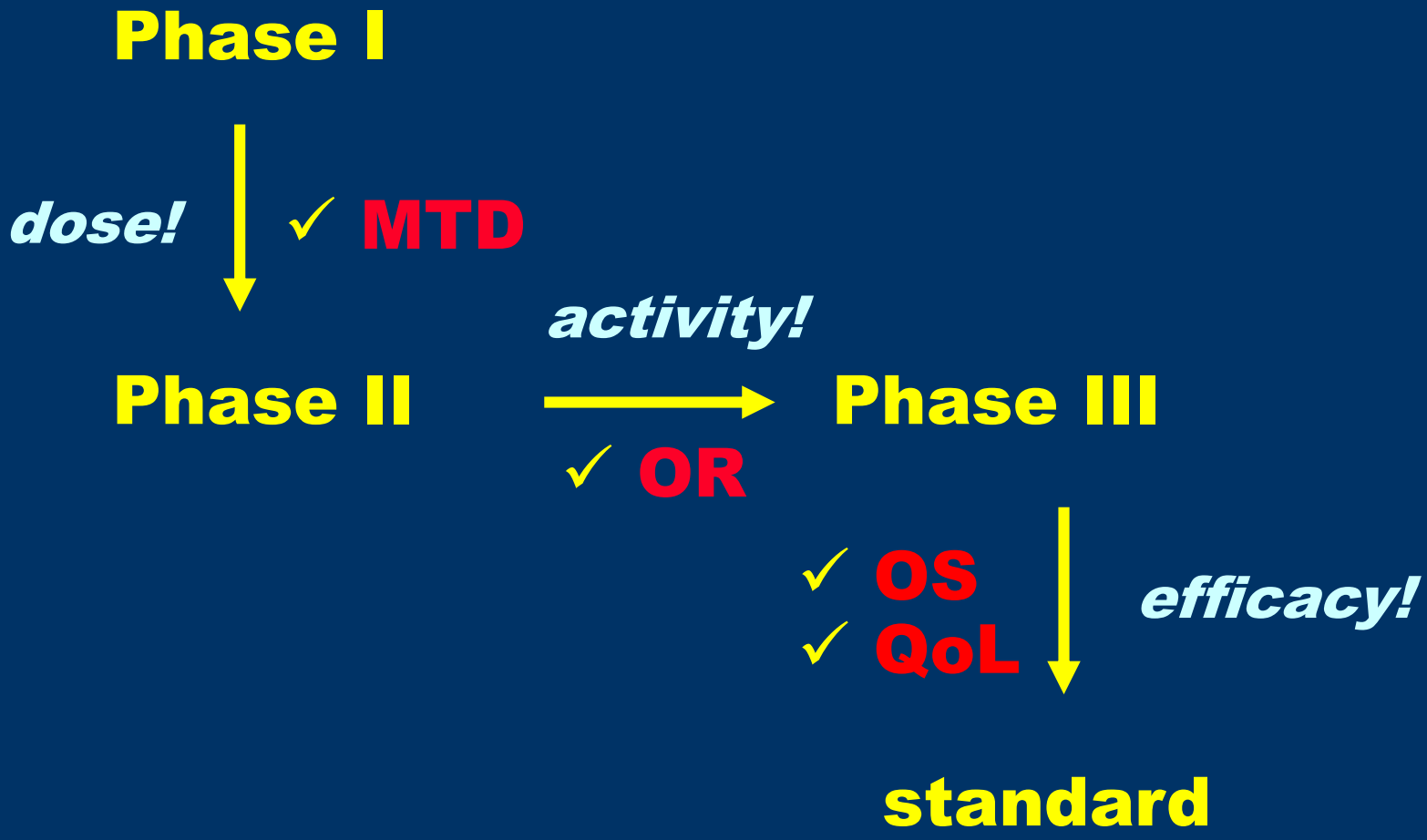
- ✓ tumor response
- ✓ toxicity

Phase 1 studies



- ✓ maximum tolerated dose
- ✓ toxicity

Clinical studies



Phase I

dose!

✓ **MTD**

activity!

Phase II → **Phase III**

✓ **OR**

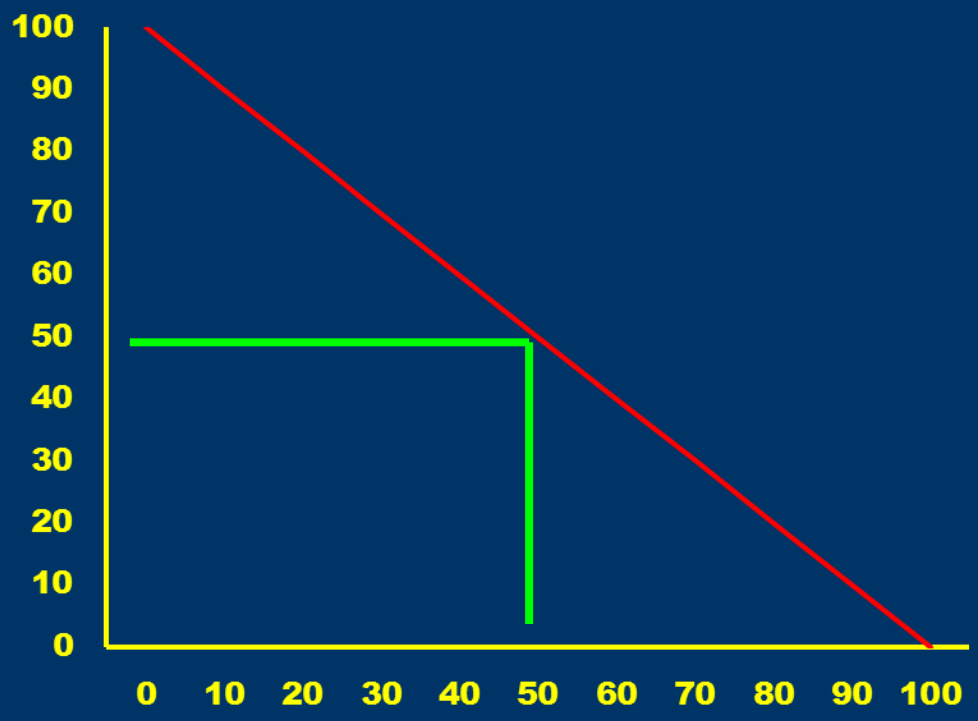
✓ **OS**

✓ **QoL**

efficacy!

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overall survival…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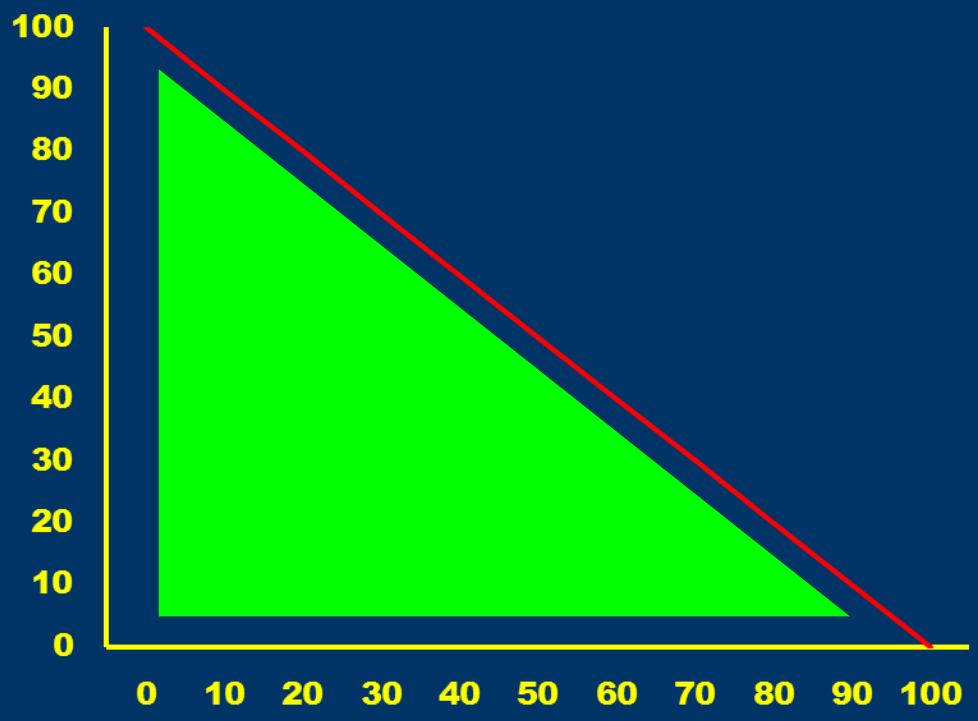
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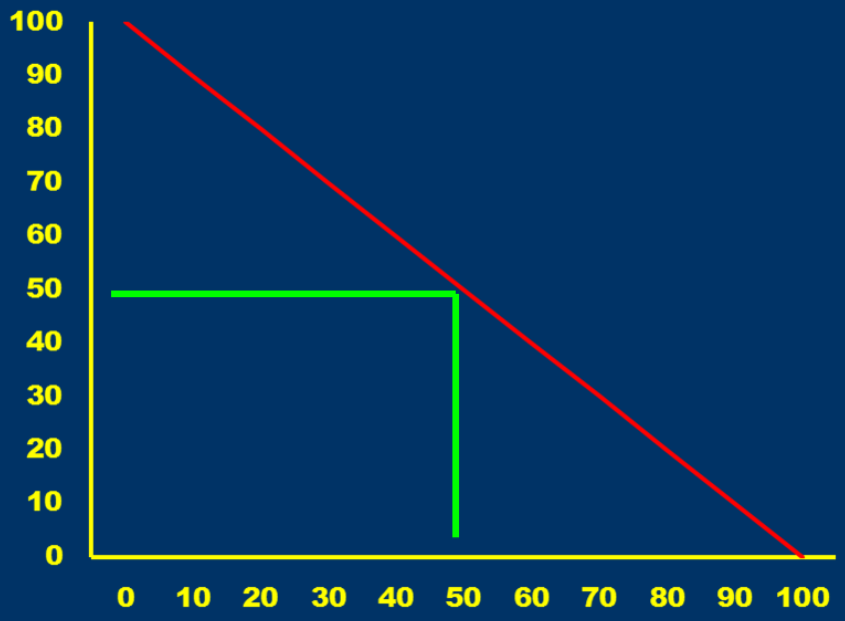
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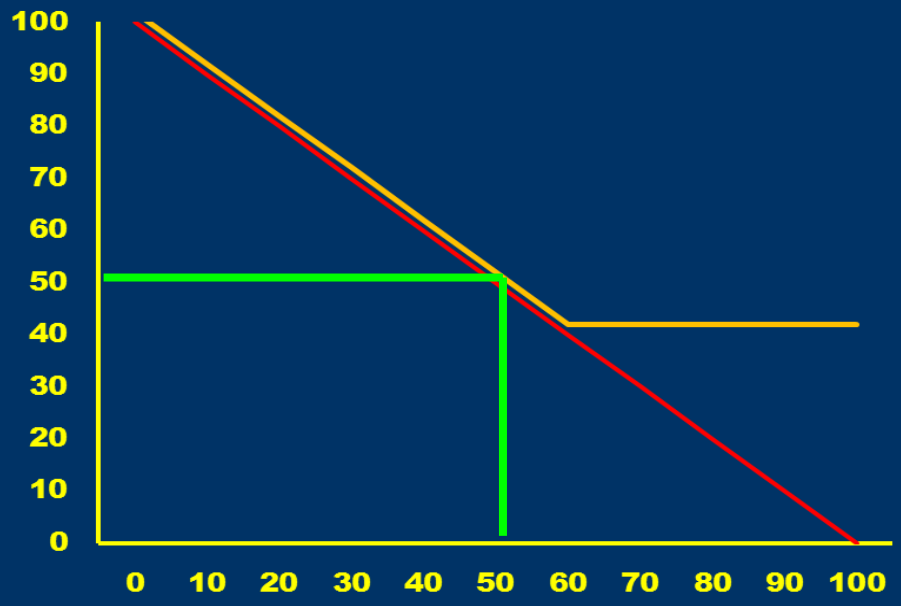
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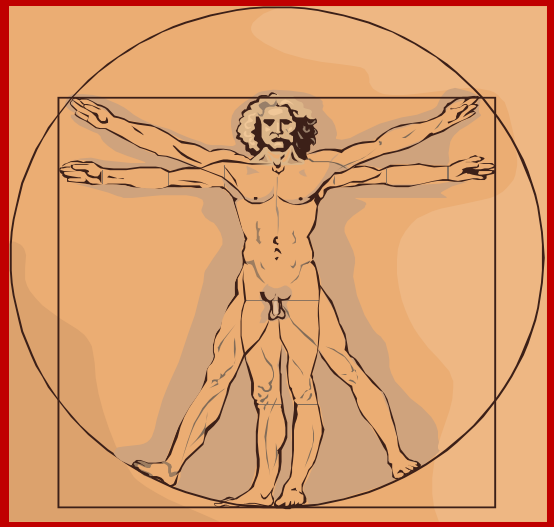
Quality of life…

physical

mental



spiritual

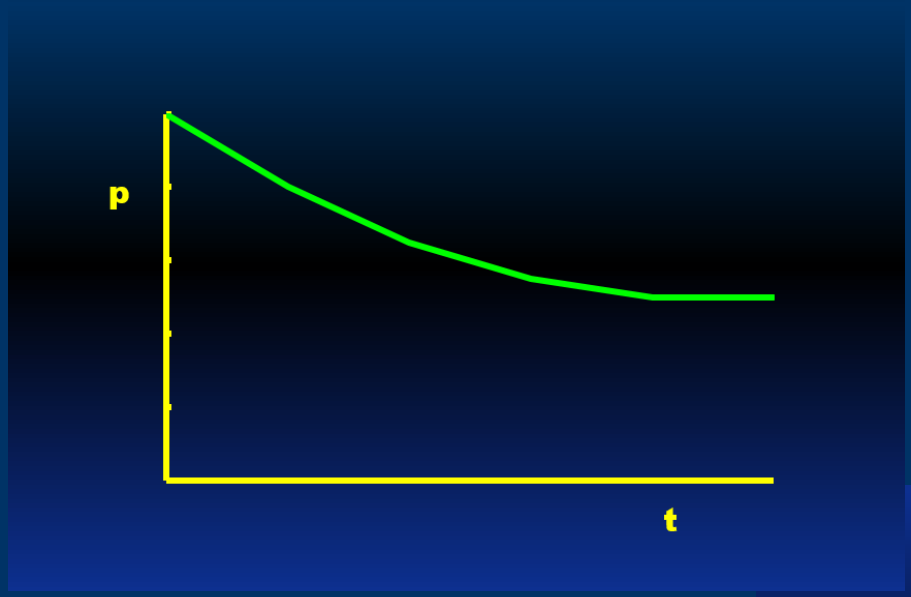
social

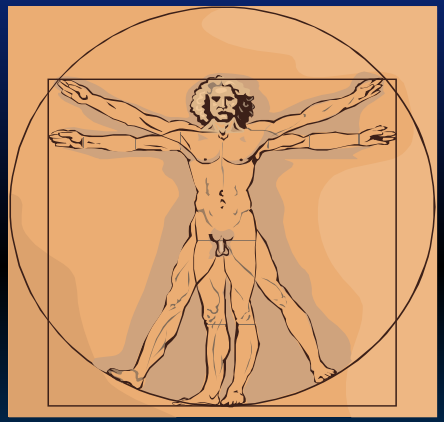
well being

"Health is a state of complete
physical, mental, and social well-being
and not merely the absence of disease or infirmity"

World Health Organization, 1948

Survival and Quality of life





Toxicity...

Am J Clin Oncol (CCT) 5: 649-655, 1982.

Toxicity and response criteria of the Eastern Cooperative Oncology Group

Martin M. Oken, M.D.[a]
Richard H. Creech M.D.[b]
Douglass C. Tormey, M.D., Ph.D.,[c]
John Horton M.D., Ch.B.,[d]
Thomas E. Davis, M.D.[c]
Eleanor T. McFadden[e]
Paul P. Carbone M.D.[c]

STANDARD CRITERIA FOR TOXICITY and for response to treatment are important prerequisites to the conduct of cancer trials. The Eastern Cooperative Oncology Group criteria for toxicity and response are presented to facilitate future reference and to encourage further standardization among those conducting clinical trials.

Reporting Results of Cancer Treatment

A. B. MILLER, MB, FRCP(C), B. HOOGSTRATEN, MD, M. STAQUET, MD, AND A. WINKLER, MD*

On the initiative of the World Health Organization, two meetings on the Standardization of Reporting Results of Cancer Treatment have been held with representatives and members of several organizations. Recommendations have been developed for standardized approaches to the recording of baseline data relating to the patient, the tumor, laboratory and radiologic data, the reporting of treatment, grading of acute and subacute toxicity, reporting of response, recurrence and disease-free interval, and reporting results of therapy. These recommendations, already endorsed by a number of organizations, are proposed for international acceptance and use to make it possible for investigators to compare validly their results with those of others.

Cancer **47:207–214, 1981.**

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Blood and lymphatic system disorders

Adverse Event	1
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mm <LLN - 100 g/L
Definition: A disorder characterized by an reduction in the mucous membranes, shortness of breath, palpitations of t	
Bone marrow hypocellular	Mildly hypocellular or <=2 reduction from normal cellularity for age
Definition: A disorder characterized by the inability of the b	
Disseminated intravascular coagulation	-
Definition: A disorder characterized by systemic pathologic increase in the risk of hemorrhage as the body is depleted	
Febrile neutropenia	-
Definition: A disorder characterized by an ANC <1000/mm (100.4 degrees F) for more than one hour.	

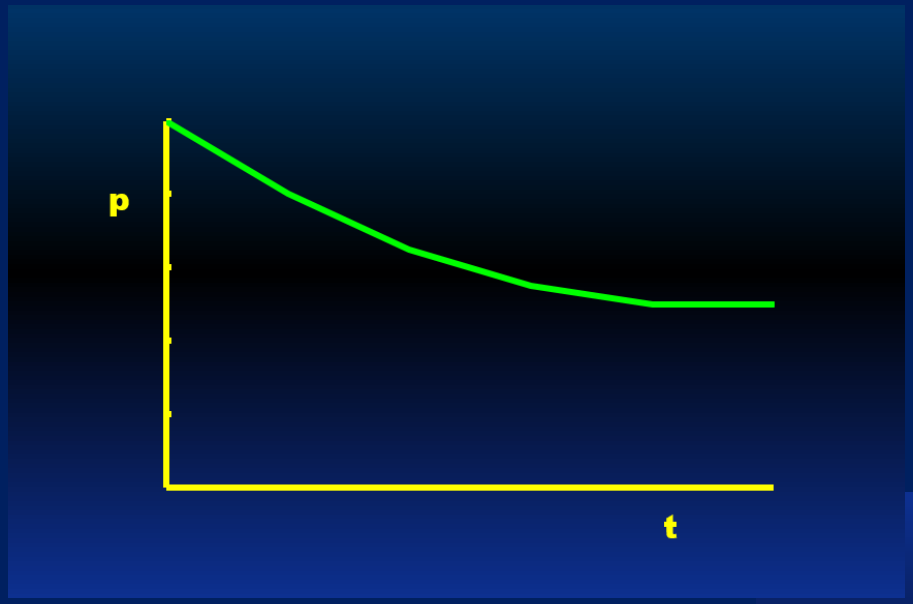
Cardiac disorders

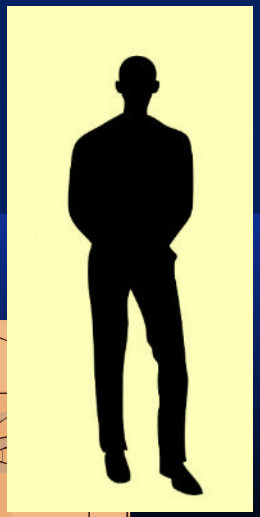
Adverse Event	1
Definition: A disorder characterized by a dysrhythmia without disturbance originates above the ventricles.	
Atrial flutter	Asymptomatic, intervention not indicated
Definition: A disorder characterized by a dysrhythmia with orga in the atria.	
Atrioventricular block complete	-
Definition: A disorder characterized by a dysrhythmia with com	
Atrioventricular block first degree	Asymptomatic, intervention not indicated
Definition: A disorder characterized by a dysrhythmia with a de beyond 0.2 seconds; prolongation of the PR interval greater th	
Cardiac arrest	-
Definition: A disorder characterized by cessation of the pumpir	

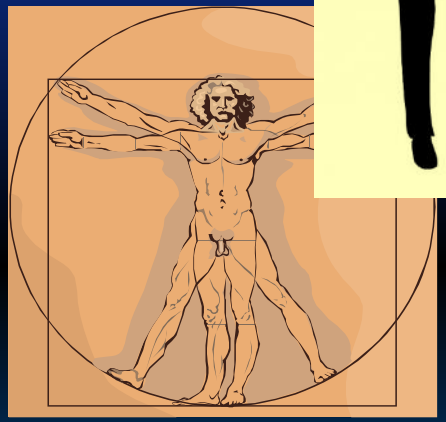
Skin and subcutaneous tissue disorders

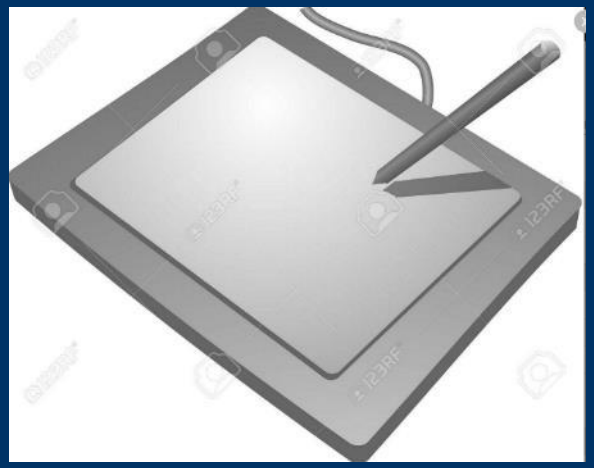
	Grade				
Adverse Event	1	2	3	4	5
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location.					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.					

Survival and Quality of life









PROs / PRO-Ms

patient's self reports on their functioning
&
well-being

Selection of the appropriate PRO questionaire in the target population

self vs interwiever vs computer administration

response format
(verbal descriptor vs numeric rating scale)

generic vs disease specific

single vs multi-items scale

focus on assessment
(severity, frequency, interference, bother)

level of psychometry evidence
(validity, reliability, ...)

...

SAcral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO)

Trial name: **SACRO**

Study code: **ISG -2016-SACRO**

Sponsor's Name and Address: Italian Sarcoma Group
c/o Istituti Ortopedici Rizzoli
Via di Barbiano, 1/10 – 40136 Bologna - Italy

Sponsor's Telephone Number: +39 051 63.66.740

Sponsor's Fax Number: +39 051 63.66.627

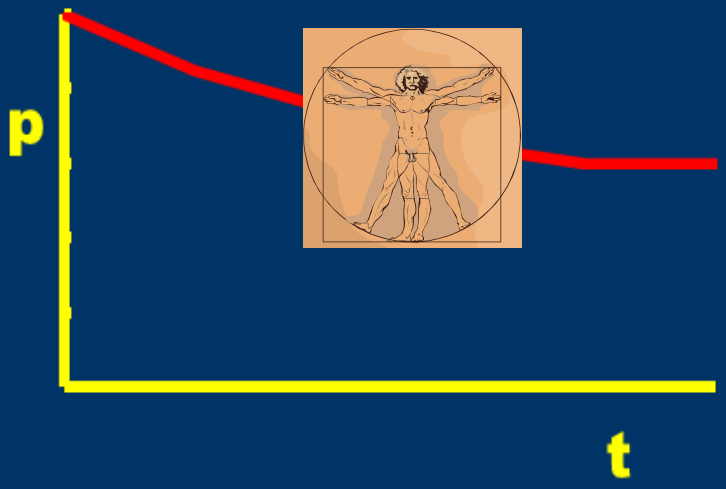
Study Number/Version/Date: Vers 1.0. 07 July 2016

Type: No Profit

Founding: **Chordoma Foundation**

The undersigned confirm that they agree to conduct the study under the conditions described in this protocol

Quality-adjusted life expectancy (QUALE)

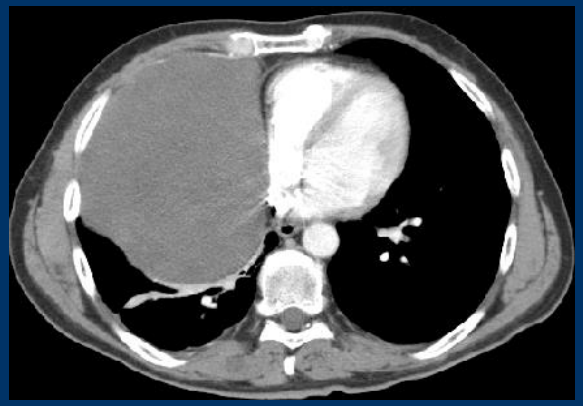


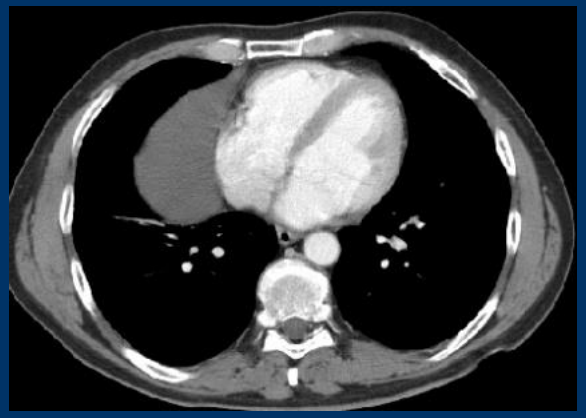
= LE x U

Tumor response…

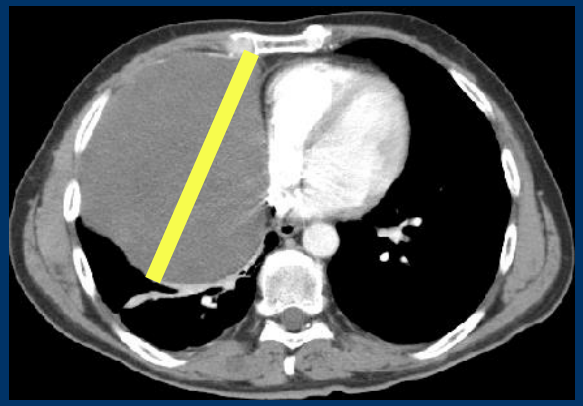
CR	complete response
PR	partial response
SD	stable disease
PD	progression

Tumor response

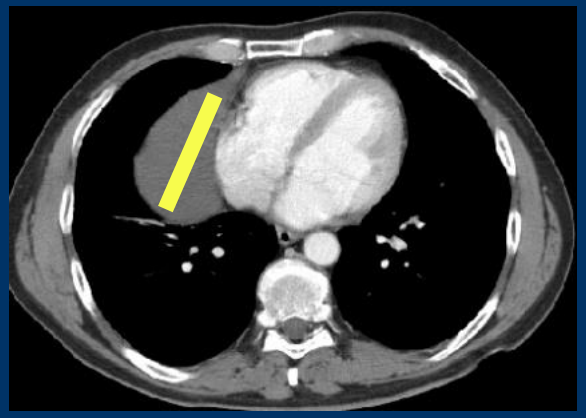




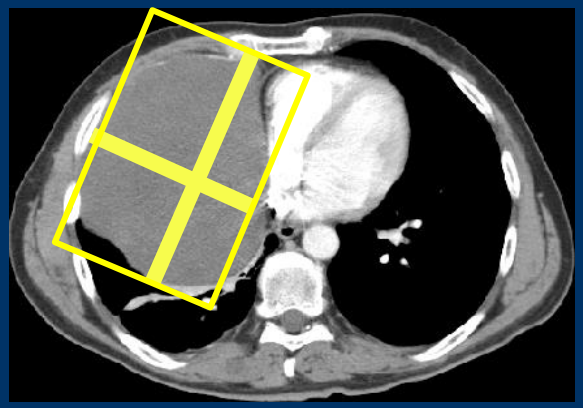
Tumor response



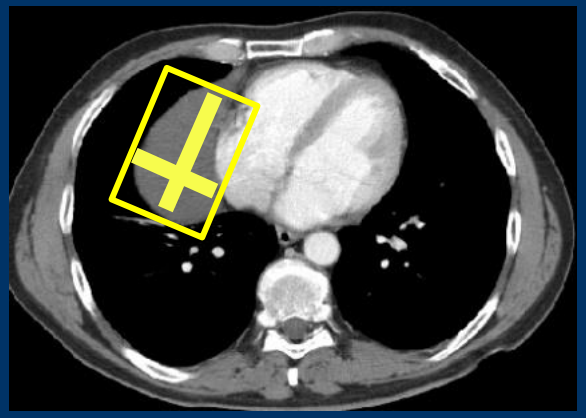
>30%
reduction



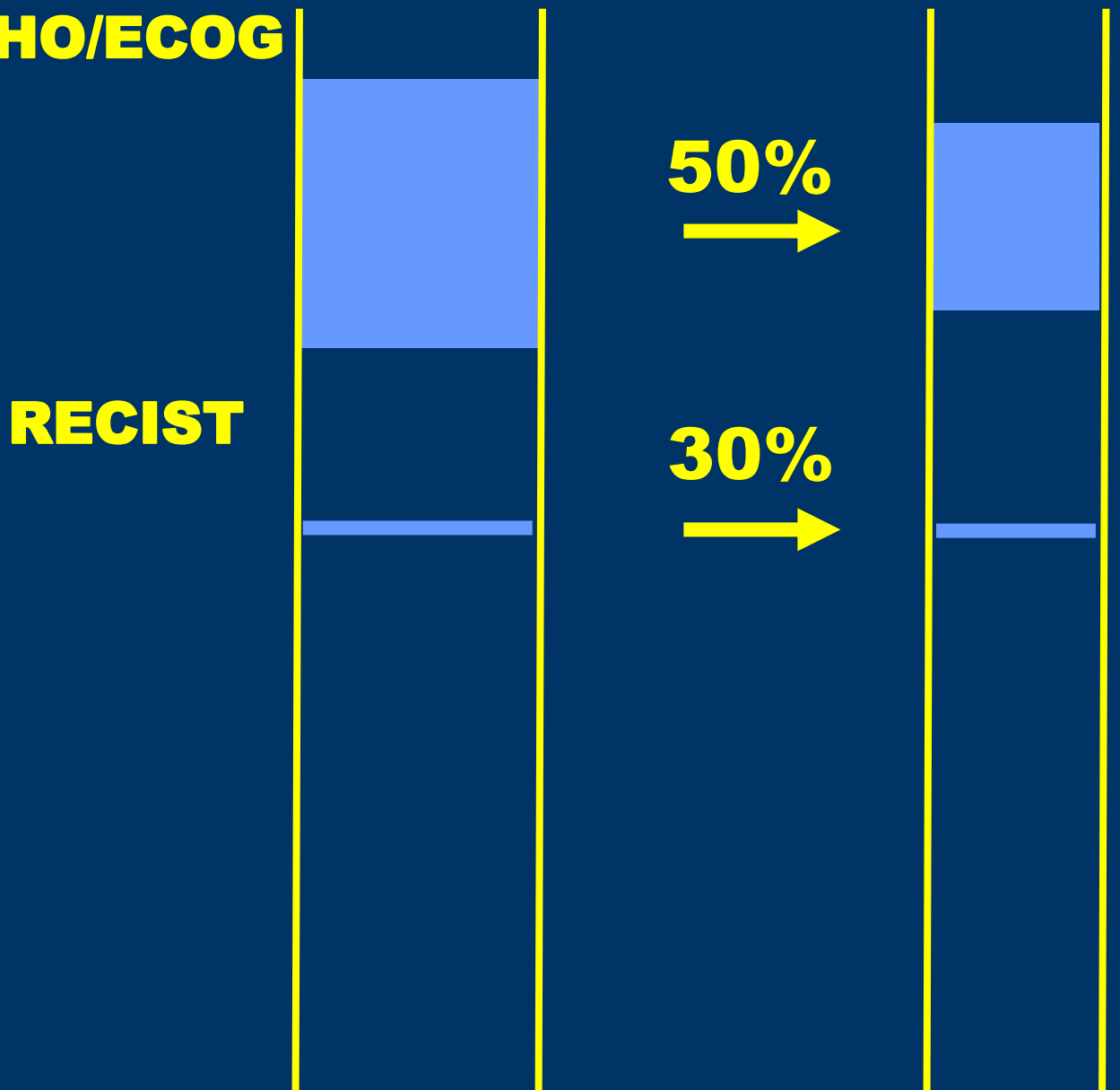
Tumor response



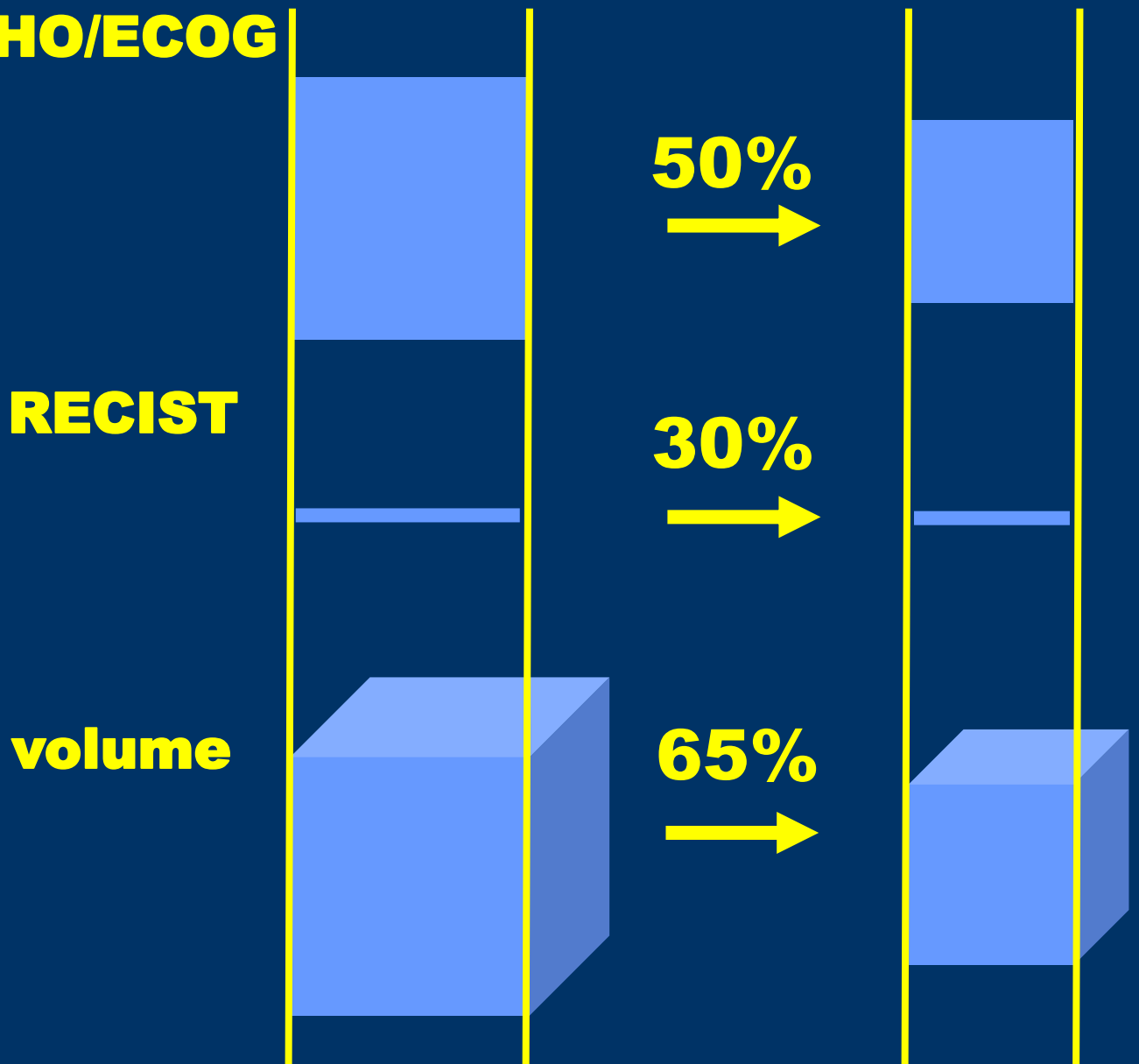
>50%
reduction



Tumor response



Tumor response



THE USE OF THE NITROGEN MUSTARDS IN THE PALLIATIVE TREATMENT OF CARCINOMA

With Particular Reference to Bronchogenic Carcinoma

DAVID A. KARNOFSKY, M.D.,* WALTER H. ABELMANN, M.D.,
LLOYD F. CRAVER, M.D., and JOSEPH H. BURCHENAL, M.D.†

PERFORMANCE STATUS

Definition	%	*Criteria*
Able to carry on normal activity and to work. No special care is needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospitalization is indicated although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

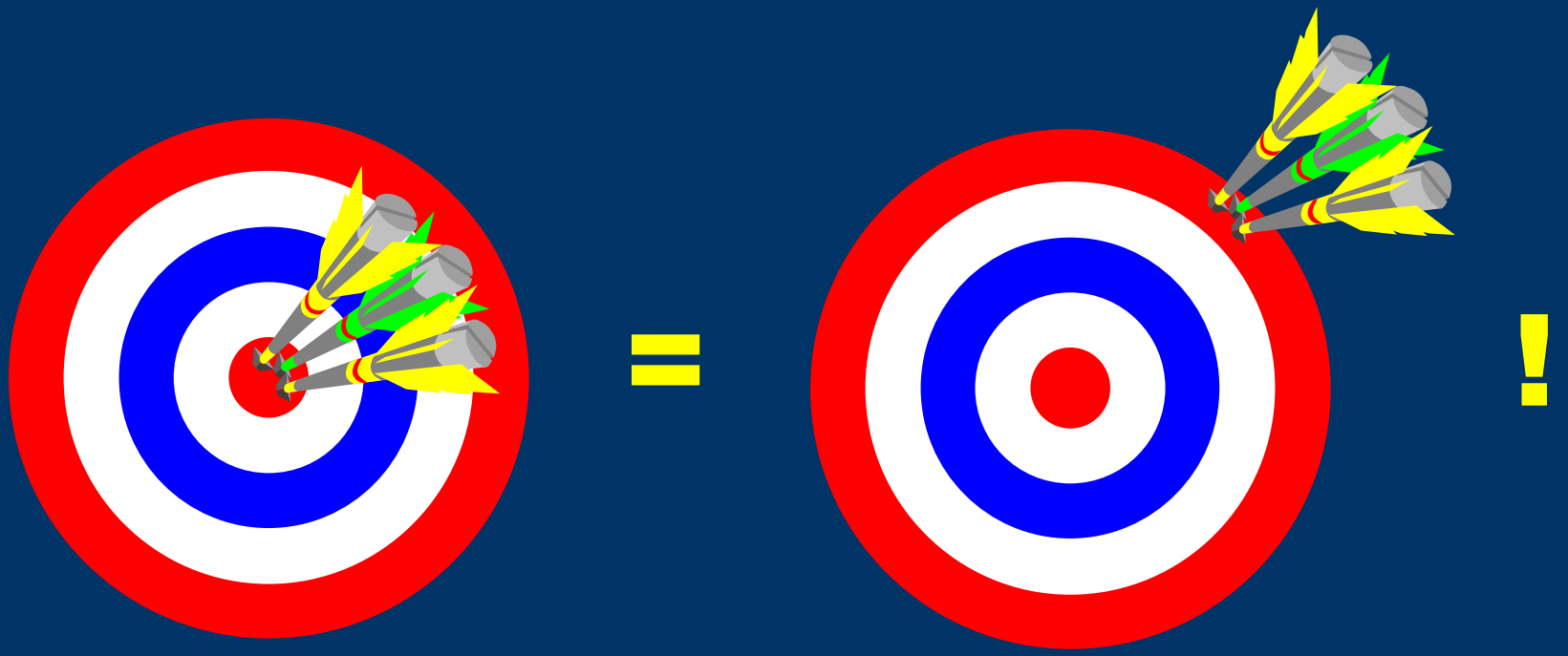
CARCINOMA OF THE LUNG

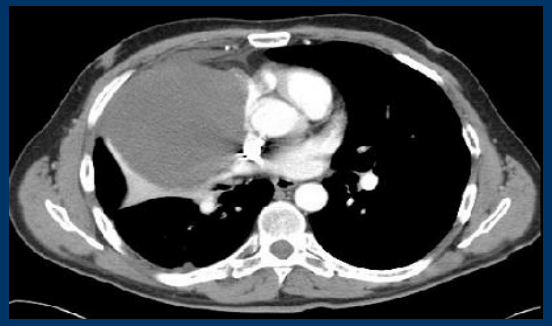
Per Cent of Patients Showing Objective and Subjective Improvement and Change in Performance Status Following the Combination of HN_2 and Roentgen-Ray Therapy

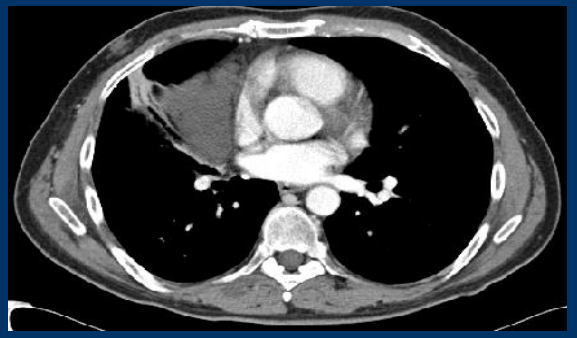
		% Improvement						*Performance status % Change*						
		Subjective			*Objective*									
Group	*No. cases*	*G*	*F*	*O*	*++*	*+*	*0*	*—10*	*0*	*10*	*20*	*30*	*40*	*50*
Anaplastic	6	50	33	17	67	16	17	0	33	16	17	16	0	17
Epidermoid	6	0	67	33	0	50	50	0	67	17	16	0	0	0
Total group	14	43	36	21	28	36	36	0	36	14	29	14	0	7

Cancer 1948;1:634

Reproducibility …







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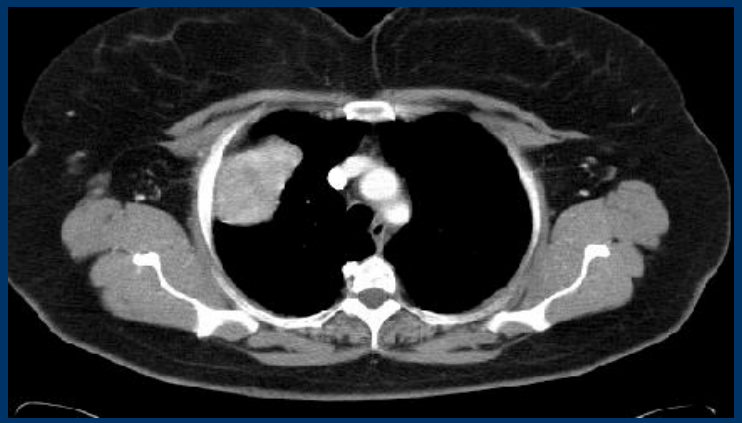
course 2

course 6



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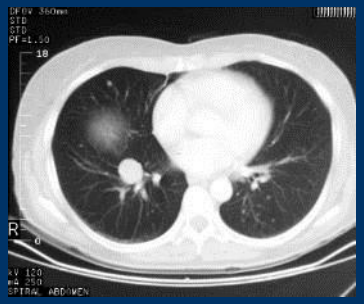
course 2



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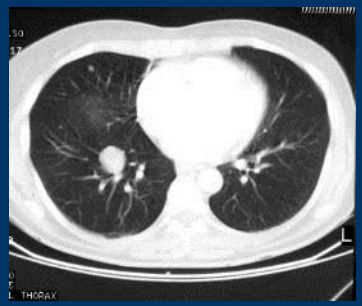
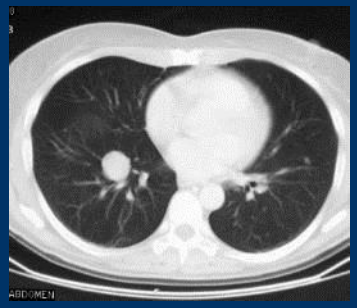
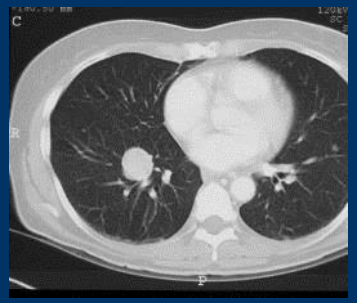


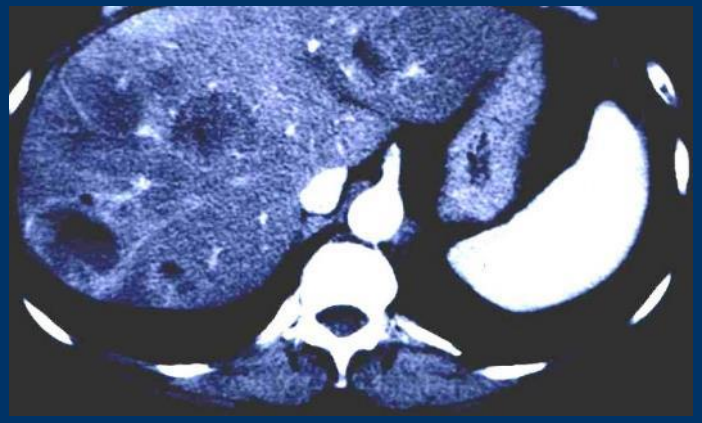
course 2

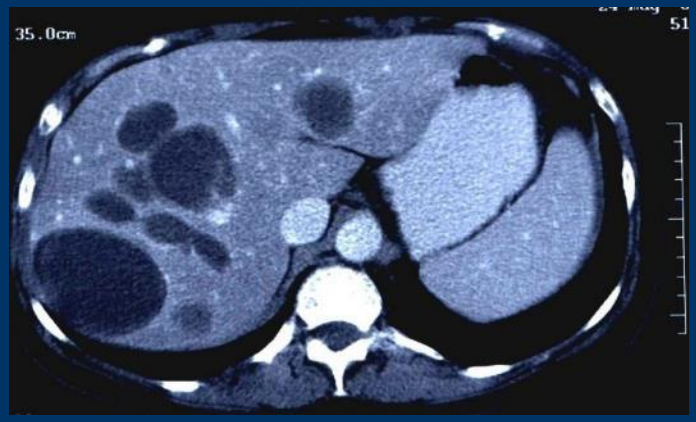


course 4



course 9

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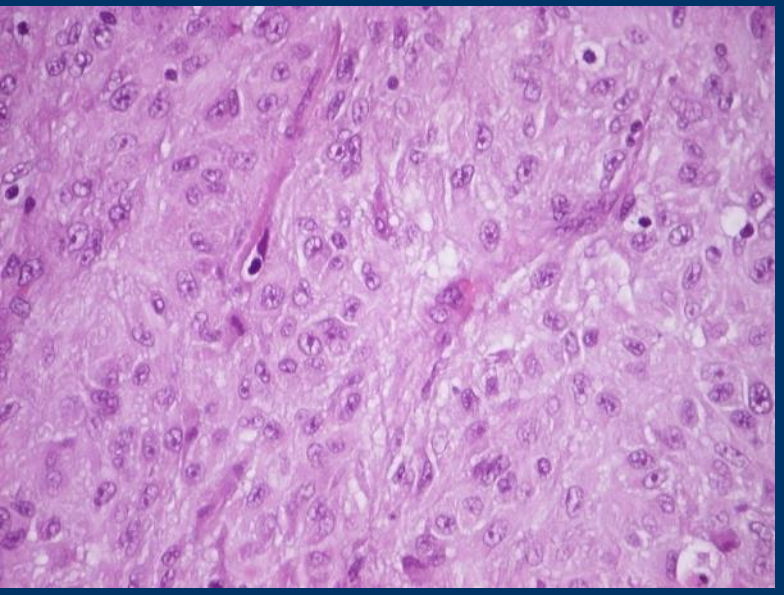
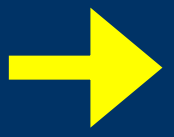
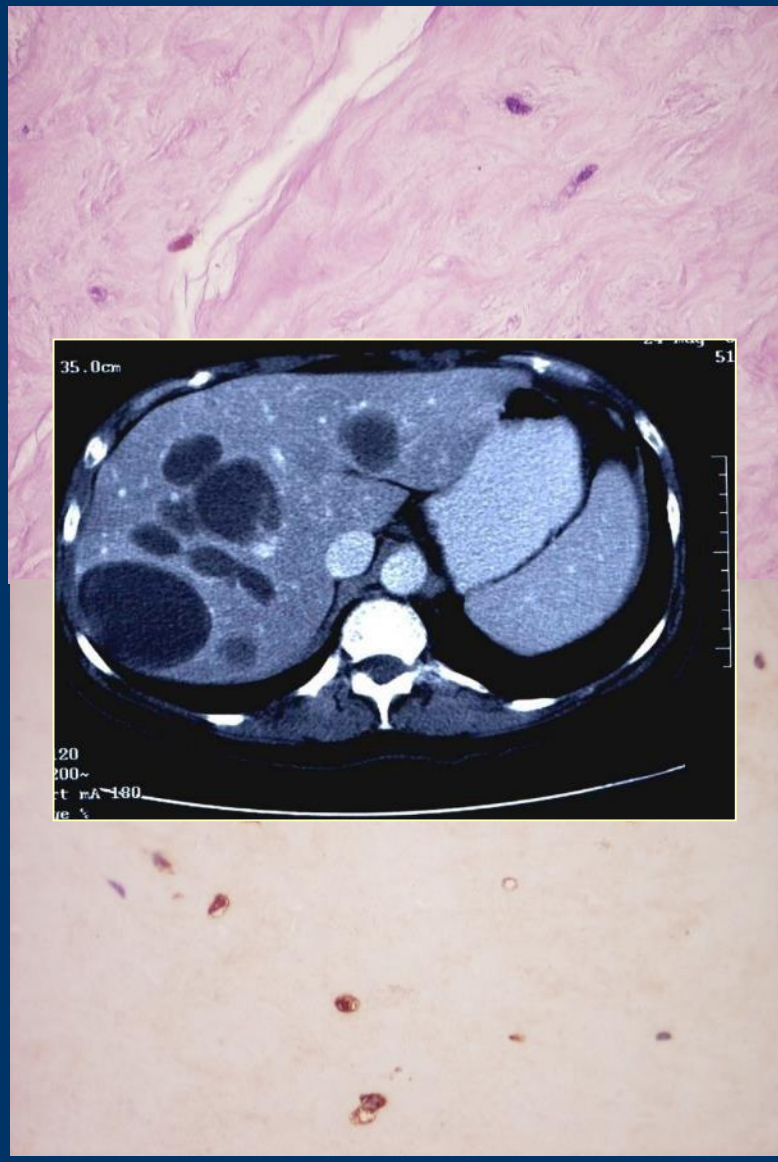
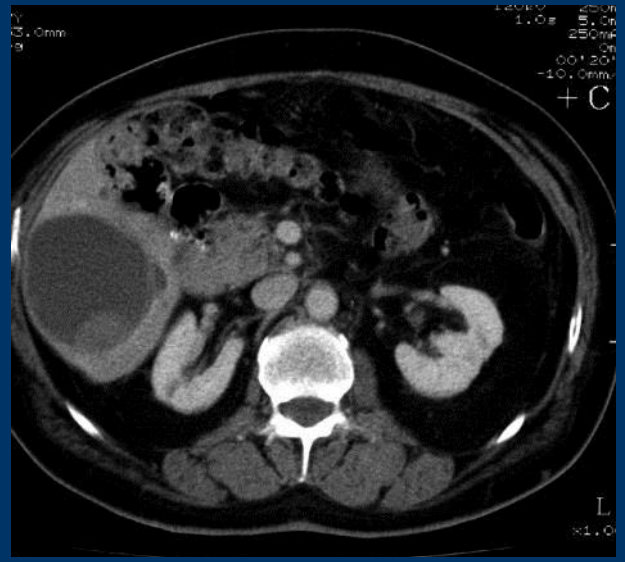


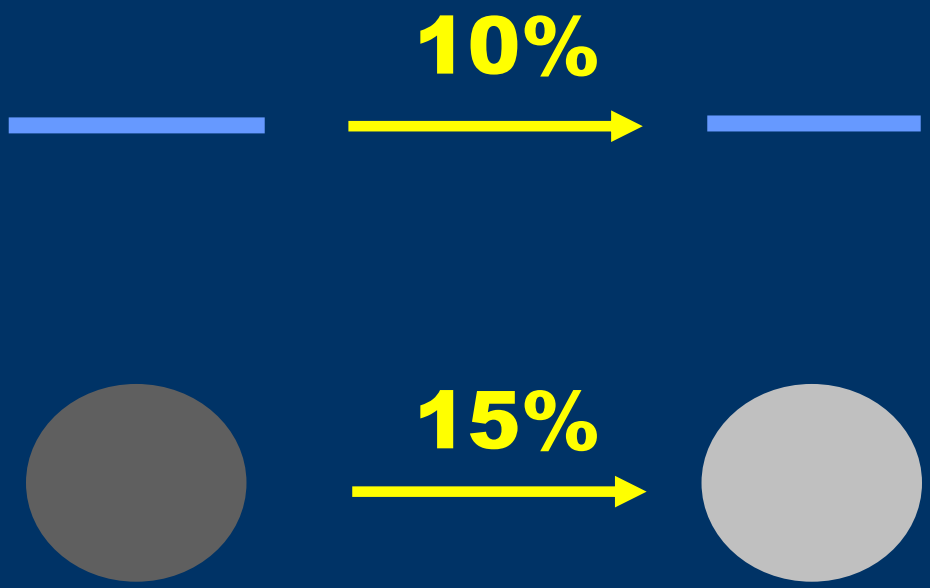


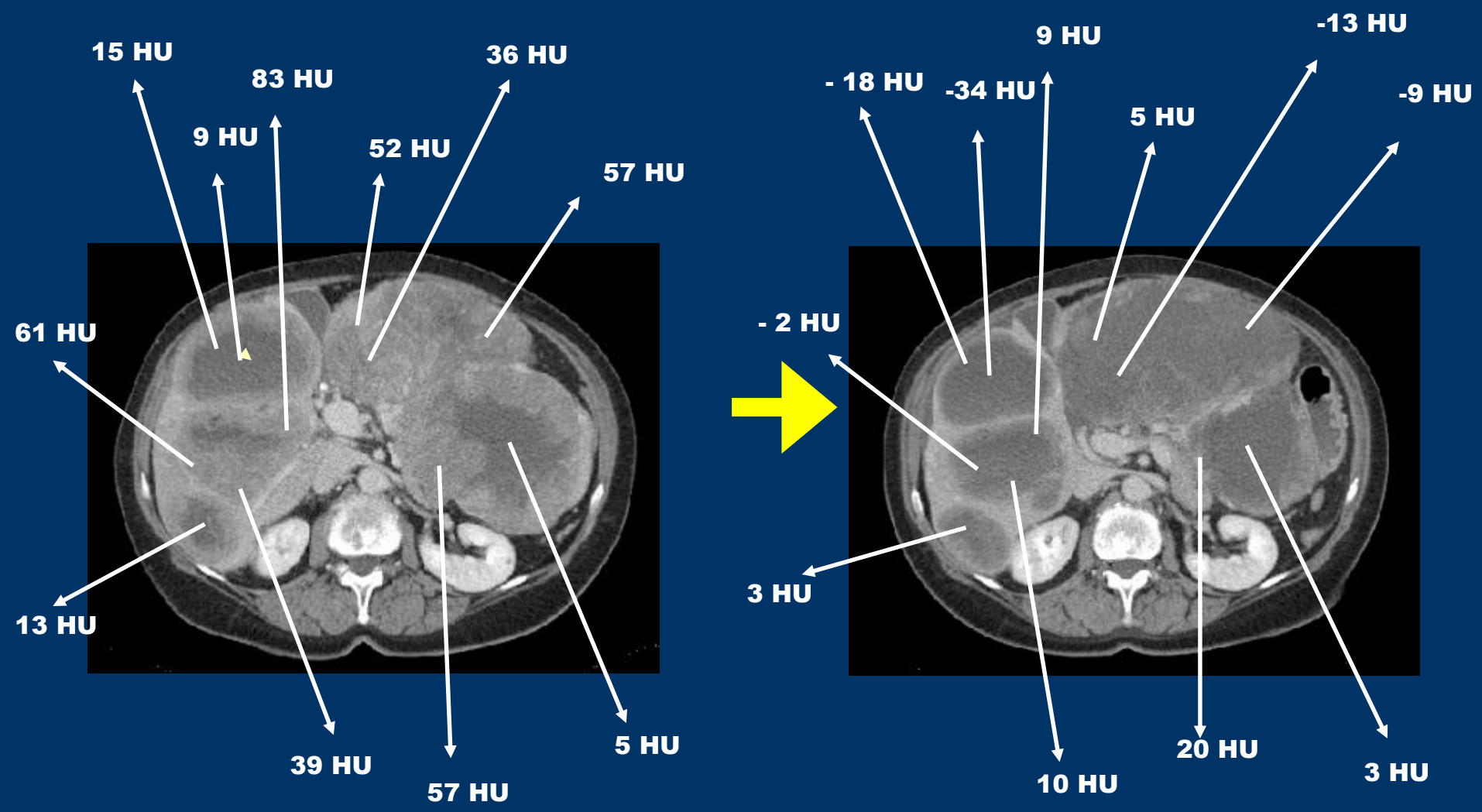

35.0cm
51
120
200~
rt mA 480



Tumor response

Choi's




15 HU
83 HU
36 HU
9 HU
52 HU
57 HU
61 HU
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39 HU
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-13 HU
- 18 HU
-34 HU
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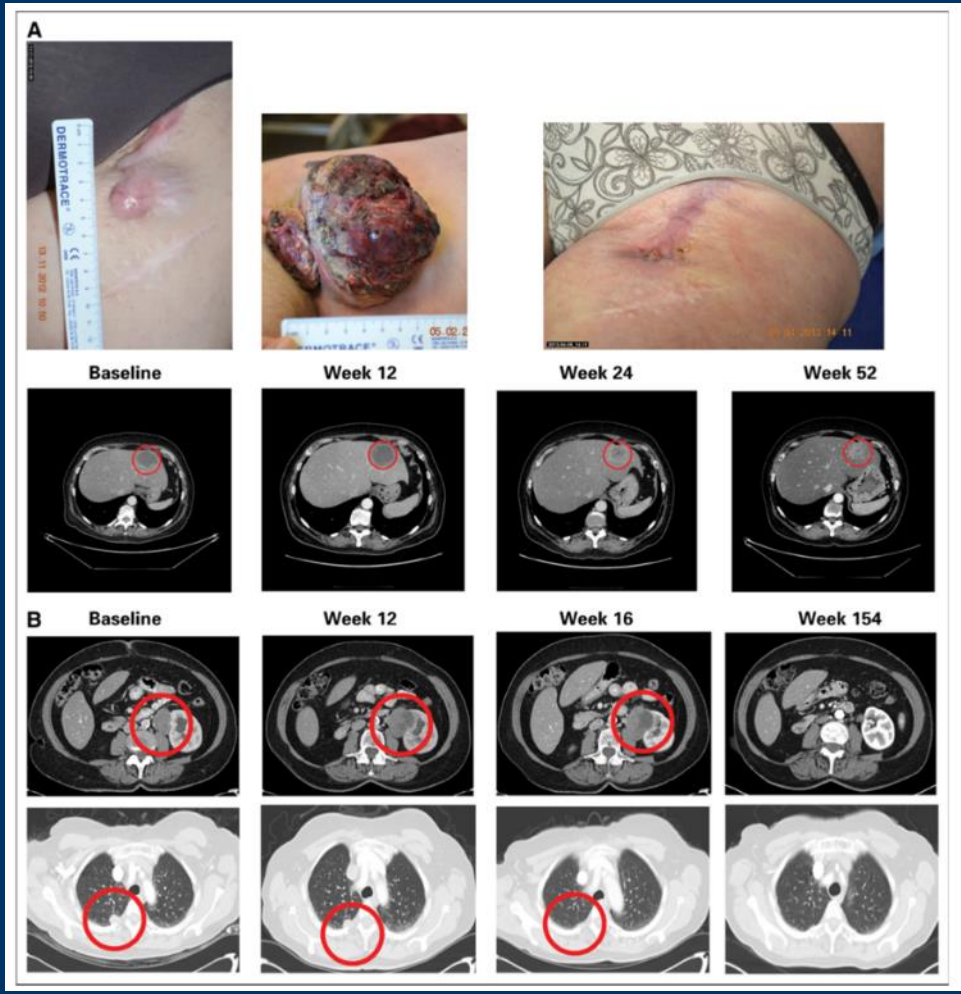
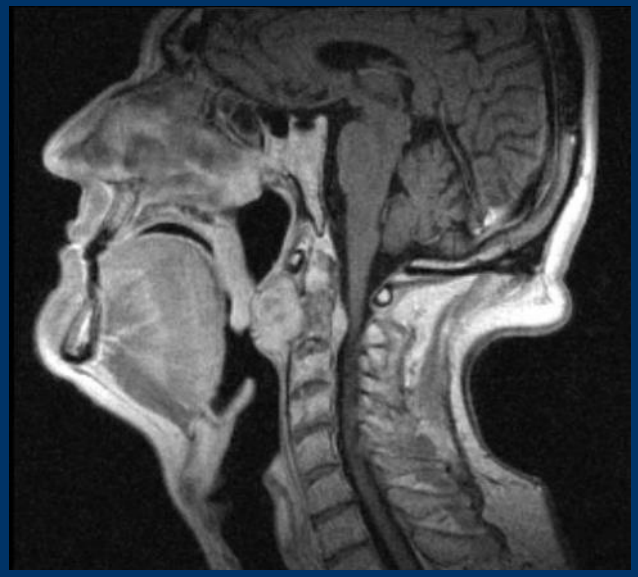
Pseudoprogression



Hodi FS et al. JCO 2016; 34:1510



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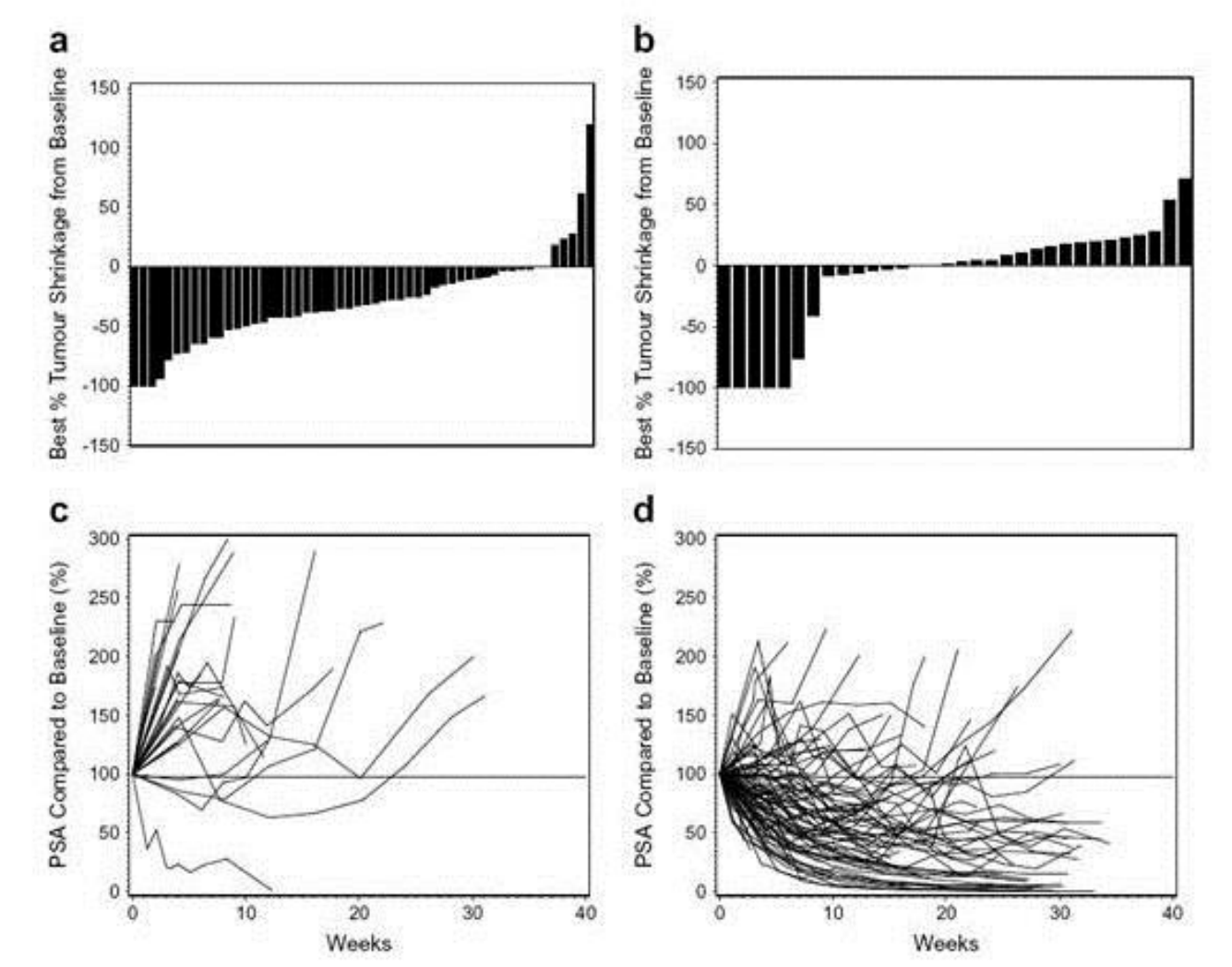
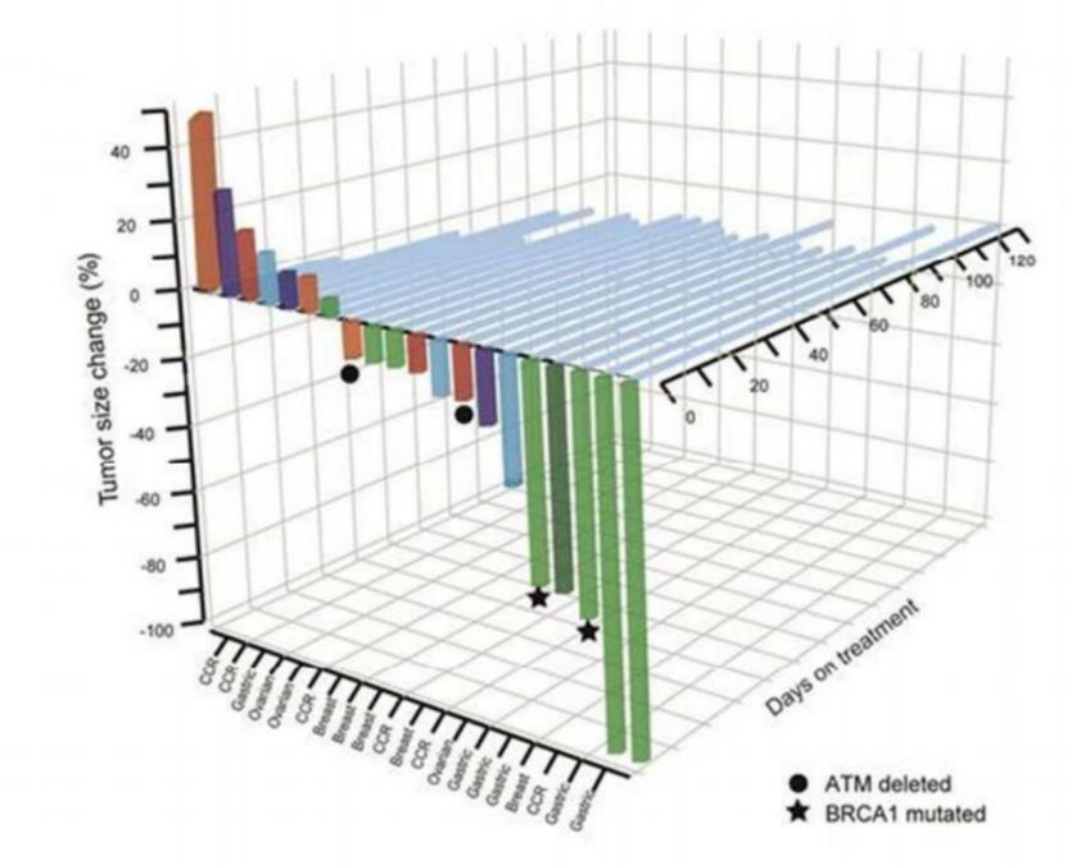
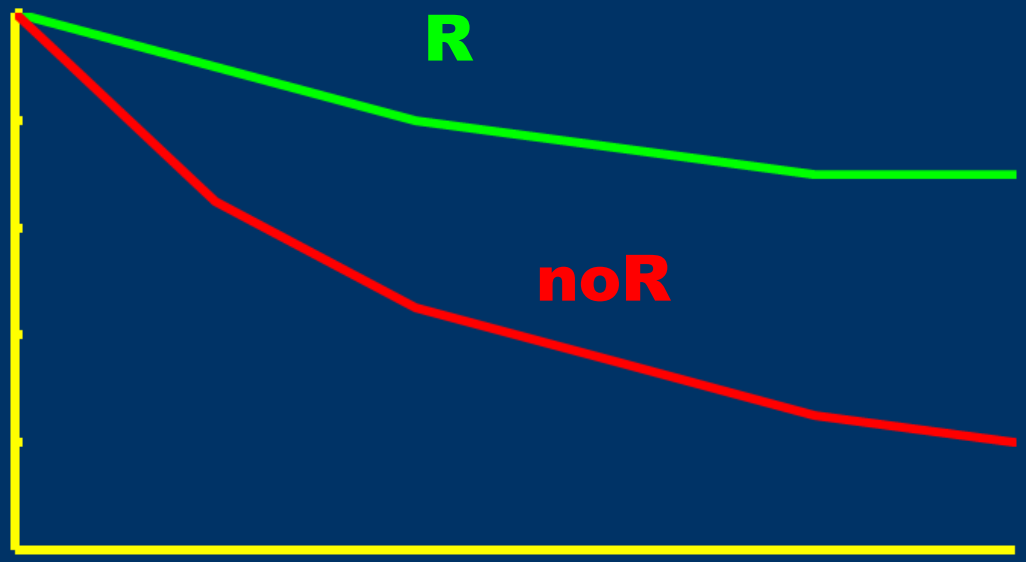


Booth CM et al. Eur J Cancer 2008;44:25

3D Waterfall plots



Castanon E et al. Ann Oncol 2016 Dec 19 [Epub]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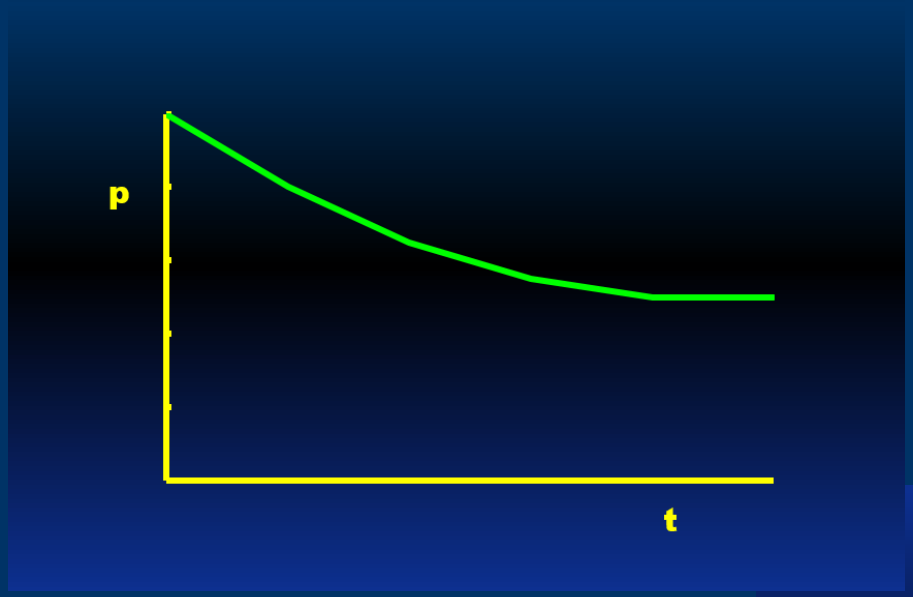
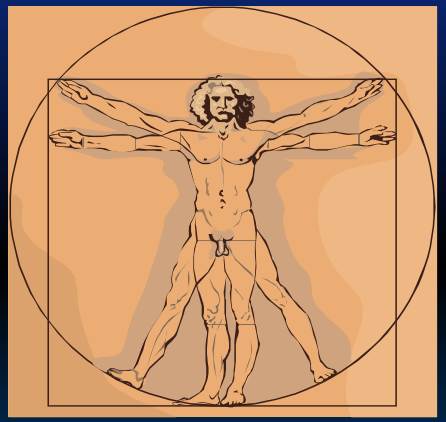
Survival and Quality of life …





… clinical trial end-points

NATURAL

Overall survival
Quality of life

SURROGATE

SURROGATE END-POINT:
a measure of effect of a specific treatment that may correlate with a real clinical end-point but does not necessarily have a guaranteed relationship

Freedom from…

Time to progression

Progression-free survival

- PD
- death

Progression-free interval

- PD

OPEN FOR DISCUSSION !

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