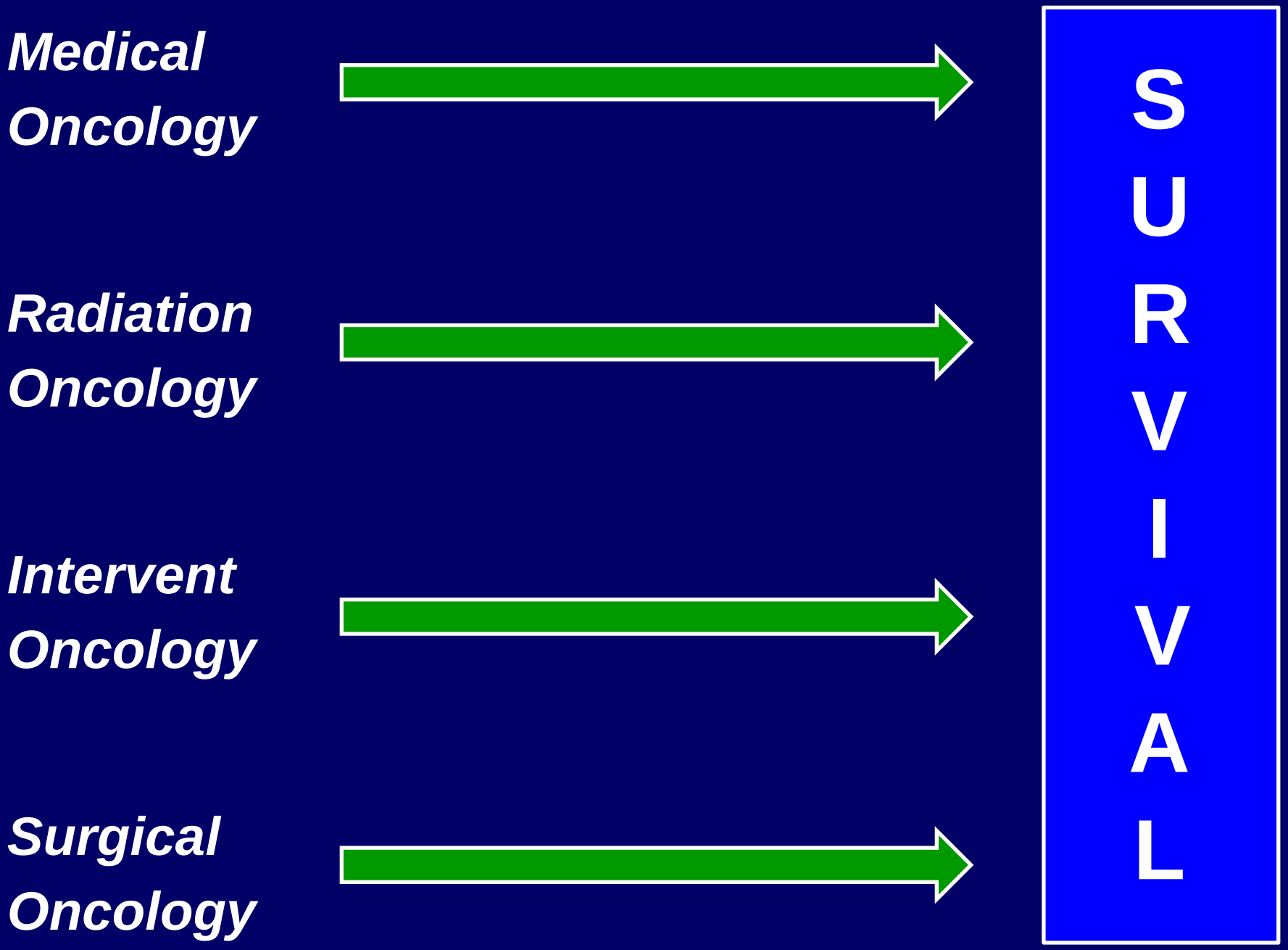
Interventional Oncology Series

New Horizons of Interventional Oncology:

The Future May Be Now

Ablation Assessment: Can We Get Beyond Contrast Enhancement?

Riccardo Lencioni, MD, FSIR, EBIR


Medical Oncology
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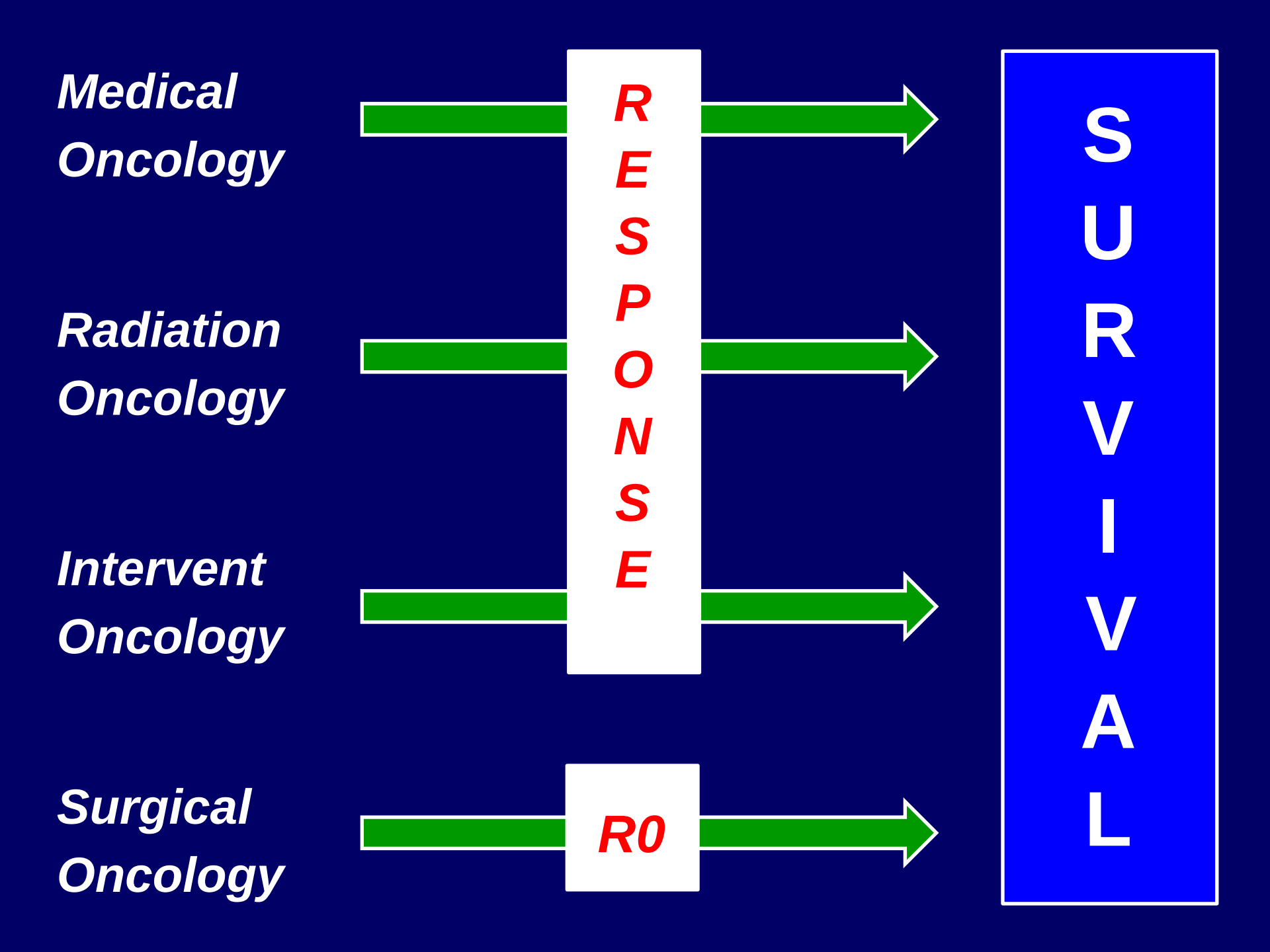
Medical Oncology
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Response Evaluation Criteria in Solid Tumors (RECIST)

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan T. van Oosterom, Michaele C. Christian, Steve G. Gwyther

Anticancer cytotoxic agents go through a process by which their antitumor activity—on the basis of the amount of tumor shrinkage they could generate—has been investigated. In the late 1970s, the International Union Against Cancer and the World Health Organization introduced specific criteria for the codification of tumor response evaluation. In 1994, several organizations involved in clinical research combined forces to tackle the review of these criteria on the basis of the experience and knowledge acquired since then. After several years of intensive discussions, a new set of guidelines is ready that will supersede the former criteria. In parallel to this initiative, one of the participating groups developed a model by which response rates could be derived from unidimensional measurement of tumor lesions instead of the usual bidimensional approach. This new concept has been largely validated by the Response Evaluation Criteria in Solid Tumors Group and integrated into the present guidelines. This special article also provides some philosophic background to clarify the various purposes of response evaluation. It proposes a model by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment. Methods of assessing tumor lesions are better codified, briefly within the guidelines and in more detail in Appendix I. All other aspects of response evaluation have been discussed, reviewed, and amended whenever appropriate. [J Natl Cancer Inst 2000; 92:205–16]

A. Preamble

Early attempts to define the objective response of a tumor to an anticancer agent were made in the early 1960s *(1,2)*. In the mid- to late 1970s, the definitions of objective tumor response were widely disseminated and adopted when it became apparent that a common language would be necessary to report the results of cancer treatment in a consistent manner.

The World Health Organization (WHO) definitions published in the 1979 *WHO Handbook (3)* and by Miller et al. *(4)* in 1981 have been the criteria most commonly used by investigators around the globe. However, some problems have developed with the use of WHO criteria: 1) The methods for integrating into response assessments the change in size of measurable and "evaluable" lesions as defined by WHO vary among research groups, 2) the minimum lesion size and number of lesions to be recorded also vary, 3) the definitions of progressive disease are related to change in a single lesion by some and to a change in the overall tumor load (sum of the measurements of all lesions) by others, and 4) the arrival of new technologies (computed tomography [CT] and magnetic resonance imaging [MRI]) has led to some confusion about how to integrate three-dimensional measures into response assessment.

These issues and others have led to a number of different modifications or clarifications to the WHO criteria, resulting in a situation where response criteria are no longer comparable among research organizations—the very circumstance that the WHO publication had set out to avoid. This situation led to an initiative undertaken by representatives of several research groups to review the response definitions in use and to create a revision of the WHO criteria that, as far as possible, addressed areas of conflict and inconsistency.

In so doing, a number of principles were identified:

1) Despite the fact that "novel" therapies are being developed that may work by mechanisms unlikely to cause tumor regression, there remains an important need to continue to describe objective change in tumor size in solid tumors for the foreseeable future. Thus, the four categories of complete response, partial response, stable disease, and progressive disease, as originally categorized in the *WHO Handbook (3)*, should be retained in any new revision.
2) Because of the need to retain some ability to compare favorable results of future therapies with those currently available, it was agreed that no major discrepancy in the meaning and the concept of partial response should exist between the old and the new guidelines, although measurement criteria would be different.
3) In some institutions, the technology now exists to determine

Affiliations of authors: P. Therasse, J. Verweij, M. Van Glabbeke, A. T. van Oosterom, European Organization for Research and Treatment of Cancer, Brussels, Belgium; S. G. Arbuck, R. S. Kaplan, L. Rubinstein, M. C. Christian, National Cancer Institute, Bethesda, MD; E. A. Eisenhauer, National Cancer Institute of Canada Clinical Trials Group, Kingston, ON, Canada; J. Wanders, New Drug Development Office Oncology, Amsterdam, The Netherlands; S. G. Gwyther, East Surrey Healthcare National Health Service Trust, Redhill, U.K.

Correspondence to: Patrick Therasse, M.D., European Organization for Research and Treatment of Cancer Data Center, Avenue Mounier 83/11, 1200 Brussels, Belgium (e-mail: pth@eortc.be).

See "Note" following "References."

EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer[a,], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]*

[a]National Cancer Institute of Canada – Clinical Trials Group, 10 Stuart Street, Queen's University, Kingston, ON, Canada
[b]GlaxoSmithKline Biologicals, Rixensart, Belgium
[c]European Organisation for Research and Treatment of Cancer, Data Centre, Brussels, Belgium
[d]Memorial Sloan Kettering Cancer Center, New York, NY, USA
[e]Mayo Clinic, Rochester, MN, USA
[f]RadPharm, Princeton, NJ, USA
[g]Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA
[h]Schering-Plough, Kenilworth, NJ, USA
[i]East Surrey Hospital, Redhill, Surrey, UK
[j]National Cancer Research Network, Leeds, UK
[k]Erasmus University Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed:* based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a short axis of ⩾15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

* *Corresponding author:* Tel.: +1 613 533 6430; fax: +1 613 533 2411.
E-mail address: eeisenhauer@ctg.queensu.ca (E.A. Eisenhauer).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.10.026

J Natl Cancer Inst 2000;92:205-216

Eur J Cancer 2009;45:228-247

Response Evaluation Criteria in Solid Tumors (RECIST)

- **Complete Response (CR)**
  - *Disappearance of all target lesions*
- **Partial Response (PR)**
  - *At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter*
- **Stable Disease (SD)**
  - *Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD*
- **Progressive Disease (PD)**
  - *At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started*

Response Assessment after Loco-Regional Therapy in HCC: RECIST Criteria are Useless

Evaluation of Tumor Response After Locoregional Therapies in Hepatocellular Carcinoma

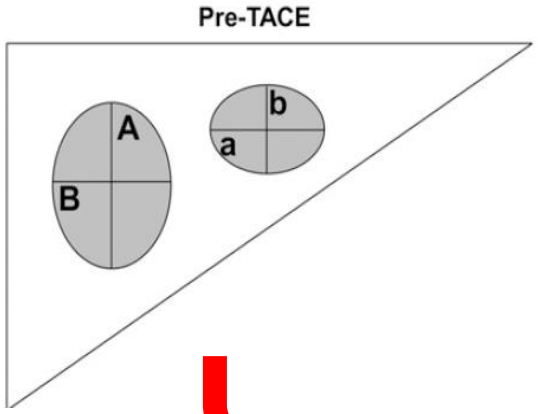
Are Response Evaluation Criteria in Solid Tumors Reliable?

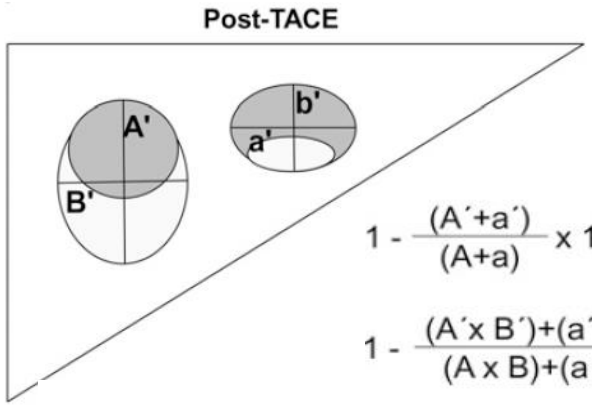
RECIST missed all complete responses and underestimated the extent of partial tumor response, wrongly assessing the therapeutic efficacy of locoregional therapies.

Forner A et al. Cancer 2009;115:616-623

Assessing the Response to Loco-Regional Therapy: Size vs Enhancement Criteria

Size criteria

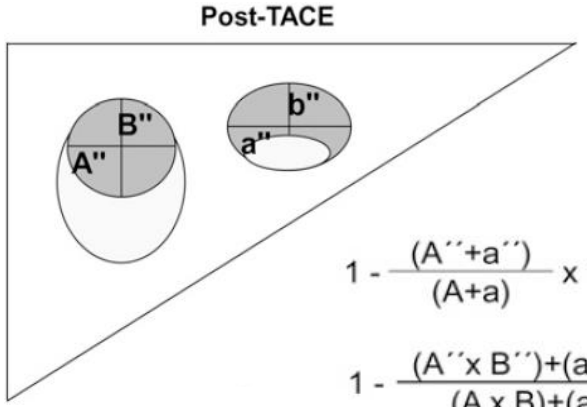




$$1 - \frac{(A' + a')}{(A + a)} \times 100\ (\%)$$: by RECIST

$$1 - \frac{(A' \times B') + (a' \times b')}{(A \times B) + (a \times b)} \times 100\ (\%)$$: by WHO

Enhancement criteria

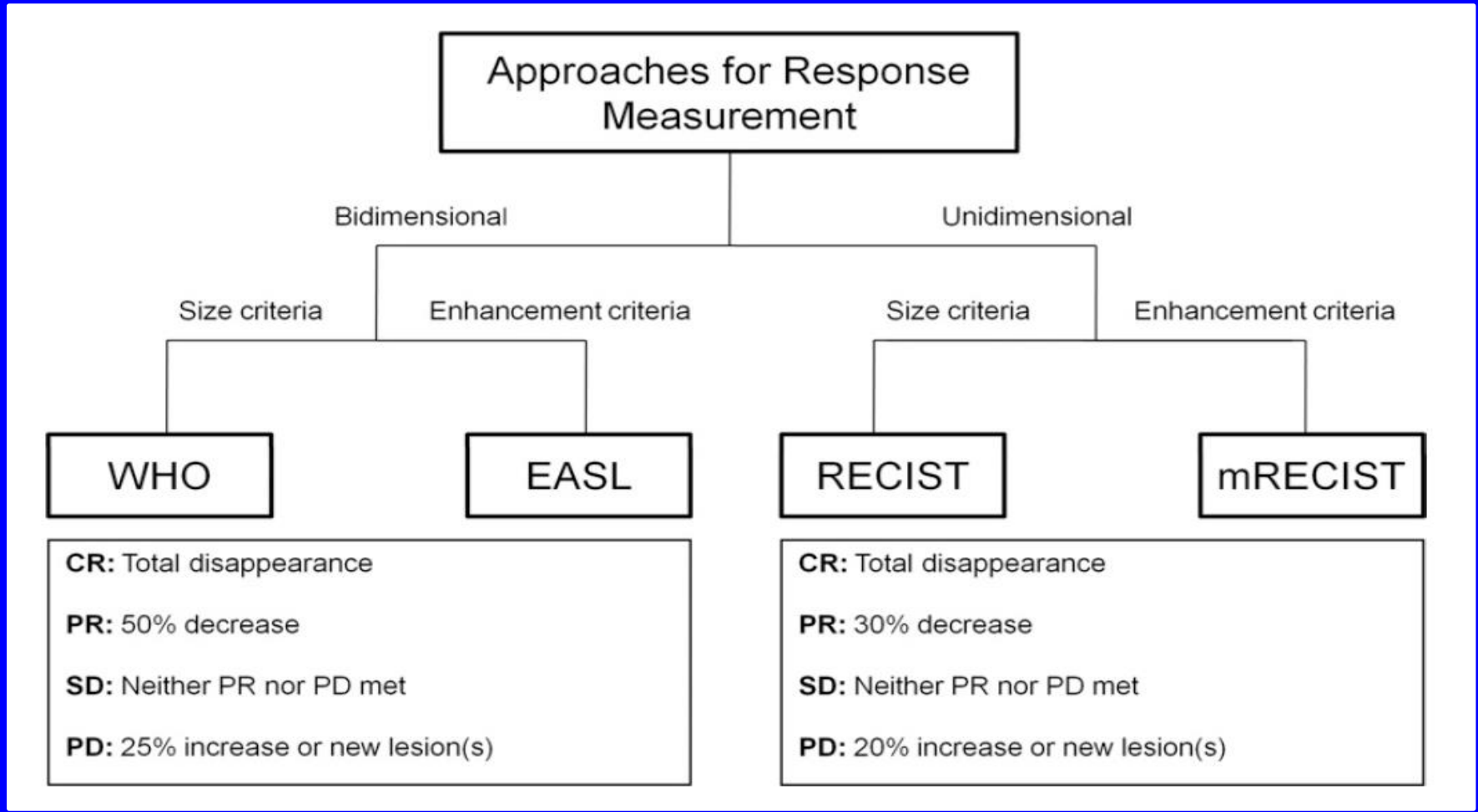


$$1 - \frac{(A'' + a'')}{(A + a)} \times 100\ (\%)$$: by mRECIST

$$1 - \frac{(A'' \times B'') + (a'' \times b'')}{(A \times B) + (a \times b)} \times 100\ (\%)$$: by EASL

Shim JH et al. Radiology 2012;262:708-718

Assessing the Response to Loco-Regional Therapy: Size vs Enhancement Criteria



Shim JH et al. Radiology 2012;262:708-718

Modified RECIST (mRECIST) for HCC

Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma

Riccardo Lencioni, M.D.,[1] and Josep M. Llovet, M.D.[2,3]

Table 3 Overall Response Assessment in mRECIST: Responses for All Possible Combinations of Tumor Responses in Target and Nontarget Lesions with or without the Appearance of New Lesions

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

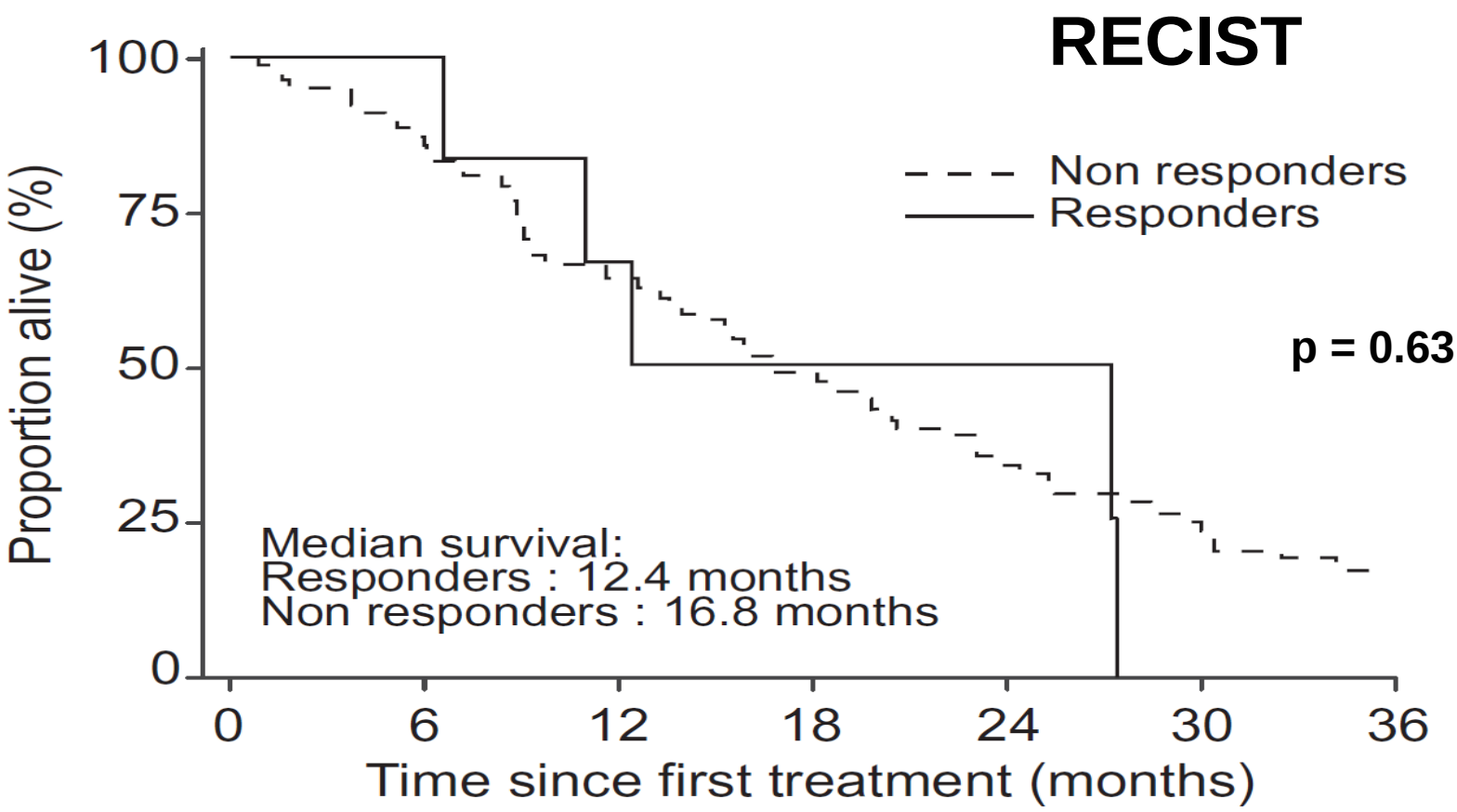
Lencioni R, Llovet JM. Semin Liver Dis 2010;30:52-60

Target Lesions Response: RECIST vs mRECIST

	RECIST	*mRECIST for HCC*
CR	**Disappearance of all target lesions**	**Disappearance of any intratumoral arterial enhancement in all target lesions**
PR	**≥ 30% decrease in the sum of diameters of target lesions** *(reference: baseline sum diameter)*	**≥ 30% decrease in the sum of diameters of viable (enhancing) target lesions**
SD	**Any cases that do not qualify for either PR or PD**	**Any cases that do not qualify for either PR or PD**
PD	**≥ 20% increase in the sum of diameters of target lesions** *(reference: smallest sum diameter)*	**≥ 20% increase in the sum of diameters of viable (enhancing) target lesions**

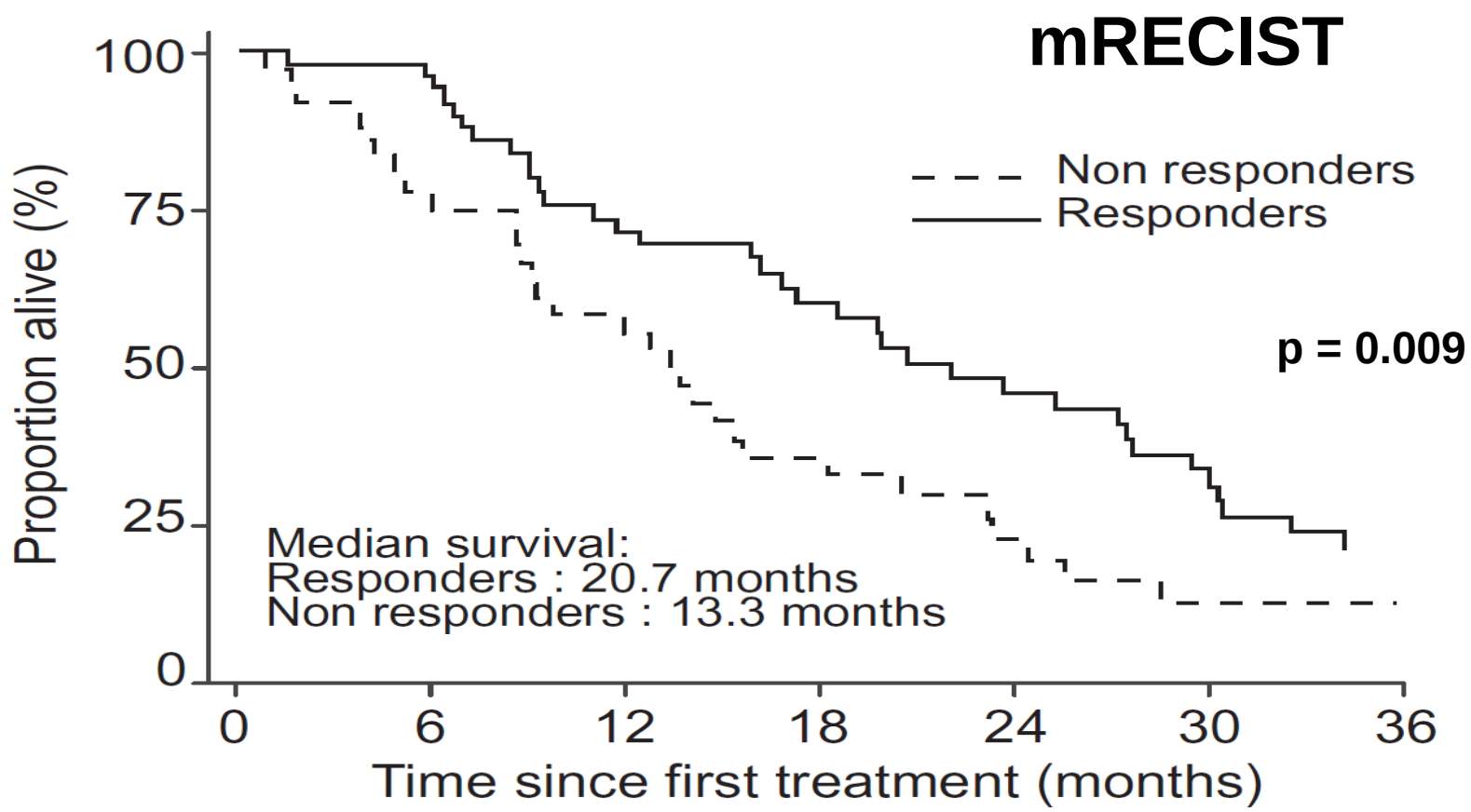
Lencioni R, Llovet JM. Semin Liver Dis 2010;30:52-60

RECIST vs mRECIST in HCC Patients Treated with TAE / DEB-TACE



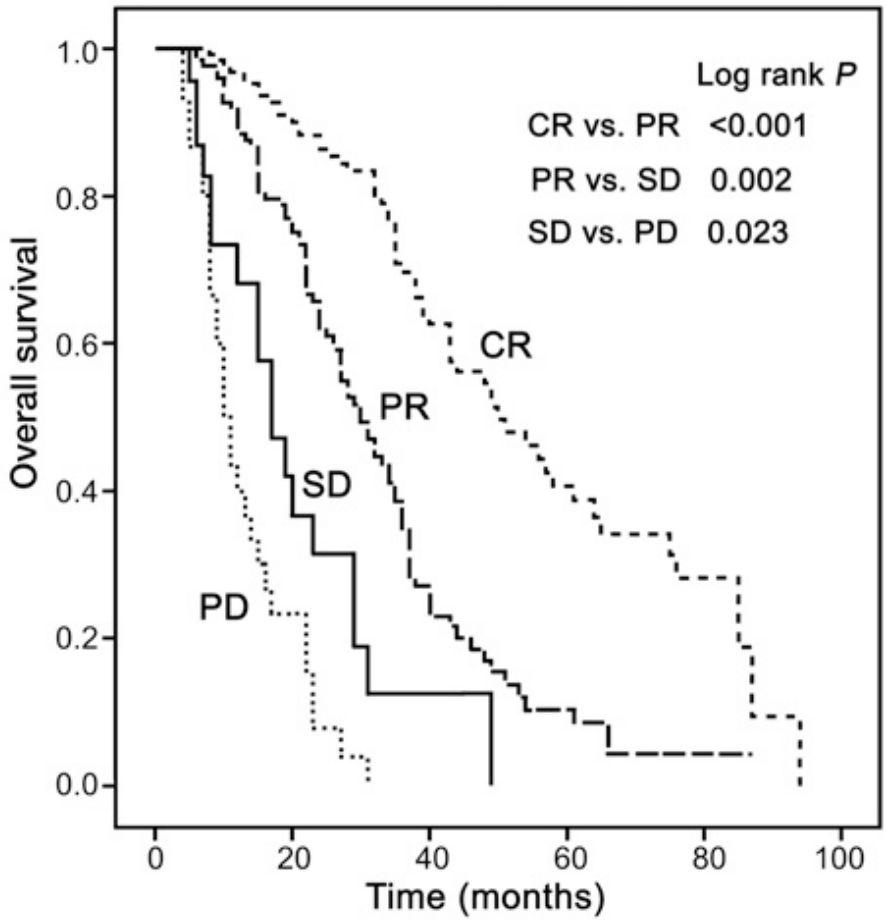
Gillmore R et al. J Hepatol 2011;55:1309-1316

RECIST vs mRECIST in HCC Patients Treated with TAE / DEB-TACE



Gillmore R et al. J Hepatol 2011;55:1309-1316

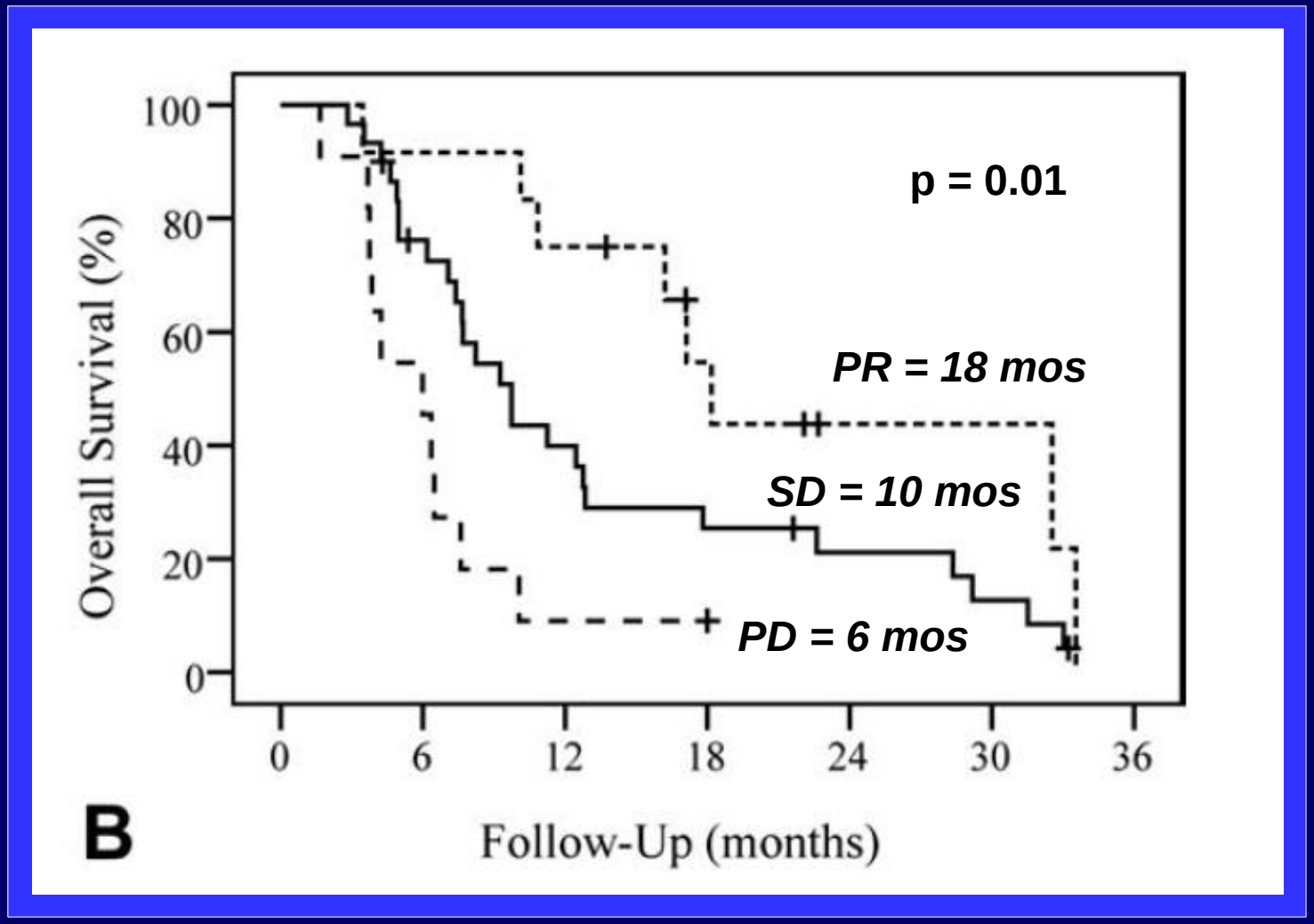
Overall Survival According to Tumor Response by mRECIST after TACE



Response	HR*
CR	1.0
PR	2.75 (1.96, 3.87)
SD	6.32 (3.67, 10.90)
PD	16.06 (9.76, 26.43)

Shim JH et al. Radiology 2012;262:708-718

Overall Survival According to Tumor Response by mRECIST in Patients Receiving Sorafenib



Edeline J et al. Cancer 2012;118:147-156

Management of Hepatocellular Carcinoma: 2012 EASL-EORTC Clinical Practice Guidelines

Assessment of response should be based on the modification of the RECIST criteria (mRECIST)

(recommendation 2B)

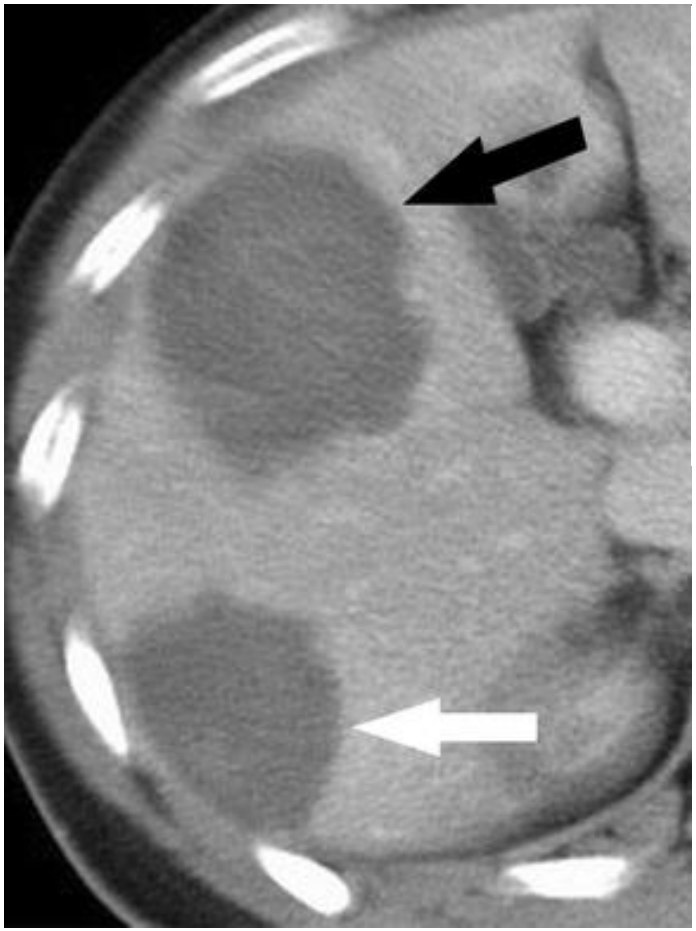
Table 5. Assessment of response comparing RECIST and mRECIST.*

Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of one or more non-target lesions	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
mRECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.	
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.	
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.	
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.	

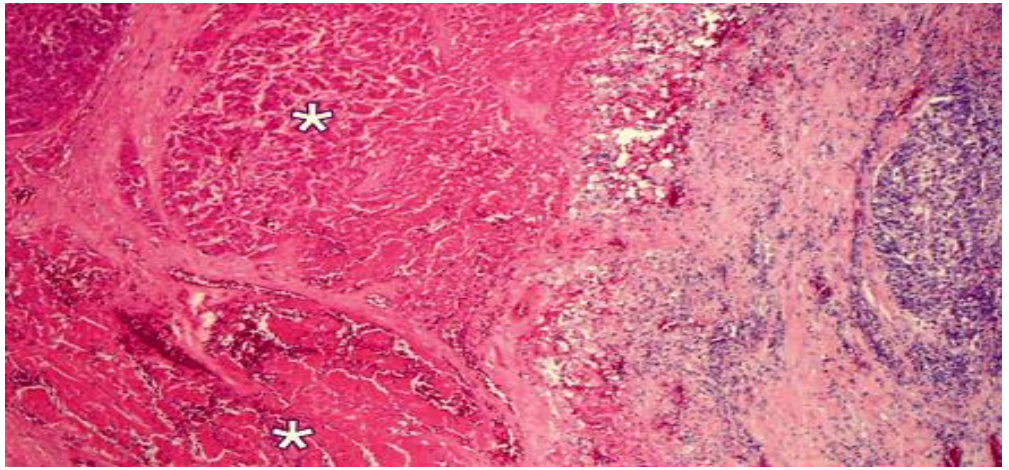
RECIST, Response Evaluation Criteria In Solid Tumors; mRECIST, modified Response Evaluation Criteria In Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.
*Adapted from Llovet *et al.* [149] and Lencioni and Llovet [100].

Llovet JM, Ducreux M, Lencioni R, et al. J Hepatol & Eur J Cancer, 2012

Enhancement Criteria vs Histologic Findings after RFA Bridging to OLT for HCC



Imaging Findings	Histologic Findings		
	Positive	Negative	Total
Positive	4	0	4
Negative	7	33	40
Total	11	33	44



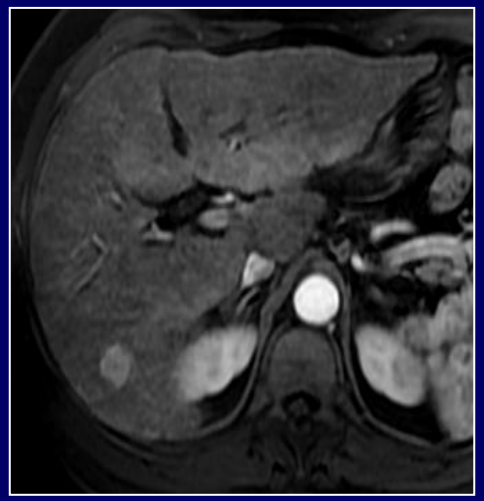
Lu DSK et al. Radiology 2005;234:954-960

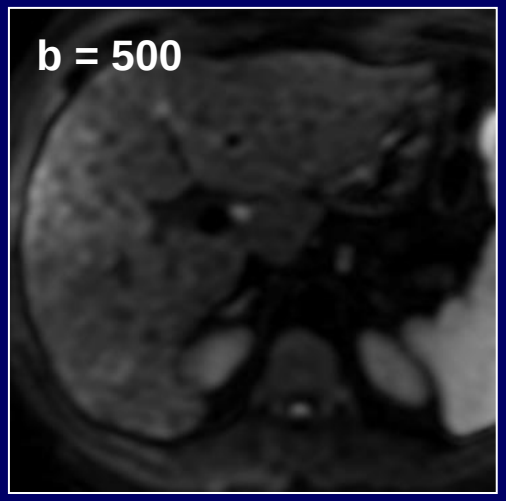
Ablation Assessment: Can We Get Beyond Contrast Enhancement?

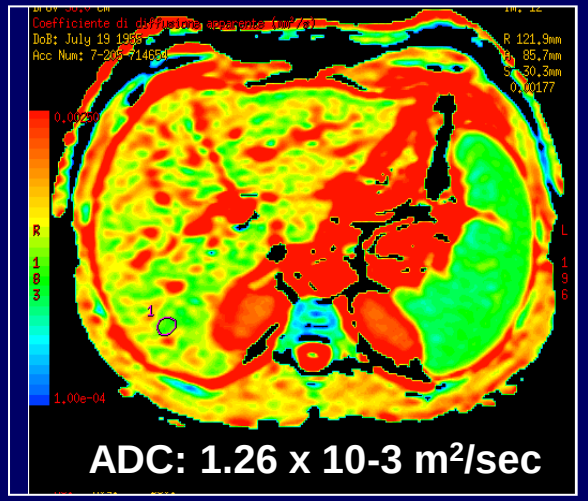
NO

Response Assessment after IRE of HCC: Dynamic Imaging vs Diffusion-weighted MRI

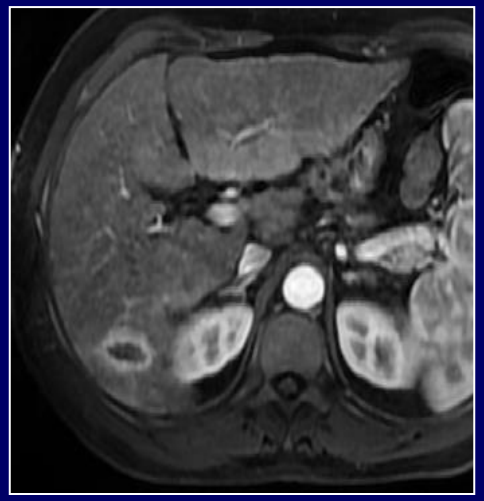
Baseline

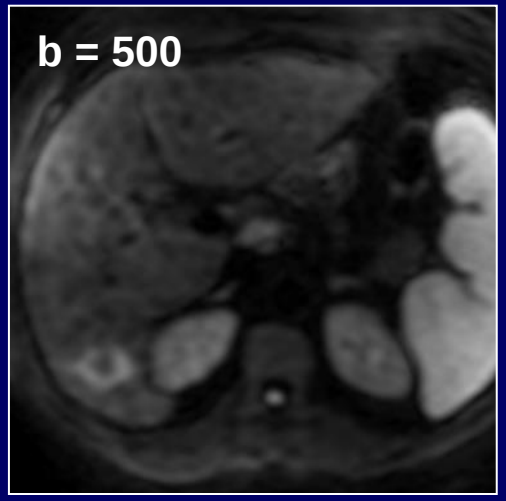


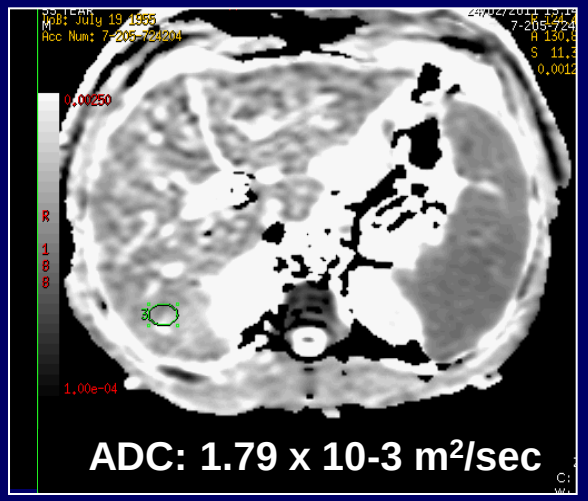




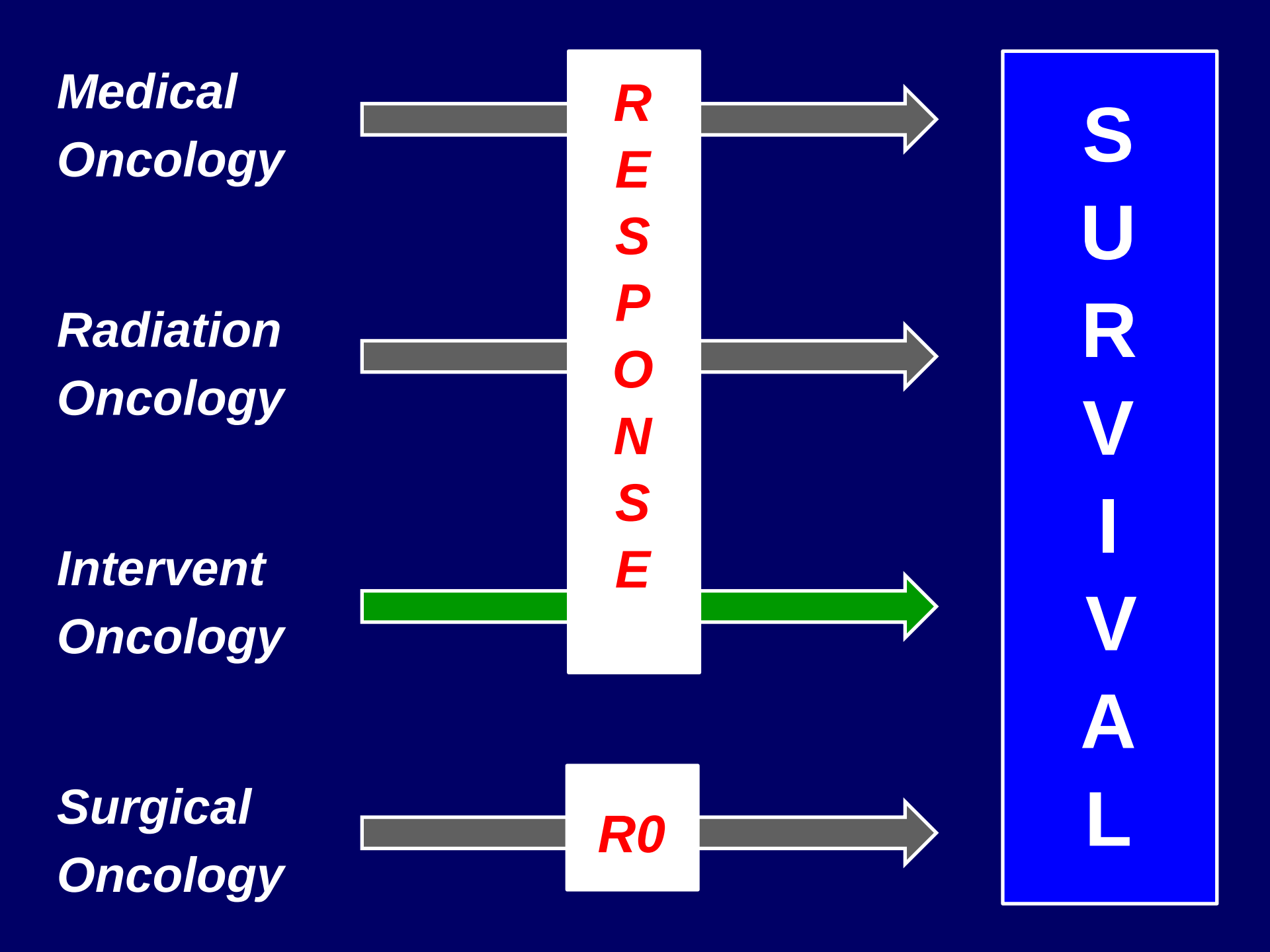
24 hrs post IRE

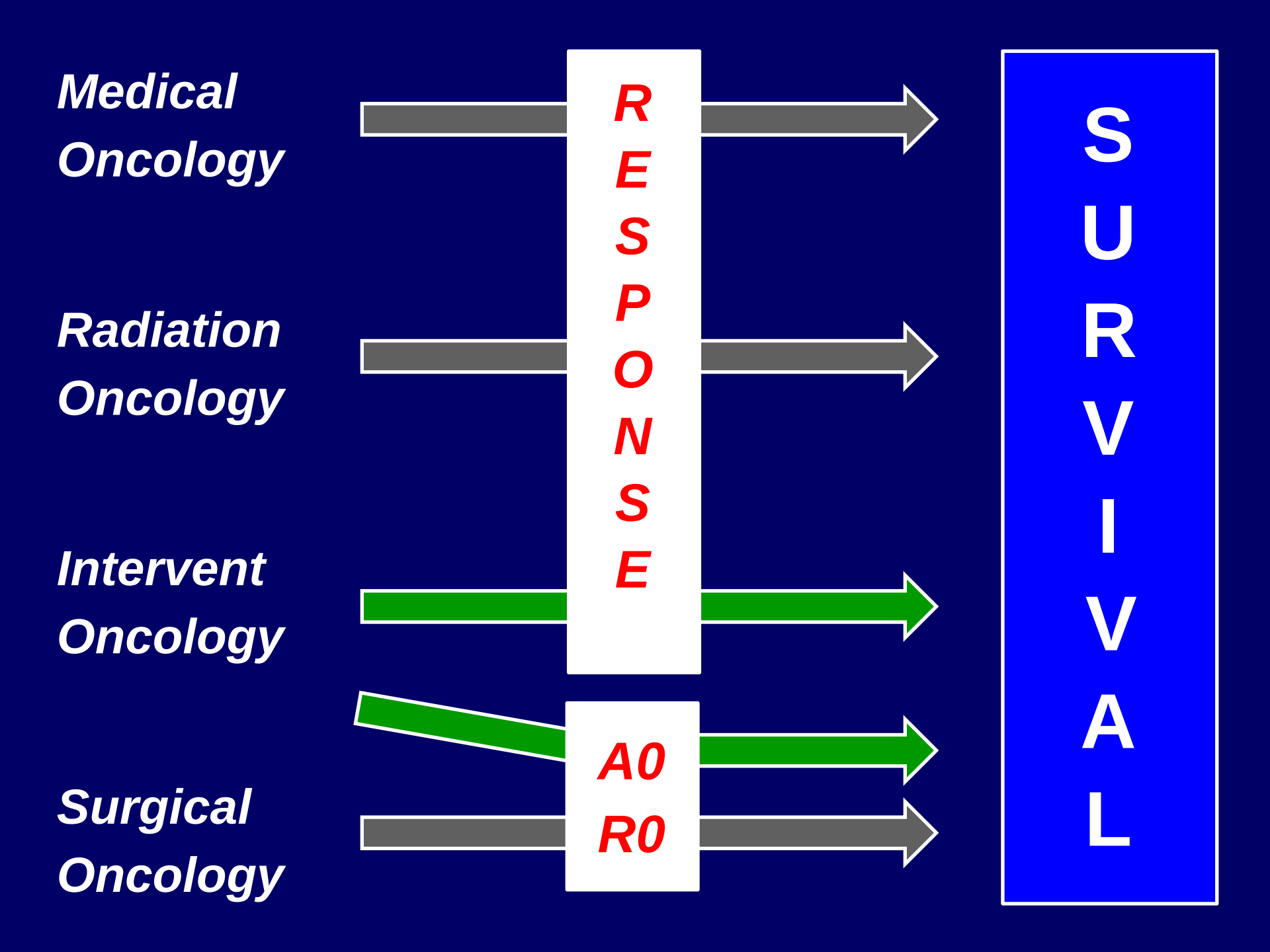




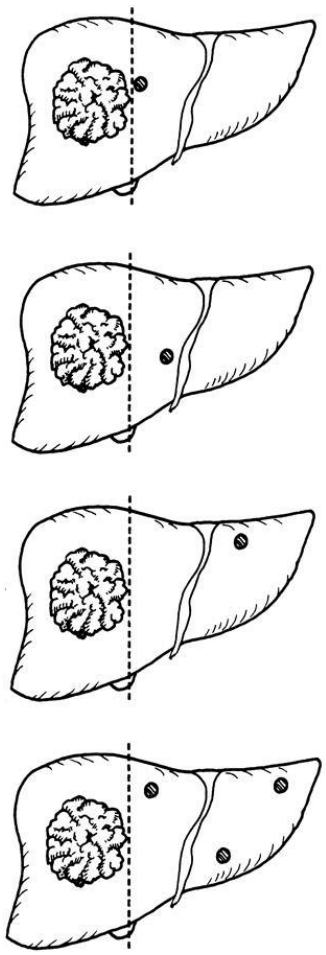


Lencioni R. Presented at RSNA 2011


Medical Oncology
Radiation Oncology
Intervent Oncology
Surgical Oncology
RESPONSE
R0
SURVIVAL


Medical Oncology
Radiation Oncology
Intervent Oncology
Surgical Oncology
RESPONSE
A0
R0
SURVIVAL

Postoperative Recurrence Rate in Patients with Positive vs Negative Resection Margins



Type 1:

Marginal recurrence

Type 2:

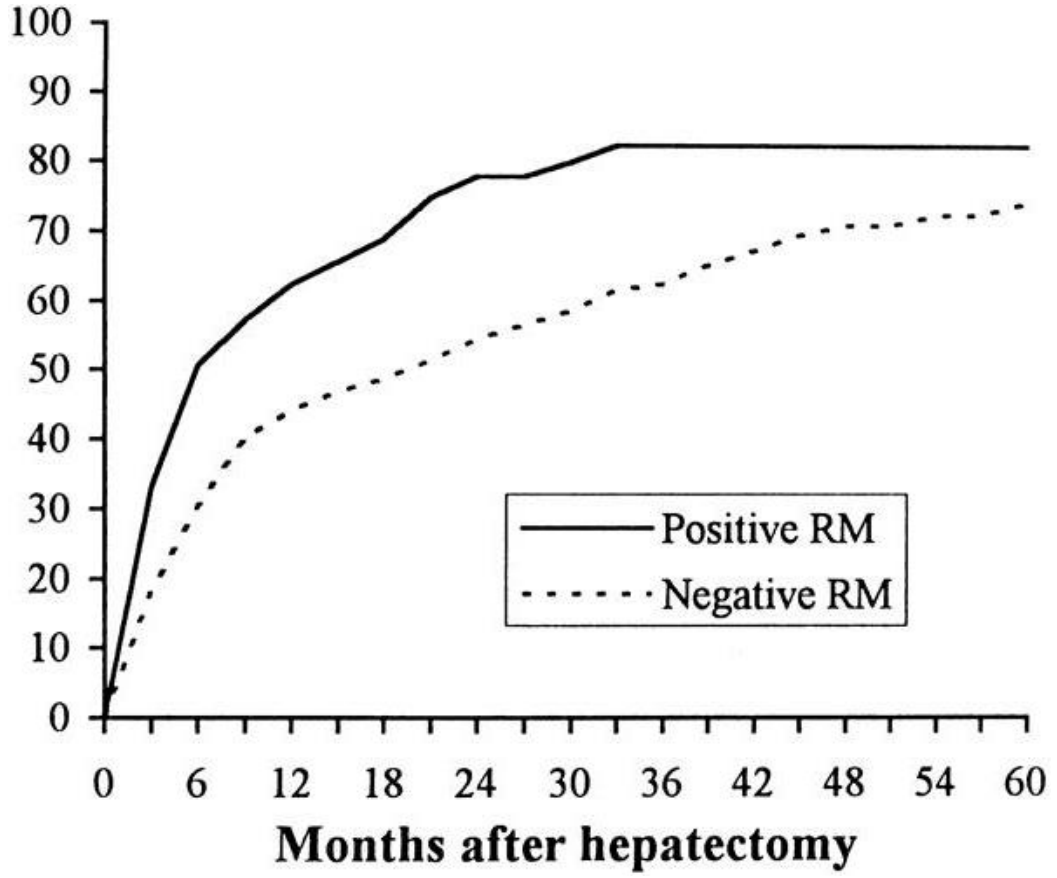
Recurrence at an adjacent segment

Type 3:

Recurrence at a distal segment

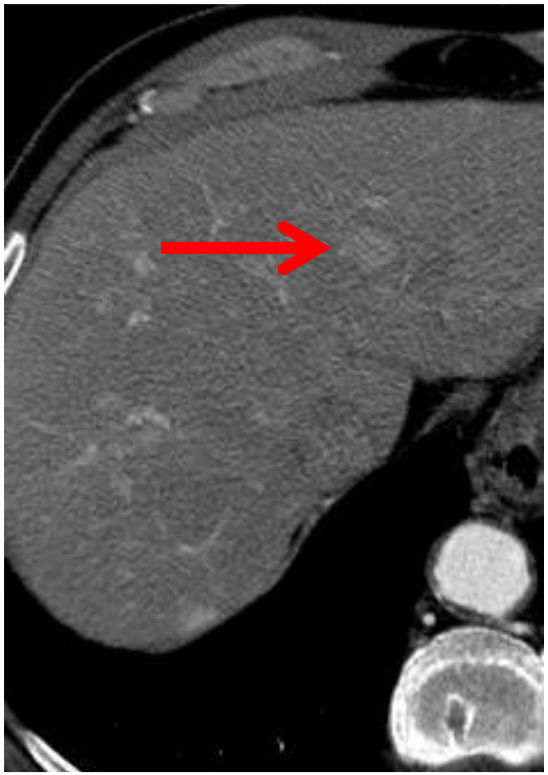
Type 4:

Multisegmental recurrence

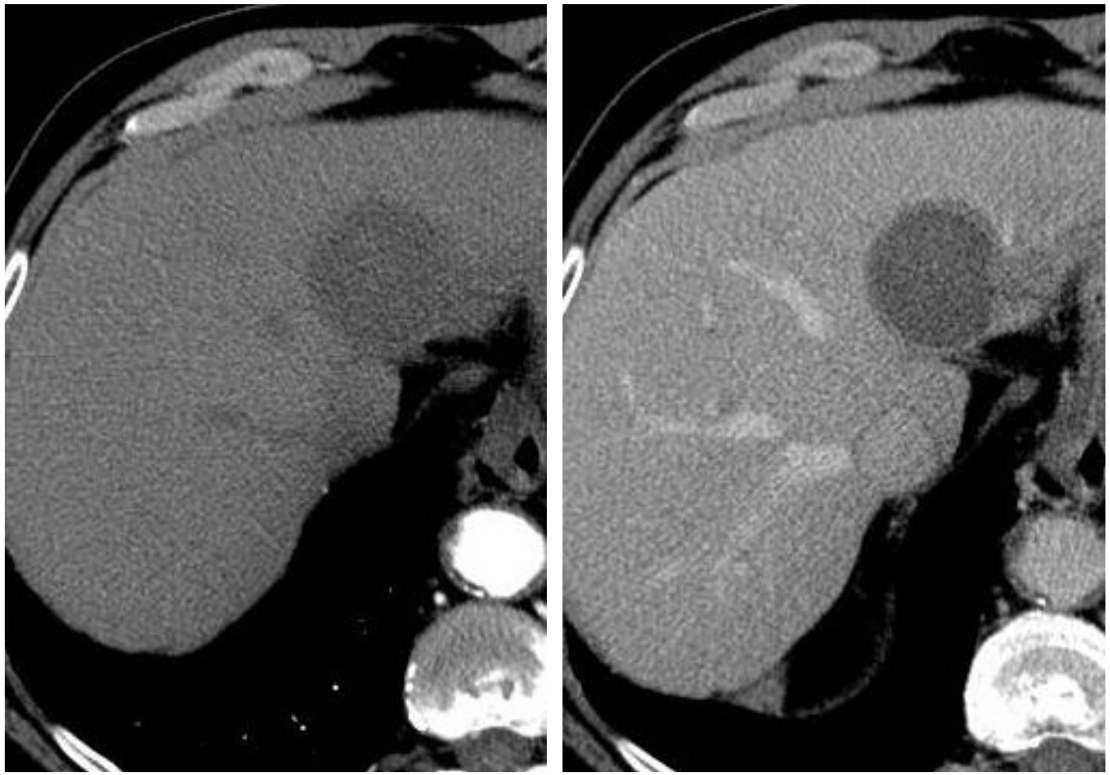


Poon RTP et al. Ann Surg 2000;231:544-551

Assessment of the Ablation Margin after RFA of Small HCC



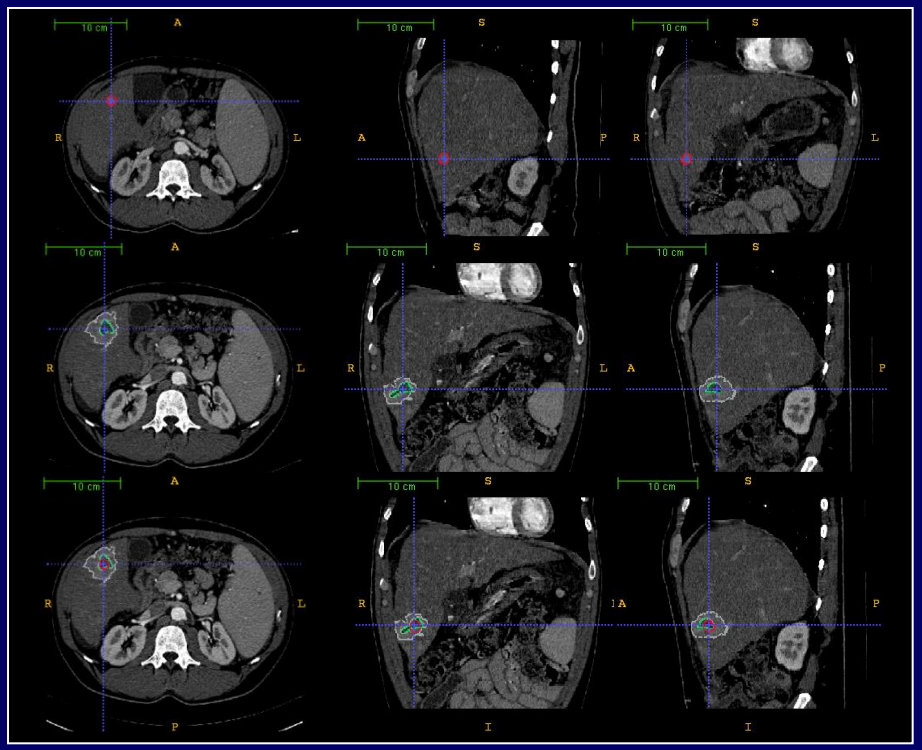
Baseline



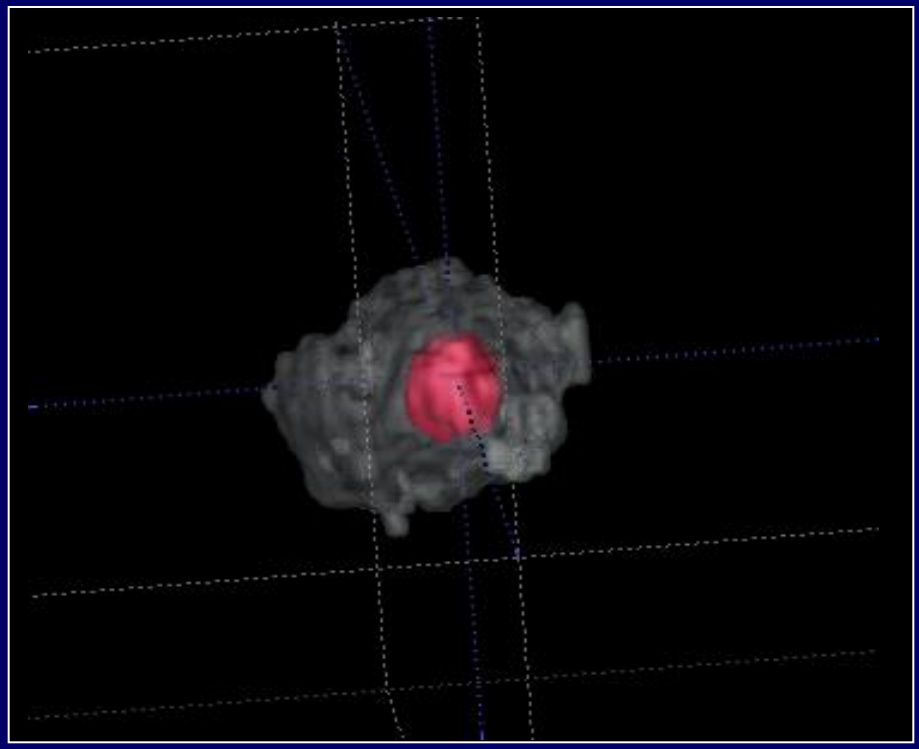
Post RFA

Lencioni R. Personal Communication

Volumetric Assessment of the Ablation Margin after IRE for HCC



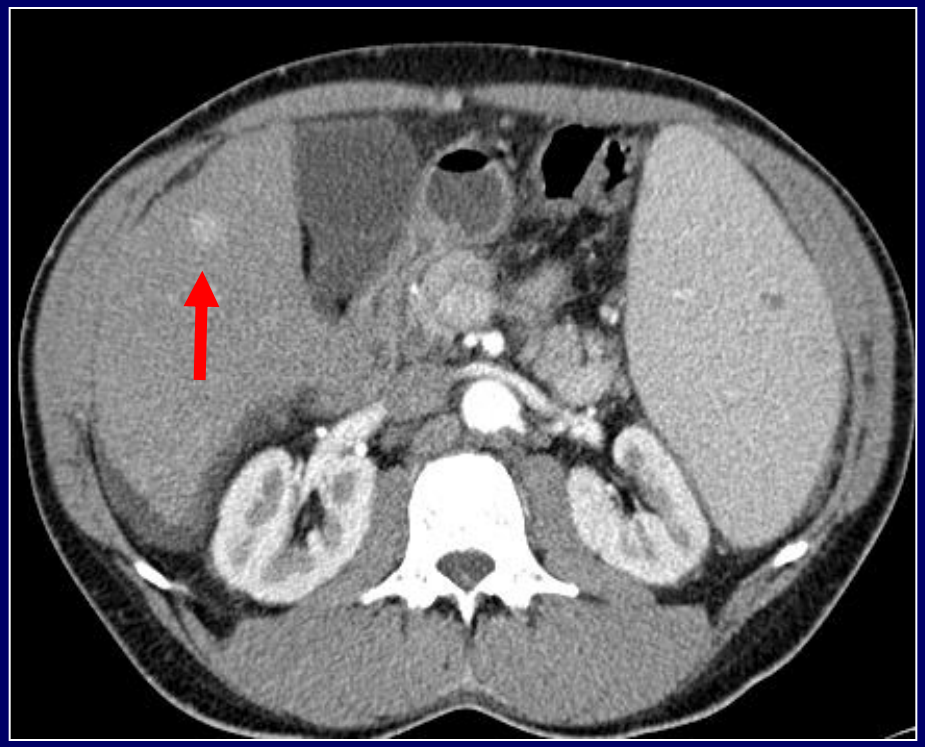
Semi-automatic segmentation volume method (SVM, INTIO Inc.)



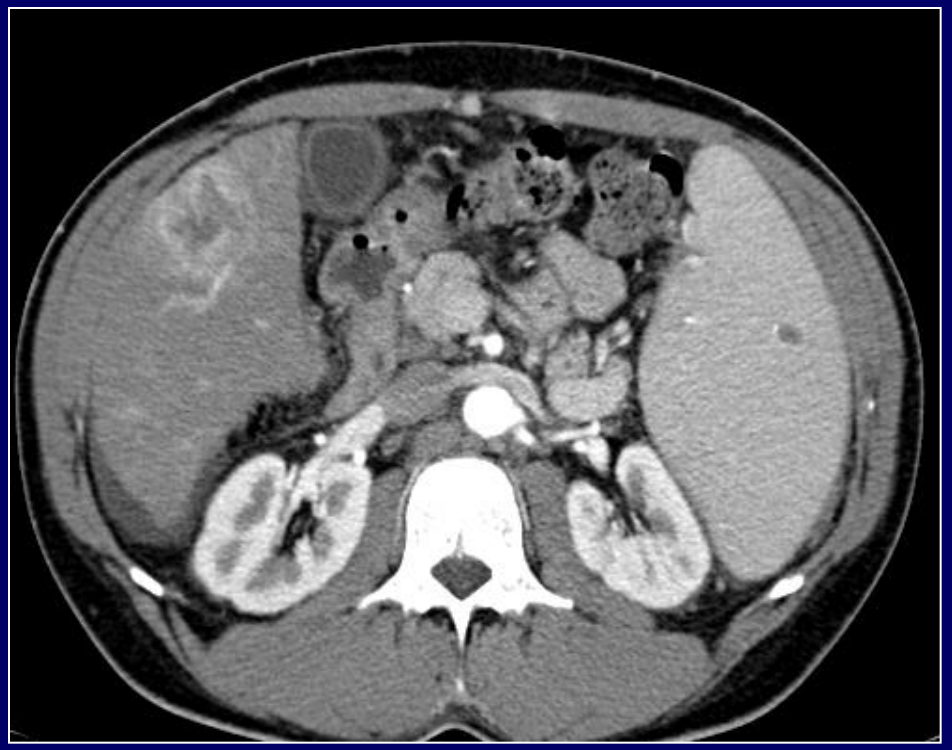
Segmented tumor overlaying on ablation volume

Lencioni R. Presented at RSNA 2011

Volumetric Assessment of the Ablation Margin after IRE for HCC



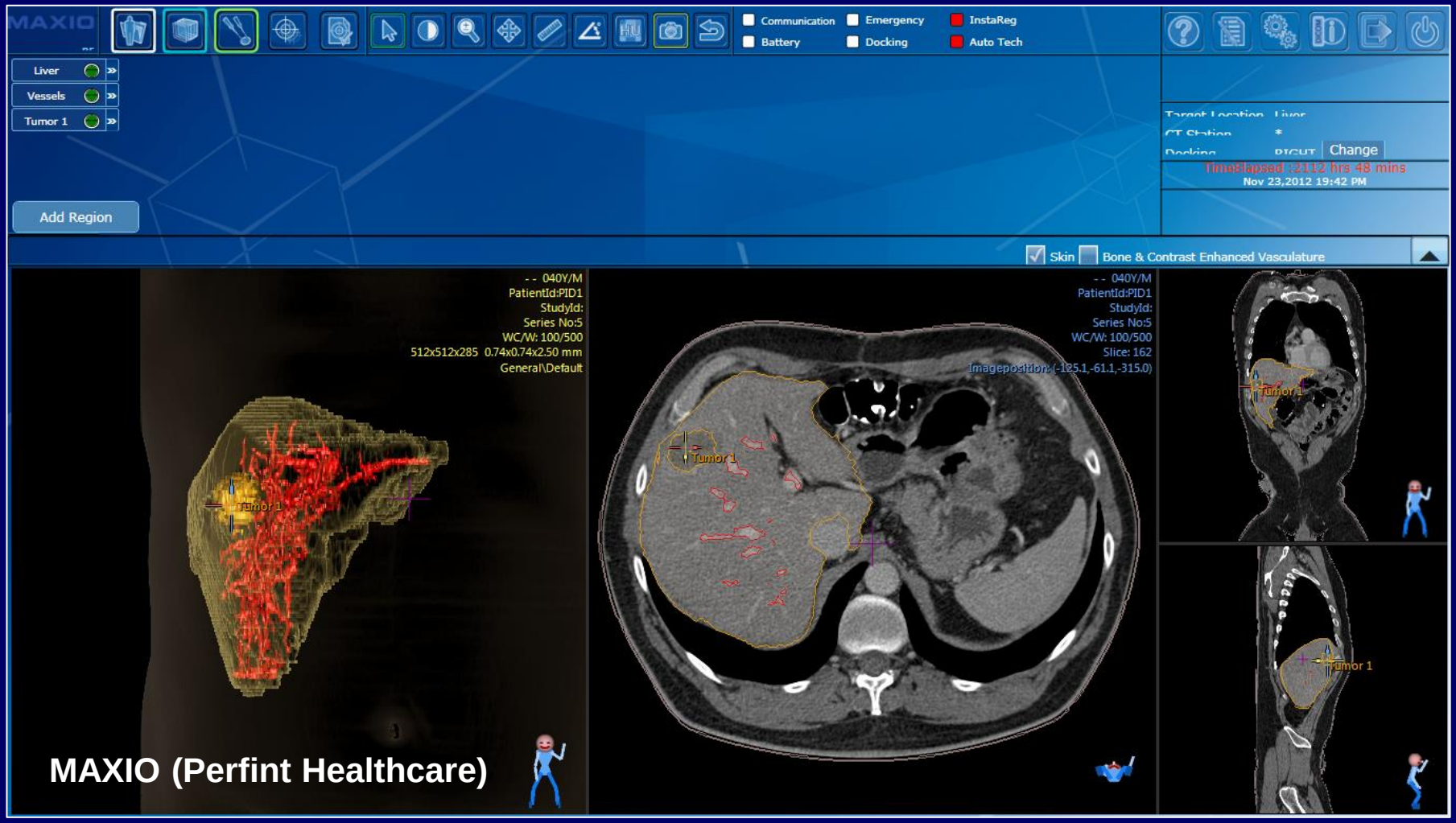
Pre-treatment – Arterial phase



Post-treatment (72 hrs) – Arterial phase

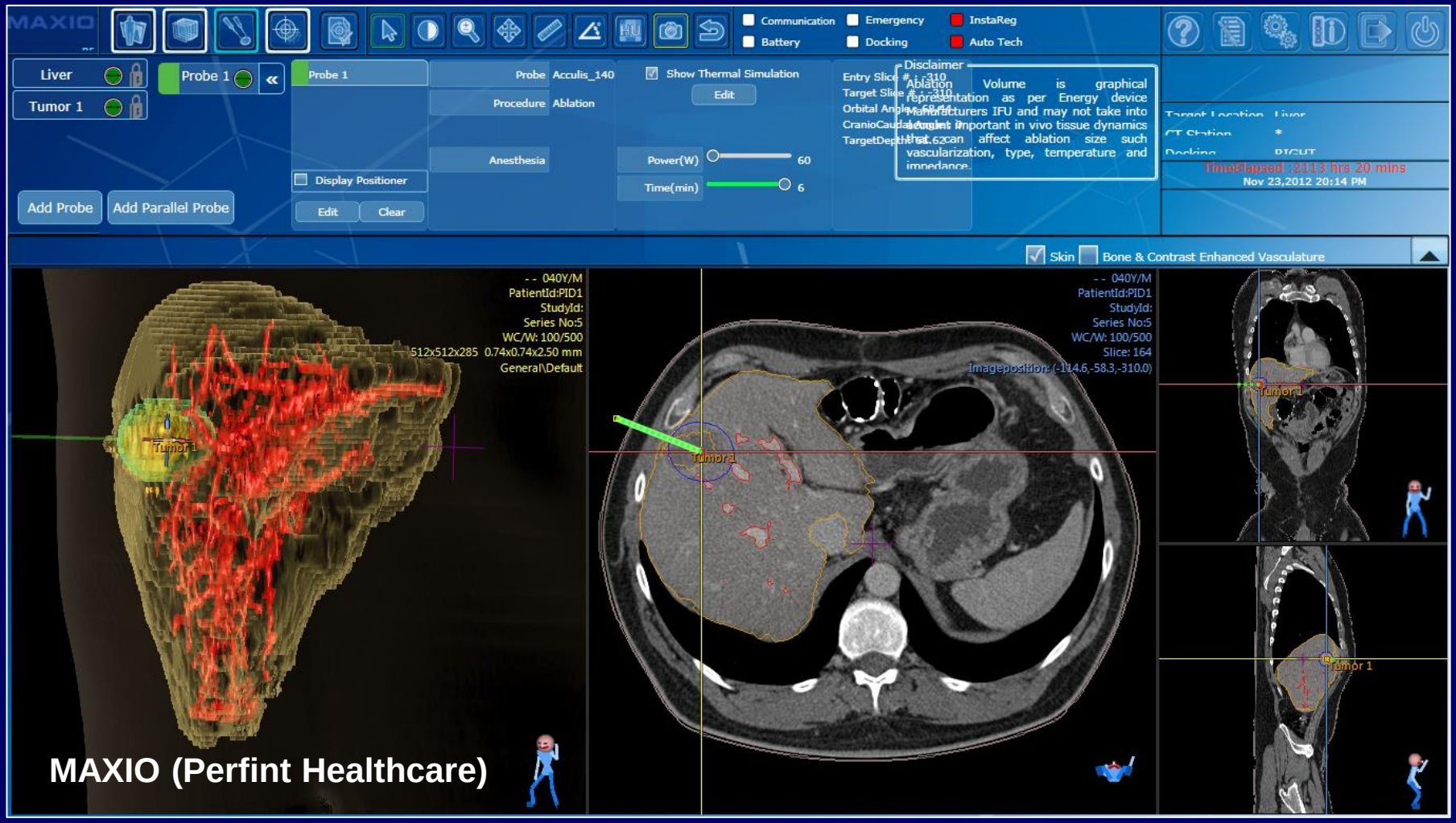
Lencioni R. Presented at RSNA 2011

Volumetric Planning and Robotic Assistance for an "A0" Ablation Strategy



Lencioni R. Personal Communication

Volumetric Planning and Robotic Assistance for an "A0" Ablation Strategy



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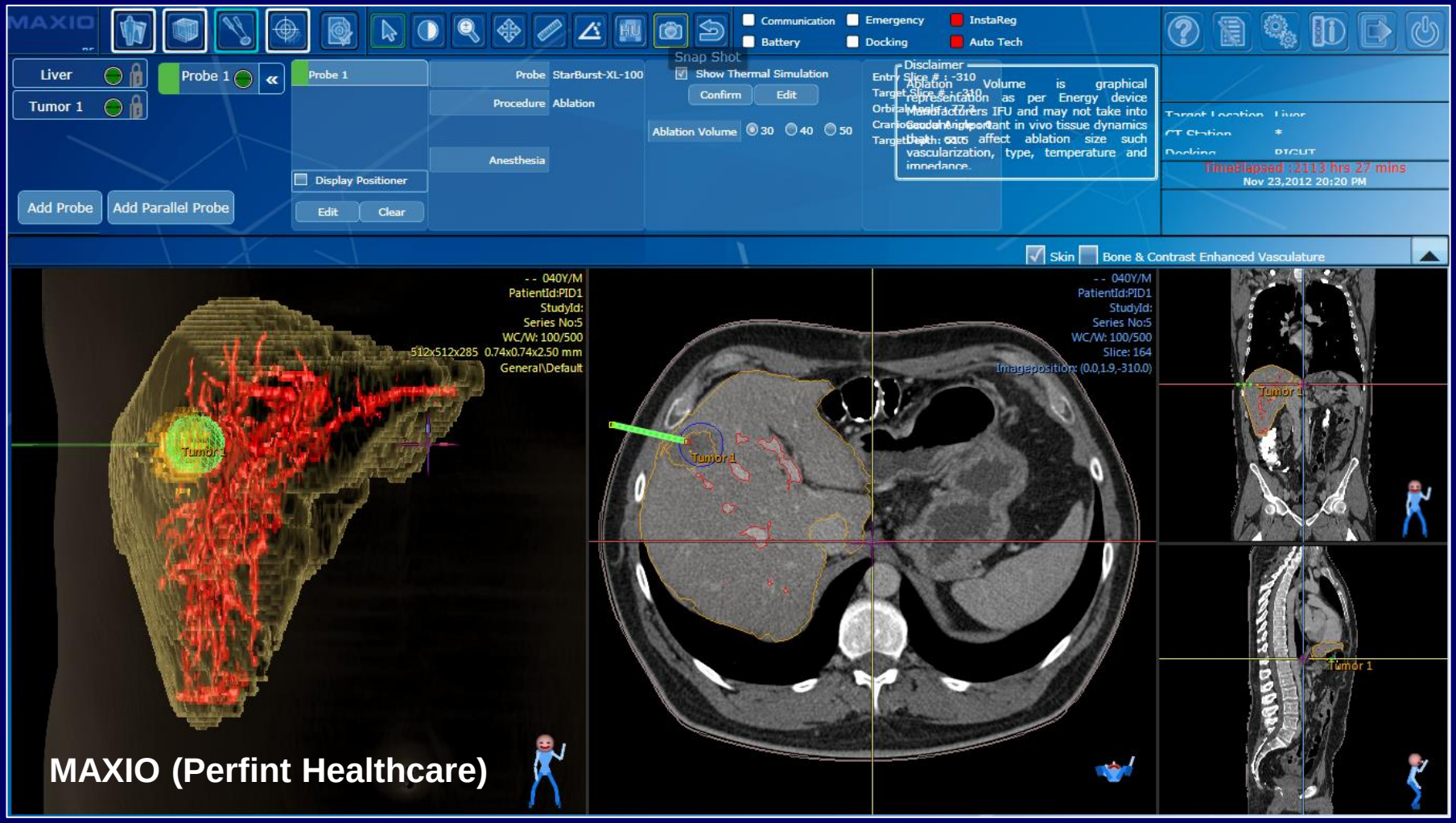

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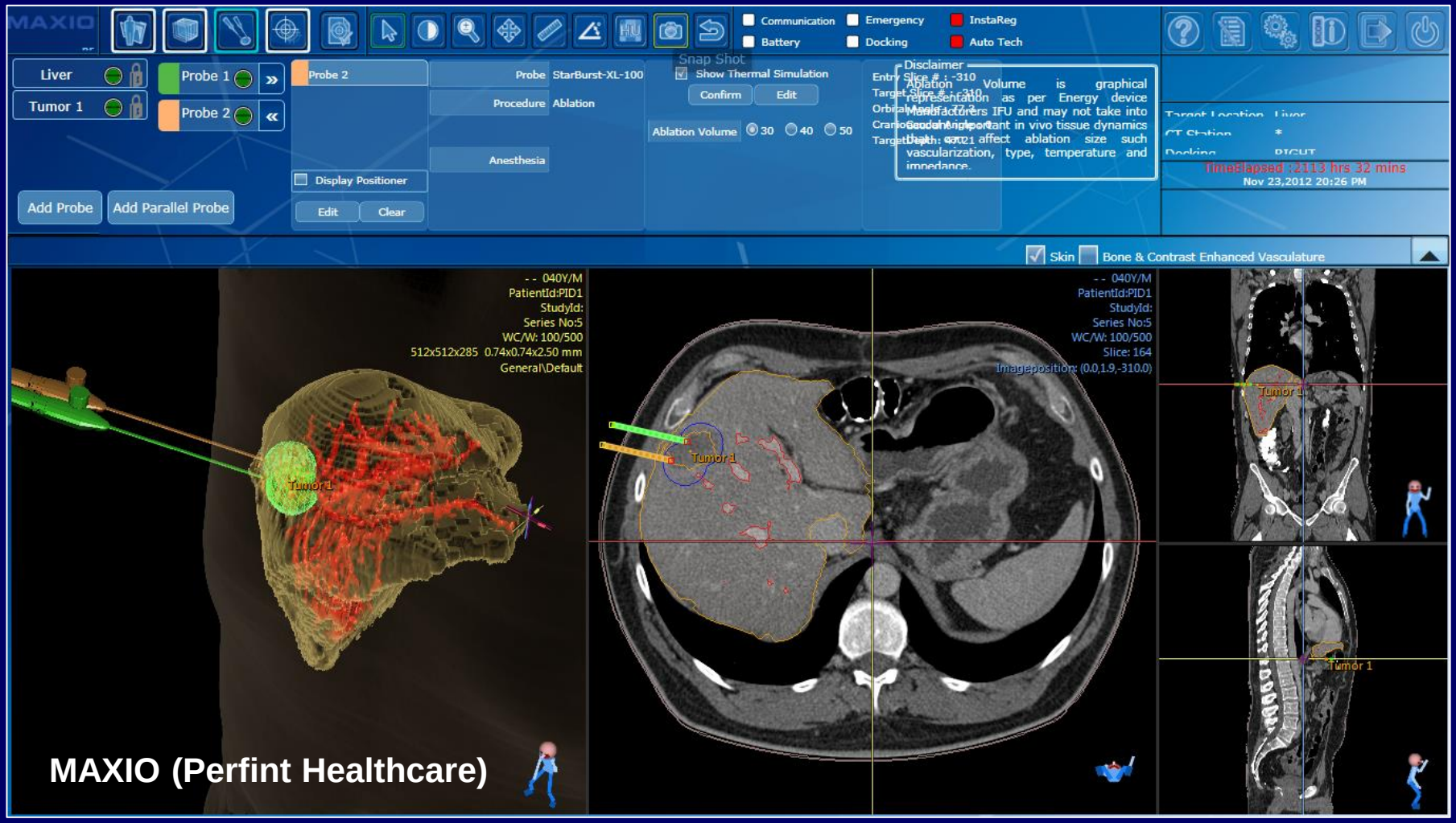

Lencioni R. Personal Communication

Ablation Assessment: Can We Get Beyond Contrast Enhancement?

- **Contrast-enhanced radiologic imaging is the basis of current response evaluation criteria for HCC**
- **Novel imaging approaches do not seem to be able to overcome the main limitation of dynamic imaging, ie the inability to detect tiny foci of residual viable tumor**
- **Volumetric techniques provide objective documentation of the ablation margin and thus appear as the best method to confirm “A0” treatment**
- **Volumetric planning of the ablation strategy, including selection of device, approach, and treatment protocol should become standard of care for clinical practice**