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San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro**



Società Italiana di Radiobiologia

Radioterapia stereotassica ablativa: metastasi polmonari

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OUTLINE

- ◆ **Endpoint and patient selection**
- ◆ **Dose & fractionation for local control**
- ◆ **SABR and radiobiology**
- ◆ **Appropriate technology**

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Lung oligometastases

Local treatments:

- Metastasectomy
- SABR
- Radiofrequency ablation

Symptoms → palliation

What is the aim of SBRT for lung metastases?

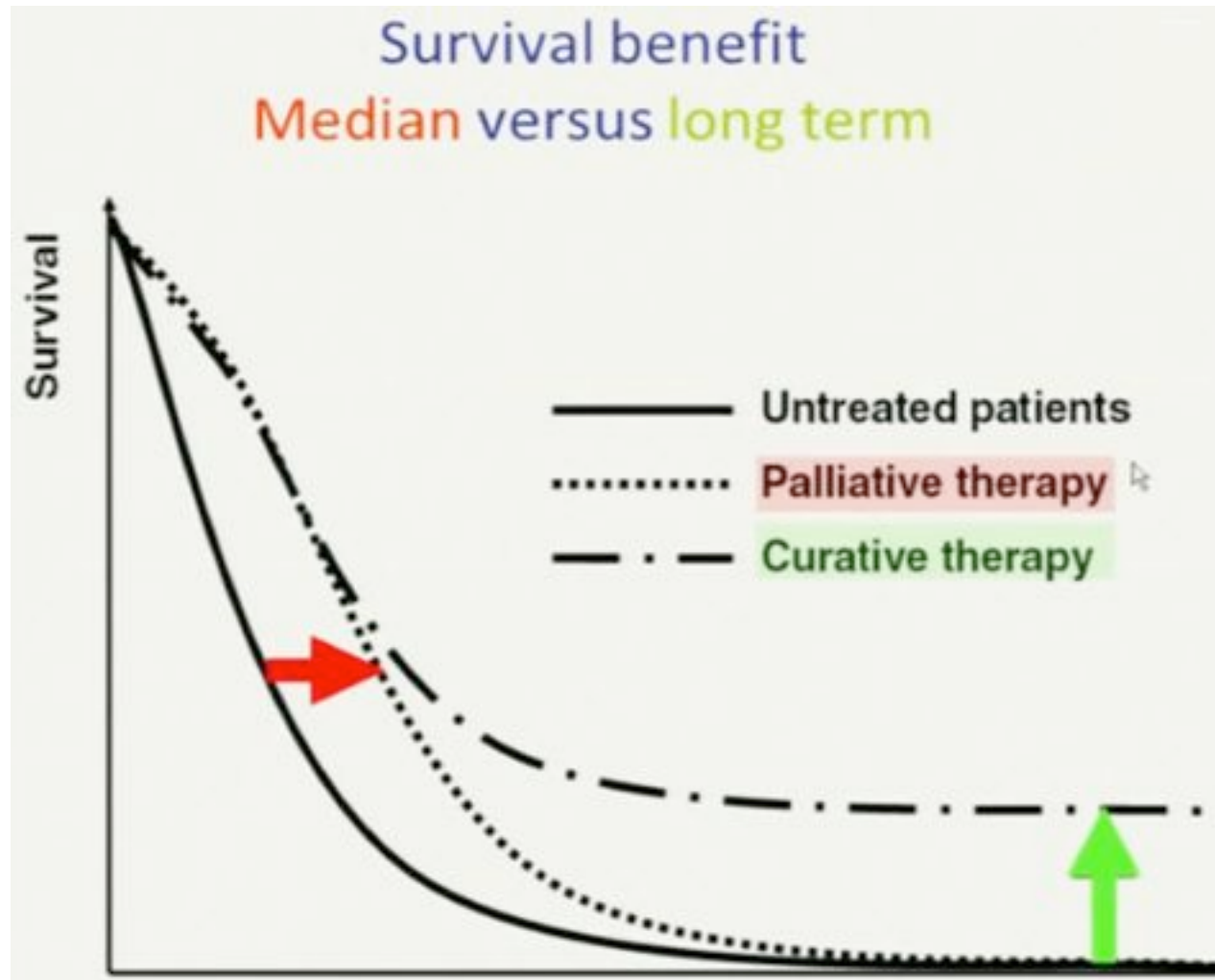
◆ Is it local control sufficient to prolong survival?

Local control might translate into clinical benefit



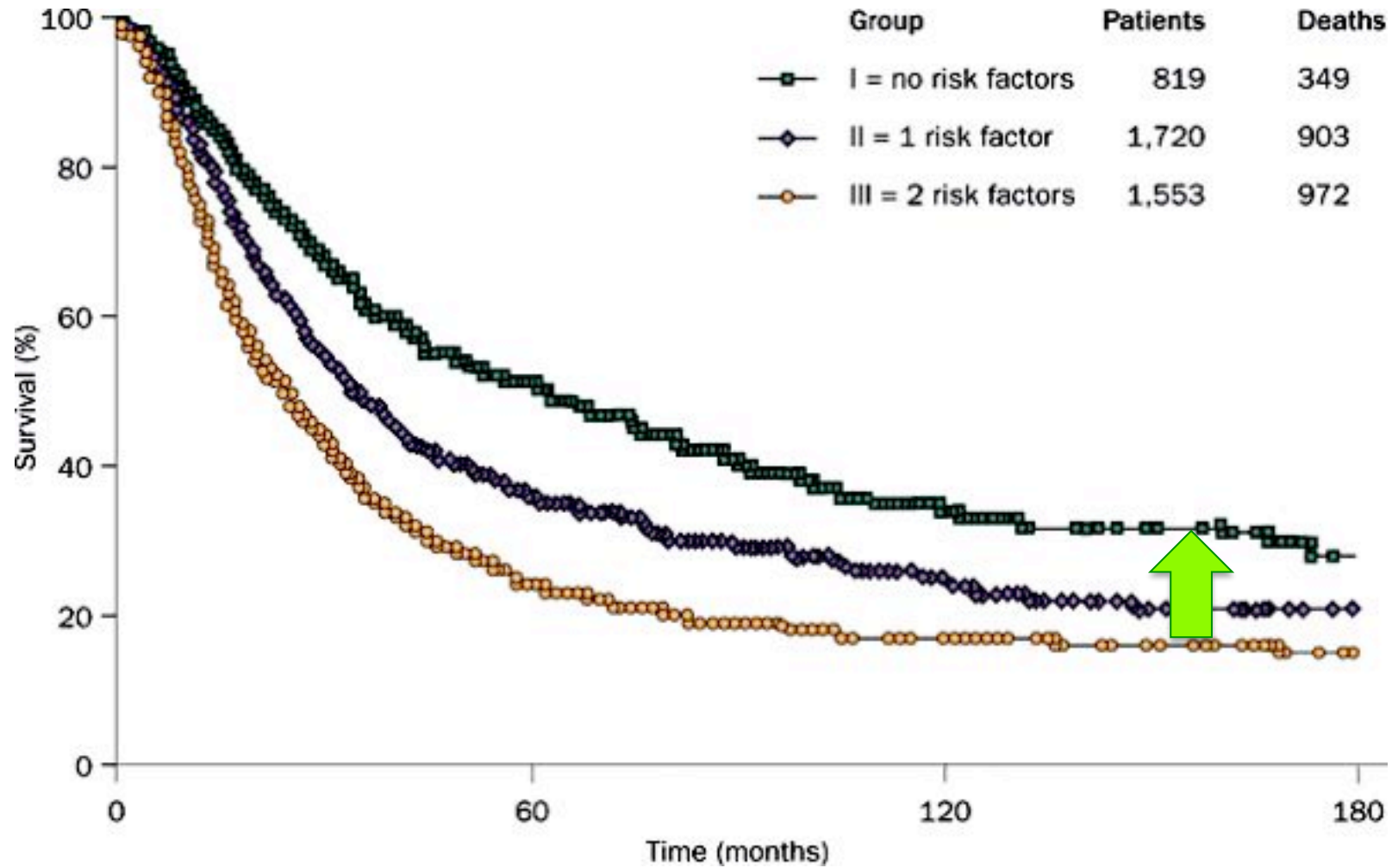
from L.B. Marks

SABR improve median or long term survival?



Cutsem et al Eur J Canc 2006


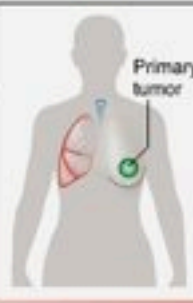


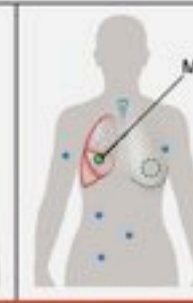
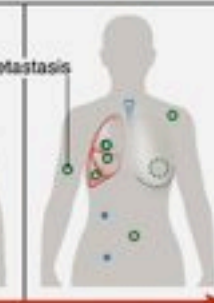
Is there a curative opportunity?



Weichselbaum, R. R. & Hellman, S. (2011) Oligometastases revisited *Nat. Rev. Clin. Oncol.*



Reshaped biological and functional framework of tumor metastases

						
Status	Pre-neoplasm Subclinical	Primary (-) CTCs and/or DTCs	Primary (+) CTCs and/or DTCs	Dormancy	Oligometastases	Systemic metastases
Focus	Management of primary tumor		Prevention of metastasis		Treatment of metastasis	
Challenge	Early detection and prevention Identify high-risk patients		Prevent local and distant relapse Drug resistance of DTCs		Early detection of relapse Heterogeneity and drug resistance	
New tools	Diagnostic markers	Prognostic markers	Profiling of primary tumor, metastases, CTCs and/or DTCs for accurate targeting Biomarkers and imaging technologies for disease monitoring Biomarkers for therapeutic efficacy			
Possible treatment strategies	Prophylactic treatment Vaccination	Surgery, radiotherapy (+) Systemic therapy		Targeted therapy against driver oncogenes and their pathways tailored by genetic makeup of tumor cells		
		Long-term adjuvant treatment (for high-risk patients): • Metronomic chemotherapy and anti-angiogenesis • Targeting common driver oncogenes and pathways • Immunotherapy • Targeting dormancy-related survival and CSC signaling and niche components			Systemic therapy Immunotherapy Stroma-targeting treatments Palliative radiation and/or surgery	
		Surgery stereotactic radiotherapy				
Possible new targets		DTC and/or CTC survival pathways; stem cell features; tumor-stroma crosstalk and niche factors Activation of metastasis-suppressive signaling				

Lung oligometastases

True oligometastases:

- **Metastases is hierarchical in time and number**
- **Intermaediate stage of restricted metastatic capacity**
- **Oligoprogression**

Biological & Clinical markers for metastases treatment

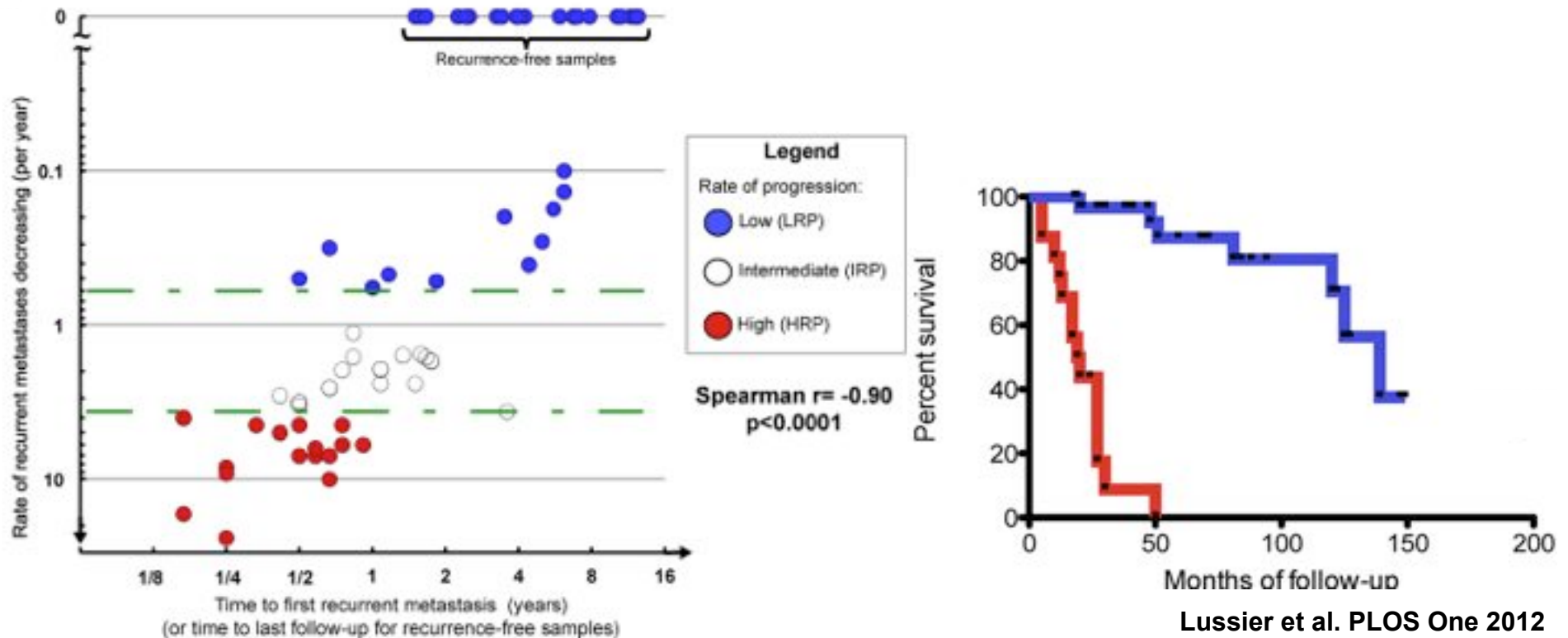
Primary goal to treat oligometastatic disease is to identify the oligometastatic state

- ◆ Number
- ◆ Dimension and size distribution
- ◆ Synchronous and metachronous metastases
- ◆ Organ distribution
- ◆ Growth rate
- ◆ Resectability of metastases
- ◆ Feasibility of SABR or RFA
- ◆ Primary tumor controlled
- ◆ New molecular characteristics

Oligo- and Polymetastatic Progression in Lung Metastasis(es) Patients Is Associated with Specific MicroRNAs

(63 patients with ≤ 5 resected lung lesions)

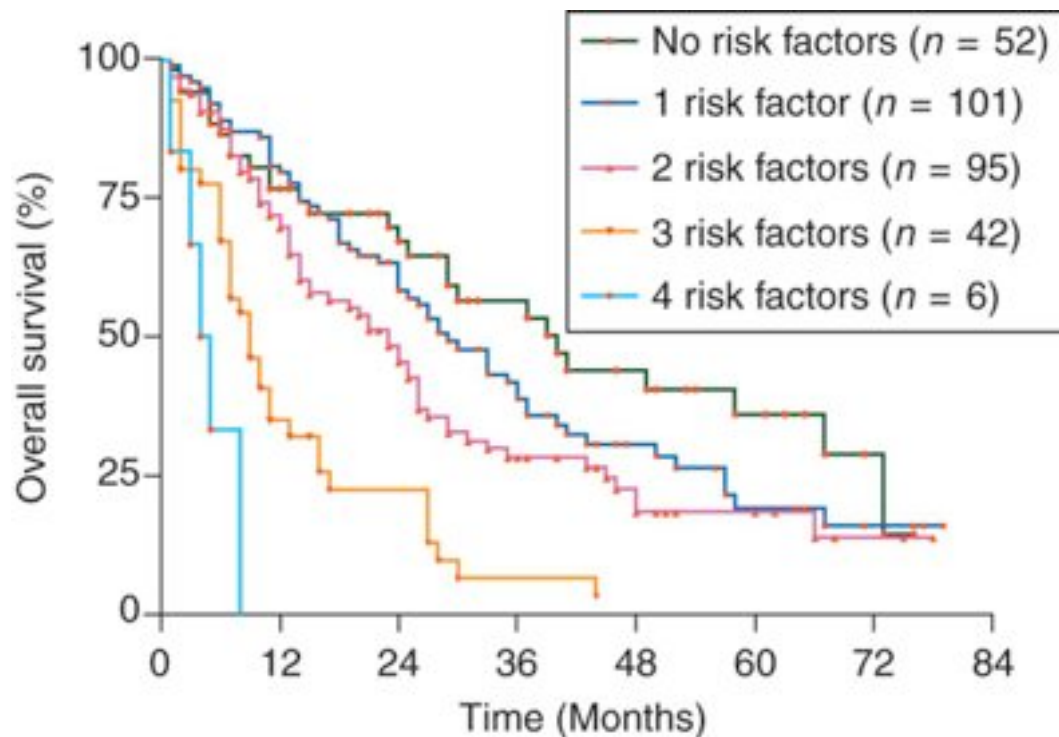
- ◆ Oligo and polimetastatic are distinct disease
- ◆ “True” oligometastatic may be recognize at a molecular level



If oligometastases are in lung and in extrapulmonary sites

Stereotactic radiotherapy for oligometastatic cancer: a prognostic model for survival

(309 patients with ≤ 5 lesions in single or multiple sites)



Risk factors

- ◆ Non adenocarcinoma
- ◆ Intracranial oligometastases
- ◆ Synchronous metastases
- ◆ Male gender

Which endpoint is aimed for SABR?

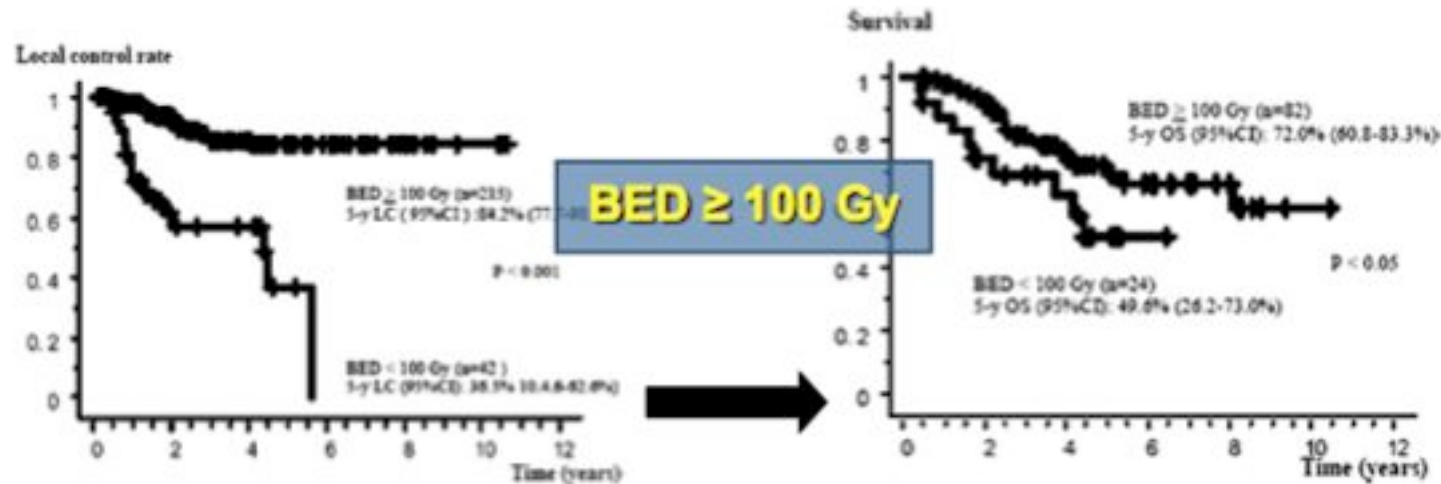
- ◆ In asymptomatic patients the aim is to improve survival without symptoms
- ◆ “true” oligometastases increase long term survival rate ----- “cure”
- ◆ Slowly progression multiple metastases----- increase time to failure local strategy and postpone systemic treatment/toxicity
- ◆ Multiple metastases responding to chemo----- increase median survival



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The magic number



Onishi, JTO 2007

- ◆ No clear consensus on the best fractionation schedule
- ◆ Consensus on BED $>$ 100 or slightly lower

Dose & Outcomes

- ◆ The 1-year LC probability is in a range of 70%-100%
- ◆ The 2-year weighted OS rate is 54% (range 39%-84%)

Alongi, Arcangeli, Filippi et al *The Oncologist* 2012

Wide fractionation

- ◆ **10-12 Gy x 5** (USA) or **7.5 Gy x 8** (Europe) for lesions within 2 cm of the tracheobronchial
- ◆ **18 Gy x 3** or **34 Gy x 1** for peripheral tumor

Chmura S et al. *Semin Thoracic Surg* 2014



Single shot

Not much data about single fraction for metastases

- ◆ 1-year LC of 93.4% and 2-year OS of 70.5% with **26 Gy** in single fraction
- ◆ Low acute and late toxicity rate
- ◆ Valid alternative to fractionated schedule and to surgery

Filippi et al *TCRT 2013*

If single-fraction SABR comparable

- ◆ It may improve treatment compliance and reduce costs
- ◆ It may be helpful in multiple lung metastases
- ◆ It may be helpful in patients with lung and extrathoracic oligometastases



Dose & Outcomes

- ◆ Fractionation schedule can be influenced by the primary histology?
- ◆ The number of lesions can influence the fractionation schedule?
- ◆ Are certain histologies associate with worse outcomes?
- ◆ Without randomized trials is difficult to evaluate outcomes

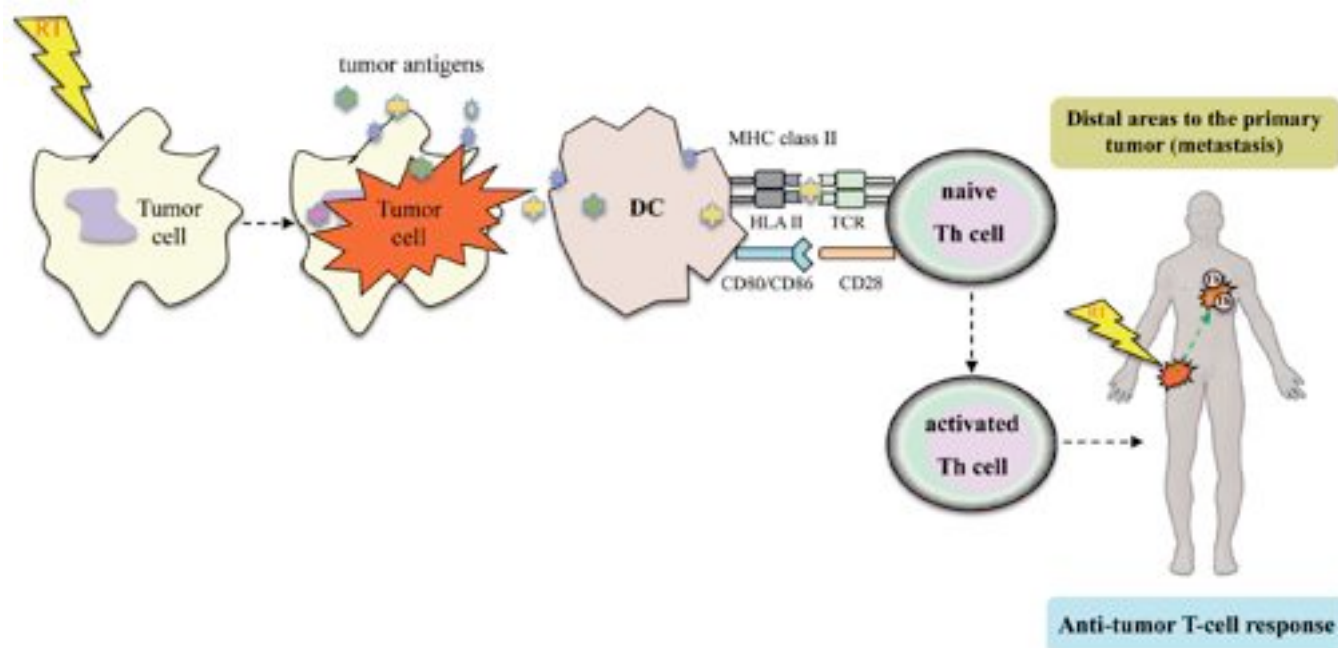


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Not only a local effect for SABR

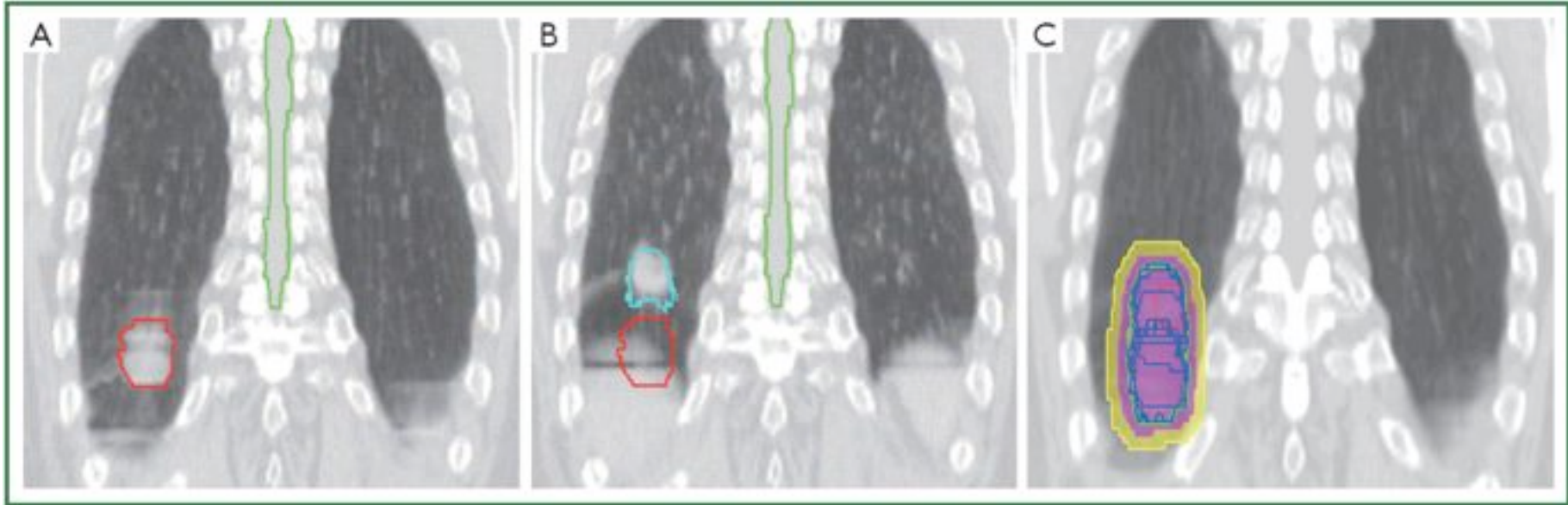
- ◆ Sphingomyelinae mediated endothelial apoptosis may increase tumor control by antiangiogenic effect (*Garcia-Barros, Science 2003*)
- ◆ Immuno-modulated effect T-cell mediated from ablative dose, resulted in reduction on target tumor and an **abscopal effect** on distant metastases (*Lee, Blood 2009; Demaria IJROBP 2004*)



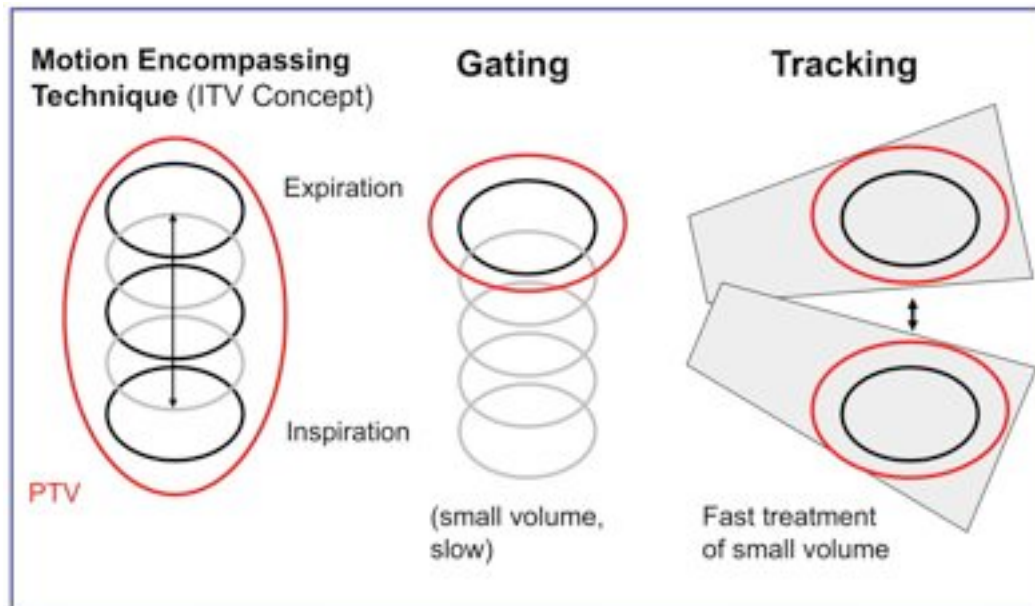
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Technical goal in lung SABR: reduce ITV



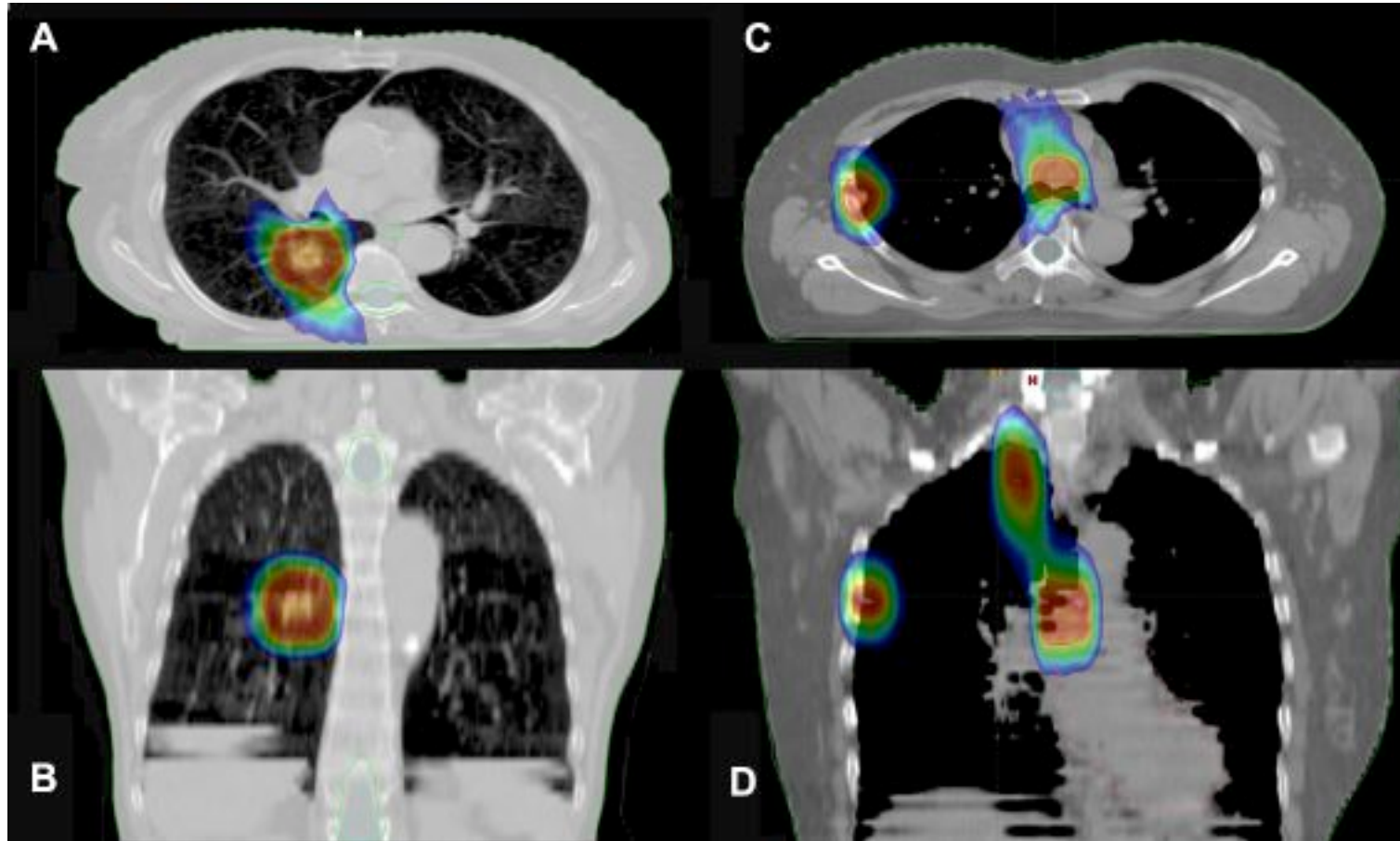
Carry K. J Tor Dis 2014



Lung S. SPS

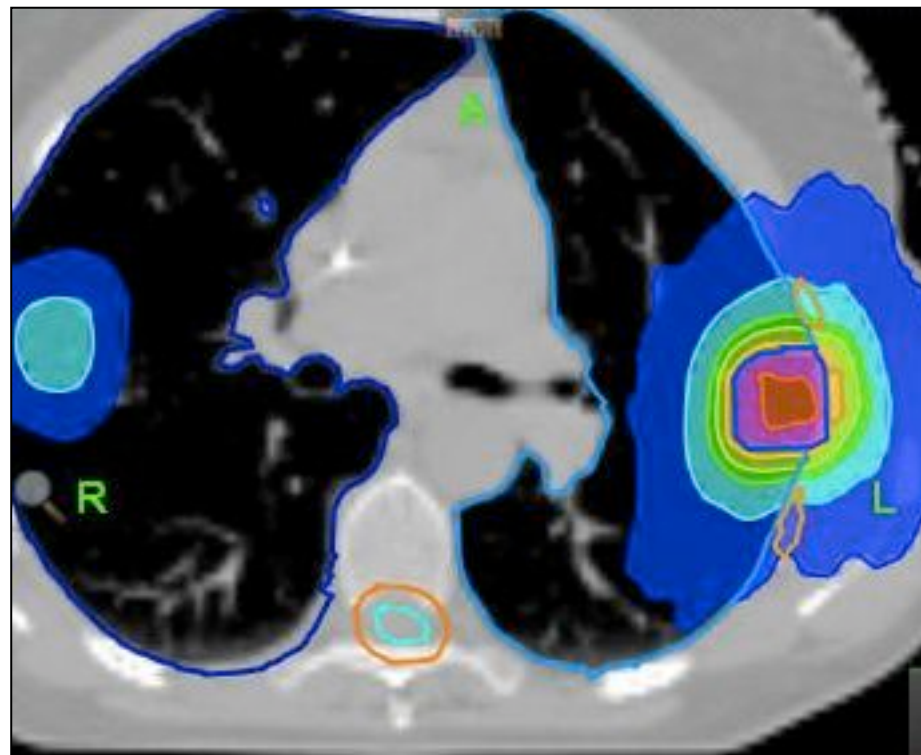
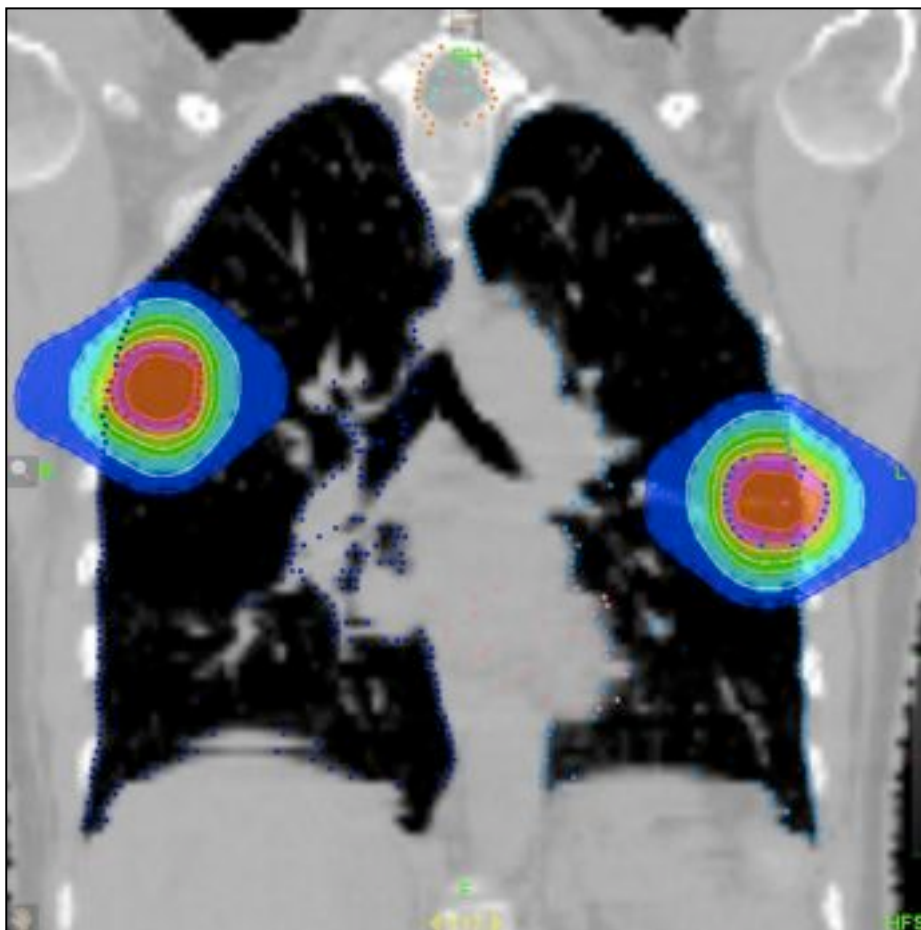


Technical goal in lung SABR: reduce ITV

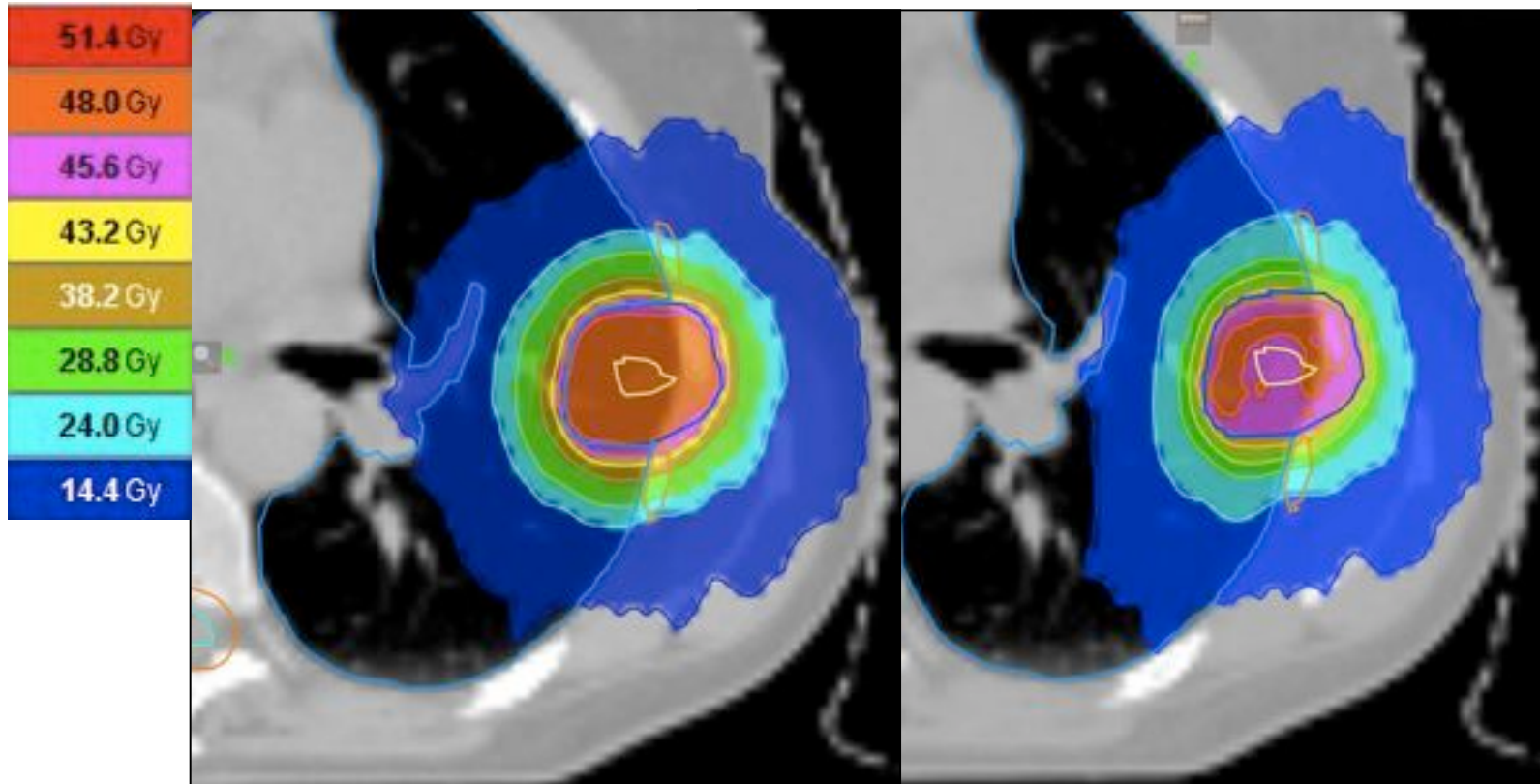


Specially for multiple lung targets

Volumetric IMRT can treat simultaneously



Volumetric IMRT can treat simultaneously



Sequentially (2 plans)

Simultaneously

BOT (1+2)
Around 21 minutes

BOT around 12 minutes

BOT: Beam On Time



Summary

- ◆ SABR for lung metastases it's feasible and effective in LC as well as for primary NSCLC and metastasectomy
- ◆ Identify clinical and biological markers to recognize “true” oligometastatic can shift the paradigm from a prolonged survival to “cure”
- ◆ Prospective randomized clinical trials are ongoing to identify the most appropriate fractionation and the impact of SABR in “oligometastatic” disease not limited to lung (COMET) (RTOG 1312). Attempt PFS and OS benefits for specific histology (RTOG 1312, breast metastases) and possible interaction with systemic therapy.
- ◆ Important to know the advantages and limits of own technology to avoid treatment delivery errors

SABR in lung metastases

Thank you