



# Systemic treatment in isolated lung metastases of STS: state of the art

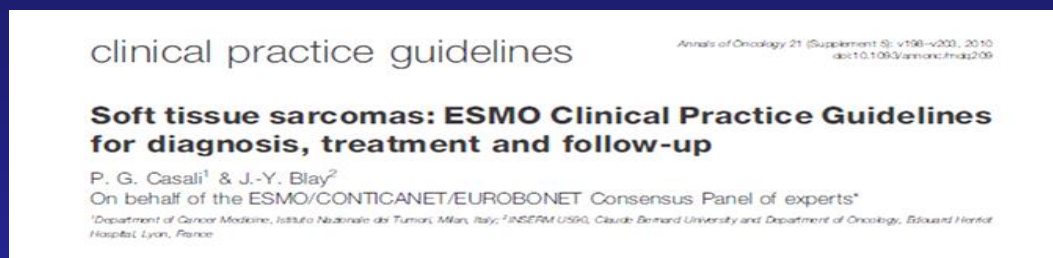


**Axel Le Cesne**  
**Gustave Roussy, Villejuif, France**

*ESMO, 28th of September 2014*

# Isolated lung metastases in STS

## ESMO 2012 recommendations



1) Metachronous resectable lung metastases without extrapulmonary disease are managed with surgery, if complete excision of all lesions is feasible.

**Comments: for a surgeon excision of all lesions is always/often feasible... ..whatever the number of mets...(until 250, *Treasure et al, BJM 2013*)**

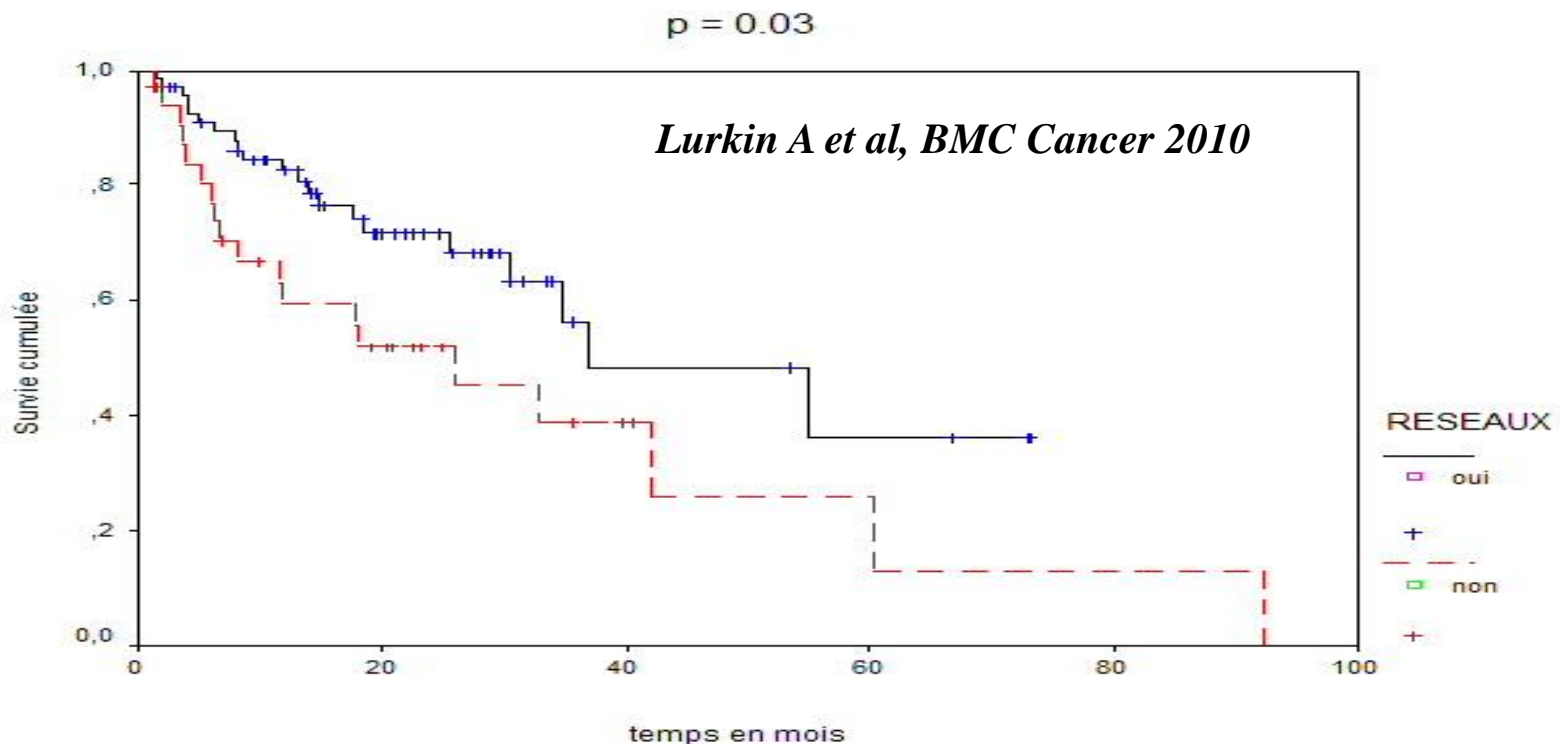
2) Chemotherapy may be added to surgery as an option. Chemotherapy is preferably given **before** surgery, in order to assess tumor response and thus modulate the length of treatment.

**Comments: if medical oncologists see the patients in first!**  
**Poor responders to CT are not in the published surgical series...**  
**.....biais in the interpretation of results**

# Isolated lung metastases

## impact of « sarcoma » tumor boards

### Distant metastasis and multidisciplinary assessment (« good clinical practice »)



clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v191-v203, 2010  
doi:10.1093/annonc/mdq209

**Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

P. G. Casali<sup>1</sup> & J.-Y. Blay<sup>2</sup>

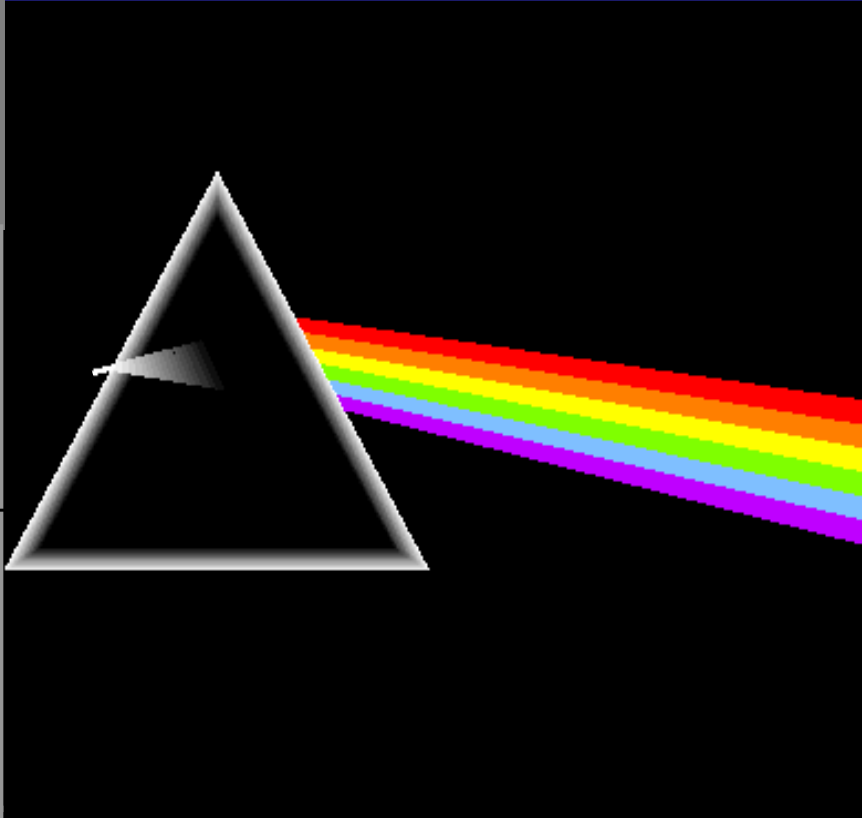
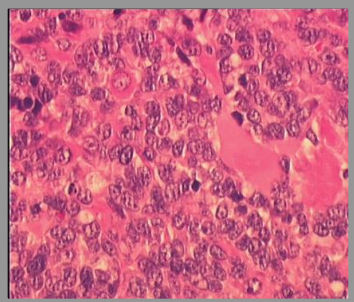
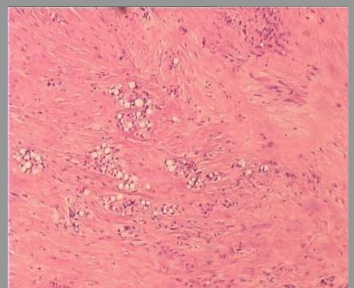
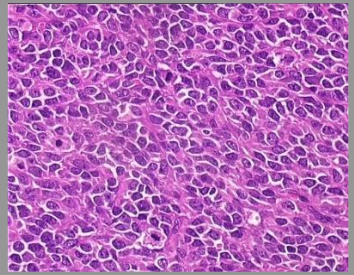
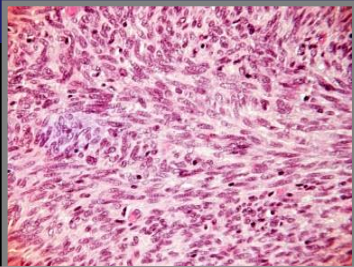
On behalf of the ESMO/CONCICANET/EUROBONET Consensus Panel of experts\*

\*Department of Cancer Medicine, Istituto Nazionale dei Tumori, Milan, Italy; <sup>1</sup>INSERM U950, Claude Bernard University and Department of Oncology, Edouard Belin Hospital, Lyon, France

**Advanced disease in STS: The decision-making is complex, depending on diverse presentations and histologies, and **should always be multidisciplinary****



# 21<sup>st</sup> century: to understand our mistakes and sarcoma complexity



A

Rainbow

Of

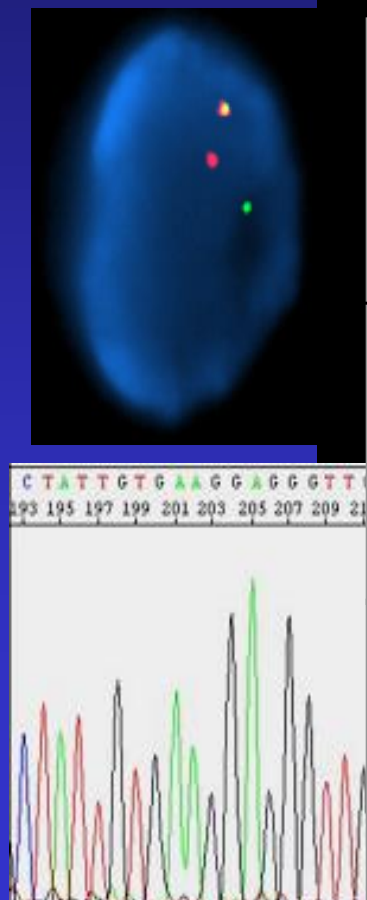
Different

Sarcoma

Subtypes

At least 50 histological subtypes,  
multiple primary sites, size, grade, age...  
**100 patients with isolated lung metastases**  
**included in retrospective surgical/medical series**  
**= 100 different diseases!!**

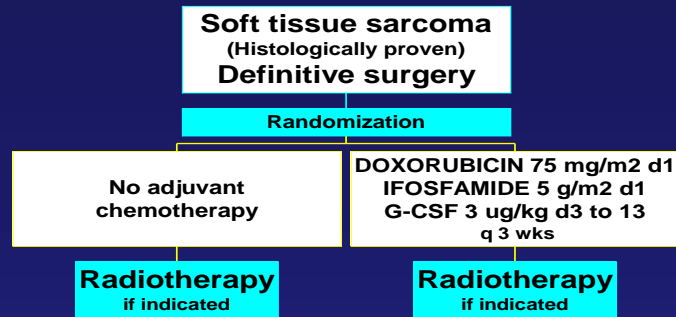
*Courtesy of G. Demetri*



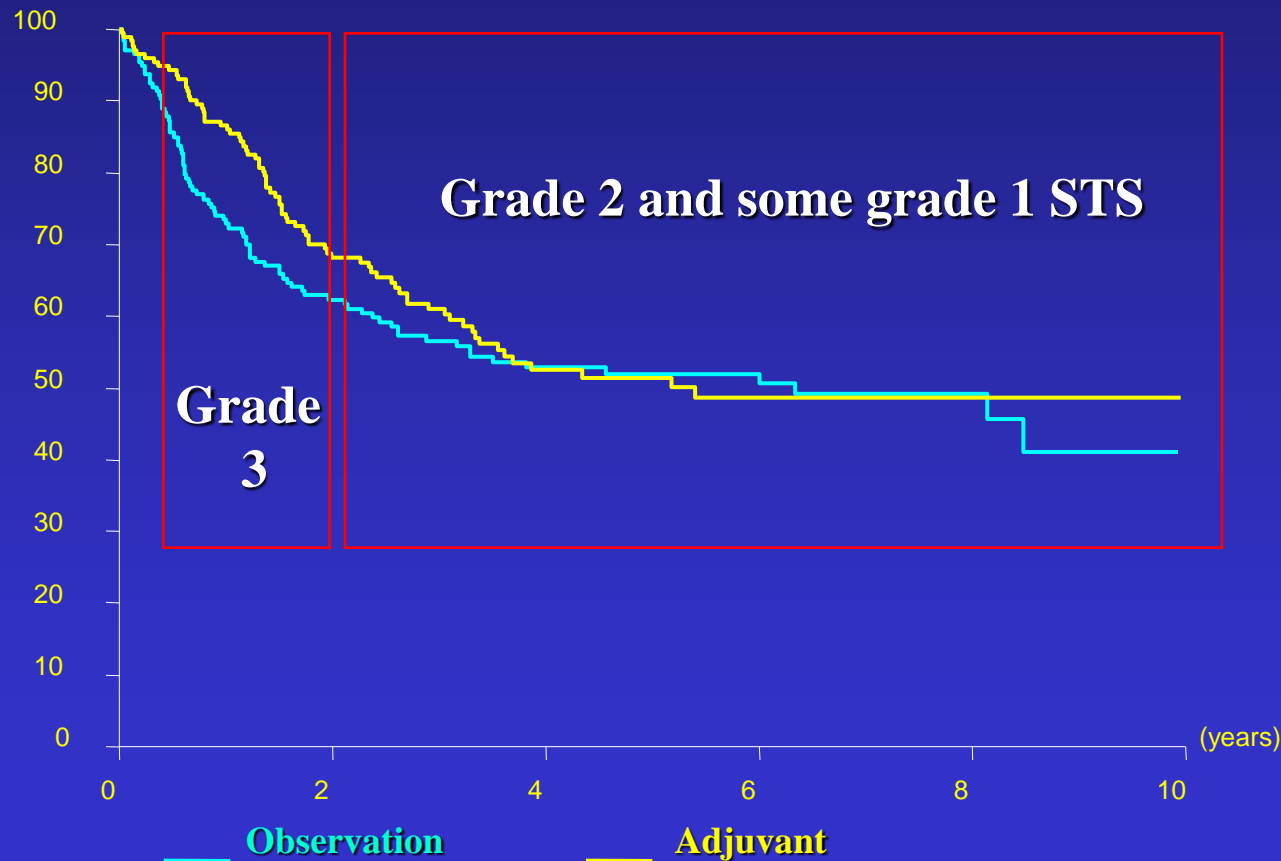


# STS – Adjuvant CT

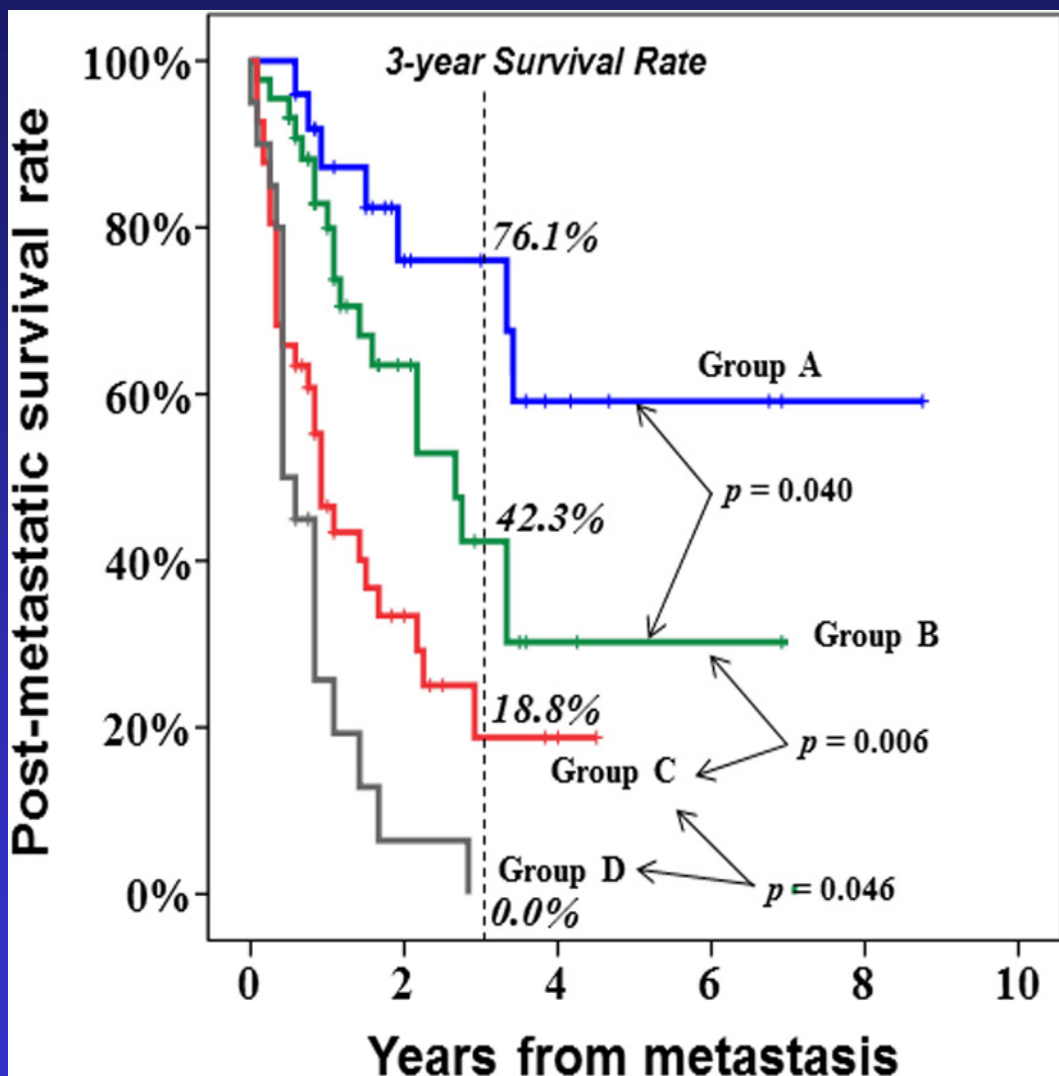
## EORTC 62931



### Relapse free survival



# Post-metastasis survival in extremity STS: Prognostic factors



**Gpe A:** low grade/metastasectomy

**Gpe B:** low grade/ no  
metastasectomy, DFI  $\geq 1$  yr  
high grade / metastasectomy

**Gpe C:** low grade / no  
Metastasectomy, DFI  $< 1$  yr  
High grade / no metastasectomy  
DFI  $\geq 1$  yr

**Gpe D:** High grade / no  
Metastasectomy, DFI  $< 1$  yr

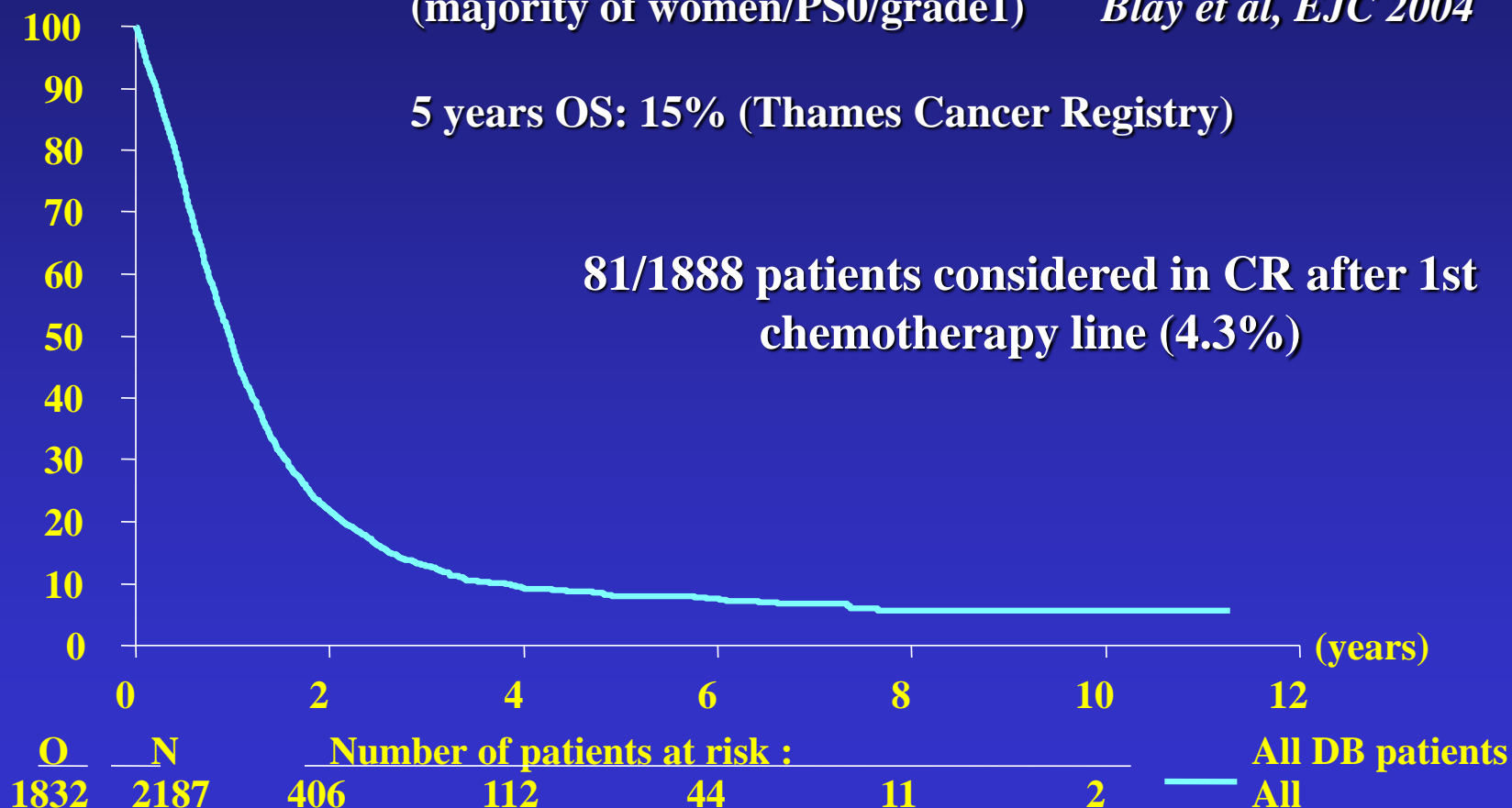


# Advanced STS: A “potentially curable” disease for oncologist...?

5 years OS: 8% of all pts included in clinical trials  
(majority of women/PS0/grade1) *Blay et al, EJC 2004*

5 years OS: 15% (Thames Cancer Registry)

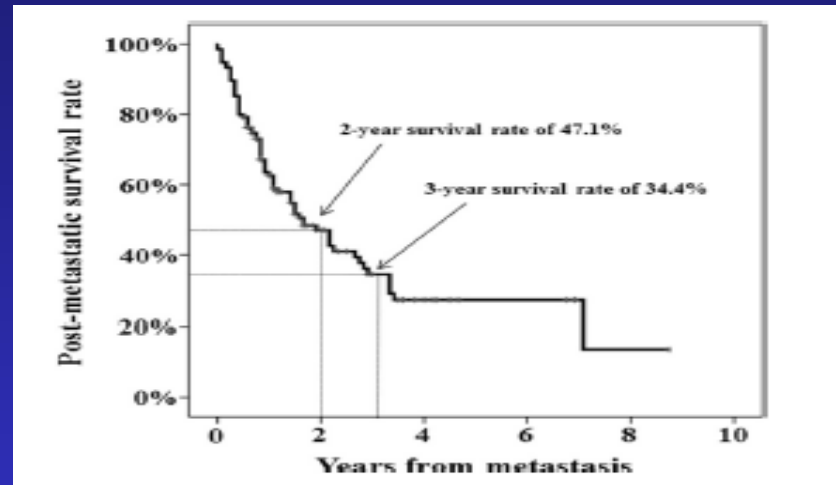
81/1888 patients considered in CR after 1st  
chemotherapy line (4.3%)



# Isolated lung metastases: a “curable” disease for surgeons!

- The words « cure » or « curative » are used in 7/18 surgery reports and in NICE guidance (National Institute for Health and Clinical Excellence) for metastatic soft tissue sarcoma!

- 5 years overall survival  
in all series: 20 to 50%  
30% in *S. kang et al, EJC 2014*



20 to 50% of all pts with advanced STS seen in Oncology Department ??

« In the absence of control data, quantifying the difference in survival among patients who have metastasectomy, and attributing it to metastasectomy rather than selection for metastasectomy, is bad science »

“A randomized controlled trial is necessary if we are to see the signal from the noise in this area of clinical practice”

(*T. Treasure et al, BMJ 2013*)

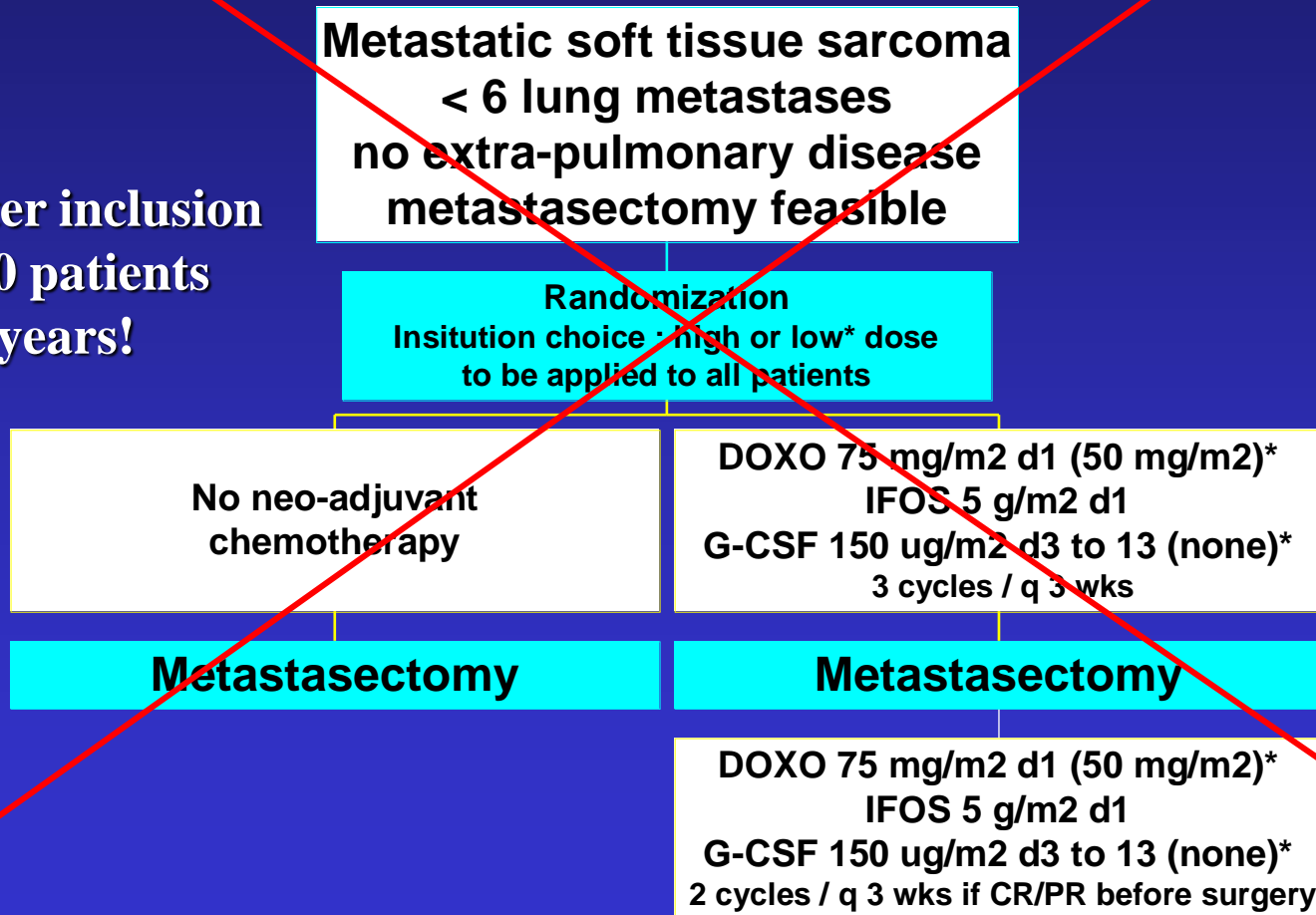


# STUDY 62933 : DESIGN

Study coordinator: A. van Geel, Rotterdam

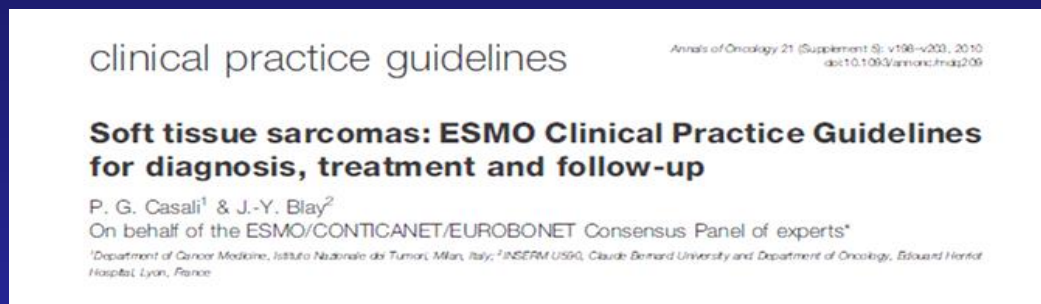
Chart Title

Closed after inclusion  
of 37/340 patients  
in 4 years!

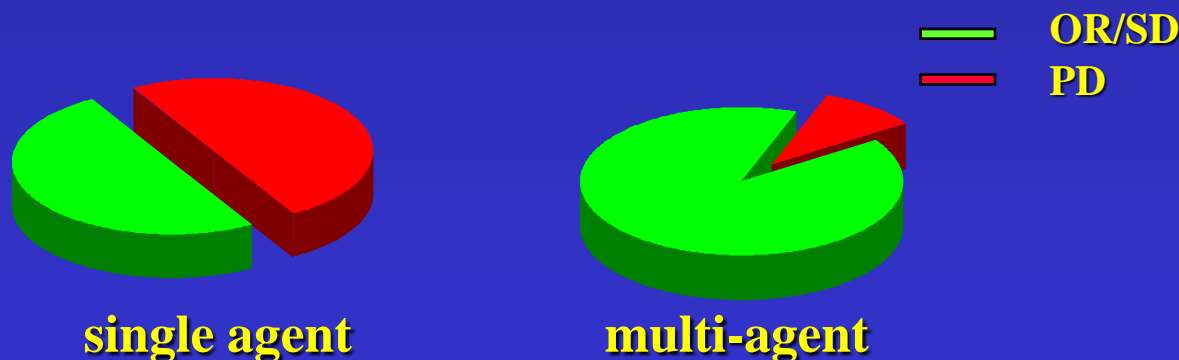


# Advanced disease in STS

## ESMO 2012 recommendations



**Multi-agent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, especially when a tumor response is felt to be able to give an advantage and patient performance status is good.**





# Advanced STS Poly- vs monoCT



Authors	Schedule	N	OR		Survival
Muss	A/AC	104	NS		NS
Omura	A/AD	146	NS		NS
Borden	A/AD	186	AD = 30 %	(p = 0.02)	NS
Lerner	A/AD	66	AD : 44 %	(leiomyo S)	NS
Santoro	A/AI/CYVADIC	449	NS		NS
Borden	A/AVd	295	NS		NS
Edmonson	A/AI/APM	262	AI = 34 %	(p = 0.03)	NS
Antman	AD/MAID	340	MAID : 32 %	(p = 0.002)	NS
Judson	A/AI	415	AI: 26%	(p = 0.0006)	NS

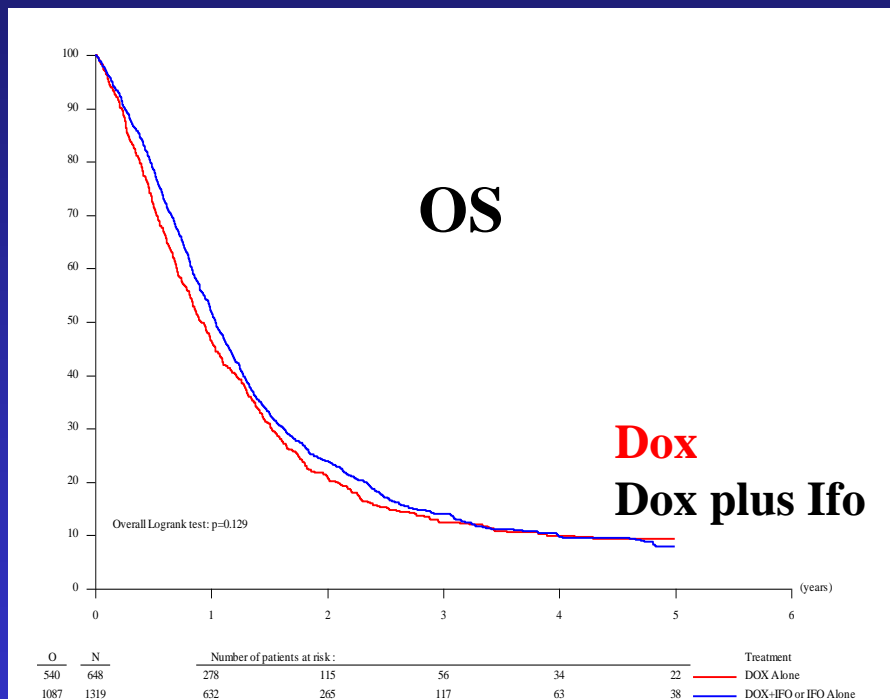


# STS – advanced STS

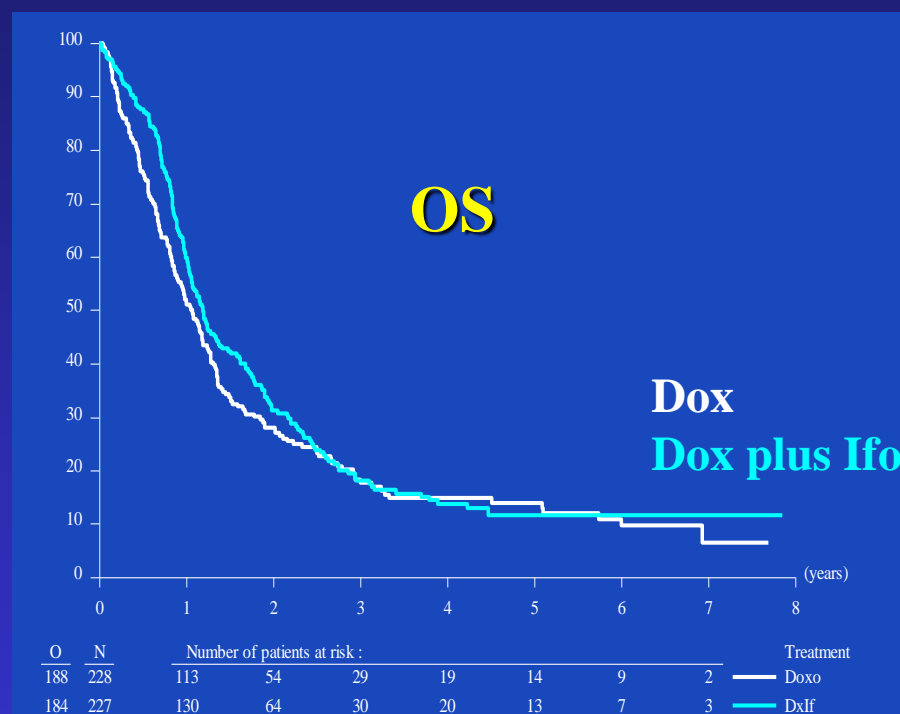
## Advantage of polyCT ?

EORTC Database

EORTC 62012



*S. Sleijfer et al, 2009*

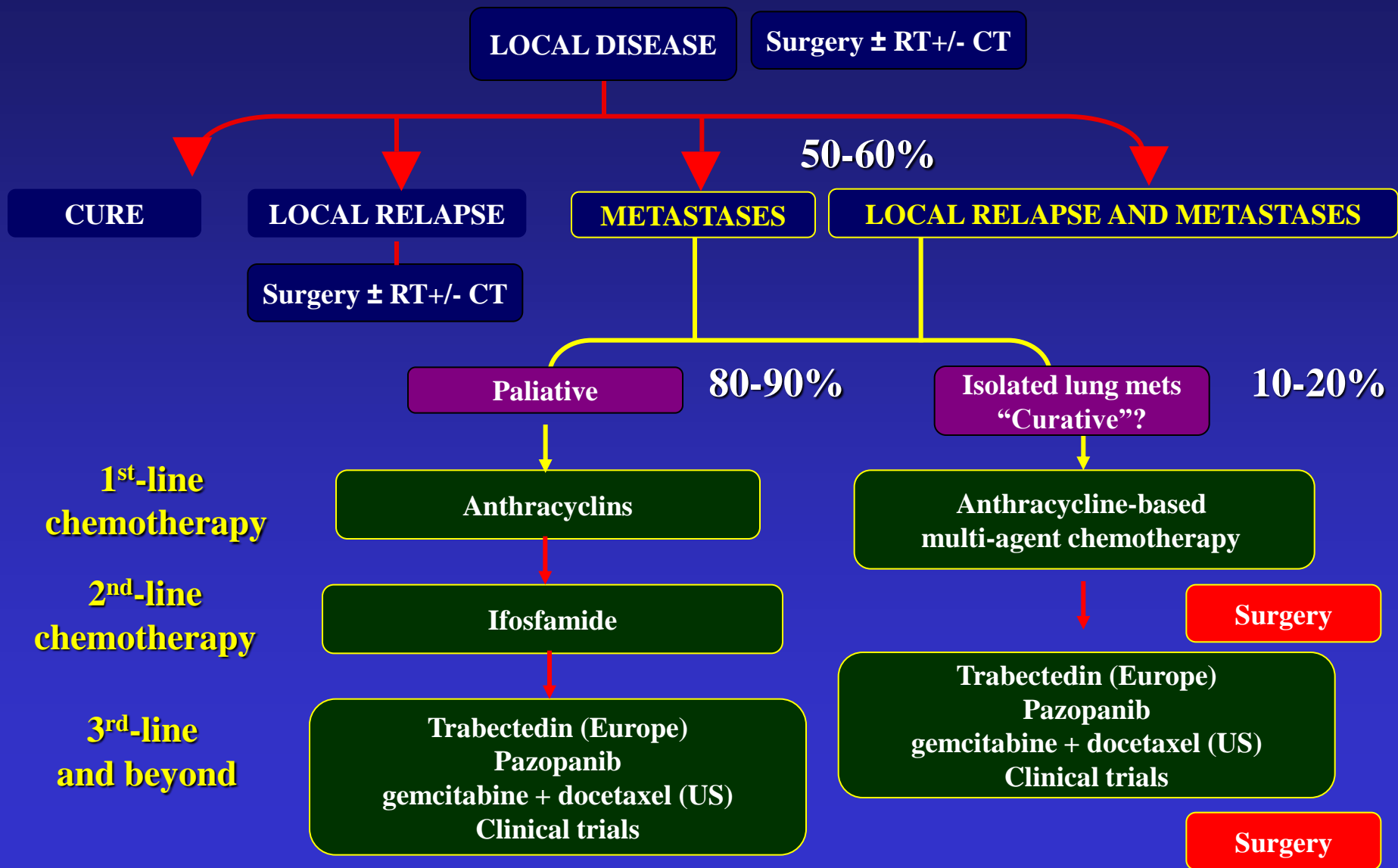


*Judson et al, LO 2014*

The impact of surgery of residual lung mets after an adapted polyCT should be apparent if the rate of pts with resectable isolated lung metastases was high!



# General treatment algorithm in STS



## ORIGINAL ARTICLE

Response to preoperative chemotherapy in patients undergoing resection of pulmonary metastasis from soft tissue sarcoma – a predictor of outcome?

HEGE O. OHNSTAD<sup>1</sup>, ØYVIND S. BRULAND<sup>1,2</sup>, INGEBORG TAKSDAL<sup>3</sup>,  
BODIL BJERKEHAGEN<sup>4</sup>, MAJA NENADOVIC<sup>4</sup>, GUNNAR SÆTER<sup>1</sup>,  
LARS H. JØRGENSEN<sup>5</sup> & KIRSTEN SUNDBY HALL<sup>1</sup>

# Isolated lung metastases

## Selection of patients with CT

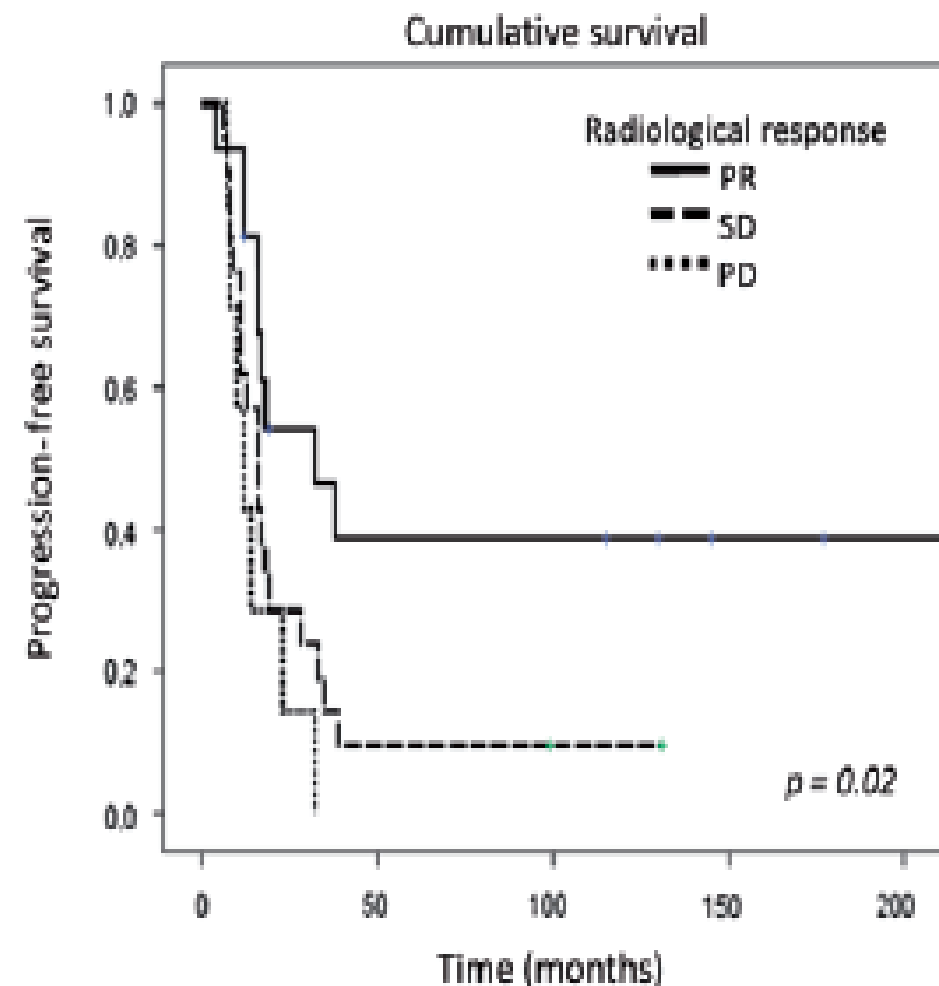
**N = 93**

**Surgery alone: 41**

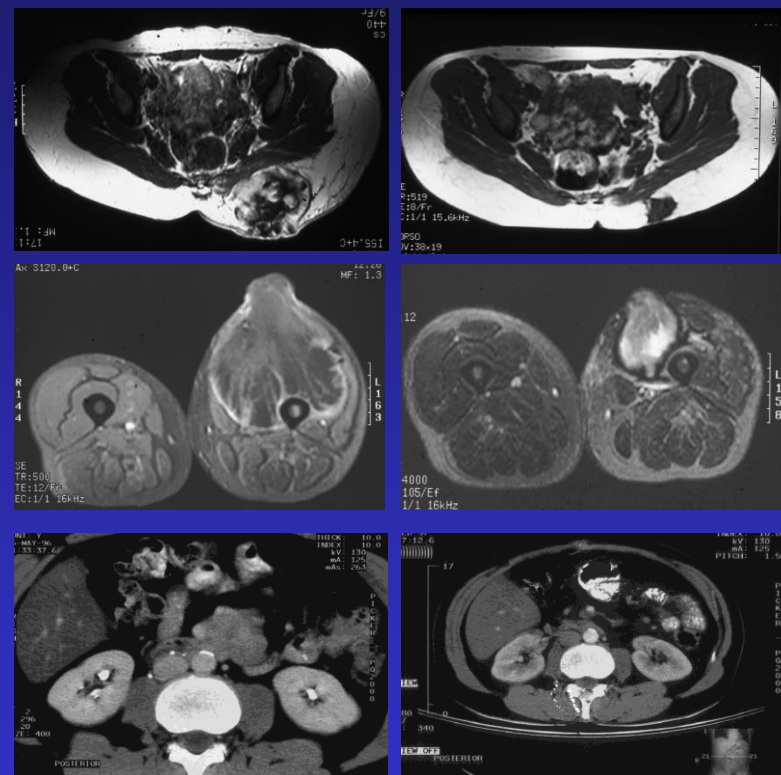
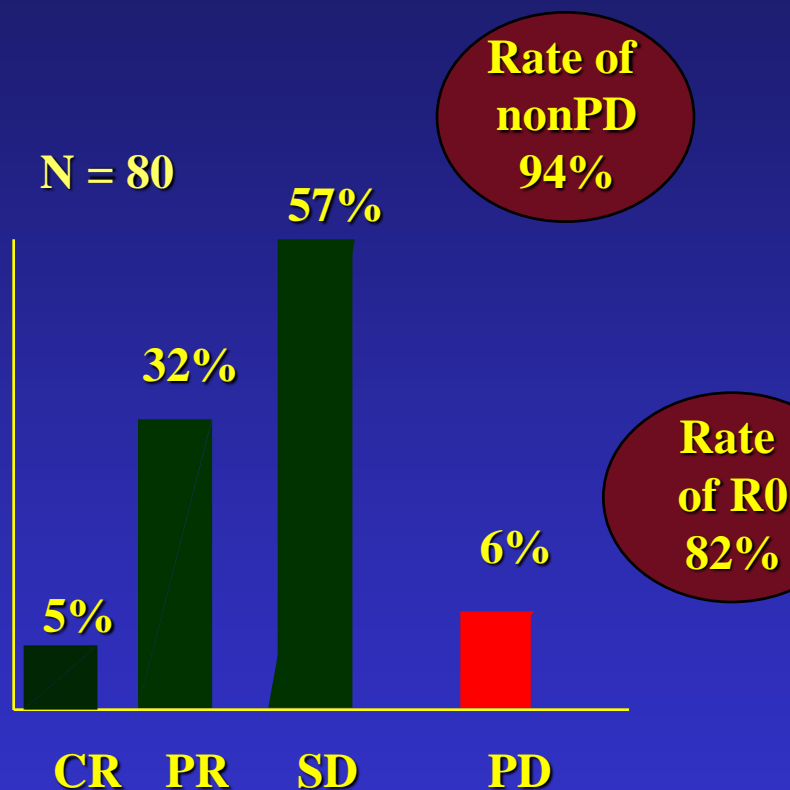
**CT then surgery: 52**

**Both histological and radiological responses to pre-operative CT seems to be prognostic in STS pats undergoing complete pulmonary metastasectomy**

**Pre-operative CT « selects »  
Good/poor candidates for surgery**



# Induction CT in STS



*Ruiz et al, EJC 2011*

clinical practice guidelines

Annals of Oncology 21 (Supplement 5):v196-v200, 2010  
doi:10.1093/annonc/mdk209

**Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

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<sup>1</sup>Department of Cancer Medicine, Istituto Nazionale dei Tumori, Milan, Italy; <sup>2</sup>INSERM U950, Claude Bernard University and Department of Oncology, Bioclinical Research Center, Lyon, France

**If the decision is made to use CT as upfront treatment, it may well be used preoperatively, at least in part.**  
**A local benefit may be gained, *facilitating surgery***

# Isolated lung metastases of STS in 2014

## « Take home messages »

- **The first step:** no surgery, no emergency (metachronous mets = synchronous infra-clinical mets!)
- **The second step:** pluridisciplinary discussion in a « sarcoma » tumor board
- **The third step:** strategy depending of mets evolution after two consecutive CT scan (size and number)

**Increase in size, not in  
number (gde 1-2)**

**Planned  
Surgery**

**« Adjuvant » CT  
if naive pts?**

**Increase in both size and  
number (gde 3)**

**Systemic treatments**

**Planned  
Surgery in  
responders?**

**Majority of tumors will be seen in « sarcoma » tumor boards!  
Registry at diagnosis of lung metastases!**



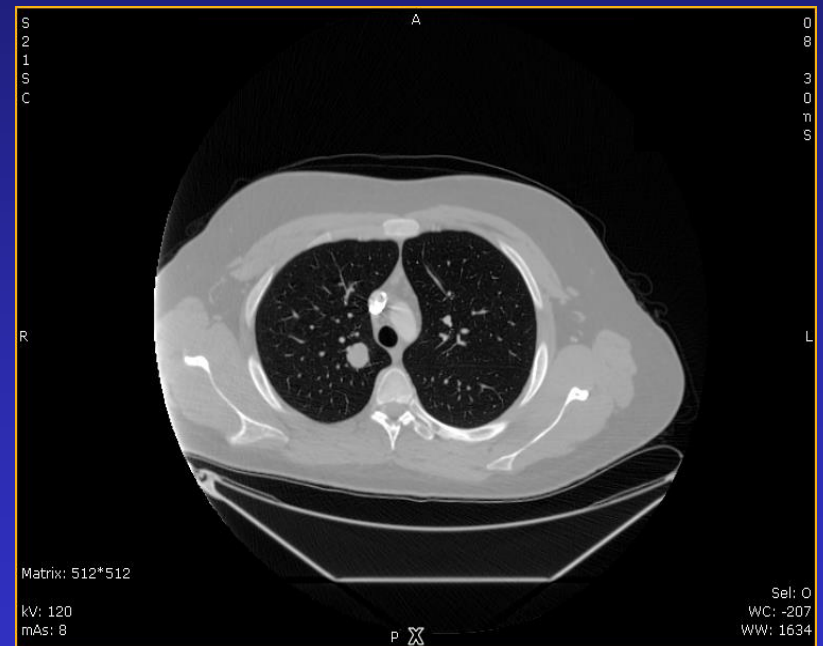
# Isolated lung metastases of STS

## « initial surveillance »

**D1**



**2-3 months later**



**Increase in size, not in number**

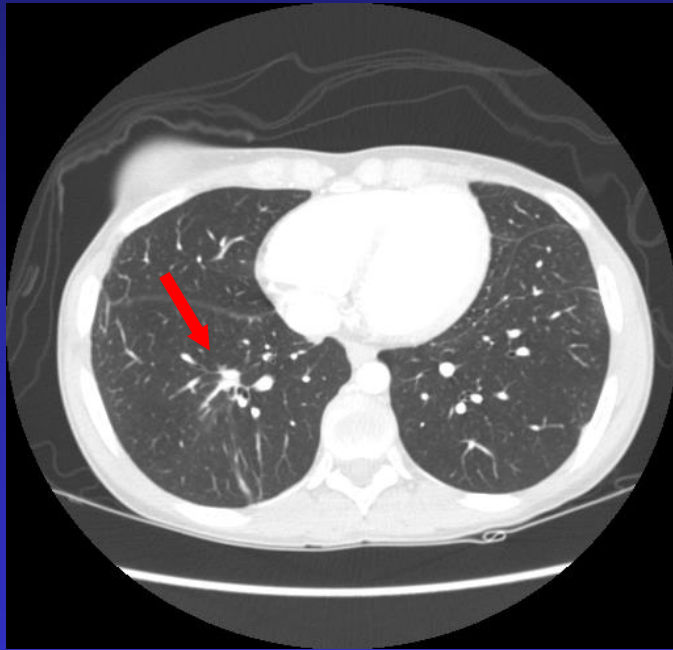
**No systemic treatment**

**Planned Surgery/locoregional approaches**

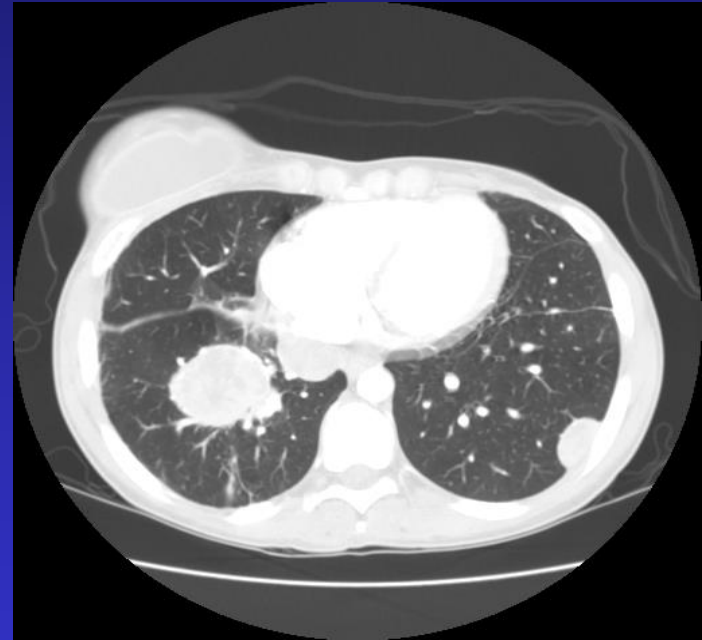
# Isolated lung metastases of STS

## « initial surveillance »

D1



2-3 months later



Increase in both size  
and number

**Systemic  
treatments**

Planned  
Surgery in  
responders?

# Future of CT in isolated lung mets in front line?

## Active drug/regimen in 2014

### Histological subtype

### Agents

**Dedifferentiated Liposarcoma**

**Doxorubicin +/-Ifosfamide**

**Myxoid liposarcoma**

**Trabectedine+/-Doxorubicin**

**Angiosarcoma**

**Paclitaxel**

**Uterine leiomyosarcoma**

**Gemcitabine + Docetaxel  
Doxorubicine + Trabectedine**

**Leiomyosarcoma**

**Doxorubicin + Dacarbazine  
Doxorubicin + Trabectedine**

**Synovialosarcoma**

**Ifosfamide**

**DFSP**

**Imatinib**

**Giant Cell Tumor**

**Denosumab**

**Planned surgery in responders...first step of personalized treatment!**



# Systemic treatment in isolated lung metastases of STS: state of the art

## Questions/Discussions

**Axel Le Cesne**  
**Gustave Roussy, Villejuif, France**

*ESMO, 28th of September 2014*