

# Aggressive and Minimally Invasive Surgery is Justified for Pulmonary Metastasis of Sarcoma

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\*no disclosures\*



# Pulmonary Metastatectomy

## History

- 1927: 1<sup>st</sup> pulmonary metastasectomy performed in Europe by Divis
- 1939: 1<sup>st</sup> pulmonary metastasectomy in North America by Barney and Churchill
- 1947: 1<sup>st</sup> published series by Alexander and Haight
- 1965: Thomford proposed criteria for surgical resection
- 1990s: Early VATS experience
- 1997: International Registry of Lung Metastases published by Pastorino et al.

# Pulmonary Metastatectomy

## Clinical Objectives

- Long term survival (curative)
- Prolong survival
- Avert complications (palliative)
- Reduce symptoms (palliative)

## Lingering Questions

- Indications / limitations
- Risk factors / Risk:Benefit

# Pulmonary Metastatectomy

## Existing Literature

- International Registry of Lung Metastasis (1997)
  - 2,173 sarcoma metastatectomies
  - 1945-1995
  - Three major risk factors: **Resectability, Disease-free interval, Number of lesions**
- Subsequent Series
  - Increase in number of reports since 2008
  - Sample size generally < 100
  - Conflicting observations regarding impact of: DFI, number of lesions, tumor size
  - Role of VATS?

# Pulmonary Metastatectomy: UCSF Experience

## Hypotheses

- Minimally invasive surgery and evolving thoracic surgical management can expand previous indications for pulmonary metastectomy
- Evolving risk factors can be identified to better guide therapeutic decision making

# Pulmonary Metastatectomy: UCSF

## Methods (1)

- Retrospective analysis of **192 procedures in 145 patients** with primary sarcomas
  - 1996 - 2009, **162 R0 resections in 118 patients**
  - Chart review and death database query
- Outcomes
  - Survival
  - Time to recurrence
  - Repeat procedures (resectable recurrence)
  - Survival after recurrence/resection

# Pulmonary Metastatectomy: UCSF Methods (2)

- Predictors
  - Demographics
  - Disease free interval
  - Lesion size, number
  - Primary sarcoma type
  - Extent of disease (bilateral, number of lobes)
  - Extrapulmonary metastasis
  - Operative approach, extent of resection
  - Use of chemotherapy
  - Primary tumor grade
  - Recurrence (interval, repeat resection)

# Pulmonary Metastatectomy: UCSF Methods (3)

- Statistics
  - Kaplan-Meier analysis
    - 2-, 3-, 5-, 10-year survival
    - Median survival
  - Cox proportional hazards models
    - Univariate
    - Multivariate models
      - Stepwise construction based on historical factors and clinical factors
  - Fisher's exact,  $\chi^2$ , Mann-Whitney tests



# Pulmonary Metastatectomy: UCSF

## Patient Characteristics (1)

Age (Mean $\pm$ SD)	46.5 $\pm$ 15
Male, N (% total)	62 (52.5%)
Disease Free Interval, years (mean $\pm$ SD )	2.53 $\pm$ 3.28
Bilateral metastasis, N (% total)	49 (41.5%)
Number of lesions (% total):	
1	40 (34%)
2	21 (18%)
3	17 (14%)
4+	39 (33%)
Size of biggest lesion (% total):	
0-3 cm	74 (63%)
>3 - 5 cm	20 (17%)
> 5 cm	24 (20%)
Extra-pulmonary Disease, N (% total)	11 (9.3%)
Chemotherapy, N (% total)	91 (77%)

# Pulmonary Metastatectomy: UCSF

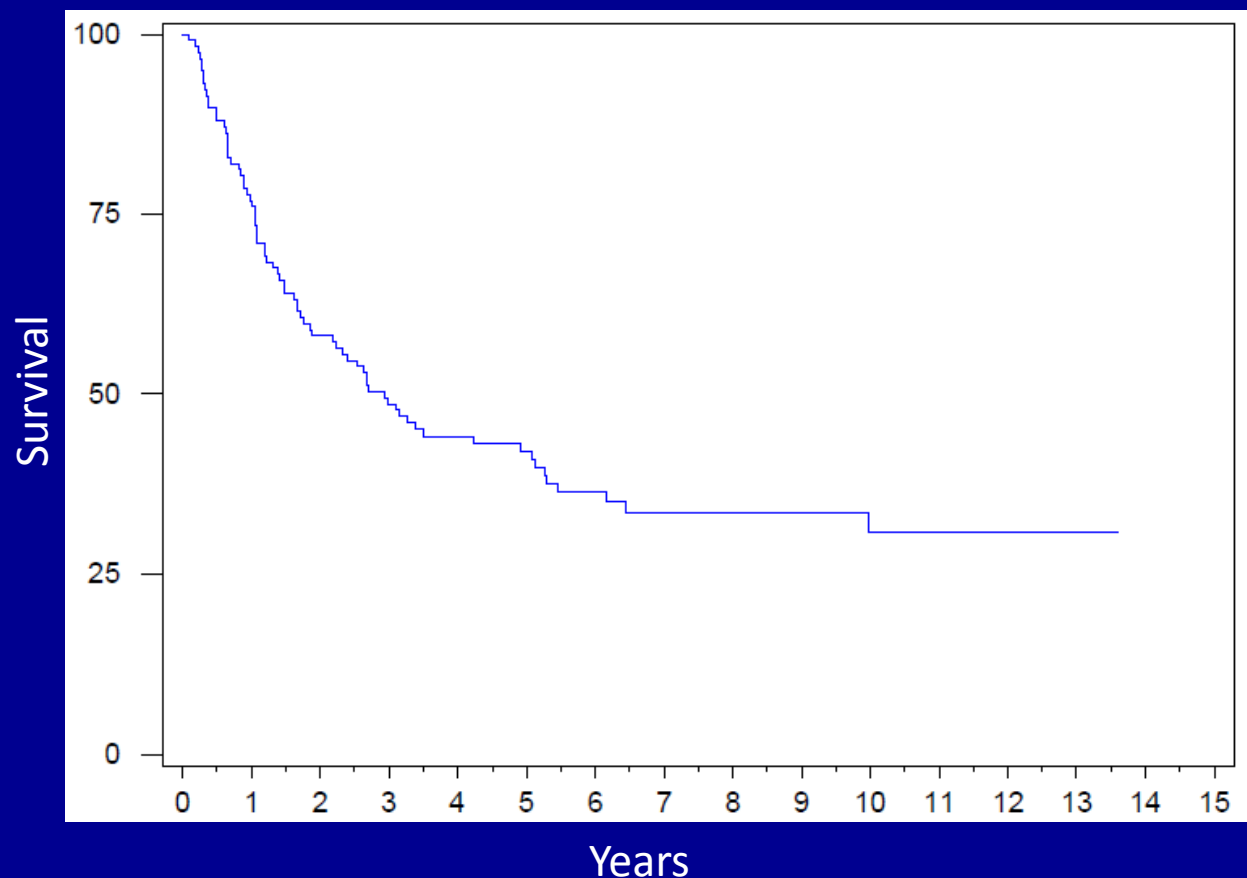
## Patient Characteristics (2)

Primary Tumor, N (% total):	
Pleomorphic Undifferentiated Sarcoma	14 (12%)
Osteosarcoma	19 (16%)
Synovial Sarcoma	16 (13%)
Leiomyosarcoma	29 (25%)
Spindle Cell	6 (5%)
Liposarcoma	6 (5%)
Other	28 (24%)
Surgical Approach, N (% total):	
VATS	44 (37%)
Thoracotomy	67 (57%)
Procedure, N (% total):	
Wedge resection	82 (70%)
Anatomic resection	26 (22%)
En bloc extrapulmonary resection	10 (8%)

# Pulmonary Metastatectomy: UCSF

## Survival

- Median survival = 35 months (95% CI 23 – 61)
- 3-, 5-, and 10-year survivals 48%, 42%, 31%



# Pulmonary Metastatectomy: UCSF

## Survival - Risk Factors

### Univariate analysis

Predictor	Hazard Ratio (95% CI)	P-value
Metastasis synchronous to primary	2.7 (1.5-5.1)	0.001
Extra-pulmonary metastasis	2.0 ( 0.97-4.2)	0.06
Need for anatomic resection	1.6 (0.95-2.8)	0.07

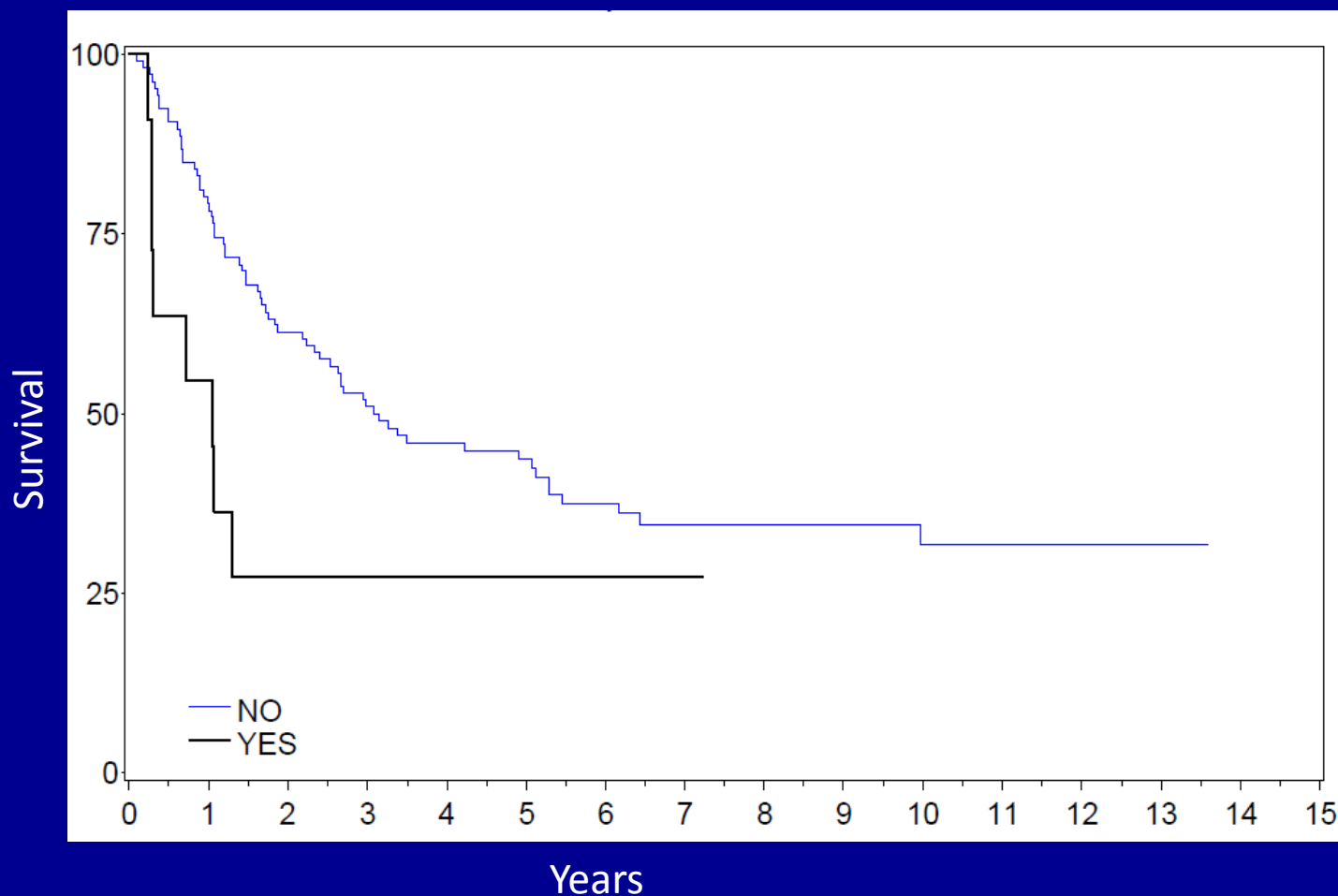
### Multivariate analysis\*

Metastasis synchronous to primary	3.0 (1.4-6.6)	0.005
Need for anatomic resection	2.6 (1.3-4.9)	0.004

\*Adjusted for lesions size, lesion number, DFI, extra-pulmonary lesions

# Pulmonary Metastatectomy: UCSF

Extra-pulmonary disease



# Pulmonary Metastatectomy: UCSF

## Survival - Risk Factors

### Univariate analysis - Traditional Predictors

Predictor	Hazard Ratio (95% CI)	P-value
Disease Free Interval <sup>†</sup>	0.88-1.03	0.23
Number of lesions	0.4-2.7	0.81
Size of biggest lesion (continuous)*	0.9-1.1	0.82
Bilateral metastasis	0.7-1.8	0.61
Sarcoma subtype (except Ewing' s/small blue cell)	-	>0.4

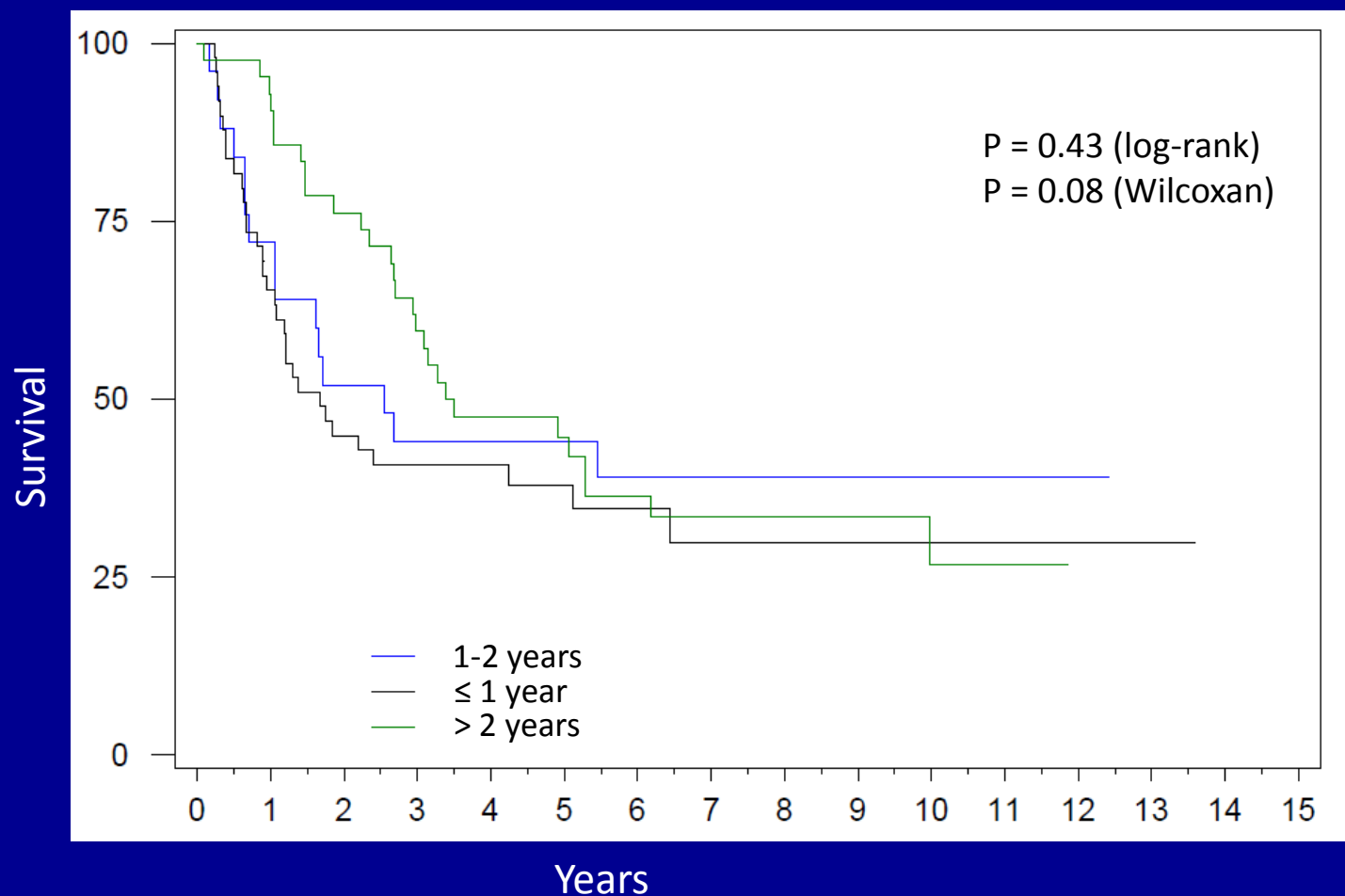
<sup>†</sup>Proportional Hazards P-value = 0.005

\*HR = 2.0 (95% CI 1.1-3.6, P=0.02) for lesions 3.1-5.0 cm

HR = 0.805 (95%CI 0.4-1.5, P=0.49) for lesions > 5 cm

# Pulmonary Metastatectomy: UCSF

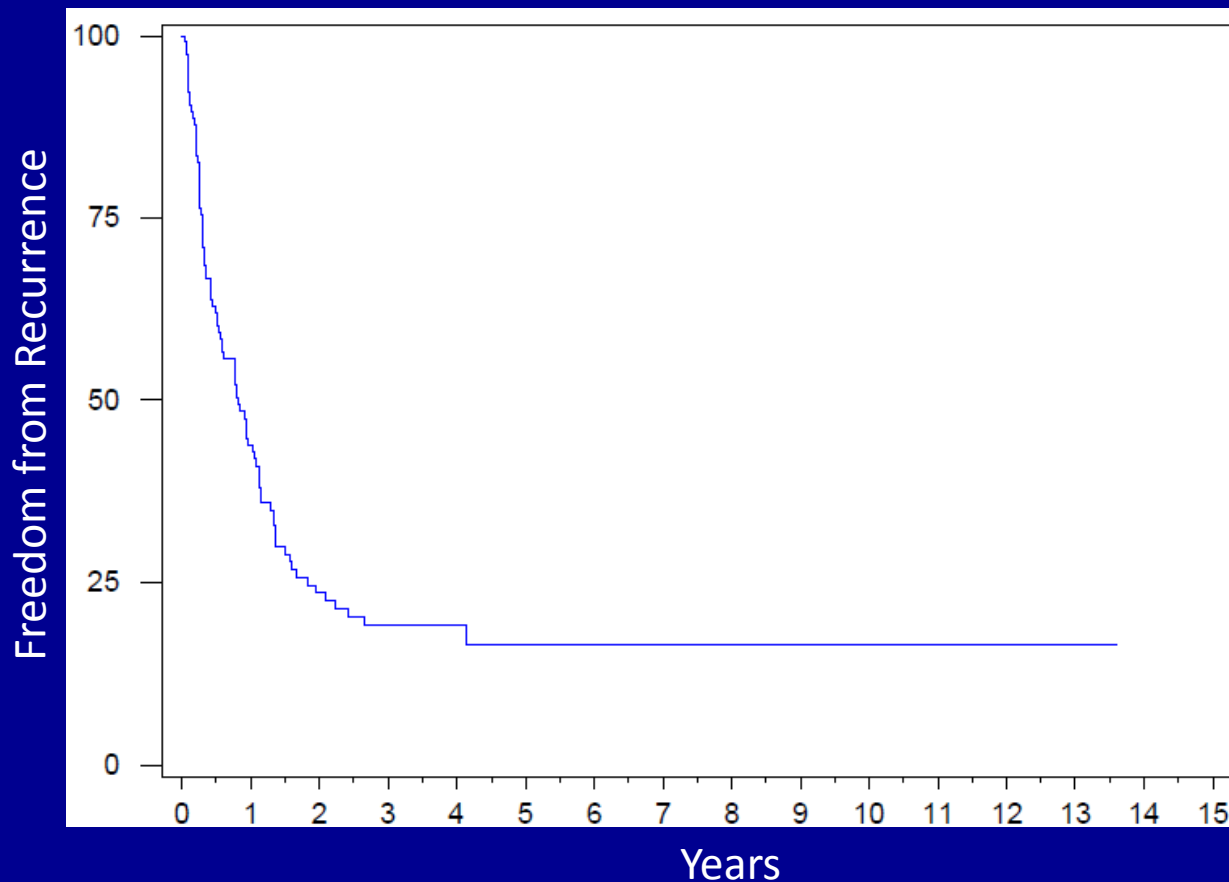
## Disease Free Interval



# Pulmonary Metastatectomy: UCSF

## Time to Recurrence

- 3-, 5-, and 10-year recurrence rates:  
81%, 83%, 83%



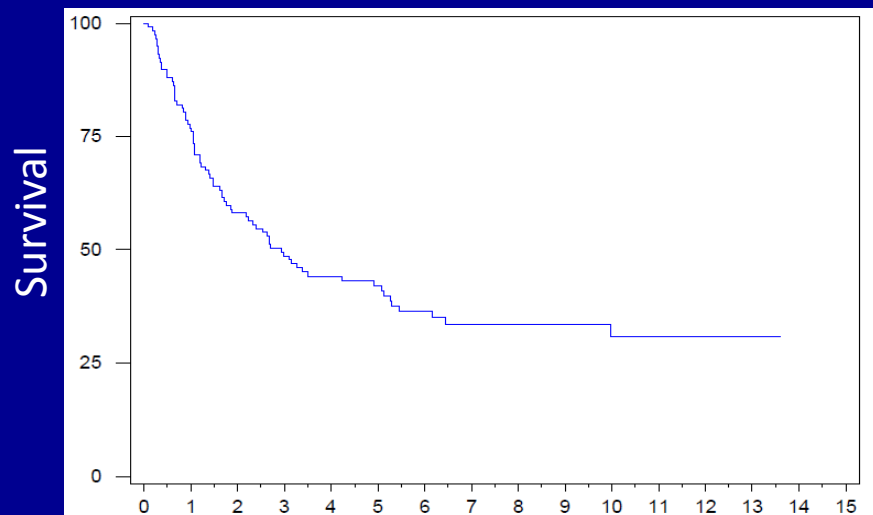


# Pulmonary Metastatectomy: UCSF

## Recurrence

- Resectable vs. Unresectable

### Initial Resection

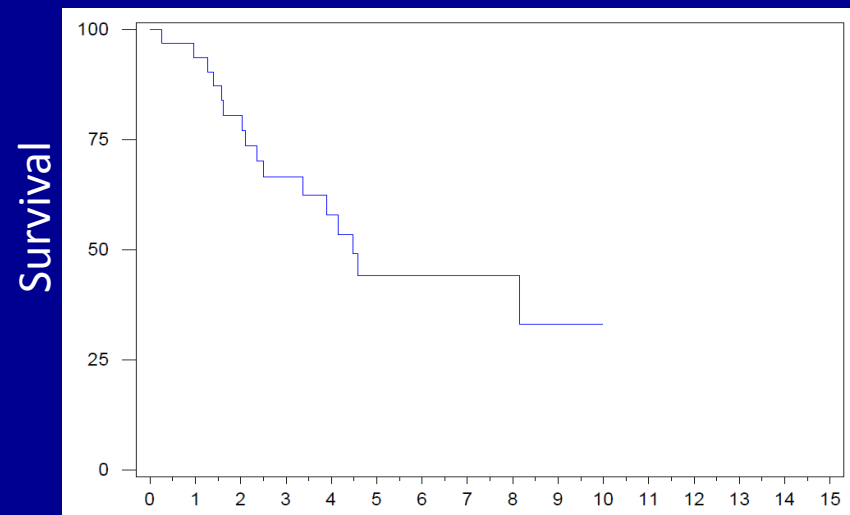


Years from initial resection

Median Survival: 35 mos

5-yr Survival: 42%

### Repeat Resection



Years from repeat resection

Median Survival: 54 mos

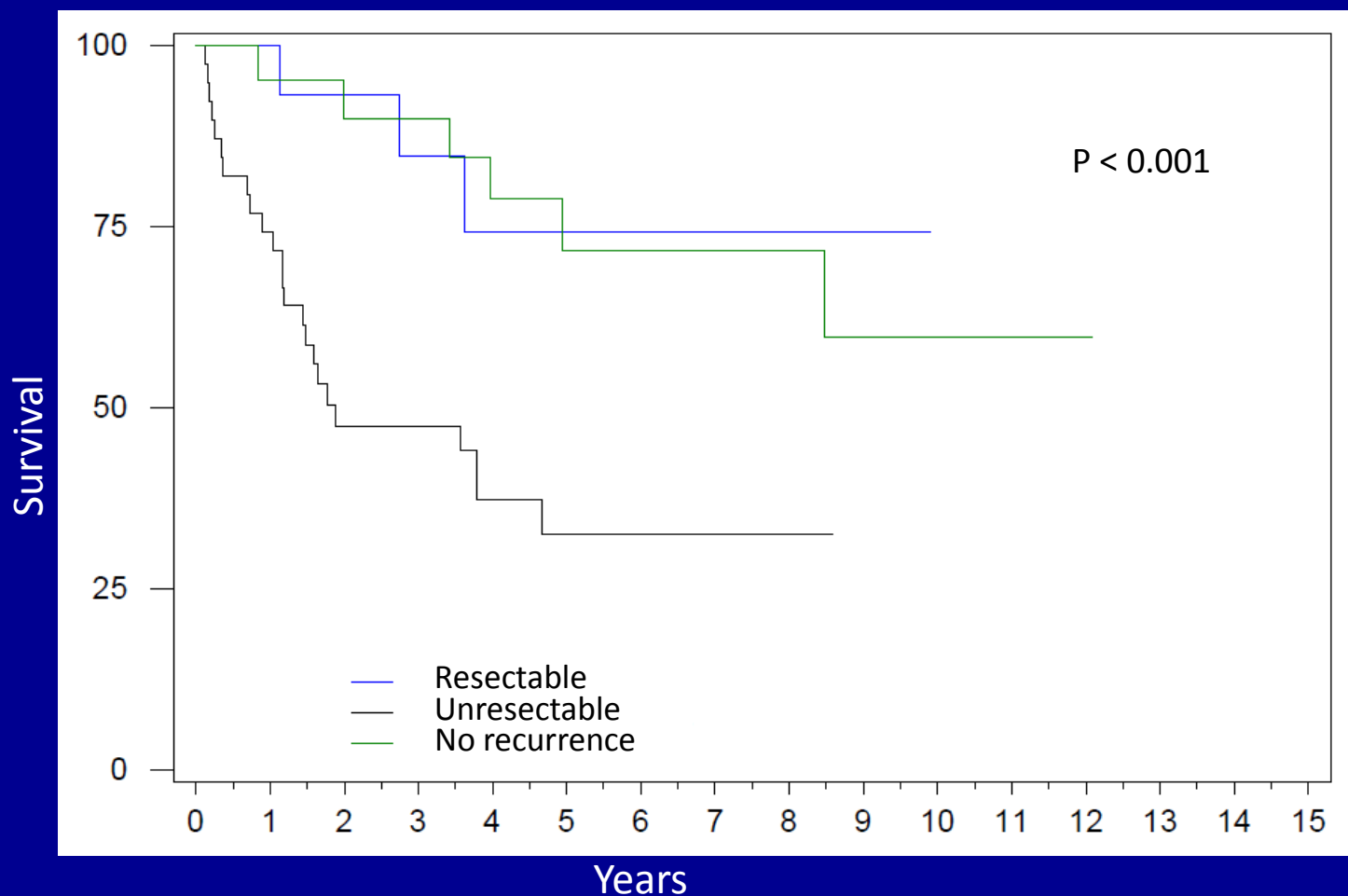
5-yr Survival: 44%

Interval to Recurrence: **HR = 0.33** (95%CI 0.10-1.06, P=0.06)

# Pulmonary Metastatectomy: UCSF

## Resectable vs. Unresectable Recurrence

- Survival beyond 18 months



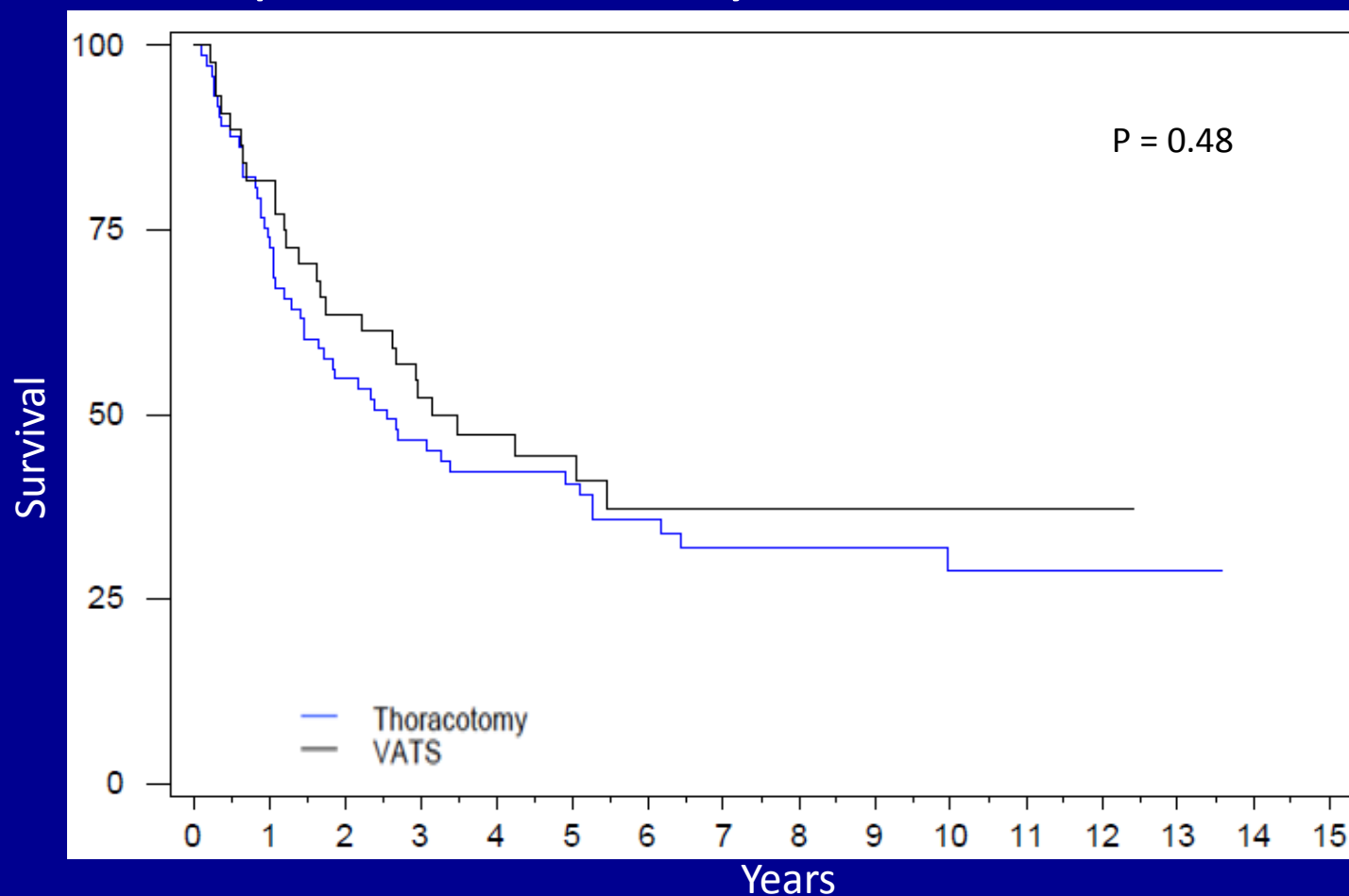
# Pulmonary Metastatectomy: UCSF

## Evolution of Therapeutic Approach: 1996-2002 vs. 2003-2009

- Increase in use of VATS over time
  - 47% vs. 18% of cases (P=0.002)
- Increase in number of lesions over time
  - Mean of  $4.8 \pm 5.0$  vs.  $2.1 \pm 1.4$  (P =0.003)
  - 33% vs. 15% of patients with >5 lesions (P=0.04)
- Decrease in size of biggest lesions over time
  - Mean of  $2.9 \pm 3.2$  cm vs.  $5.8 \pm 4.8$  cm (P= <0.0001)
  - 27% vs. 8% of patients with largest lesion  $\leq 1$  cm (P= 0.02)

# Pulmonary Metastatectomy: UCSF

## Evolution of Therapeutic Approach: VATS vs. Open Thoracotomy



# Pulmonary Metastatectomy: UCSF

## Evolution of Therapeutic Approach:

### VATS vs. Open Thoracotomy

- No difference in **Number of Lesions**
- No difference in **Time to Recurrence**
- No difference in rate of **Unresectable Recurrence**
- No difference in **Survival**
- Repeat operation for resectable disease after initial

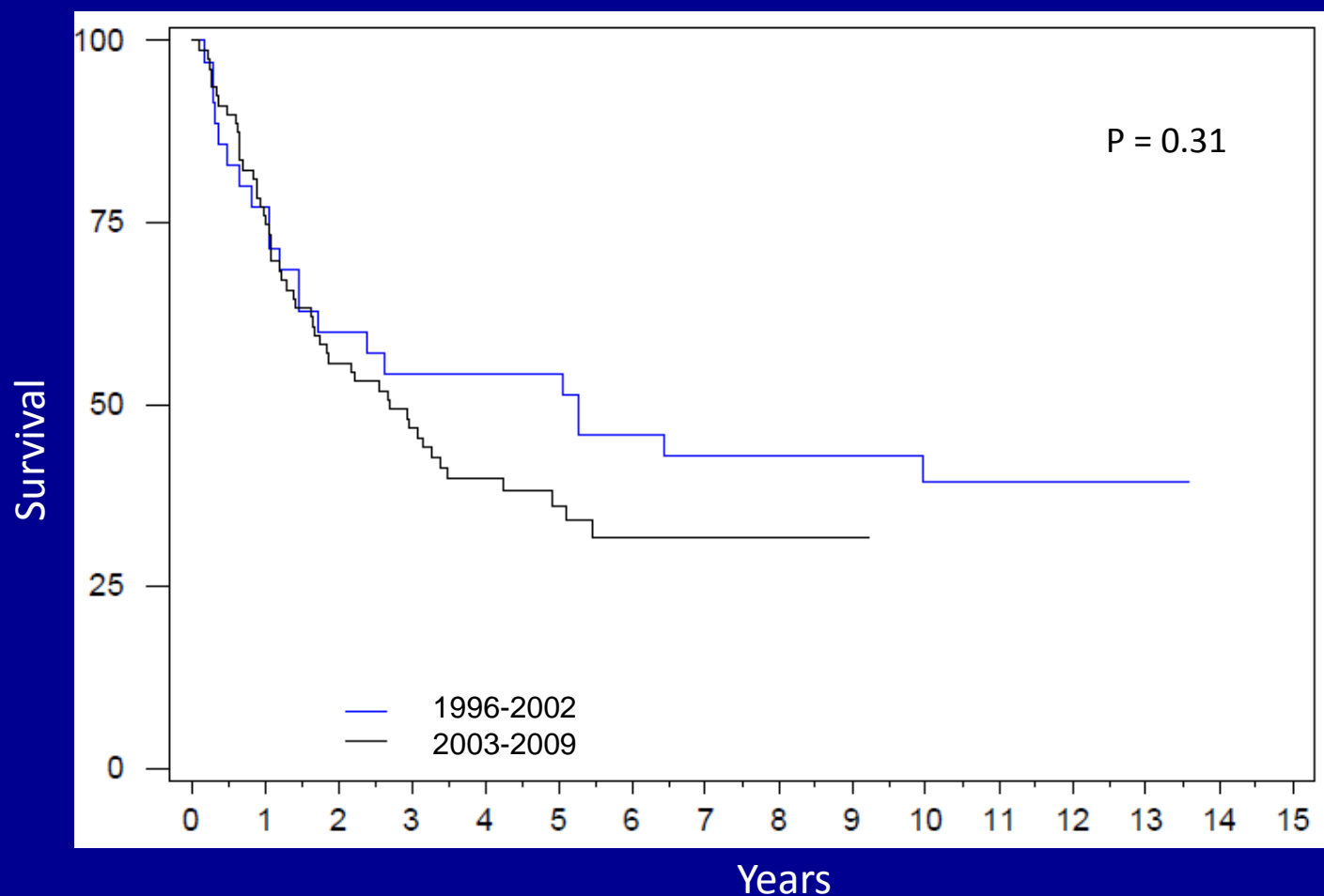
### VATS vs. Thoracotomy

- **100% vs. 79%,  $P = 0.11$  (Fisher's exact test)**
  - Repeat operation for resectable disease after initial
- ### Wedge vs. Anatomic Resection

- **97% vs. 50%,  $P = 0.01$  (Fisher's exact test)**

# Pulmonary Metastatectomy: UCSF

Evolution of Therapeutic Approach:  
1996-2002 vs. 2003-2009



# Pulmonary Metastatectomy: UCSF

## Conclusions (1)

- Median survival of 3 years can be achieved with aggressive pulmonary metastatectomy
  - **31% long-term cure**
- Initial disease free interval may affect 3-year but not long-term survival, though synchronous metastasis is an ominous finding
- Although extra-pulmonary metastasis and a need for anatomic resection may influence survival, bilateral metastases and the number and size of lesions, if fully resectable, likely do not impact survival

# Pulmonary Metastatectomy: UCSF

## Conclusions (2)

- Although most patients recur, recurrences may not impact prognosis if they remain fully resectable
- Time to recurrence may be a predictor of survival after recurrence
- Increasing use of VATS and an aggressive approach to number of lesions does not impact survival or recurrence