Surgery for (Metachronous) Multiple Primary Lung Cancers

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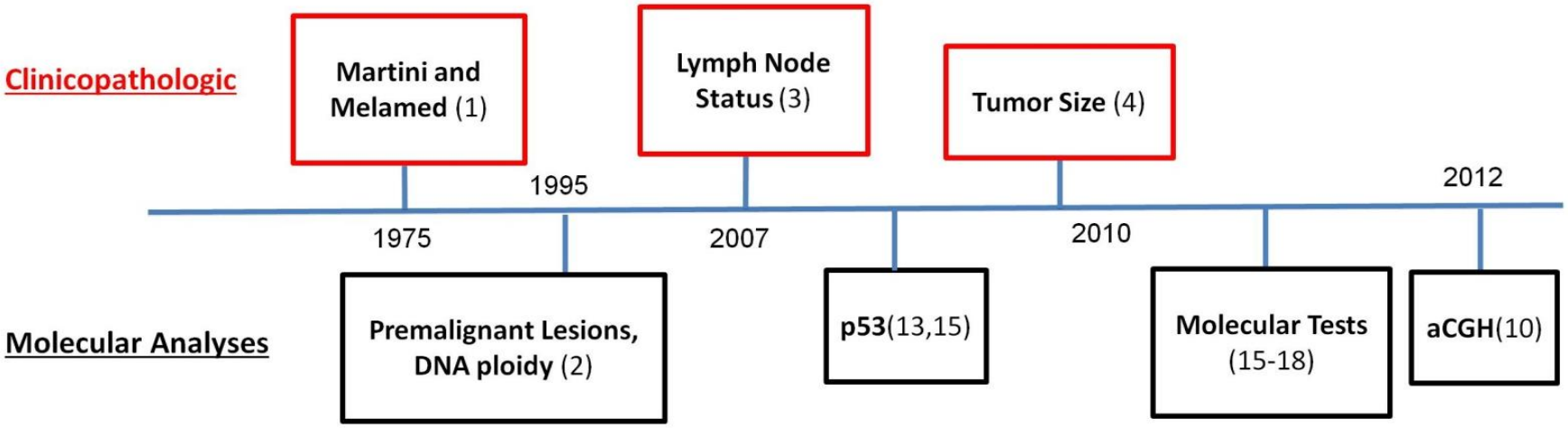
Multiple primary lung cancers

Data on 50 patients with multiple separate primary carcinomas of the lung are presented. Eighteen had synchronous tumors and 32 had metachronous tumors, the intervals between diagnoses varying from 4 months to 16 years. Histologic patterns in the two different carcinomas were the same in 31 patients, most commonly epidermoid, and they were different in 19 patients. The problems involved in establishing the diagnosis of multiple primary lung cancers, the choice of treatment, and the expectation for survival are discussed.

Nael Martini, M.D.,* and Myron R. Melamed, M.D.** (by invitation),
New York, N. Y.

***J Thorac Cardiovasc Surg* 1975**

How Do We Define Multiple Lung Cancers?



Martini-Melamed Criteria

1. Tumors with different histology
2. Time interval between initial and second cancer >2 yrs
3. In tumors with the same histology
- 2+ of the following:
- Tumors in different lobes of same lung
- Tumors in contralateral lung, no shared lymph node basin
4. Tumors associated with pre-malignant condition
5. No systemic metastases
6. No mediastinal spread

Multiple Primary Lung Cancers

Comparative Genomic Hybridization

Objectives

- Mutational profiles and aCGH in 24 clinically determined MLC tumor pairs
- Assess whether these tests can replicate Martini-Melamed classification, through concordant tumor clonality.

Results

- Mutational profiling contradicted clinical criteria in 4/24 cases (17%)
  - 4 cases deemed metastasis, where clinical criteria classified as MLCs
  - 1 case deemed to be MLCs, where clinical criteria classified as metastasis
- 4 pairs deemed 'equivocal' by aCGH, had matching mutational profiles

Conclusion/Criticisms

- Small dataset; likely MPLC cases already pre-selected

Girard et al. *Clin Cancer Res* 2009

Molecular/Genomic Analyses on MPLCs

Do They Help?

- **p53 status (protein, mutations, LOH)**
  - ~ 10 studies
  - Correlation is between 35 to 66% for MPLC
- **EGFR mutations**
  - 2 studies
  - No real correlations
- **KRAS**
  - Very little information; no meaningful correlations

Conclusions: at present, Martini-Melamed Classification the best, most clinically relevant criteria

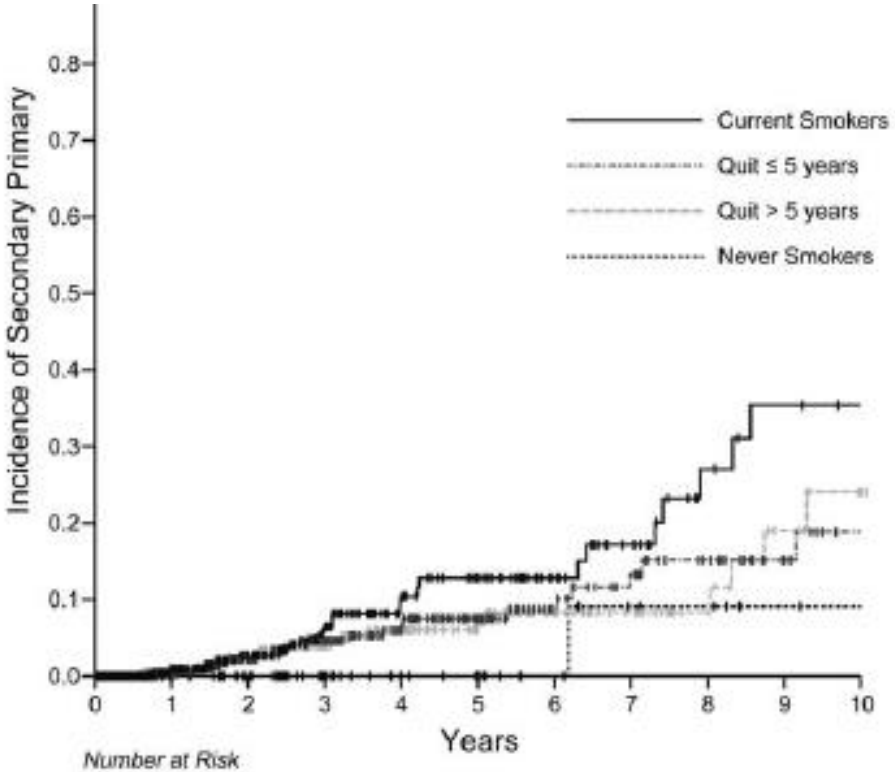
Loukeri AA et al. *Clin Lung Cancer* 2015

Smoking History and SPLCs

- Single institution, retrospective study (1995-2009) of 1484 pts with 66 pts (4%) developing SPLC
  - Incidence at 5 years - 8%
  - Incidence at 10 years - 16%
- Risk of developing a SPLC at 5 yrs related to smoking history
  - Never smoker: 0%
  - Quit > 5 years: 7%
  - Quit < 5 years: 11%
  - Active smoker: 13%
- Development of SPLC related to pack years on MVA
  - 8% increase per 10 pack years (p=0.03)

Boyle JM et al. *Cancer* 2015

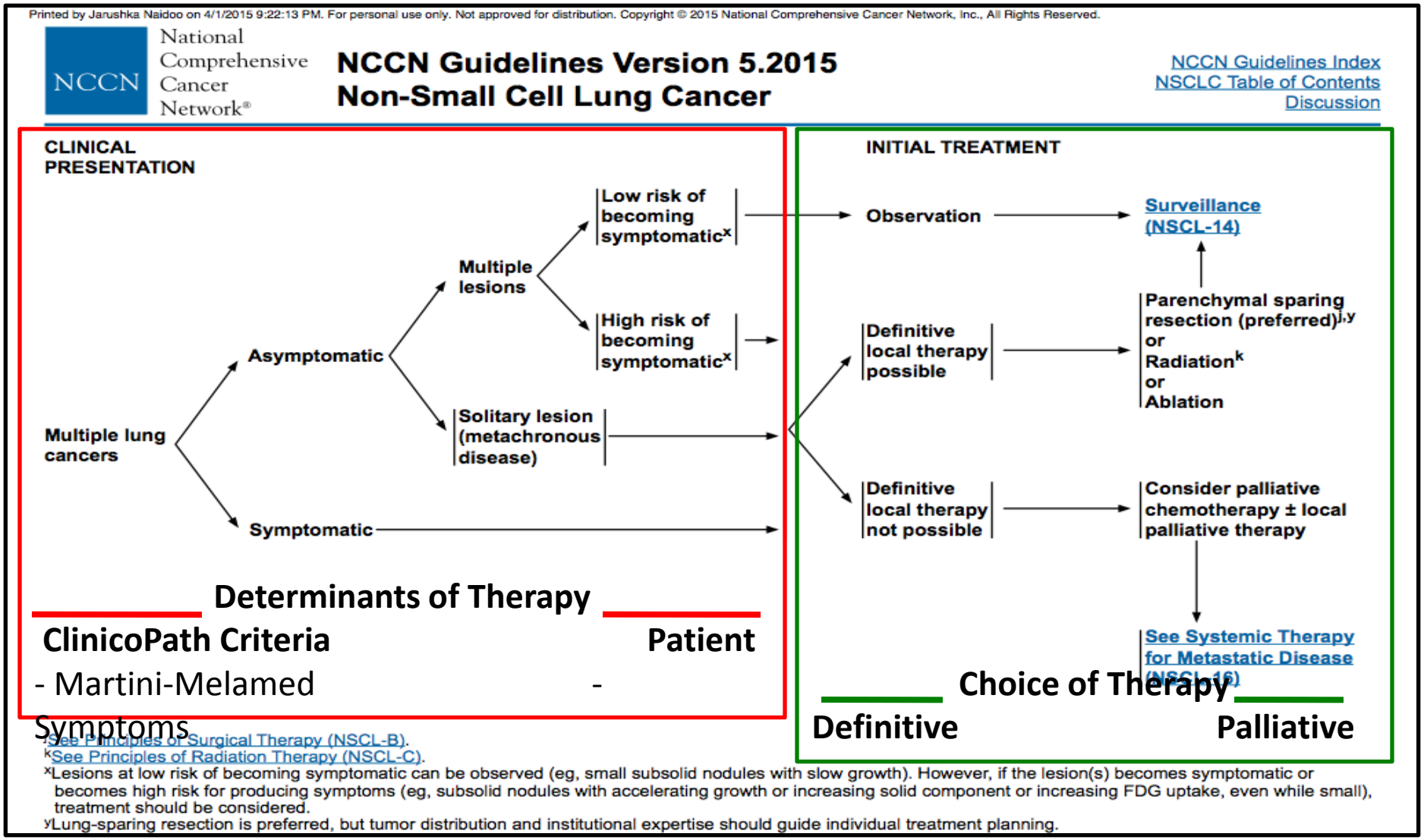
Rate of SPLC Stratified by Smoking Status



Boyle JM et al. *Cancer* 2015

Multiple Lung Cancers

How do we assess and treat these tumors?



Non-Small Cell Lung Cancer Guidelines, NCCN 20th edition, 2015: Zauderer, Kris, MSKCC submission

Surgical Principles for Resection of MPLCs

- Surgically stage the mediastinum
- Preop biopsy of second lesion not always helpful
- Both lesions must be resectable
- Often a combination of lobar and sublobar resections
- Consider SBRT or ablative therapies for second tumor not amenable for resection
- If metachronous, then often a sublobar resection
- No data on VATS vs. open

Surgical Principles for Resection of MPLCs

- Identical histology with primary = 64%
- Majority of series are adenocarcinoma histology
- Extent of resection for MPLC
  - Sublobar resection = 26%
  - Lobectomy = 40%
  - Pneumonectomy = 22%
- Post-operative mortality (0-26%)
  - Average is 6.5%
  - Higher when pneumonectomy performed

Loukeri AA et al. *Clin Lung Cancer* 2015

What is the Prognosis of Patients With MPLCs?

- **Median OS in SEER database[1]**

- Stage IV NSCLC: 4 months
- Synchronous MLCs (n=1858): 22 months
- Metachronous MLCs (n= 33): 29 months

1. Bhaskarla et al. *J Surg Res* 2010

- **Improved OS of surgically resected MPLCs [2]**

- Adenocarcinoma histology (median OS: 67.2 mos. vs. 36.2 mos. adeno vs. other histologies, p<0.01)
- Bilateral lesions
- T<3cm
- N0 disease
- Age<70 years
- Female sex

2. Tanvetyon et al. JTO 2015

Prognosis and MPLCs

- Systematic review of 22 studies from 1975-2013 (1796 pts)
- No difference in OS of metachronous and synchronous MPLCs if OS starts at diagnosis of the second tumor
- No difference in OS
  - Based on same or different tumor histologies
  - Ipsilateral vs. contralateral

- Single institution study of 161 pts
- T > 2 cm (p=0.003) , pack year smoking (0.005)
- Sublobar resection and node-positive disease not predictive of prognosis

Jiang L et al. *Lung Cancer* 2015
Hamaji M et al. *JTCVS* 2013

Multiple Primary Lung Cancers

MSKCC Experience

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Multiple Primary Lung Cancers

MSKCC Experience

- Retrospective review from 2008-2013
- R0 resection for cstage IA-IIIA NSCLC
- Excluded carcinoid and GGO lesions
- Martini-Melamed criteria to discern MPLCs
- Identified 113 patients (prior study from MSK identified 130 patients 1995-2007)