Surgery for (Metachronous) Multiple Primary Lung Cancers

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David R. Jones, MD
Professor & Chief, Thoracic Surgery
Co-Director, Druckenmiller Center for Lung Cancer Research

Memorial Sloan Kettering Cancer Center

More Science. Less Fear.
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.
How Do We Define Multiple Lung Cancers?

**Clinicopathologic**
- Martini and Melamed (1)
- Lymph Node Status (3)
- Tumor Size (4)

**Molecular Analyses**
- Premalignant Lesions, DNA ploidy (2)
- p53(13,15)
- Molecular Tests (15-18)
- aCGH(10)

**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

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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

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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

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

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Multiple Lung Cancers
How do we assess and treat these tumors?

Determined by Therapy
ClinicoPath Criteria
- Martini-Melamed
- Symptoms

Patient

Definitive

Palliative

Choice of Therapy

Determinants of Therapy

INITIAL TREATMENT

Multiple lesions

Low risk of becoming symptomatic

High risk of becoming symptomatic

Definitive local therapy possible

Definitive local therapy not possible

Consider palliative chemotherapy ± local palliative therapy

Observation

Surveillance (NSCL-14)

Parenchymal sparing resection (preferred) or Radiation or Ablation

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

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

- 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

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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
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)