SURGERY FOR SYNCHRONOUS LUNG TUMORS

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Definition and implication for treatment

- **Synchronous Primary Lung Cancers**
  - Aggressive local treatment

- **Primary lung cancer with Lung metastasis**
  - Palliative systemic therapy
Epidemiology MPLC

- 6% of all tumors
- Rate of operability 44-76% in surgical series
- 20-40% are synchronous (rate increase if review of previous CT scan is performed)
- About half has the same histology

Riquet et al ANN Thor Surg 2008
### Table 1
Criteria for diagnosis of second primary lung cancer.

<table>
<thead>
<tr>
<th>Criteria for Diagnosis of Second Primary Lung Cancer</th>
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<tbody>
<tr>
<td><strong>Martini and Melamed criteria</strong></td>
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<tr>
<td><strong>Synchronous MPLC</strong></td>
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<tr>
<td>A. Tumors physically distinct and separate</td>
</tr>
<tr>
<td>B. Histological type</td>
</tr>
<tr>
<td>1. Different</td>
</tr>
<tr>
<td>2. Same, but in different segments, lobes, or lungs, if</td>
</tr>
<tr>
<td>a. Origin from carcinoma in situ</td>
</tr>
<tr>
<td>b. No carcinoma in common lymphatics</td>
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<tr>
<td>c. No extrapulmonary metastases at the time of diagnosis</td>
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<tr>
<td><strong>Metachronous MPLC</strong></td>
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<tr>
<td>A. Histologically different</td>
</tr>
<tr>
<td>B. Histologically identical, if</td>
</tr>
<tr>
<td>1. Free interval between cancers ≥ 2 years, or</td>
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<tr>
<td>2. Origin from carcinoma in situ</td>
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<tr>
<td>3. Second cancer in different lobe or lung, but:</td>
</tr>
<tr>
<td>a. No carcinoma in common lymphatics</td>
</tr>
<tr>
<td>b. No extrapulmonary metastases at time of diagnosis</td>
</tr>
<tr>
<td><strong>Antakli et al. modifications</strong></td>
</tr>
<tr>
<td>A. Different histological conditions</td>
</tr>
<tr>
<td>B. Same histological condition with two or more of the following</td>
</tr>
<tr>
<td>1. Anatomically distinct</td>
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<tr>
<td>2. Associated premalignant lesion</td>
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<tr>
<td>3. No systemic metastases</td>
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<tr>
<td>4. No mediastinal spread</td>
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<tr>
<td>5. Different DNA ploidy</td>
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Table 2—Definition of Satellite Nodules, MPLCs, and Pulmonary Metastases

- **Satellite nodules from primary tumor**
  - Same histology
  - And same lobe as primary cancer
  - And no systemic metastases

- **MPLCs**
  - Same histology, anatomically separated
  - Cancers in different lobes
  - And no N2,3 involvement
  - And no systemic metastases

- **Same histology, temporally separated**
  - \( \geq 4 \text{-yr interval} \) between cancers
  - And no systemic metastases from either cancer

- **Different histology**
  - Different histologic type
  - Or different molecular genetic characteristics
  - Or arising separately from foci of carcinoma in situ

- **Hematogenously spread pulmonary metastases**
  - Same histology and multiple systemic metastases
  - Same histology, in different lobes
  - And presence of N2,3 involvement
  - Or \(< 2 \text{-yr interval} \)
Satellite nodules: 10% of patients had a second lesion detected preoperatively; nearly 60% were benign.

A patient should not be denied a curative approach on the basis of a second pulmonary nodule.

13. In patients with suspected or proven lung cancer and a satellite nodule within the same lobe, it is recommended that no further diagnostic workup of a satellite nodule be undertaken. Grade of recommendation, 1B.

14. In patients with a satellite lesion within the same lobe as a suspected or proven primary lung cancer, evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be performed as dictated by the primary lung cancer alone and not modified because of the presence of the satellite lesion. Grade of recommendation, 1C.

15. In patients with NSCLC and a satellite focus of cancer within the same lobe (and no mediastinal or distant metastases), resection via a lobectomy is the recommended treatment. Grade of recommendation, 1B.
Synchronous primaries

A synchronous second focus of lung cancer in a different lobe is easily defined as a second primary lung cancer when the two sites are of different histologic types. Cancers may also be distinguished on the basis of different molecular genetic characteristics. In the absence of molecular analysis, it is difficult to distinguish two synchronous cancers that are of the same histologic type as separate primary lung cancers.

One proposed requirement for classification as synchronous second primary lung cancers is that there be no mediastinal node involvement and no sites of distant metastases when the two cancers are of the same histologic type.

Invasive mediastinal staging and extrathoracic imaging is recommended as N2 is considered a contraindication to surgery. Shen et al. Chest 2007

In patients who have two synchronous primary NSCLCs and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

In patients (not suspected of having a second focus of cancer) who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is recommended, provided that the patient has adequate pulmonary reserve and there is no N2 nodal involvement. Grade of recommendation, 1C

In patients who have a metachronous NSCLC and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C
There is no consensus on staging.

Whether staging should be based on a combination of all tumors with one TMN designation, or each tumor separately is ambiguous.

- IASLC: “multiple synchronous primary tumors should be staged separately” “The highest T category and stage of disease should be assigned” “Pts should be treated according to the stage of the highest one” including both same or different histology.

- American Joint Committee On Cancer (AJCC): ”The IASLC guideline implies that the TNM classification can be applied to both same and different histology between primary and secondary tumors”, but the AJCC guideline only fits for tumors with the same histological subtype.

- The 2012 manual of UICC (Union for International Cancer Control) suggests, “A tumor in the same organ with a different histologic type is counted as a new tumor”.

Multiple tumor nodules in the same lobe reclassified from T4 to T3

Multiple tumor nodules in the same lung but different lobe reclassified from M1 to T4

Multiple tumors in contralateral lung as M1a

<table>
<thead>
<tr>
<th>Category</th>
<th>6th Edition</th>
<th>7th Edition</th>
<th>Reason for Revision*</th>
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<tbody>
<tr>
<td><strong>Tumor</strong></td>
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<tr>
<td>Size</td>
<td>T1: ≤3 cm</td>
<td>T1a: ≤2 cm</td>
<td>5-year survival rate = 77%</td>
</tr>
<tr>
<td></td>
<td>T1b: &gt;2 cm but ≤3 cm</td>
<td>T1b: &gt;2 cm but ≤3 cm</td>
<td>5-year survival rate = 71%</td>
</tr>
<tr>
<td></td>
<td>T2: &gt;3 cm</td>
<td>T2a: &gt;3 cm but ≤5 cm</td>
<td>5-year survival rate = 58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2b: &gt;5 cm but ≤7 cm</td>
<td>5-year survival rate = 49%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3: &gt;7 cm</td>
<td>5-year survival rate = 35%</td>
</tr>
<tr>
<td>Tumor nodule(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>separate from primary mass</td>
<td>T4</td>
<td>T3</td>
<td>5-year survival rate = 28% (similar to that for T3 and better than that for T4)</td>
</tr>
<tr>
<td>Same lung and lobe as primary mass</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>M1</td>
<td>T4</td>
<td>5-year survival rate = 22% (similar to that for T4)</td>
</tr>
<tr>
<td>Same lung but not same lobe as primary mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral lung</td>
<td>M1</td>
<td>M1a</td>
<td>5-year survival rate = 3% (consistent with that for other intrathoracic metastatic disease)</td>
</tr>
</tbody>
</table>

| **Node**                   |             |             |                     |
| Lymph node map             | Lymph node staging primarily from the MD-ATS (Mountain-Dresler–American Thoracic Society) map | New IASLC lymph node map published (Fig 7) | New IASLC map reconciles differences between earlier lymph node maps and provides new descriptions of the nodal anatomy with respect to anatomic borders to ensure accurate localization of lymph nodes (cf. Table 3) |
| Malignant pleural or pericardial effusion | T4          | M1a         | 5-year survival rate = 2% (similar to that for tumors in the intrathoracic metastatic category, compared with a 5-year survival rate of 15% in other patients with T4 tumors |
| Metastasis                 | M0: absent  | M0: absent  |                     |
|                            | M1: present | M1a: local thoracic metastatic disease | Additional nodules in the contralateral lung (M1a) result in a median survival time of 10 months and a 1-year survival rate of 45% for stage IV metastases result in a median survival time of 6 months and a 1-year survival rate of 22% |
7th TNM examples

T3: same lobe

T4: different lobes

M1: different lung
• MPLC better OS than intrapulmonary metastasis

• No difference in OS whether same or different histology

• No difference in OS between unilateral and bilateral MPLT

• S-MPLC have shorter OS than M-MPLC patients from the diagnosis of first tumor, but same OS when started from the diagnosis of the second tumor
Conclusions MPLC metanalysis

Need of a MPLC staging system

Surgical approach is an option for pts with a new primary tumor

Still ambiguity in diagnosing the second primary cancer

ACCP: second primary tumor should be defined by an experienced multidisciplinary team

Jiang, Lung cancer 2014
• 467 pts with resection of multifocal lung cancer in multiple lobes > poor prognostic factors: advanced age, male gender and unilateral tumour location

• bilateral cancers = more favourable prognosis > patients more likely to be those with true multiple cancers, and benefitting most from surgery because of non-metastatic disease.
Survival was similar for major or minor resection, same or different histology, 2 or more than 2 nodules.

SMLC with more than 2 nodules were 13% of the cases and showed 5 yy srv of 40%

Conclusions: effort should be done to understand the nature of multiple nodules however surgery actually should be seriously considered for the treatment of Multiple lung nodules whatever metastatic or not

Deschamps J Thor Cardiovasc Surg 1990
Riquet 2008

**Fig 3.** Survival of lung cancer patients without lymph node involvement (N0) with either no prior malignancy (curve 3), multiple metachronous tumors (curve 2), or multiple synchronous tumors (curve 1).

**Fig 2.** Survival of lung cancer patients without prior malignancy (curve 3), lung cancer patients with multiple metachronous tumors (curve 2), and lung cancer patients with multiple synchronous tumors (curve 1).

- **N0 tumors**
  - (3) 1495 984 660 417 221
  - (2) 89 44 20 11 5
  - (1) 55 33 15 5 1

- **All tumors**
  - 3: LC
  - 2: M-MPLC
  - 1: S-MPLC

Riquet

*Ann Thorac Surg 2008*
What is the optimal management of multifocal lung cancer?
2nd ESMO Consensus Conference: Ann Onc 2015

- Surgical data from retrospective analyses. Current evidence supports surgery as up-front approach for patients with SMLC in multiple lobes, either ipsilateral or contralateral.
- Recent studies of patients undergoing resection of multiple nodules – two synchronous tumours in most of cases – and without evidence of lymph node involvement have demonstrated 5-year survival rates greater than 50%.
- No consensus exists on the optimal type of surgery for patients with multifocal lung cancer, although lobectomy for the main tumour plus sublobar resection of the smaller nodule(s) seems a reasonable approach.
- If surgery is not feasible, other approaches such as local ablative (SABR) and/or systemic therapy should be considered. All treatment decisions should be taken within the context of a multidisciplinary tumour board.

- What is the optimal management of multifocal lung cancer? Complete resection is recommended whenever possible.
8 of 14 studies > no significant difference in OS and PFS when at least one sublobar resection (wedge resection or segmentectomy) was performed (613)

2 studies > absence of anatomical resection (in the form of lobectomy or bilobectomy) had a negative impact on survival (n = 210)
### Extension of resection
- Lobectomy and wedge: 13
- Segmentectomy and wedge: 1
- Bilateral wedge: 5

### Approach
- Sternotomy: 5
- VATS bilateral: 13

### Tumor type
- ADK: 84
- SCC: 3

In conclusion, for a selected number of patients with SBMLC whose diagnosis was based on HRCT, single-stage bilateral surgical treatment may be associated with favorable outcomes in cases where complete resection of lesions is determined to be feasible. Patients with SBMLC also need careful follow-up after resection, however, owing to the possibility of development of new primary lesions or recurrences.
FDG PET and multiple tumors

PET with FDG reflects the metabolic activity and proliferative potential of malignant tumors, enable the selection of an appropriate extent of resection for each lesion in cases of multifocal lung denocarcinoma.

Next-generation sequencing of several cancers has revealed that solid tumors harbor tens to hundreds of somatic chromosomal rearrangements and thousands of single-nucleotide variations (SNVs). Both of these types of alterations have been used to investigate lineage relationships in tumors from the same individual.

Clinical use is still limited.
10% of patients with a screen detected tumor had multifocal synchronous disease at diagnosis.

6% has developed a new primary tumor of the lung during 5 years. These subjects, already having lung surgery, can badly tolerate a second surgery: limited resection or SABR for metachronous tumors.

Veronesi G et al JTO 2014
Veronesi et al JTO 2014
Multiple, bilateral pure GGOs that are technically not completely resectable or in patients at high risk for surgical resection can be managed by radiologic surveillance, particularly when follow-up imaging has established stability or very slow growth.

Sometimes, one of these lesions shows an increase in size or in the solid component of the GGO while the other lesions remain stable. In this setting, the enlarging lesion should be treated independently as a presumed lung cancer. Same-lobe malignant lesions are usually best managed by lobectomy.

When bilateral synchronous malignant lesions are present, the amount of cardiopulmonary reserve of each patient will determine the extent of lung resection.
SABR
101 pts who received for second primary

SURGERY
RIQUET ET AL
SUMMARY

- Need of a MPLC staging system
- Ambiguity in diagnosing the second primary cancer
- Surgical resection is the primary treatment
- 5 years OS about 30%-50% pre screening era 65 to 80% among screen cancers
- Lobectomy plus sublobar resections seems a reasonable approach
- No difference according to number of lesions, whether histology is the same or different, if unilateral or bilateral MPLT
- PET of help to define the treatment strategy
- Sabr is a potentially curable alternative approach to surgery