Surgical Management of Multifocal Lung Cancer

11th Annual Masters in Minimally Invasive Thoracic Surgery

September 22, 2018

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Disclosures

Consultant Scanlan Instruments

No conflicts of interest related to this presentation
Multifocal Lung Cancer: T3/T4 /M1 vs Separate Primaries

- Histology (may not be known until after surgery)
- Synchronous vs Metachronous
- Laterality
- Solid vs GGO
- Node involvement
- Extent of resection
Clinical scenario: otherwise healthy 60-year-old man with RUL and LLL pulmonary nodules posed to the 6373 members of the IASLC:

1. Would you recommend surgery, and the extent?
2. What other measures to complete the staging?
3. Would chemotherapy or RT be indicated?

- 221 responses (3.5%) from multiple specialists
63% recommended surgery for this scenario

Surgeons more likely to recommend surgery

Most would obtain PET/CT scan to rule out distant metastases and MRI to rule out brain metastases

In the absence c-N disease, most would not stage the mediastinum by EBUS or mediastinoscopy

When surgery not recommended, respondents commonly recommended RT
<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Resection of RUL (lobectomy)</td>
<td>42 (30.2)</td>
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<tr>
<td>Resection of anterior segment of RUL (segmentectomy)</td>
<td>24 (17.3)</td>
</tr>
<tr>
<td>Resection of anterior segment of RUL and posterior segment of RLL</td>
<td>24 (17.3)</td>
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<tr>
<td>Resection of involved RUL wedge</td>
<td>9 (6.5)</td>
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<tr>
<td>Resection of involved RUL and RLL wedges</td>
<td>39 (28.0)</td>
</tr>
<tr>
<td>Right pneumonectomy</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Stage</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>T0</td>
<td>No primary tumor detected</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≥ 1 cm but ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≥ 2 cm but ≤ 3 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 3 cm but ≤ 5 cm or tumor with any of the following features:</td>
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<tr>
<td></td>
<td>- Involves main bronchus regardless of distance from the carina but without involvement of the carina</td>
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<tr>
<td></td>
<td>- Invades visceral pleura</td>
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<tr>
<td></td>
<td>- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 3 cm but ≤ 5 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures:</td>
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<tr>
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<td>- Chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium</td>
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<tr>
<td>T2a</td>
<td>Tumor &gt; 3 cm but ≤ 4 cm in greatest dimension</td>
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<tr>
<td>T2b</td>
<td>Tumor &gt; 4 cm but ≤ 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 5 cm but ≤ 7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures:</td>
</tr>
<tr>
<td></td>
<td>- Diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor &gt; 7 cm in greatest dimension or associated with separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Single extrathoracic metastasis</td>
</tr>
<tr>
<td>M1c</td>
<td>Multiple extrathoracic metastases in one or more organs</td>
</tr>
</tbody>
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The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

T3
Tumor >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium

T4
Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina

M1
Distant metastasis present

M1a
Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer

- Systematic review of literature by the Staging and Prognostic Factors committee of IASLC to develop recommendations to distinguish 2nd primary lung cancers
- Mechanism of metastasis, determination of clonality, and outcomes of patients with resected tumors

• Easier to prove that 2 tumors are different than that they are the same: finding similarities is not enough as most 2nd primary lung cancers are of the same histologic subtype

• Few criteria are reliable alone:
  • Different histologic cancer types or
  • Matching DNA breakpoints by sequencing

Characteristics that are suggestive but associated with potential misclassification include:

- Presence or absence of biomarkers
- Imaging characteristics
- Presence or absence of nodal involvement
Molecular driver results from primary tumors and their metastases compared (45 patients, cohort 1)

69 patients with a total of 154 synchronous or metachronous lung carcinomas were identified, and pathologic findings compared with driver mutation

Each patient was assigned a highest potential T or M category on the basis of clinical, histopathologic, and molecular findings (cohort 2)
The concordance rate of EGFR, KRAS, BRAF, and ALK mutations was 96% in cohort 1.

In cohort 2, 36% of same-lobe nodules were MPLC, 40% were IPM, and 24% were noninformative.

82% of multiple lobe nodules were MPLCs, 7% were IPM, 11% noninformative.

Of metachronous tumors, 53% were MPLCs.

OS was 100% at 2 y, 95% at 3 y, 80% at 4 y.
1997-2010: 47 bilateral synchronous lung cancers
96%: at least 1 VATS; 60% bilateral VATS
Median LOS: 3 days; 28% had a postop Cx
11: adjuvant chemo; 8/11 full treatment regimen
3-year OS and DFS: 35% and 24%
Survival of patients whose bilateral tumors had identical histology did not differ from patients whose histology was different ($p = 0.57$)
Overall Disease-free
• Lobectomy + lobectomy (39), lobectomy + sublobar (49), sublobar + sublobar (13)

• Overall survival 5 years was 75.0%

• Sublobar resection for contralateral nodule (stage I) did not have a negative effect on 5-year survival

• Multivariate analysis: most advanced TNM stage (p=0.018) and # of lesions (p=0.001) as significant predictors of overall survival
Surgical Therapy for Bilateral Multiple Primary Lung Cancer

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• Systematic literature search performed to identify 1796 patients with MPLC in 22 studies
• OS of patients with synchronous MPLC was inferior to metachronous MPLC \( (p < 0.001) \)
• OS not different when starting from the diagnosis of the 2\textsuperscript{nd} metachronous tumor \( (p = 0.29) \)
• OS with MPLC was superior to patients with intrapulmonary metastasis \( p = 0.007 \)
Synchronous
4 synchronous GGO
R VATS upper lobe
L VATS seg 6
Observation
3 synchronous solid R VATS upper lobe L VATS seg 1-3 & 6
1. 11/05/2013 – R VATS seg 6
2. 01/04/2013 – L VATS upper lobe
3. 05/24/2013 - bronchoscopy with laser ablation
1. Stage I NSCLC, adenocarcinoma, right upper lobe
2. Stage I carcinoid, typical variant left upper lobe
3. Adenoid cystic carcinoma trachea
R VATS Upper lobectomy
Adjuvant Chemotherapy
L VATS lower lobectomy
Metachronous
1. 3/6/2006  Right VATS bilobectomy  
   T2 N0 SCC
2. 1/24/2008  Left VATS wedge resection  
   M1 SCC?
3. 3/20/2009  Left VATS wedge resection  
   M1 SCC
12/01/2008 VATS right upper lobectomy
01/23/2012: Left thoracoscopic lingular segmentectomy

Pathology
1. 3.4 cm adenocarcinoma moderately differentiated, T2N0
2. 1.1 cm adenocarcinoma moderately differentiated, T2N0
1. January 2006 Esophagogastrectomy
2. August 2007 Right thoracoscopic upper lobectomy
3. 07/22/2016 Left VATS wedge resection

1. Esophageal Cancer T2N0, poorly differentiated
2. 1.5 cm moderately differentiated adeno (TTF+) T1N0
3. 0.6 cm well differentiated adenocarcinoma pT1aN0
Multifocal Lung Cancer

Sub-lobar Resection

vs

Lobectomy

vs

SBRT
Conclusions

• Multifocal lung cancers present challenges in diagnosis, staging, and management

• Preop staging should be thorough (PET, brain, and EBUS.med), and metachronous lesions require the same staging as the first primary

• In the absence of N and M involvement, most cases of bilateral multifocal cancers are primaries

• When feasible, sublobar resection of the smaller lesion is advisable
Conclusions

• For synchronous bilateral lesions, sublobar resection of the smaller lesion first allows the 2nd operation to be better with single lung ventilation
• For unilateral lesions, MLND 1st is preferable to ascertain the absence of N2 disease
• Adjuvant chemo between procedures is an option
• SBRT for smaller lesions is also an option
GGO

• After resection of multiple GGOs, surveillance is considered, and resection of 3 GGOs is common
• Role of 4\textsuperscript{th} or 5\textsuperscript{th} or 6\textsuperscript{th} resection for GGO is uncertain
• Consider use of molecular target inhibitor (EGFR, Ros, ALK, PDL-1) in lieu of surgery
• Consider use of SBRT
## Multifocal Lung Cancer

<table>
<thead>
<tr>
<th></th>
<th>First</th>
<th>Second</th>
<th>Chemo between?</th>
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<tbody>
<tr>
<td><strong>Synchronous</strong></td>
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<tr>
<td>Unilateral</td>
<td>N0</td>
<td>Sublobar</td>
<td>Lobectomy</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Sublobar</td>
<td>Lobectomy</td>
</tr>
<tr>
<td><strong>Bilateral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>Sublobar</td>
<td>Lobectomy</td>
<td>N/A</td>
</tr>
<tr>
<td>N1</td>
<td>Sublobar</td>
<td>Lobectomy</td>
<td>No</td>
</tr>
<tr>
<td><strong>Metachronous</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>N0</td>
<td>Lobar</td>
<td>? Lobe</td>
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<tr>
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<td><strong>Bilateral</strong></td>
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<td>N0</td>
<td>Lobar</td>
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<td>Consider</td>
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<tr>
<td>N1</td>
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<td>Consider</td>
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