The Impact of Adjuvant Chemotherapy in Pulmonary Large Cell Neuroendocrine Carcinoma (LCNC)
Disclosure

None
Background

Torino, Italy
LCNC

- Rare tumor (2% to 3% of all resected primary lung cancers)
- Preoperative diagnosis is often impossible
- Clinical behavior and prognosis similar to SCLC
- Surgery alone is insufficient to treat LCNC, even in early stages
Biologically related to Neuroendocrine tumors, but still considered a variant of LCCs, and therefore, accordingly treated
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N° pts</th>
<th>5-y OS</th>
<th>5-y OS Stage I</th>
<th>Recurrence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Yuste et al.</td>
<td>2000</td>
<td>22</td>
<td>21 %</td>
<td>33 %</td>
<td>59 %</td>
</tr>
<tr>
<td>Takey et al.</td>
<td>2003</td>
<td>87</td>
<td>57 %</td>
<td>67 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Battafarano et al.</td>
<td>2004</td>
<td>45</td>
<td>30 %</td>
<td>33 %</td>
<td>49 %</td>
</tr>
<tr>
<td>Paci et al.</td>
<td>2004</td>
<td>48</td>
<td>21 %</td>
<td>27 %</td>
<td>NA</td>
</tr>
<tr>
<td>Rossi et al.</td>
<td>2005</td>
<td>83</td>
<td>NA</td>
<td>33 %</td>
<td>65 %</td>
</tr>
<tr>
<td>Veronesi et al.</td>
<td>2006</td>
<td>144</td>
<td>42 %</td>
<td>52 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Sarkaria et al.</td>
<td>2011</td>
<td>100</td>
<td>NA</td>
<td>58 %</td>
<td>38 %</td>
</tr>
</tbody>
</table>
LCNC

- Due to its rarity and the lack of RCT, the optimal treatment is still debated

- Few clinical papers evaluated the role of induction/adjuvant CT
3 years ago...

The ESTS Lung NETs-WG was created with the aim to:

- create a group of physicians worldwide expert in NETs
- develop scientific knowledge on such rare neoplasms
2014:
14 Centres  2054 patients

- Atypical Carcinoid: 61%
- LCNC: 16%
- Mixed Tumor: 5%
- SCLC: 5%
- Typical Carcinoid: 1%
- Unspecified: 12%
Aim of the study

Torino, Italy
Aim of the study

- To evaluate the possible adjuvant CT effect on LCNC survival
- To assess clinicopathologic prognostic factors in a surgically-based population of patient with LCNC
Methods

Torino, Italy
Pier Luigi Filosso, MD
University of Torino, Department of Thoracic Surgery

460 patients with LCNC surgically treated between 1992-2014 in 14 Centers

- 28 patients with missing information on vital status

432 Patients

- 32 patients with missing information concerning adjuvant chemotherapy

400 patients

median FU: 38 months

% FU completeness: 94%
LCNC diagnosis

✓ All the histological samples were reviewed by local NETs expert Pathologists

✓ LCNC definitive diagnosis was made according to:
  2004 WHO Lung Tumors Classification criteria
  Travis’ histological guidelines for NETs diagnosis
NET morphological/immunohistochemical characteristics:

- Neuroendocrine morphology (organoid nesting, palisading rosettes and trabeculae)
- High mitotic rate (11 or more)
- Abundant necrosis
- Large cell size
- Low nuclear/citoplasm ratio
- Tumor cells positive for neuroendocrine markers: Synaptophysin, Chromogranin A, CD56
Retrospective multicentre study

- Outcome measure: overall survival (OS)
- Cox proportion hazard model with shared frailty (for center heterogeneity)

Demographics
- Age
- Gender
- Smoking habit

Clinical variables
- Previous malignancy
- Tumor site
- PS (ECOG)

Tumor-related variables
- Stage (TNM 7° edition)

Treatment variables
- Type of surgical resection
- Completeness of resection
- Use of chemotherapy
Results

Torino, Italy

Pier Luigi Filosso, MD
University of Torino, Department of Thoracic Surgery
<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median – IQR-)</td>
<td>66 (58-72)</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>252</td>
<td>63</td>
</tr>
<tr>
<td>Smokers (current/former)</td>
<td>99</td>
<td>25</td>
</tr>
<tr>
<td>Previous malignancy</td>
<td>99</td>
<td>25</td>
</tr>
<tr>
<td>pTNM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>185</td>
<td>48</td>
</tr>
<tr>
<td>II</td>
<td>110</td>
<td>29</td>
</tr>
<tr>
<td>III</td>
<td>76</td>
<td>20</td>
</tr>
<tr>
<td>IV</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>53 (44 CT; 9 RT)</td>
<td>13</td>
</tr>
<tr>
<td>Adjuvant CT</td>
<td>146</td>
<td>37</td>
</tr>
<tr>
<td>Adjuvant RT</td>
<td>38</td>
<td>10</td>
</tr>
</tbody>
</table>

400 pts
Type of surgery

- Mediastinoscopy: 1 case
- Extended Resection: 14 cases
- Pneumonectomy: 43 cases
- Bilobectomy: 9 cases
- Sleeve lobectomy: 7 cases
- Lobectomy: 263 cases
- Segmental resection: 24 cases
- Wedge Resection: 38 cases

R0 resection: 360 cases (97%)
Median FU: 38 months
FU completeness: 94%

213 patients died
(69 in the adjuvant CT group)
Overall survival

Median OS: 43 months

3-y surv rate: 54 %
5-y surv rate: 45 %
OS according to adjuvant CT administration

A slight improvement in OS was observed in those who received adjuvant CT (HR 0.82; 95%CI: 0.62-1.09, P=0.17)
Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant Chemotherapy YES vs NO (adjusted for the below factors)</td>
<td>0.74 (0.53 to 1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>1.03 (1.01 to 1.04)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.18 (0.87 to 1.59)</td>
<td>0.28</td>
</tr>
<tr>
<td>Previous Malignancy</td>
<td>1.01 (0.73 to 1.39)</td>
<td>0.94</td>
</tr>
<tr>
<td>ECOG PS&gt;=2</td>
<td>1.62 (1.21 to 2.16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vascular Invasion</td>
<td>1.29 (0.95 to 1.77)</td>
<td>0.11</td>
</tr>
<tr>
<td>pTNM II vs I</td>
<td>1.4 (0.98 to 2.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>III/IV vs I</td>
<td>2.57 (1.76 to 3.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year of Surgery 2000-2007 vs 1992-1999</td>
<td>0.74 (0.49 to 1.12)</td>
<td>0.15</td>
</tr>
<tr>
<td>2008-2014 vs 1992-1999</td>
<td>0.61 (0.38 to 0.95)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

An evidence of a higher OS in adjuvant CT was observed.
### Subgroup Analysis for the effect of administration of adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95%CI)</th>
<th>P-Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.74 (0.53 to 1.02)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>&lt;65</td>
<td>0.69 (0.43 to 1.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;=65</td>
<td>0.8 (0.52 to 1.21)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Female</td>
<td>0.83 (0.49 to 1.42)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.7 (0.48 to 1.02)</td>
<td></td>
</tr>
<tr>
<td>Previous Malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.8 (0.56 to 1.14)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.56 (0.29 to 1.08)</td>
<td></td>
</tr>
<tr>
<td>Vascular Invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.65 (0.4 to 1.06)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.96 (0.6 to 1.56)</td>
<td></td>
</tr>
<tr>
<td>pTNM</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>I</td>
<td>0.71 (0.36 to 1.41)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0.75 (0.44 to 1.28)</td>
<td></td>
</tr>
<tr>
<td>III-IV</td>
<td>0.76 (0.44 to 1.3)</td>
<td></td>
</tr>
</tbody>
</table>

The subgroup analysis did not show any subset of patients that significantly benefited from adjuvant CT administration.
Conclusions
✓ We observed a signal of an improved survival in LCNC patients treated with adjuvant CT

✓ We did not identify a particular subset of patients in which adjuvant CT might be more appropriate

✓ Prospective data collection (ESTS prospective database), will hopefully help to define more tailored treatment strategy for such aggressive neoplasm
Thank you very much for your attention

Torino, Italy
Cause of death

- Unknown: 30
- Tumor related: 130
- Treatment complications: 5
- Non tumor related: 48
Local recurrences: 61
(26 in the adjuvant CT group)

Distant MTS: 140
(59 in the adjuvant CT group)
Stage I OS

3-y surv rate: 63 %
5-y surv rate: 51 %
Statistical analysis

Kaplan-Meier method: probabilities of survival

Cox proportional hazards regression model with shared frailty: effect of adjuvant CT on OS

Effect modifications by subgroups: inclusion in the model an interaction term between the covariate indicating adjuvant CT and the subgroup covariate of interest, adjusting for the others
NET morphological/immunohistochemical characteristics:

- Neuroendocrine morphology (organoid nesting, palisading rosettes and trabeculae)
- High mitotic rate (11 or more)
- Abundant necrosis
- Large cell size
- Low nuclear/citoplasm ratio
- Tumor cells positive for neuroendocrine markers:
  - Synaptophysin
  - Chromogranin A
  - CD56
Study limitations:

✓ retrospective and multicenter design
✓ long recruitment period
✓ possible inherent treatment selection bias
(pts receiving CT may have been selected among those with better clinical/functional conditions)
Future directions:

✓ Future clinical trials might be "ad hoc" designed and new (biological) drugs might be tested to treat such aggressive neoplasms
LCNC:

- Due to its rarity and the lack of RCT, LCNC’s optimal treatment is still debated
- Few clinical papers evaluated the role of induction/adjuvant CT
Recent increased incidence: 2.3 – 2.8 cases/100,000/year (diagnostic techniques improvement; lung cancer screening programs diffusion)

Yao JC: J Clin Oncol. 2008 Jun 20;26:3063-72