Treatment of Older Adult Patients with Non-Small Cell Lung Cancer

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Moderated by Mark Geisler
NCCN, Conferences and Meetings Department

The U.S. Population Is Aging

Incidence of Lung Cancer Increases With Age

U.S. incidence of lung cancer by age


Chemotherapy in elderly patients (≥ 65)
SEER Database between 1997 and 2002

A: First-line
n = 21285
B: 2nd line
n = 2026

% pts receiving CT:
20.4% in 1997
27.8% in 2002


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Elderly Lung Cancer Patients are Under-Represented on Clinical Trials

- 60% of lung cancer patients are ≥60
- 35% - 40% of lung cancer patients are ≥70
- Elderly representation on Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>% ≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td>E5592</td>
<td>15%</td>
</tr>
<tr>
<td>S9509/9305</td>
<td>19%</td>
</tr>
<tr>
<td>E1594</td>
<td>20%</td>
</tr>
<tr>
<td>CALGB 9730</td>
<td>27%</td>
</tr>
<tr>
<td>UNC</td>
<td>29%</td>
</tr>
</tbody>
</table>

CHALLENGES SPECIFIC TO ELDERLY PATIENTS

- Heterogeneity in functional status
- Age-related organ function decline
- Alterations in Pharmacokinetics (excretion, metabolism, distribution and absorption)
- Polypharmacy
- Compromised immune responses
- Lower marrow regenerative capacity
- Comorbid conditions
- Quality of life issues (in relation to life expectancy)
**CARG (The Cancer and Aging Research Group) model for predicting chemotherapy toxicity in older adults**

- Age ≥72 years
- Cancer type GI or GU
- Chemotherapy dosing, standard dose
- Number of chemotherapy drugs, polychemotherapy
- Hemoglobin <11 g/dL (male), <10 g/dL (female)
- Creatinine clearance (Jelliffe, ideal weight) <34 mL/min
- Hearing, fair or worse
- Number of falls in last six months, one or more
- IADL (instrumental activities of daily living): Taking medications, with some help/unable
- MOS (Medical Outcomes Study): Walking one block, somewhat limited/limited a lot
- MOS: Decreased social activity because of physical/emotional health, limited at least sometimes

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**Ability of (A) risk score versus (B) physician-rated Karnofsky performance status (KPS) to predict chemotherapy toxicity.**

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Patient is 85 year old female with newly diagnosed lung adenocarcinoma with mets to liver and bones. Negative for EGFR mutation, ALK or ROS-1 rearrangement. She has ECOG performance status of 1 and no significant co-morbidities.

What would be the best approach for first line treatment?

1. Supportive Care Only
2. Single agent Vinorelbine
3. Single agent Gemcitabine
4. Carboplatin and Pemetrexed
5. Carboplatin, Paclitaxel and Bevacizumab

Treatment of Elderly Patients with Metastatic NSCLC

- Is chemotherapy better than best supportive care?
- Platinum based therapy or non-platinum?
- Single agent vs doublet?
- Bevacizumab or not?
- Other targeted agents?
The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS): Chemo vs BSC.

Vinorelbine 30 mg/m² days 1 & 8 every 21 days vs supportive care

1-year Survival 14% vs 32%

Favorable QoL Overall

- Worsening
- Improvement

Physical functioning
Role functioning
Emotional functioning
Cognitive functioning
Social functioning
Global health status

Patients at Risk
Vinorelbine 76
Control 78

Weeks
Control arm
Vinorelbine arm

Median OS 21 vs 28 weeks
(P=0.03)
HR 0.65 (95% CI, 0.45 to 0.93)


The MILES phase III trial: gemcitabine + vinorelbine vs vinorelbine vs gemcitabine in elderly advanced NSCLC patients

NSCLC
70+ years old
Chemotherapy naïve
Stage IIIB or IV
PS 0-2

Randomize

- vinorelbine 30 mg/m² d1,8 Q 3 weeks
- gemcitabine 1200 mg/m² d1,8 Q 3 weeks
- gemcitabine 1000 mg/m² d1,8 vinorelbine 25 mg/m² d1,8 Q 3 weeks

Cesare Gridelli et al. JNCI 2003 Vol. 95, N0 5
### ITT Analysis of Efficacy

<table>
<thead>
<tr>
<th></th>
<th>VNR</th>
<th>GEM</th>
<th>VNR+GEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients (n)</td>
<td>233</td>
<td>233</td>
<td>232</td>
</tr>
<tr>
<td>Stage IIIB (%)</td>
<td>29</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>18</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Time to Progression (wk)</td>
<td>18</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Median Survival (weeks)</td>
<td>36 (30-45)</td>
<td>28 (25-34)</td>
<td>30 (27-36)</td>
</tr>
<tr>
<td>HR</td>
<td>1.17 (vs VNR)</td>
<td>1.06 (vs GEM)</td>
<td></td>
</tr>
<tr>
<td>1 yr survival (%)</td>
<td>41%</td>
<td>26%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Cesare Gridelli et al. JNCI 2003 Vol. 95, N0 5.

### ECOG 5592: Elderly Data

- Patients randomized to cisplatin 75 mg/m^2 &
  - etoposide 100 mg/m^2 d 1-3
  - paclitaxel 135 mg/m^2
  - paclitaxel 250 mg/m^2 + G-CSF
- BREAKDOWN by Elderly (≥ 70) v “Young” (<70)
  - Elderly: ↑ cardiovascular (p=0.0089) + resp (p=0.0441) co-morbidities

<table>
<thead>
<tr>
<th>Age ≤ 70</th>
<th>N</th>
<th>RR (%)</th>
<th>TTP (mo)</th>
<th>MS (mo)</th>
<th>1 YS (%)</th>
<th>2 YS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>488</td>
<td>21.5</td>
<td>4.37</td>
<td>9.05</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>≥70</td>
<td>86</td>
<td>23.3</td>
<td>4.30</td>
<td>8.53</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.666</td>
<td>0.294</td>
<td>Log rank 0.2857</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ↑ leukopenia (p=0.0001) and neuropsych tox (0.0025) in ≥ 70 yrs
- No difference baseline QoL, Trial outcome index

**French Intergroup study (IFCT-0501)**

- **NSCLC**
  - Stage III-IV
  - Age 70-89
  - PS 0-2
  - n = 451

Randomize:
- vinorelbine
  - or gemcitabine*
- carboplatin + paclitaxel
- erlotinib 150 mg/d

**Stratification by center, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV**


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**Progression Free Survival (PFS)**

- **Doublet chemotherapy**
  - Median PFS: **6.1** months (95% CI 5.5-6.9)
  - 1-year PFS: 15.4% (95% CI 10.8-20.8)
- **Monotherapy**
  - Median PFS: **3.0** months (95% CI 2.6-3.9)
  - 1-year PFS: 2.3% (95% CI 0.8-5.3)

Overall Survival (OS)

- **Doublet chemotherapy**
  - Median OS = **10.3** months (95% CI 8.3-13.3)
  - 1-year survival 45.1% (95% CI 38.2-51.8)
- **Monotherapy**
  - Median OS = **6.2** months (95% CI 5.3-7.4)
  - 1-year survival 26.9% (95% CI 21-33.1)


Adverse Events

- Overall well tolerated
- Grade 3 or 4 neutropenia was more common with the combination compared with monotherapy (48 versus 12 percent).
- Ten deaths (4.4 percent) in the combination arm were attributed to treatment, compared with three (1.3 percent) in the monotherapy group.

Stage IIIb/IV NSCLC
No prior treatment for metastatic disease
PS 0-1
N = 1,050

Patients had no active brain metastases or ≥ grade 2 neuropathy at baseline

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ab-P/C (n=521)</th>
<th>P/C (n=531)</th>
<th>All Patients (N=1052)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) years</td>
<td>60 (28, 81)</td>
<td>60 (24, 84)</td>
<td>60 (24, 84)</td>
</tr>
<tr>
<td>&lt;65 years, n (%)</td>
<td>360 (69)</td>
<td>348 (66)</td>
<td>708 (67)</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>161 (31)</td>
<td>183 (34)</td>
<td>344 (33)</td>
</tr>
</tbody>
</table>

Socinski, et al. 2010 ASCO LBA7511

Carbo/paclitaxel vs. carbo/nab-paclitaxel

Socinski, et al. JCO 30:17, 2012
Overall Survival

![Graph showing Overall Survival with HR=0.583, 95% CI [0.388, 0.875] and P-value=0.009.](image)

Socinski et al, ASCO 2011, Abstr 7551

### Ongoing prospective studies of nab-paclitaxel for elderly patients with NSCLC

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Title</th>
<th>Treatment</th>
<th>Primary Outcome</th>
</tr>
</thead>
</table>
| NCT02151149 | Phase IV study of nab-paclitaxel (A) in Combination With carboplatin (C) as First Line Treatment in Elderly Subjects With Advanced NSCLC (Abound.70+) | Arm A: A 100 mg/m2 IV on Days 1, 8, and 15 and C AUC = 6 every 21-day  
Arm B: A 100 mg/m2 IV on Days 1, 8, and 15 and C AUC = 6 every 28-day | Peripheral neuropathy or myelosuppression |
| NCT01702844 | Phase II, single arm Study of the tolerability of weekly A as second line treatment for elderly patients with NSCLC | A 100 mg/m2 IV on Days 1, 8, and 15 every 28 days | Grade 3 or worse toxicity after 6 cycles or 3 weeks after discontinuation of treatment |
| NCT02590003 | A Randomized Phase II Trial of Combination Versus Single Agent Chemotherapy in High-risk Elderly Patients With Advanced NSCLC | Arm A: A 100 mg/m2 IV on Days 1 and 8 and C AUC = 5 every 16.8-day  
Arm B: A 100 mg/m2 IV on Days 1 and 8 every 21-day | Progression Free Survival |

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### Cis/pem vs. cis/gem elderly data (Nonsquamous patients)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Age &lt; 65 Years n = 319 (67.2%)</th>
<th>Age ≥ 65 Years n = 157 (33.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pem + Cis (n = 217)</td>
<td>Placebo (n = 102)</td>
</tr>
<tr>
<td></td>
<td>Pem + Cis (n = 103)</td>
<td>Placebo (n = 54)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (2.7)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (1.4)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (2.7)</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (0.5)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Diarrhea Without Colostomy</td>
<td>1 (0.5)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

HR OS (all favor pem):
- Subgroup <65: 0.62
- Subgroup >65: 0.87
- Subgroup <70: 0.63
- Subgroup >70: 0.81

### JMEN elderly data: pem vs. placebo

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Age &lt; 65 Years n = 815 (67.2%)</th>
<th>Age ≥ 65 Years n = 398 (32.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pem + Cis (n = 390)</td>
<td>Gem + Cis (n = 425)</td>
</tr>
<tr>
<td></td>
<td>Pem + Cis (n = 215)</td>
<td>Gem + Cis (n = 183)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (2.8)</td>
<td>34 (8.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>45 (11.9)</td>
<td>107 (25.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>23 (5.9)</td>
<td>43 (10.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>15 (3.8)</td>
<td>34 (8.0)</td>
</tr>
<tr>
<td>Diarrhea Without Colostomy</td>
<td>6 (1.5)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26 (6.7)</td>
<td>15 (3.5)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>2 (0.5)</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (8.2)</td>
<td>17 (4.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (6.9)</td>
<td>29 (6.8)</td>
</tr>
</tbody>
</table>

HR OS (all favor pem):
- Subgroup <65: 0.89
- Subgroup >65: 0.75
- Subgroup <70: 0.83
- Subgroup >70: 0.85

Treatment Scheme of ECOG 4599

Non-squamous NSCLC
Absence of brain metastasis
ECOG PS 0 or 1
Informed consent

RANDOMIZE

carboplatin (AUC 6)
paclitaxel 200 mg/m²
bevacizumab 15 mg/kg*

* Bevacizumab continued as monotherapy for CR/PR/SD after 6 cycles

Ramalingam, JCO 26:1, 2008

Subset Analysis of ECOG 4599: Elderly patients treated with bevacizumab in combination with carboplatin and paclitaxel

### Safety in E4599

Incidence of gr 3–5 AEs was significantly higher for PCB vs. PC alone

<table>
<thead>
<tr>
<th>Age</th>
<th>PC + Bev</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3–5 toxicity &lt;75 years</td>
<td>63%</td>
<td>48%</td>
</tr>
<tr>
<td>Grade 3–5 toxicity ≥75 years</td>
<td>81%</td>
<td>56%</td>
</tr>
<tr>
<td>Grade 5 toxicity ≥75 years</td>
<td>8%</td>
<td>2%</td>
</tr>
</tbody>
</table>

\(^{\text{P} < .005}\)

Rates for discontinuations due to AEs also higher for PC + Bev vs. PC alone

<table>
<thead>
<tr>
<th>Age</th>
<th>PC + Bev</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75 years</td>
<td>17% (65/375)</td>
<td>12% (49/401)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>29% (17/59)</td>
<td>19% (8/43)</td>
</tr>
</tbody>
</table>


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### PointBreak

- Randomized, open-label, phase III superiority study
- pemetrexed 500 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg
- paclitaxel 200 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg

**Inclusion:**
- No prior systemic therapy for lung cancer
- ECOG PS 0/1
- Stage IIIB-IV NS-NSCLC
- Stable treated brain mets allowed

**Exclusion:**
- Peripheral neuropathy ≥Grade 1
- Uncontrolled pleural effusions

**Induction Phase**
4 cycles, q21d

**Maintenance Phase**
q21d until PD

R 1:1

**Primary Endpoint:** Overall Survival

Socinski M, et al. ASCO 2013

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## Pooled analysis of Phase III E4599 and Point Break Randomized Clinical Trials

**Treatment:** Bevacizumab + PC vs. PC

<table>
<thead>
<tr>
<th>Age</th>
<th>Bevacizumab + PC vs. PC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65-74</td>
<td>OS: HR 0.80 (0.64-1.00)</td>
</tr>
<tr>
<td></td>
<td>PFS: HR 0.62 (0.49-0.78)</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>OS: HR 0.68 (0.48-0.96)</td>
</tr>
<tr>
<td></td>
<td>PFS: HR 0.57 (0.40-0.81)</td>
</tr>
<tr>
<td>Age &lt;75</td>
<td>OS: HR 0.78 (0.68-0.89)</td>
</tr>
<tr>
<td></td>
<td>PFS: HR 0.69 (0.60-0.79)</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>OS: HR 1.05 (0.70-1.57)</td>
</tr>
<tr>
<td></td>
<td>PFS: HR 0.95 (0.62-1.44)</td>
</tr>
</tbody>
</table>

PC: paclitaxel and carboplatin

*Langer et al. Am J Clin Oncol. 2015*

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## Retrospective cohort study of Medicare beneficiaries

**Median Survival Time (months)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Survival Time (months)</th>
<th>HR Compared to BCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCP</td>
<td>9.7 (4.4–18.6)</td>
<td></td>
</tr>
<tr>
<td>CP 2006–7</td>
<td>8.9 (3.5–19.3)</td>
<td>1.01 (95% CI, 0.89–1.16; P=.85)</td>
</tr>
<tr>
<td>CP 2002–5</td>
<td>8.0 (3.7–17.2)</td>
<td>0.93 (95% CI, 0.83–1.06; P=.28)</td>
</tr>
</tbody>
</table>

Patient is 82 year old male with T3N1 M0 lung adenocarcinoma, s/p right lower lobectomy and mediastinal nodal dissection. Patient has recovered well from surgery and has ECOG performance status of 0 with no significant co-morbidities.

**What would be the appropriate adjuvant chemotherapy?**

A. No need for adjuvant chemotherapy  
B. Cisplatin and Vinorelbine  
C. Carboplatin and Paclitaxel  
D. Cisplatin, Vinorelbine and Bevacizumab

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**Adjuvant Chemotherapy**

- The standard for patients with stages IB to IIIA (high-risk) NSCLC is postoperative cisplatin-based combination chemotherapy for four cycles.

- The LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis reviewed all five cisplatin-containing trials with 4,584 patients; that study reported an overall survival benefit of 5.4% at 5 years.

An age-based analysis of the LACE data

- An age-based analysis of the LACE data showed no difference in survival among the age groups of younger than 65 (n=3269), 65 to 70 (901) and older than 70 years (n=414).

- Elderly patients received significantly lower cisplatin doses and fewer chemotherapy cycles.

- Rates of severe toxicity were comparable between groups.


Ontario Cancer Registry Data

- Outcome of elderly (≥70 years) patients (n=2763) treated before (2001–2003) or after (2004–2006) the adoption of adjuvant chemotherapy.

- The cisplatin/vinorelbine combination was the most frequently used doublet across all age groups.

- Adjuvant chemotherapy administration was associated with a significant survival benefit in the elderly (although not for patients older than 80 years, n = 282) with tolerability similar to that of patients <70 years.

Wisnivesky et al. reported the data from SEER database for 3,324 patients who were 65 years of age or older. No survival advantage was observed in patients older than age 80 years (HR, 1.33; 95% CI, 0.86 to 2.06).

Comparison of carbo vs cisplatin based adjuvant chemotherapy in SEER-Medicare database showed comparable OS benefit and a slightly better toxicity profile.


Adjuvant Chemotherapy in Elderly

- Adjuvant chemotherapy is associated with survival benefit in the elderly and therefore it should not be denied to these patients.

- The benefit of adjuvant chemotherapy has not been established in patients 80 years of age or older and should be undertaken with extra caution.

- Although there is lack of prospective data, carboplatin based regimen may be acceptable when patient is not a cisplatin candidate.
Locally Advanced NSCLC

- Elderly patients with locally advanced NSCLC are more likely to receive no treatment.
  - In one large series by Davidoff et al. based on SEER registry (n = 6325 patients, ≥66 years), 34% of these patients received no treatment at all.
  - Similarly Veterans Affairs Central Cancer Registry (n = 4635 patients, ≥65 years) reported that 35% of patients received no treatment.

- Mixed data from the retrospective analyses of large randomized trials. Most post 2000 trials showed similar benefit of CRT (concurrent or sequential) compared to younger patients with increased toxicity. (NCCTG 94-24-52, CALGB and RTOG 94-10)

JCOG0301: A randomized, phase III trial of thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with NSCLC.

- Unresectable stage IIIA or IIIB NSCLC
- Age > 70 years
- Not eligible for cisplatin
- ECOG PS 0-2
- Excluded if had COPD or uncontrolled heart disease

Randomize

Chemo-RT with weekly low dose carboplatin (n=100)

RT alone (n=100)

Carboplatin was administered (30 mg/m2) 1 h before radiotherapy for the first 20 fractions, RT consisted of 60 Gy given as 30 fractions over 6 weeks.

Median OS
Chemo-RT: 22.4 months
(95% CI 16.5–33.6)
RT: 16.9 months
(95% CI 13.4–20.3),


Adverse Events

- Higher grade 3–4 hematological toxicity in Chemo-RT group than in the radiotherapy alone group. Neutropenia (57.3% vs none), and thrombocytopenia (29.2% vs 2.0%).

- Higher Grade 3 infection in Chemo-RT group (12.5%) than with radiotherapy (4.1%).

- Similar incidences of grade 3–4 pneumonitis and late lung toxicities between groups.

Only prospective randomized study showing benefit of CRT over RT alone in elderly.

Several Limitations...
- RT alone is not considered standard treatment for fit elderly patients
- Weekly carboplatin/RT is not standard for concurrent chemo-RT for locally advanced disease.
- Study only included Asian, good performance status (96.4% pts had PS 0 and 1)
- Patients had limited co-morbidities (pts with COPD and uncontrolled heart disease were excluded).
- Study did not include geriatric functional assessment of patients.

Extrapolation of its conclusions to the general elderly western population should be made with caution.

Early Stage Disease

Limited resections and omission of systematic mediastinal lymphadenectomy can be considered in the elderly on the basis of retrospective data.

Pneumonectomy should be avoided when possible given the higher mortality associated with this procedure.

VATS might be an option for elderly since it is associated with lower incidence of postoperative morbidity.

For elderly patients who are not operable for medical reasons, SABR (stereotactic radiation) could represent an alternative with less adverse events and similar outcome, although prospective data are needed.