Radiotherapy in NSCLC: What are the ESMO Guidelines?

- The role of radiation in early stage
- RT/CT for unresectable NSCLC
- Brain metastasis
- Oligometastatic disease

Jean-Yves DOUILLARD MD PhD
Chief Medical Officer ESMO
2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up
J. Vansteenkiste1, L. Crino2, C. Dooms3, J. Y. Douillard3, C. Faivre-Finn4, E. Lim5, G. Rocco6, S. Senan7, P. Van Schil8, G. Veronesi9, R. Staehler10, S. Peters11, E. Felip12 & Panel Members12†

2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer
W. E. E. Eberhardt1, D. De Ruyscher2, W. Weder3, C. Le Péchoux4, P. De Leyn5, H. Hoffmann6, V. Westeel7, R. Staehler8, E. Felip9, S. Peters10 & Panel Members10†

clinical practice guidelines

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†
S. Novello1, F. Barlesi2, R. Califano3,4, T. Cufer5, S. Ekman6, M. Giaj-Levra7, K. Kerr8, S. Popat9, M. Reck10, S. Senan11, G. V. Simo12, J. Vansteenkiste13 & S. Peters14 on behalf of the ESMO Guidelines Committee†
Standard treatment for early lung cancer

- Around 20% of patients diagnosed with NSCLC have a localized, technically resectable, early stage disease.
- Surgical resection with lobectomy and lymph node sampling is the standard of care in medically fit patients.

- But because of comorbidities, about 25% of these patients do not have standard surgical treatment.

Rami Porta JTO 2015
The role of radiation therapy in early stage

1. Early, resectable but non-operable patients unfit for surgery
2. Resected patients: role of Post Operative Radiation Therapy (PORT)
The role of radiation therapy in early stage

1. Early, resectable but non-operable patients unfit for surgery

ESMO GUIDELINES

- The non-surgical treatment of choice for stage I NSCLC is **stereotactic ablative radiotherapy (SABR)**. The dose should be to a biologically equivalent tumour dose of ≥100 Gy, prescribed to the encompassing isodose [III, A].
- SABR for early-stage peripheral lung tumours is associated with low toxicity in patients with COPD and the elderly [III, A].
- For medically inoperable patients with tumours with a size > 5 cm and/or central location, **radical radiotherapy** using more conventional or accelerated schedules is recommended [III, A].
- In case of R1 resection (positive resection margin, chest wall), **postoperative radiotherapy** should be considered [IV, B].
SURVIVAL AND QUALITY OF LIFE AFTER STEREOTACTIC OR 3D-CONFORMAL RADIOThERAPY FOR INOPERABLE EARLY-STAGE LUNG CANCER

![Graph showing survival and quality of life outcomes](image)
## SRT in lung cancer: Results

<table>
<thead>
<tr>
<th>Author</th>
<th>N pts</th>
<th>DT(Gy)D/jour</th>
<th>Reference point</th>
<th>LC (%)</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>Timmerman 2010</td>
<td>59</td>
<td>T1 et T2</td>
<td>Edge of PTV</td>
<td>3Yr 90%</td>
<td>MS: 48 m</td>
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<tr>
<td>Baumann 2009</td>
<td>57</td>
<td>T1-T2</td>
<td>54Gy 18X3</td>
<td>3YrLC:92%</td>
<td>3y0S:60%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LRel:7%</td>
<td>3yrCSS:88%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RR:5%</td>
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<td></td>
<td></td>
<td>DM: 16%</td>
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<tr>
<td>Lagerwaard 2008</td>
<td>208</td>
<td>20-40 Gy in 2-4 fr</td>
<td>80% isodose</td>
<td>LFail R:12%</td>
<td>3yOS:52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DM:25%</td>
<td>3yrCSS:66%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Haasbeck 2010</td>
<td>203</td>
<td>Tum in 193&gt;75 yrs</td>
<td>80% isodose</td>
<td>LFR:3%</td>
<td>34 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RFR:9%</td>
<td>2y0S:64%</td>
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</tbody>
</table>

3 yr LC rate 90%

Mortality Rate in peripheral Tumors: 0 %

Morbidity Rate: <10%

Timmerman JAMA 2010, Baumann JCO 09, Acta Onco 06; Lagerwaald IJROBP 08; Haasbeck Cancer 2010
7543: Stereotactic body radiotherapy versus lobectomy for operable clinical stage IA pulmonary adenocarcinoma: Comparison of prospective clinical trials with propensity score analysis (JCOG1313-A) – Eba J et al

- **Study objective**
  - A combined analysis of two prospective studies to evaluate the effects of stereotactic body radiotherapy (SBRT) vs lobectomy on survival in patients with operable early stage NSCLC

**Key patient inclusion criteria**
- Operable NSCLC
- cT1N0M0
- Adenocarcinoma

**Primary endpoint**
- OS (adjusted with propensity score analysis*)

*Patient factors included age, sex and 2 CT findings – tumour diameter and consolidation/tumour ratio (CTR)*)

Eba et al. J Clin Oncol 2014; 32 (suppl 5; abstr 7543)
Key results

- Patients in the lobectomy group were younger than in the SBRT group (median age 62 vs 79 years, respectively; p<0.001)
- OS was longer with lobectomy among 21 patients from each group matched for the propensity score analysis

Conclusion

- Lobectomy may provide better outcomes than SBRT, but no definite conclusions can be made owing to the small sample size of the SBRT group; further studies are required

Eba et al. J Clin Oncol 2014; 32 (suppl 5; abstr 7543)
The role of radiation therapy in early stage

1. Resected patients: role of Post Operative Radiation Therapy (PORT)

- Postoperative radiotherapy in completely resected early-stage NSCLC is not recommended [I, A].
- In case of R1 resection (positive resection margin, chest wall), postoperative radiotherapy should be considered [IV, B].
Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-III A non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial

Jean-Yves Douillard, Rafael Rosell, Maria De Lena, Francesca Carpognano, Rodrg Ramlau, Jos Luis Gonzlez-Larriba, Tomasz Grodzki, Jorge Rodrigues Pereira, Alain Le Groumellec, Vito Lorusso, Claude Clary, Antonio J Torres, Jabrail Dahabreh, Pierre-Jean Souquet, Julio Astudillo, Pierre Fournel, Angel Artil-Cortes, Jacek Jassem, Leona Koobkova, Patricia His, Marcello Riggi, Patrick Hurteloup

ANITA:
5 year-survival according to treatment

<table>
<thead>
<tr>
<th></th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>62.3%</td>
<td>31.4%</td>
<td>16.6%</td>
</tr>
<tr>
<td>PORT</td>
<td>43.8%</td>
<td>42.6%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>59.7%</td>
<td>56.3%</td>
<td>34.0%</td>
</tr>
<tr>
<td>Chemotherapy + PORT</td>
<td>44.4%</td>
<td>40.0%</td>
<td>47.4%</td>
</tr>
</tbody>
</table>

Douillard JY et al. The Lancet Oncology 2006 7: 719-727
Cohort of 3395 resected pts NSCLC St II, III
Incomplete Resection: Any Role for PORT??

Survival seems improved in all pts (p<0.04)

Pts treated between 2003-2011
All; R1,R2 surgery
RT:1207 pts (35.6%)
1892 pts R1 (55.7%) 129 pts R2 (3.8%) 1374 pts R1 or R2

5 yr S\text{al} \ S 25.6%, PORT 41.4%

National Cancer Data base Wang and al, JCO 2015
LUNG ART phase III Trial (IFCT O5O3-UK group-EORTC 22055-08053)
Trial registry: NCT00410683

Completely resected NSCLC with mediastinal histo or cytologically proven nodal involvement

Possibility of adjuvant CT

Pre-op and/or Post-op CT

Control
Conformal PORT (54 Gy)

Main end-point: DFS, 700 pts needed to show a 10% difference in DFS (from 30% to 40%)

With the support of INCa (French National Cancer Institute)

Principal investigator: C Le Pechoux
The role of radiation therapy in locally advanced non-resectable NSCLC

**IMAGING: CT-SCAN**

- No enlarged LNs and peripheral tumour
- No enlarged N2 nodes but central tumour or hilar LNs
- Enlarged discrete N2 LNs
- Extensive mediastinal N2 infiltration

**INVASIVE LN RESULT**

- Not required if negative LNs on PET

**CATEGORY OF N2**

- Surgery: unforeseen N2
- Potentially resectable N2
- Unresectable N2

**THERAPEUTIC APPROACH**

- Adjuvant chemotherapy (radiotherapy)
- Dedicated multidisciplinary assessment
- Non-surgical multimodality treatment

*(Figure 1. Suggested algorithm for treatment in patients with logoregional non-small-cell lung cancer, based on imaging, invasive lymph node staging tests and multidisciplinary assessment. Reproduced from [17], by permission of Oxford University Press, on behalf of ESMO.)*
Stage III: importance of pluridisciplinary approach.

- **Very heterogenous population**
- **Several treatment available options**
  - TNM importance of nodal involvement
  - Age, PS and Co-morbidities

Importance of PET-CT and brain imaging
Stage III A and selected III B

5-year survival: 20-25% [5-45%]

- Treatment should be decided within a multidisciplinary team UPFRONT
  - Surgery? RT? Both? Tri-modality or Bi-modality? timing of CT?

- High risk of recurrence (metastatic and local)
  - Distant failure: 30 to 50%  Brain 20 to 32%

- Local Failure Rate at 3 years
  - In surgical series (15% to 60%)
  - CTRT: Loco-regional progression rate <30%

Absolute benefit in OS with concomitant CT:

<table>
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<tr>
<th>Time (y)</th>
<th>RT + conc CT (%)</th>
<th>RT + seq CT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5.3%</td>
<td>10.6%</td>
</tr>
<tr>
<td>3</td>
<td>5.7%</td>
<td>15.1%</td>
</tr>
<tr>
<td>5</td>
<td>4.5%</td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.84 [0.74;0.95], p = 0.004

Aupérin A. et al, JCO 2010
Standard of care in stage III unresectable NSCLC in 2015

- Concomitant chemoradiation: standard of care
- Decreased loco-regional progression
- Most studies 2D RT
- Dose: 52 - 70 Gy 2GyED
- Local Progression Free survival at 3 years 70%

Room for improvement!!

Absolute reduction in LRP:
At 1 year: -4.5%
At 2 years: -5.6%
At 3 years: -6.0%

HR = 0.77 (95% CI: 0.62-0.95), p=0.01

Auperin et al., JCO 2010
Conformal RT and Stage III NSCLC

- Local control is a challenge in locally advanced NSCLC
- How to improve results?
  - Dose escalation, Altered fractionation
  - More precise RT (optimized treatment planning: PET–CT based, 4D CT planning)
  - Combination of targeted agents to CTRT?
  - Immunotherapy?
Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

Prof Jeffrey D Bradley, MD, Rebecca Paulus, BS, Prof Ritsuko Komaki, MD, Gregory Masters, MD, Prof George Blumenschein, MD, Prof Steven Schild, MD, Prof Jeffrey Bogart, MD, Chen Hu, PhD, Kenneth Forster, PhD, Prof Anthony Magliocco, MD, Vivek Kavadi, MD, Yolanda I Garces, MD, Samir Narayan, MD, Puneeth Iyengar, MD, Cliff Robinson, MD, Prof Raymond B Wynn, MD, Christopher Koprowski, MD, Joanne Meng, MD, Prof Jonathan Beitler, MD, Rakesh Gaur, MD, Prof Walter Curran, MD, Prof Hak Choy, MD

The Lancet Oncology
Volume 16, Issue 2, Pages 187-199 (February 2015)
DOI: 10.1016/S1470-2045(14)71207-0

<table>
<thead>
<tr>
<th>AJCC stage</th>
<th>60Gy</th>
<th>74Gy</th>
<th>Cetux</th>
<th>No Cetux</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA/N2 + undetectable NSCLC primary</td>
<td>144 (66%)</td>
<td>131 (63%)</td>
<td>154 (65%)</td>
<td>150 (66%)</td>
</tr>
<tr>
<td>IIIB/N3 + undetectable NSCLC primary</td>
<td>73 (34%)</td>
<td>76 (37%)</td>
<td>83 (35%)</td>
<td>78 (34%)</td>
</tr>
</tbody>
</table>
unresectable IIIA (N2) disease and IIIB disease patients

Recommendation 4.3: Concurrent chemoradiotherapy is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent chemoradiotherapy is not possible—for any reason - sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative [I, A].
Radiation therapy and brain metastasis

• Brain metastasis is an issue now that patient live longer (30-60%)
• Prophylactic Cranial Irradiation PCI is not recommended in NSCLC
• Treatment of patients with brain metastasis and no driver mutation depends on the prognosis
• Prognosis to be established according to RTOG Recursive Partitioning Analysis (RPA class I, II and III)
• Patients with RTOG/RPA class III are not candidates for radiation (OS<2m)
Radiation therapy and brain metastasis

• In class I and II RPA, the radiation technic depends on the number of metastasis
  • Single lesion: Resection or Stereotactic Radio-Surgery (SRS)
  • 2-3 lesions: SRS for PRA I or II (IIB)
    • Addition of Whole Brain Radio-Therapy (WBRT) does not improve OS (IA)
  • > 3 lesions: WBRT? BSC + Steroids?
    • The randomised trial Quartz proved non-inferiority

• In symptomatic patients with no prior systemic therapy. Start systemic treatment 1st (Chemo or TKI)
  • In case of driver mutation use next generation TKI
NSCLC with Oligometastatic progression

• Radiation therapy may be indicated for symptom control (bone) or improved disease control (solitary lung or liver lesion, adrenal gland)
• In addition to continuing systemic treatment
ESMO PRECEPTORSHIP PROGRAMME
NON-SMALL-CELL LUNG CANCER
Standards of care, evolving paradigm and future perspectives
Singapore
13-14 December 2016

Radiotherapy in NSCLC: What are the ESMO Guidelines?

THANK YOU!