Curative treatment of early-stage NSCLC

Lessons learned from comparative effectiveness research and future directions

Professor Suresh Senan
VU University Medical Center, Amsterdam
• Varian Medical Systems: Speakers honoraria, research agreement

• Lilly Oncology: Advisory board
• In 1996, surgery was considered by Dutch physicians as the only curative treatment for early-stage NSCLC

• Questions encountered in the period 1996-2003:
  • “Can radiotherapy cure lung cancer?”
  • “Is any treatment justified in the unfit elderly?”
Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer

E.M. Noordijk¹, E. v.d. Poest Clement¹, J. Hermans², A.M.J. Wever³ and J.W.H. Leer¹

Departments of ¹Clinical Oncology (Division of Radiotherapy), ²Medical Statistics and ³Pneumonology, University Hospital, Leiden, The Netherlands

50 patients (no pathology in 6)
60 Gy / 20 fractions
Overall survival: 16% at 5 years
Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer

- RT can be curative in patients with operable tumors <4cm
- Inform patients about advantages/disadvantageous of surgery and RT
- Prospective randomized trial to compare surgery and RT
- Abandon the ‘wait-and-see’ policy if surgery is not possible

Noordijk EM, Radioth Oncol 1988

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<table>
<thead>
<tr>
<th>Time interval</th>
<th>Radiotherapy (n=40)</th>
<th>Operation (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>93%</td>
<td>84%</td>
</tr>
<tr>
<td>1 year</td>
<td>70%</td>
<td>71%</td>
</tr>
<tr>
<td>2 years</td>
<td>55%</td>
<td>48%</td>
</tr>
<tr>
<td>3 years</td>
<td>32%</td>
<td>39%</td>
</tr>
<tr>
<td>4 years</td>
<td>21%</td>
<td>29%</td>
</tr>
<tr>
<td>5 years</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>Median</td>
<td>27 months</td>
<td>23 months</td>
</tr>
</tbody>
</table>

Fig. 5. Type of treatment and survival.
STEREOTACTIC ABLATIVE RADIOTHERAPY (SBRT, SABR)

STEREOTACTIC RADIOTHERAPY OF MALIGNANCIES IN THE ABDOMEN
Methodological aspects

INGMAR LAX, HENRIC BLOMGREN, INGEMAR NÄSLUND and RUT SVANSTRÖM

STEREOTACTIC HIGH DOSE FRACTION RADIATION THERAPY OF EXTRACRANIAL TUMORS USING AN ACCELERATOR
Clinical experience of the first thirty-one patients

HENRIC BLOMGREN, INGMAR LAX, INGEMAR NÄSLUND and RUT SVANSTRÖM

Fig. 11  a The Elekta Stereotactic Body Frame, based on the original design of Lax and Blomgren; b the abdominal compression feature of the SBF is very effective at reducing motion associated with respiration
IASLC Textbook (2014): A technique for delivering external beam radiotherapy to an extra-cranial target
- with a high degree of accuracy
- using high doses of irradiation
- in 1-8 treatment fractions

4-dimensional CT (2003)  Treatment delivery times of <4 minutes [Ong CL, IJROBP 2012]
# Clinical trials of surgery versus SABR

## Closed randomized trials

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>ROSEL</th>
<th>STARS</th>
<th>Z4099</th>
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</thead>
<tbody>
<tr>
<td>Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials</td>
<td><a href="https://doi.org/10.1016/S1470-2045(15)00034-6">Lancet Oncol 2015</a></td>
<td>'Borderline’ operable, stage I &lt;3cm</td>
<td></td>
</tr>
<tr>
<td>'Borderline’ operable, stage I &lt;3cm</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Primary end-point</td>
<td>Local &amp; regional control, QoL treatment costs at 2- and 5-years</td>
<td>OS at 3 years</td>
<td>OS at 3 years</td>
</tr>
<tr>
<td>Secondary end-points</td>
<td>OS, pulmonary functions, QALYs, total costs</td>
<td>DSS at 3 years</td>
<td>LRR, DFS, toxicities, pulmonary function</td>
</tr>
<tr>
<td>Total enrolled</td>
<td>22 (of 920)</td>
<td>36 (of 1030)</td>
<td>10 (of 420)</td>
</tr>
</tbody>
</table>
Current SABR Guidelines

- **ESMO Guidelines** [Vansteenkiste J, 2014]
  SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.

- **NCCN Guidelines** [version 7.2015]
  SABR is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation.
Figure 1. Example of hierarchy of research design as per evidence-based medicine; *review of randomized controlled trials includes systematic reviews with or without meta-analysis. RCT = randomized controlled trial.
CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition .......

Purpose: ... is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.

Key elements in this definition:

- direct comparison of effective interventions
- in patients typical of day-to-day clinical care

Sox HC, Inst. of Medicine report, Ann Int Med 2009
In 1996, surgery was considered by Dutch physicians as the only curative treatment for early-stage NSCLC.

Questions encountered in the period 1996-2003:
- “Can radiotherapy cure lung cancer?”
- “Is any treatment justified in the unfit elderly?”
SBRT vs no treatment (US data, NCDB)

3147 pathology proven patients >70 years (2003-2006)

No treatment = 2889 (91.8%); SABR = 258 patients (8.2%)

No significant differences in Charlson/Deyo comorbidity index scores

Multivariable analysis: improved overall survival with SABR compared with observation for the entire cohort (hazard ratio, 0.64; P < .001).

Nanda RH, Cancer 2015
Survival curves for 70 to 74 years
Median survival: 8.9 mo vs 36.2 mo

Survival curves for 75 to 79 years
Median survival: 9.2 mo vs 28.3 mo

Nanda RH, Cancer 2015
Systematic review; 9 prospective studies (2010-2015)

Few clinically significant changes in HRQOL scores
Deterioration in fatigue and dyspnea in 2 studies

SABR is a well-tolerated modality for patients with ES-NSCLC who either declined or were unfit for surgery

Chen H, Clin Lung Cancer 2016
## SABR outcomes in operable stage I NSCLC

<table>
<thead>
<tr>
<th>SABR data</th>
<th>Stage</th>
<th>3-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABR – Japan Onishi H, 2011</td>
<td>T1-2N0</td>
<td>83%</td>
</tr>
<tr>
<td>SABR -Dutch Lagerwaard F, 2012</td>
<td>T1-2N0</td>
<td>85%</td>
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<tr>
<td>SABR – US (RTOG 0618) Timmerman R, 2013</td>
<td>T1-2N0</td>
<td>77%</td>
</tr>
<tr>
<td>SABR -Dutch Verstegen N, 2013</td>
<td>T1-2N0</td>
<td>80%</td>
</tr>
<tr>
<td>SABR /Japan (JCOG 0403) Nagata Y, 2015</td>
<td>T1N0</td>
<td>76%</td>
</tr>
</tbody>
</table>

## Surgical data

<table>
<thead>
<tr>
<th>Surgical data</th>
<th>Stage</th>
<th>3-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublobar resection (ACOSOG) Fernando HC, 2014</td>
<td>T1N0</td>
<td>71%</td>
</tr>
</tbody>
</table>

Confounding by indication [Walker AM, Epidemiology 1996]

Physicians choose the treatment that they think best for their patients. The distortions arise from an imbalance in prognostic factors between compared treatment groups.
Recurrences after surgery (n=1294 pts)

- Recurrence risk of 6-10% per person-year for up to 4 years, decreasing thereafter to 2%

- Risks of 2\textsuperscript{nd} primary lung cancer of 3-6% per person-year

Lou F, JTCVS 2012
Surgical salvage following SABR

- Local failure rates of 10% at 5-years after SABR in a study of 855 patients with median follow-up of 52 months [Verstegen NE, JTO 2015]

Follow-up CT scans after curative therapy

• Recommended by
  – European Society for Medical Oncology (ESMO)
  – National Cancer Centre Network (NCCN)
  – American Association for Thoracic Surgery (AATS)
  – American College of Radiology (ACR)
  – American College of Chest Physicians
  – American Society of Clinical Oncology

Hanna WC, TLCR 2015
Second tumors: treatment outcomes

Meta-Analysis of resected metachronous second NSCLC
[Hamaji M, Ann Thorac Surg 2015]

- Sublobar resections in 51.4%; Lobectomy in 34.7%
- Pooled operative mortality rate: 7% (95% CI: 3% to 11%)
- Pooled rate of 5-year OS: 46% (95% CI: 36% to 56%)

SABR outcomes in metachronous second NSCLC

- MDAH [Chang JY, Cancer 2013]: n = 101 patients. After either surgery or SABR for index tumor, incidence of grade ≥ 3 radiation pneumonitis was 3%
- VUMC [Griffioen G, JTO 2014]: n = 107 patients. Median OS was 40 months, and the 3-year OS was 60%
Generating evidence

Which follow-up strategy

- Randomized clinical trial
- Observational study
RCT or post-surgical follow-up

Intergroupe Francophone de Cancerologie Thoracique
Collaborator NCT00198341

Interventions

• **Procedure**: Radiological Arm
  Clinical Visit + X-Ray Chest

• **Procedure**: Scannographic arm
  Clinical visit + X-Ray Chest + CT-Scan + Fibroscopy (for squamous cell)

<table>
<thead>
<tr>
<th>Estimated Enrollment:</th>
<th>1744</th>
</tr>
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<tbody>
<tr>
<td>Study Start Date:</td>
<td>January 2005</td>
</tr>
<tr>
<td>Estimated Study Completion Date:</td>
<td>December 2018</td>
</tr>
<tr>
<td>Estimated Primary Completion Date:</td>
<td>December 2017 (Final data collection date for primary outcome measure)</td>
</tr>
</tbody>
</table>
Observational study: CT follow-up

Danish Lung Cancer Registry (2512 patients in Funen region, population 484,700)

University Hospital: 391 patients (2008-2013) after curative-intent surgery
After mid-2010, chest CT scans every 3 months for 2 years, followed by 6 monthly scans for 3 years

Hansen NC, ERS abstract 2015.
Generating evidence

Chest CT follow-up after head and neck cancer

- Randomized clinical trial
- Observational study
Little survival improvement seen for cancers of the oral cavity, larynx and hypopharynx

5-year survival in head-and-neck squamous cell cancer (HNSCC)\(^1\)
- All-cause mortality: 51.3% (95%CI: 50.8-51.9)
- HNSCC-specific mortality: 23.8% (95%CI: 23.3-24.2)
- Competing mortality: 27.6% (95%CI: 26.8-28.3)

Risk of second primary lung cancer (SPLC) is 5.8%, 11.4%, and 16.4% at 5, 10, and 15 years, respectively\(^2\)

\(^1\) Rose BS, J Clin Oncol 2011; \(^2\) Milano MT, Head Neck. 2012
2nd primary early-stage (ES) lung cancer after a HNSCC

- Netherlands Cancer Registry (1997-2011): Either an early-stage primary only, or SPLC after HNSCC
- Survival outcomes in pre- and post-2005 period
- Univariable and multivariable Cox regression modeling to determine factors prognostic for OS in ES-SPLC
- 21,648 patients: ES primary (n = 21,032) or SPLC (n = 616)

Louie AV, Lung Cancer 2016
2nd primary early-stage (ES) lung cancer after a HNSCC

Significant improvement in OS between treatment eras after radiotherapy ($p = 0.049$), but not for surgery or palliative care.
### New trials: surgery vs SABR

<table>
<thead>
<tr>
<th>SABRTooTH</th>
<th>POSTLIV (RTOG3502)</th>
<th>STABLE-MATES</th>
<th>VALOR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td>Lobectomy or Sublobar Resection</td>
<td>Radical Resection</td>
<td>Sublobar</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>≤ 5 cm</td>
<td>≤ 3 cm</td>
<td>≤ 4 cm</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Peripheral</td>
<td>Peripheral</td>
<td>Peripheral</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Randomization Feasibility</td>
<td>2y LRC</td>
<td>3y OS</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>n=58</td>
<td>n=76</td>
<td>n=258</td>
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<tr>
<td><strong>Sponsor</strong></td>
<td>NHS (UK)</td>
<td>RTOG/NRG/Varian</td>
<td>UTSW</td>
</tr>
<tr>
<td><strong>Principal Investigator Radiation Oncology</strong></td>
<td>Kevin Franks</td>
<td>Jinming Yu (China) Feng-Ming Kong (US)</td>
<td>Robert Timmerman</td>
</tr>
<tr>
<td><strong>Principal Investigator Thoracic Surgery</strong></td>
<td>Babu Naidu</td>
<td>Yilong Wu (China) Andrew Chang (US)</td>
<td>Hiran Fernando</td>
</tr>
<tr>
<td><strong>Co-Chair Pulmonology</strong></td>
<td>David Baldwin</td>
<td>Chunxue Bai</td>
<td></td>
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</tbody>
</table>

**ClinicalTrials.gov ID**
- SABRTooTH: NCT02629458
- POSTLIV: NCT01753414
- STABLE-MATES: NCT02468024
- VALOR: Under IRB Review

*Slide courtesy of Dr. D Moghanaki*
Large clinical databases for the study of lung cancer: Making up for the failure of randomized trials

Chi-Fu Jeffrey Yang, MD, Matthew G. Hartwig, MD, Thomas A. D’Amico, MD, and Mark F. Berry, MD

• “Analyses of large-scale data sets… can enhance quantitative evidence regarding prognosis, efficacy of interventions, and disparities in treatment.

• Although these studies have limitations and cannot replace RCTs, appropriate use of these valuable data sets can enhance current evidence and help direct future research endeavors”

Jeffrey Yang C-F, JTCVS 2016
Empowering patients in decision making

- **ESMO Magnitude of Clinical Benefit Scale** [Cherny NI, Ann Oncol 2015]. Living better; improved QoL, reduced toxicity of treatment

- **ASCO Conceptual Framework to Assess the Value of Cancer Treatment Options** [Schnipper LE, JCO 2015]. To ensure informed decision making, patients need access to both clinical and cost information about their treatment options

- **European Cancer Patients Bill of Rights** [Lawler M, The Oncologist 2014]. Article 1: Right of every European citizen to receive the most accurate information and to be proactively involved in his/her care.
Patient decision aid

http://www.keuzehulp-longkanker.nl/

Algemene informatie over de behandelopties

De standaard behandeling is een operatie. Stereotactische bestraling is een relatief nieuwe behandeling. De overleving na deze behandeling is even goed als bij een operatie. Dit heeft uit studies naar het effect van stereotactische bestraling. De twee behandelingen zijn echter nog niet één op één vergelijkbaar met elkaar.

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Er zijn twee behandelingen voor een vroeg stadium longkanker:

- Een operatie om de tumor te verwijderen. Hiervoor is een ziekenhuisopname nodig.
- Stereotactische bestraling om de tumor dood te stralen. Dit is een poliklinische behandeling; een ziekenhuisopname is niet nodig.

Collaborators: EMGO+ Institute for Health and Care Research, radiotherapy, pulmonology and thoracic surgery

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- W Hopmans (EMGO+)
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Frank Lagerwaard

Pulmonologists and surgeon

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Egbert Smit
Rick Paul

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David Palma
Alex Louie