Operable lung tumors:
Surgery or Stereotactic ablative radiotherapy

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VU University Medical Center
Disclosures

Research grants: Varian Medical Systems, ViewRay Inc.
Advisory boards – Eli Lilly, AstraZeneca, Merck
ESMO Guidelines [Vansteenkiste J, 2013]
SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.
# Operable NSCLC: SABR outcomes

Table 1. Overall survival and treatment-related mortality in patients with operable stage I lung cancer treated with stereotactic ablative body radiotherapy

<table>
<thead>
<tr>
<th>Author, Year [Reference]</th>
<th>Design</th>
<th>Patients (n)</th>
<th>Median age (yr)</th>
<th>Treatment-related mortality rate (%)</th>
<th>3-yr OS (%)</th>
<th>5-yr OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uematsu et al., National Defense Medical College, Tokozawa, Japan, single institution, 2001 [31]</td>
<td>Retrospective</td>
<td>29</td>
<td>71</td>
<td>0</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Lagerwaard et al., VU University, single institution, 2011 [32]</td>
<td>Retrospective</td>
<td>177</td>
<td>76</td>
<td>30-day rate, 0; potentially 1.1 overall</td>
<td>85</td>
<td>51</td>
</tr>
<tr>
<td>Nagata et al., Ishikura et al., JCOG 0403, multi-institutional, 2010–2011 [33, 34]</td>
<td>Prospective phase II</td>
<td>64</td>
<td>79</td>
<td>0</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Timmerman et al., RTOG 0618, 2013 [35]</td>
<td>Prospective phase II</td>
<td>26</td>
<td>72</td>
<td>0</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Onishi et al., Japan, multi-institutional, 2011 [36]</td>
<td>Retrospective</td>
<td>87</td>
<td>74</td>
<td>0</td>
<td>80</td>
<td>62–72</td>
</tr>
<tr>
<td>Komiyama et al., Japan, multi-institutional, 2015 [37]</td>
<td>Retrospective</td>
<td>661</td>
<td>75</td>
<td>0.5</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: JCOG, Japan Clinical Oncology Group; OS, overall survival; RTOG, Radiation Therapy Oncology Group.

Siva S, Oncologist 2016
## Randomized trials of SABR vs surgery

<table>
<thead>
<tr>
<th></th>
<th>VALOR (USA)</th>
<th>POSTILV (China)</th>
<th>SABRTooth (UK)</th>
<th>STABLE-MATES (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility criteria</strong></td>
<td>Tumor ≤5cm (peripheral and central)</td>
<td>Tumor ≤3 cm, fit for lobectomy or pneumonectomy</td>
<td>High-risk operable, peripheral tumors ≤5cm,</td>
<td>High-risk operable, patients pre-randomized</td>
</tr>
<tr>
<td><strong>Primary End-point</strong></td>
<td>5-year overall survival</td>
<td>2-year local-regional control</td>
<td>Average recruitment rate of 3 pts/month for a 15 month period</td>
<td>3-year overall survival</td>
</tr>
<tr>
<td><strong>Secondary end-points</strong></td>
<td>QoL, patterns of failure, cause of death</td>
<td>OS, DFS, site-specific failure, Time to LR failure and DM</td>
<td></td>
<td>PFS, failure patterns, toxicity, and 5-year overall survival</td>
</tr>
<tr>
<td><strong>Planned accrual</strong></td>
<td>670</td>
<td>76</td>
<td>54 (feasibility phase)</td>
<td>258</td>
</tr>
</tbody>
</table>

- Late toxicity, 2nd tumors, overall survival
- Data on early deaths, toxicity, QoL
Accepted Manuscript

The Slippery Slope of Non Operative Therapy in Early Stage Lung Cancer: Snake Oil For Our Surgically Fit Patients?

Lara W. Schaheen, MD, Jonathan D’Cunha, MD, PhD

PII: S0022-5223(17)31178-9
DOI: 10.1016/j.jtcvs.2017.06.009

Lung cancer randomized controlled trials should compare stereotactic body radiation therapy with observation, NOT surgery

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0022-5223/$36.00
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http://dx.doi.org/10.1016/j.jtcvs.2017.06.009
NCDB study: SBRT versus no treatment

3147 pathology-proven cases >70 years in US National Cancer Database (2003-2006)
2889 patients (92%) underwent no treatment & 258 patients (8%) had SBRT

Similar Charlson/Deyo comorbidity index scores

Median survival with only observation: 10.1 months
Median survival with SABR: 29 months

Nanda RH, Cancer 2015
Survival after a lobectomy (1996-2012)

Overall Survival stratified by predicted DLCO

972 patients who underwent lobectomy without induction therapy for stage I NSCLC (T1-2N0M0) from 1996 to 2012

Evaluated using Kaplan-Meier approach and a multivariable Cox proportional hazard model
SABR vs. Surgery in Early Lung Cancer: A Meta-analysis of Propensity Score-Adjusted Studies

Hanbo Chen, WCLC 2017
SABR vs. Surgery in Early Lung Cancer: A Meta-analysis of Propensity Score-Adjusted Studies

**Primary Overall Survival meta-analysis:**
statistically significant differences favouring surgery, both after lobectomy and sublobar resection

**Primary Disease-specific Survival meta-analysis:**
no statistically significant differences (neither lobectomy nor sublobar resection)
ASTRO Guidelines [Videtic GM, Pract Rad Oncol 2017]: For patients with “standard operative risk” (i.e. with anticipated operative mortality of <1.5%) and stage I NSCLC, SABR is not recommended as an alternative to surgery outside of a clinical trial.

Endorsed by the European Society for Radiotherapy & Oncology, the Royal Australian and New Zealand College of Radiologists, and the International Association for the Study of Lung Cancer.
30- and 90-day mortality after surgery

Fig 1. Thirty-day and 90-day postoperative mortality for lung cancer resection in contemporary series. Weighted average calculated from the sum of individual mortality events in all studies/total patient numbers in all studies. Only series from unique data sets are included, with the exception of Rueth et al.² and Hu et al.³ which report SEER-Medicare data from nonoverlapping years. Data sets for other series displayed include Bryant et al (University of Alabama at Birmingham),⁴ Greillier et al (Hopitaux de Marseille), Cheung et al (Florida State Registries), He et al (Guangzhou), Haasbeek et al (Netherlands Registry), St Julien et al (Veterans Affairs), Damhuis et al (Rotterdam Registry), Powell et al (English Registry), Landreneau et al (University of Pittsburgh), and Samson et al (National Cancer Database).
Dutch surgical mortality after a lobectomy
Netherlands Cancer Registry

https://shop.iknl.nl/shop/kankerzorg-in-beeld-de-oudere-patiënt-(2016)/123187
### English NLCA: 90-day mortality after a lobectomy

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Performance status</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>(1–2%)</td>
<td>(1–2%)</td>
<td>(2–4%)</td>
<td>(3–10%)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>2534</td>
<td>1467</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4%</td>
<td>6%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3–6%)</td>
<td>(5–7%)</td>
<td>(5–12%)</td>
<td></td>
</tr>
<tr>
<td>70–80</td>
<td>1361</td>
<td>1420</td>
<td>219</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>7%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3–9%)</td>
<td>(5–10%)</td>
<td>(8–25%)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>263</td>
<td>377</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

95% confidence intervals are presented in brackets below the risk%, with the total number in each group underneath.

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O'Dowd EL, Lung Cancer 2016
NCDB: Post-Treatment Mortality for Early-Stage NSCLC

A  30-Day Mortality

% Mortality

Age

B  90-Day Mortality

% Mortality

Age

Stokes WA, JCO in press
NCDB: Post-Treatment Mortality for Early-Stage NSCLC

A 30-Day Mortality

- ≤55
- 56-60
- 61-65
- 66-70
- 71-75
- 76-80
- >80

All Ages - interaction p = 0.027

Hazard Ratio

0.1 0.25 0.5 1 2.5 5 10 15

increased mortality with SBRT \(\leftarrow\) increased mortality with surgery

B 90-Day Mortality

- ≤55
- 56-60
- 61-65
- 66-70
- 71-75
- 76-80
- >80

All Ages - interaction p < 0.001

Hazard Ratio

0.1 0.25 0.5 1 2.5 5 10 15

increased mortality with SBRT \(\leftarrow\) increased mortality with surgery

Stokes WA, JCO in press
Non-cancer deaths after stage I NSCLC

Resected stage I NSCLC at MSKCC [Eguchi T, JCO 2017]
SABR: Criticisms by surgeons

- Treatment without pathology
- Lack of long-term follow-up
- Lack of nodal staging
- Recurrences
- No randomized trials
- Depriving patients of the only curative option
Clinical stage I NSCLC: Audit of Dutch MDT’s

Dutch surgical papers: ≤6% risk of benign disease in resected lesions

Dutch Lung Surgery Audit: Of 1555 clinical stage I NSCLC cases, the final diagnosis was benign disease in 0.8% [Heineman D, ATS 2016]

Intraoperative diagnosis (IOD) in lung cancer [Verhaegen A, 2017]

For segmentectomy, lobectomy, bilobectomy and pneumonectomy, the rates of IOD were 55%, 39%, 23% and 11%, respectively
IOD rates highest in small tumors (cT1A - 59%), and varied between hospitals (range 15%-65%)

## SABR: Recurrence patterns in stage I NSCLC

<table>
<thead>
<tr>
<th>Recurrences</th>
<th>Local</th>
<th>Regional</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td>VU University Med Ctr</td>
<td>10.5%</td>
<td>12.7%</td>
<td>20%</td>
</tr>
<tr>
<td>676 patients; median follow-up of 33 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD Anderson Hospital</td>
<td>11%</td>
<td>12%</td>
<td>21%</td>
</tr>
<tr>
<td>912 patients; median follow-up of 59 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


2. Brooks E, IJROBP 2017 and update at ASCO (Abstr 8501)
<table>
<thead>
<tr>
<th></th>
<th>Proceed with treatment</th>
<th>Treatment discouraged</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO 2014</td>
<td>Yes, if MDT agrees</td>
<td></td>
</tr>
<tr>
<td>ASTRO 2017</td>
<td>Yes, if MDT agrees</td>
<td>In some regions</td>
</tr>
<tr>
<td>Asian Guidelines 2016</td>
<td>No</td>
<td>Early biopsy preferred</td>
</tr>
</tbody>
</table>

MDT = multi-disciplinary team

Salvage surgery possible post-SABR

- Chen F, J Thoracic Oncology, 2010
- Neri S, J Thoracic Oncology, 2010
- Hamamoto Y, Japan J Radiology 2012
- Hamaji M, J Thoracic Oncology, 2015
- Verstegen N, Radioth Oncol 2016
- Antonoff MB, JTCVS 2017
Second lung tumors in treated stage I NSCLC

855 post-SABR patients from VUMC [Verstegen NE, JTO 2015]

1294 surgical cases from MSKCC [Lou F, JTCVS 2012]
Stage I NSCLC: Doctors attitudes

- 126 pulmonologists, surgeons and radiation oncologists; binary choice experiment using vignettes with hypothetical cases.

- 55% of oncologists considered surgery and SABR to be equal treatment options, ranging from 49% of pulmonologists, 18% of thoracic surgeons and 83% of radiation oncologists.
Dutch trends in early-stage NSCLC

Netherlands Cancer Registry:
Treatment utilization by diagnosis year (n = 21,032 patients)

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis year 1997-1999</th>
<th>Diagnosis year 2009-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>62%</td>
<td>60%</td>
</tr>
<tr>
<td>Radiation</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td>Palliative therapy</td>
<td>19%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Louie AV, Lung Cancer 2016
Patient decision aids

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

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

- Timmermans DRM (EMGO+)
- Damman O (EMGO+)
The patient’s right to know

JUDGMENT

Montgomery (Appellant) v Lanarkshire Health Board (Respondent) (Scotland)
Informed patient decisions

I just want surgery

I just want SBRT

Hmm... there was so much I didn’t know

Informed Uncertainty

Uninformed Preferences

VALOR

Courtesy of Dr. Drew Moghanaki, PI of VALOR study
Thank you for your attention
IPF is a chronic, progressive fibrotic interstitial lung disease of unknown origin.

HRCT images: usual interstitial pneumonia (UIP) pattern.

- UIP pattern, with extensive honeycombing: basal predominant, peripheral predominant reticular abnormality, with multiple layers of honeycombing.
- Possible UIP pattern; peripheral predominant, basal predominant reticular abnormality with moderate amount of ground glass abnormality, but without honeycombing.

Raghu G, AJRCCM 2011