Debate: Which treatment for screening detected tumors? The radiotherapeutic approach

Professor Suresh Senan
Department of Radiation Oncology
VU University medical center, Amsterdam

SABR - a definition

High-precision image-guided RT characterized by:
- Accurate target definition
- Reproducible patient / tumor positioning
- Multiple fixed beams or arc delivery

Features of SBRT delivery
- Very high biological doses
- Delivery in 3-8 sessions
- Steep dose-gradients
Examples of treatment units

Treatment machines that permit CT scans of non-diagnostic quality to be made
Poorer outcomes after SABR have been reported [Bral S, 2007 and 2010; Nagata Y, 2010]

**Dutch ‘Risk-adapted’ protocols**

- **3 fractions** of 18 Gy (1 week)
  
  *T1 tumors without extensive contact with thoracic wall or mediastinum*

- **5 fractions** of 11 Gy (1.5 weeks)
  
  *T1 tumors with broad contact with chest wall or mediastinum, and any T2 tumors*

- **8 fractions** of 7.5 Gy (3.5 weeks)
  
  *Tumors adjacent to pericardium or hilum*

Lagerwaard FJ, 2008
SABR is well tolerated

Toxicity is uncommon [Nguyen N, 2008]

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient no.</th>
<th>Types of complications</th>
<th>Death from treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagerwaard et al.</td>
<td>206</td>
<td>6 grade 3 pneumonitis, 4 rib fractures</td>
<td>0%</td>
</tr>
<tr>
<td>Koto et al.</td>
<td>31</td>
<td>3 chronic thoracic pain</td>
<td>0%</td>
</tr>
<tr>
<td>Fritz et al.</td>
<td>40</td>
<td>1 grade 3 pneumonitis</td>
<td>0%</td>
</tr>
<tr>
<td>Onishi et al.</td>
<td>257</td>
<td>2 rib fractures</td>
<td>0%</td>
</tr>
<tr>
<td>Zimmermann et al.</td>
<td>30</td>
<td>14 pneumonitis, 3 grade 3–4 dermatitis, 4 rib fractures</td>
<td>0%</td>
</tr>
<tr>
<td>Baumann et al.</td>
<td>138</td>
<td>1 grade 3 pneumonitis, 1 fracture</td>
<td>0%</td>
</tr>
<tr>
<td>Onimaru et al.</td>
<td>41</td>
<td>2 atelectasis, 2 rib fractures, 1 pneumonitis</td>
<td>0%</td>
</tr>
<tr>
<td>Beiter et al.</td>
<td>75</td>
<td>2 pleural effusion, 1 pneumothorax</td>
<td>0%</td>
</tr>
<tr>
<td>Guckenberger et al.</td>
<td>38</td>
<td>4 pneumonitis</td>
<td>0%</td>
</tr>
<tr>
<td>Nymans et al.</td>
<td>45</td>
<td>3 atelectasis, 2 rib fractures</td>
<td>0%</td>
</tr>
<tr>
<td>Zimmermann et al.</td>
<td>70</td>
<td>4 grade 3 pneumonitis, pleural effusion, decline in pulmonary function test, and skin reaction</td>
<td>6 (8.5%)</td>
</tr>
<tr>
<td>Ricardi et al.</td>
<td>43</td>
<td>3 grade 3 pneumonitis, 1 rib fracture</td>
<td>0%</td>
</tr>
<tr>
<td>Xie et al.</td>
<td>43</td>
<td>1 grade 3 pneumonitis</td>
<td>0%</td>
</tr>
</tbody>
</table>

Patient-scored quality of life maintained after SABR in >500 patients [van der Voort van Zyp N 2010; Widder J, 2011; Lagerwaard F, in press]

What is the evidence to show that SABR is curative in stage I nsclc?
SBRT outcomes in stage I NSCLC

Phase 2 North American multi-center study [Timmerman R, 2010]

SBRT in 3 fractions to biopsy-proven lesions measuring ≤5 cm
• Median FUP (all patients) was 34.4 months (4.8-49.9 mo)
• 3-year primary tumor control was 97.6% (95% CI, 84.3%-99.7%)
• 3-year local-regional control was 87.2% (95% CI, 71.0%-94.7%)

Phase 2 Scandinavian multi-center study [Baumann P, 2009]

70% of patients had a tissue diagnosis of malignancy
• Median follow-up of 35 months (4-47 months)
• 3-year local control rates of 92%.
• Local relapse in 7%; regional relapses in 5%

Single institution outcomes

Stage I NSCLC results at VUMC

<table>
<thead>
<tr>
<th>3 year endpoints</th>
<th>PA + (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>55.4%</td>
</tr>
<tr>
<td>Local control</td>
<td>90.4%</td>
</tr>
<tr>
<td>Regional control</td>
<td>90.3%</td>
</tr>
<tr>
<td>Distant control</td>
<td>79.6%</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>72.1%</td>
</tr>
</tbody>
</table>

Verstegen NE, 2011
SABR operable patients

177 patients (24% of referrals to VUmc)

![Graph showing survival of operable vs. inoperable patients](image)

- Median survival: 5.1 years
- 30-day mortality: 0%
- 2-year survival: 88%
- 3-year survival: 85%
- 5-year survival: 51%

Predicted 30-day mortality for lobectomy (Thoracoscore): 2.6%

Lagerwaard F, 2011

NCI levels of evidence

- Randomized controlled trials and meta-analysis
- Controlled trials where allocation is non-random (e.g., allocation by birth date or chart number)
- Population-based consecutive series
- Others

Advantages of population-based studies

- Reflect real-world outcomes
- Reduce selection bias
- Next strongest study design after controlled trials

Population-based time-trend studies

- Netherlands Cancer Registry (2001-2009)
- Population - 16 million
- 4605 patients with stage I NSCLC aged ≥75 years

North Holland/Flevoland (1999-2007)
- Population - 3 million
- 843 patients with stage I aged ≥75 years

Palma D, 2010

Palma D, 2010 Haasbeek CJ, in press

Dutch national study (2001-2009)

4605 stage I NSCLC patients aged ≥75 years

- Radiation Therapy
- Surgery
- Neither

<table>
<thead>
<tr>
<th>Year</th>
<th>Radiation Therapy</th>
<th>Surgery</th>
<th>Neither</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2003</td>
<td>37%</td>
<td>31%</td>
<td>32%</td>
</tr>
<tr>
<td>2004-2006</td>
<td>36%</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>2007-2009</td>
<td>37%</td>
<td>38%</td>
<td>25%</td>
</tr>
</tbody>
</table>

* estimated utilization of SABR in radiotherapy group was >75%,

Haasbeek C, in press
Dutch national study (2001-2009)

Survival

Haasbeek C, in press

All patients
Median 16.4 → 24.4 months

Surgery
Median 35.7mo → not reached
90 day mortality 11.5% → 7.0%

Radiotherapy
Median 16.8 → 26.1 months

No treatment
Median 6.6 months

Dutch surgical results representative?

- US Nationwide Inpatient Sample [Finlayson E, 2006]
- US CanCORS data [Billmeirs SE, 2011]
- French national thoracic data (Epithor®) [Rivera C, 2011]
- Spanish NATCH trial [Felip E, 2010]
- Differences in 30-day and 90-data mortality [Bryant AS, 2010; Rivera C, 2011; Fernando HC, 2011]
With 2 curative options available for patients with a stage I-II NSCLC, it is important to establish a diagnosis before initiating treatment.

Objections voiced by surgeons

- SABR without pathology
- No invasive nodal staging (ESTS guidelines)
- SABR is comparable to a wedge resection (= inferior)
- Limited follow-up – late recurrences may occur
- Anectodal (bronchial necrosis; ‘holes’ in esophagus)

Clinical vs pathological diagnosis

Stage I NSCLC results at VUMC

<table>
<thead>
<tr>
<th>3 year endpoints</th>
<th>PA+ (n=209)</th>
<th>PA– (n=393)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>55.4%</td>
<td>54.4%</td>
<td>.93</td>
</tr>
<tr>
<td>Local control</td>
<td>90.4%</td>
<td>91.5%</td>
<td>.92</td>
</tr>
<tr>
<td>Regional control</td>
<td>90.3%</td>
<td>87.9%</td>
<td>.83</td>
</tr>
<tr>
<td>Distant control</td>
<td>79.6%</td>
<td>79.8%</td>
<td>.95</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>72.1%</td>
<td>73.2%</td>
<td>.98</td>
</tr>
</tbody>
</table>

Calculated mean probability of malignancy [Herder G, CHEST 2005]

- 94.8% (95% CI 94.3-95.4%)
- 92.5% (95% CI 91.8-93.3%)

Verstegen NE, 2011
SABR after a clinical diagnosis?

Clinical diagnosis only as % of all SABR cases

Princess Margaret Hosp [Taremi M, 2012]: 29%
Sandinavian [Baumann P, 2009]: 33%
Dutch national registry [Haasbeek C, in press]: 30%
VUMC data: approximately 65%

Dutch surgical data show ≤6% benign lesions
• Van Tinteren H [Lancet 2002]
• Herder G [JCO 2006]
• Senan S [submitted]

Consider toxicity of VATS in multicenter setting:
≥ Gr 3 complications in 7.4%;
30-day mortality of 2.7% (Swanson S, 2007)

CT screening trials: Benign histology

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Type</th>
<th>Age (40–74)</th>
<th>No. of Rounds</th>
<th>% Recall</th>
<th>Total LC</th>
<th>% LC</th>
<th>% Stage I</th>
<th>No. of Surgery</th>
<th>% Benign</th>
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</thead>
<tbody>
<tr>
<td>Shinshu Univ</td>
<td>O</td>
<td>5483</td>
<td>3</td>
<td>10</td>
<td>63</td>
<td>1.1</td>
<td>81</td>
<td>72</td>
<td>22</td>
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<tr>
<td>Hitchi</td>
<td>O</td>
<td>7965</td>
<td>2</td>
<td>8.9</td>
<td>40</td>
<td>0.5</td>
<td>78</td>
<td>57</td>
<td>30</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>O</td>
<td>1520</td>
<td>5</td>
<td>37</td>
<td>66</td>
<td>4.3</td>
<td>55</td>
<td>70</td>
<td>18*</td>
</tr>
<tr>
<td>LEICAP</td>
<td>O</td>
<td>31567</td>
<td>2</td>
<td>13</td>
<td>484</td>
<td>1.5</td>
<td>85</td>
<td>—</td>
<td>8*</td>
</tr>
<tr>
<td>LUSG</td>
<td>O</td>
<td>3642</td>
<td>2</td>
<td>31</td>
<td>80</td>
<td>2.2</td>
<td>50</td>
<td>88</td>
<td>37</td>
</tr>
<tr>
<td>Milan Unipoly</td>
<td>O</td>
<td>5189</td>
<td>2</td>
<td>11</td>
<td>92</td>
<td>1.8</td>
<td>66</td>
<td>104</td>
<td>14</td>
</tr>
<tr>
<td>Torino</td>
<td>O</td>
<td>3352</td>
<td>2</td>
<td>18</td>
<td>65</td>
<td>1.9</td>
<td>65</td>
<td>48</td>
<td>18*</td>
</tr>
<tr>
<td>LSS</td>
<td>R</td>
<td>1460</td>
<td>2</td>
<td>—</td>
<td>36</td>
<td>2.3</td>
<td>48</td>
<td>39</td>
<td>45*</td>
</tr>
<tr>
<td>DLCT</td>
<td>R</td>
<td>2052</td>
<td>0</td>
<td>8.7</td>
<td>17</td>
<td>0.8</td>
<td>53</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>NELSON</td>
<td>R</td>
<td>7757</td>
<td>2</td>
<td>27</td>
<td>144</td>
<td>1.86</td>
<td>67</td>
<td>—</td>
<td>27</td>
</tr>
<tr>
<td>ITALUNG</td>
<td>R</td>
<td>1406</td>
<td>0</td>
<td>30</td>
<td>20</td>
<td>1.5</td>
<td>50</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>

* Data combined with Ref. 12.
* O, observational; R, randomized; no., subjects in the LDCT screening arm only; total LC, all cases detected throughout the study period, including interval cases.
SABR without invasive nodal staging

- Nodal recurrence after SABR approx 10% (Chi A, 2010)
- Nodal recurrence rates despite surgical staging (Grills I, 2010; Saynak M, 2011; Senan S, submitted)
- Fitness to undergo post-op chemotherapy after upgrading (Felip E, 2010; Puri V, 2012)

Post-surgical relapse rates: ‘old data’

<table>
<thead>
<tr>
<th>Surgical Stage</th>
<th>5-Year Survival (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Local</td>
</tr>
<tr>
<td>I A</td>
<td>T1N0M0</td>
<td>67</td>
</tr>
<tr>
<td>I B</td>
<td>T2N0M0</td>
<td>57</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
<td>55</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>T3N0M0</td>
<td>38</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N1M0</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>T1-3N2M0</td>
<td>23</td>
</tr>
</tbody>
</table>

Table 1. Expected Outcome Following Surgical Resection in Operable Non-Small-Cell Lung Cancer

Pisters et al. JCO 2005
SABR is not comparable to a wedge resection

Grills I, 2010

Local failure after complete resection of N0–1 NSCLC

Saynak M, 2011
Stage I NSCLC: Recurrence patterns

Stage I-II NSCLC treated using either SABR or VATS-lobectomy: Outcomes of a propensity score-matched analysis (Verstegen N, submitted)

- 86 VATS-lobectomy and 527 SABR patients eligible
- Nodal staging in VATS group in accordance with ESTS guidelines

- Matching covariates:
  - Gender - Age
  - cTNM - Tumor diameter
  - Histology - Tumor location
  - FEV 1% - WHO score
  - Charlson comorbidity

Propensity score-matched analysis

Results under embargo
Long-Term Excess Mortality in NSCLC

12,148 patients aged 45-74 years, stage I–III NSCLC, from Netherlands Cancer Registry

Janssen-Heijnen M, 2011

SEER review of 5-year NSCLC survivors;

31, 206 patients (1988-2001): Approximately half of the deaths in 5-year survivors are categorized as due to lung cancer

Hubbard MO, 2012
Winning the Battle, Losing the War: The Noncurative “Curative” Resection for Stage I Adenocarcinoma of the Lung

N = 285 patients from Cleveland Clinic

Fig 5. Survival after resection and competing risks for recurrence of adenocarcinoma of the lung. (A) Overall survival after index resection. Format is as in Fig 1A. (B) Competing risks depiction of death without recurrence, and cancer recurrence after index operation. All patients start alive at index operation. The three curves sum to 100% at each point in time.

Murthy SC, 2010

Risk of delaying treatment of lung cancer

Progression of non-small-cell lung cancer during the interval before stereotactic body radiotherapy

CLINICAL INVESTIGATION   IJROBP 2011

Mean increase rate (%)  AD  SQ

Volume increase rate (%)  

Waiting time (weeks)
Risk of delaying treatment for lung cancer

N= 210 tumors

Nawa T, 2012

Approach to screen-detected tumors

• Establish guidelines for therapeutic intervention in screen-detected ‘tumors’

• SABR should be discussed as a standard option if therapy is indicated for a screen-detected early-stage lung cancer
  – Local control rates similar to surgery
  – Less toxicity reported than VATS
  – Screen-detected cancers are at low risk for occult nodal metastases
    (exceptions: central lesions, intense PET +ve, SCLC)