Stereotactic ablative radiotherapy (SABR) for early-stage lung cancer

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Amsterdam, The Netherlands
• Research support: Varian Medical Systems
Overview

- Treatment guidelines and delivery
- Toxicity of SABR
- New developments - MR-guided SABR
- Follow-up after SABR
- Treatment of operable patients
SABR is a technique for delivering high-dose radiotherapy to an extra-cranial target with high precision

- Tumors up to 5 cm; minimal delivered dose $BED_{10} \geq 100$ Gy

When SABR is unavailable, a hypofractionated radiotherapy schedule with a high biologically equivalent dose is advised in patients with early-stage NSCLC who are unfit for surgery

ESMO Clinical Practice Guidelines, Vansteenkiste J, Ann Oncol 2013
SABR delivery at VUMC (standard cases)

Patient positioning

4-Dimensional CT (2003)

Linear accelerator

Cone-beam CT

VMAT delivery (2008)
SABR delivery: ‘risk-adapted’ fractionation

Dutch fractionation schedules [Hurkmans C, Rad Onc 2009]

- **3 fractions of 18 Gy**: T1 lesions, not adjacent to chest wall
- **5 fractions of 11 Gy**: T1 lesions with broad chest wall contact, and T2 lesions
- **8 fractions of 7.5 Gy**: central lesions with limited overlap with mediastinum
**SABR: Long-term follow-up data**

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timmerman R, ASTRO 2014</td>
<td>Multicenter phase II trial</td>
<td><strong>Median 4 years</strong> (7.2 years for surviving patients)</td>
</tr>
<tr>
<td>Lindberg K, Acta Oncol 2015</td>
<td>Multicenter phase II trial</td>
<td><strong>Median 3.5 years</strong> [median 5 years in 34 patients with follow-up of &gt; 36 month]</td>
</tr>
<tr>
<td>Verstegen N, JTO 2015</td>
<td>Single institution</td>
<td><strong>Median 4.3 years</strong></td>
</tr>
</tbody>
</table>
Post-SABR recurrences: 855 patients

- Median follow-up: **52 months**
- Actuarial local control rate at 5 years of 91%
- **54%** had isolated local tumor recurrences (LR)
- **13%** had LR **combined** with regional recurrence.

**Incidence of SPLC and local recurrence per year**

Verstegen NE, JTO 2015
Early stage NSCLC in inoperable elderly

- NCDB analysis (2003-2006)
- 3147 pathology-proven cases aged ≥70 years
- SBRT in 258 patients (8.2%) and no treatment in 2889 (91.8%)
- No significant differences in Charlson/Deyo comorbidity index scores

Median survival:
Observation: 10.1 months
SABR: 29 months

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

Nanda RH, Cancer 2015
Stage IA NSCLC (SEER 2004-2012)

Haque W, AJCO 2016
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Systematic review; 9 prospective studies (2010 to 2015)

Few clinically significant changes in HRQOL scores after SABR. Deteriorations in fatigue and dyspnea reported in just 2 studies

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

Chen H, Clin Lung Cancer 2016
## Incidence of chest wall toxicity in dedicated studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median F/U</th>
<th>CW pain (%)</th>
<th>Rib fracture (%)</th>
<th>Median onset (mo)</th>
<th>Dose/Fx</th>
<th>Grade (pain)</th>
<th>Grade (fracture)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andolini [12]</td>
<td>347</td>
<td>19 mo</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>18–72 Gy/6–24 fx</td>
<td>27</td>
<td>-</td>
</tr>
<tr>
<td>Creach [26]</td>
<td>146</td>
<td>22.5 mo</td>
<td>15</td>
<td>8</td>
<td>12.6</td>
<td>50–54 Gy/3–5 fx</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Dunlap [25]</td>
<td>60</td>
<td>11.1 mo</td>
<td>32</td>
<td>8</td>
<td>7.1</td>
<td>21–60 Gy/3–5 fx</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Kim [32]</td>
<td>118</td>
<td>22 mo</td>
<td>27</td>
<td>38</td>
<td>17</td>
<td>36–60 Gy/3–4 fx</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nambu [53]</td>
<td>177</td>
<td>27 mo</td>
<td>21</td>
<td>23</td>
<td>21.2</td>
<td>48–70 Gy/4–10 fx</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Stephans [27]</td>
<td>45</td>
<td>18.8 mo</td>
<td>22</td>
<td>-</td>
<td>8.8</td>
<td>60 Gy/3 fx</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Taremi [30]</td>
<td>46</td>
<td>24.9 mo</td>
<td>46</td>
<td>37</td>
<td>21</td>
<td>54–60 Gy/3 fx</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Welsh [37]</td>
<td>265</td>
<td>10.3 mo</td>
<td>22</td>
<td>3</td>
<td>6</td>
<td>50 Gy/4 fx</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>Bongers [34]</td>
<td>500</td>
<td>33 mo</td>
<td>11</td>
<td>2</td>
<td>8</td>
<td>60 Gy/3–8 fx</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>Woody [29]</td>
<td>102</td>
<td>25 mo</td>
<td>20</td>
<td>4</td>
<td>3.8</td>
<td>48–60 Gy/3–8 fx</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Mutter [28]</td>
<td>126</td>
<td>16 mo</td>
<td>43</td>
<td>4</td>
<td>9</td>
<td>40–60 Gy/3–5 fx</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>Pettersson [31]</td>
<td>33</td>
<td>29 mo</td>
<td>-</td>
<td>39</td>
<td>8.8</td>
<td>45 Gy/3 fx</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CW: Chest wall.  
F/U: Follow-up.  
Fx: Fraction.

2 - 39 %  
1 - 19 %

Shaik T, Cancer Treat Rev 2014
• Bahig H, Prac Rad Oncol 2016
  • 504 SABR patients (6% had preexisting Interstitial Lung Disease)
  • Grade ≥ 3RP of 4% in entire cohort
  • Grade ≥ 3 RP in 2% of patients without ILD
  • Grade ≥ 3 RP in 32% of patients with ILD
  • Grade 5 RP in 21% of patients with ILD

• Chen H, Proceedings WCLC 2016 (P1.05-061)
  • Systematic review: SABR-related mortality rate in IPF of 16%
Moderately central vs ‘ultracentral’ tumors

SABR appears feasible
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patient selection</th>
<th>Fractionation (fx) schemes</th>
<th>Number of patients</th>
<th>Median FU</th>
<th>G3 or higher toxicity</th>
<th>Survival</th>
<th>Disease control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woody, 2015 IJROBP</td>
<td>NSCLC ≥5 cm 2003-2014 (single institution)</td>
<td>5x10Gy, 8x7.5Gy, 10x5Gy, or other</td>
<td>N = 40</td>
<td>10.8 mo</td>
<td>N = 3 (7.5%) → lobar collapse, pleural effusion, pneumonitis. − G5 tox: 3%</td>
<td>Median OS: 19.9 mo 18 mo survival 60%</td>
<td>Local failure: 7.5%  Locoreg control @18 mo: 64.4%  Distant failure: 32.5%  Median DFS: 14.4 mo</td>
</tr>
<tr>
<td>Verma, 2016 Cancer</td>
<td>NSCLC ≥5 cm 2004-2016 (multi-institutional)</td>
<td>3x18Gy, 4x12Gy, 5x10Gy, or other ≤5 fx schemes</td>
<td>N = 92</td>
<td>12.0 mo</td>
<td>N = 6 (6.5%)  G3: n= 5  G4: n = 0  G5: n = 1</td>
<td>Median OS: 21.4 mo 2 yr survival: 46%</td>
<td>Local failure: n = 15%  Local control 1 yr: 95.7%  Distant failure: 21%  Median DFS: 32.4 mo</td>
</tr>
<tr>
<td>Verma, 2016 IJROBP</td>
<td>NSCLC ≥5 cm 2004-2012 (NCDB)</td>
<td>48, 50, 54, or 60 Gy in ≤10 fx</td>
<td>SABR: 171 SABR-chemo: 30</td>
<td>41.1 mo</td>
<td>Not reported</td>
<td>Median OS: 25.1 mo 3 yr survival: 33%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Peterson, 2016 Clinical Lung Cancer</td>
<td>Node-negative NSCLC &gt; 5cm (single institution)</td>
<td>Median radiation dose/fraction: 50Gy in 5 fractions</td>
<td>N = 41</td>
<td>15.2 mo</td>
<td>G3: n = 2 (4.8%)  Shortness of breath  Pneumonitis − G4/G5: n = 0</td>
<td>Median OS: 17.5 mo 2 yr survival: 34%</td>
<td>Local failure: 4.8%  Distant failure: 31%</td>
</tr>
<tr>
<td>Tekatli, JTO 2017</td>
<td>NSCLC ≥5 cm 2003-2014 (single institution)</td>
<td>5x11Gy, 5x12Gy, or 8x7.5Gy</td>
<td>N = 63</td>
<td>54.7 mo</td>
<td>N= 19 (30%)  − Pneumonitis most common  − G5 tox: 19%</td>
<td>Median OS: 28.3 mo 3 yr survival: 42%</td>
<td>Local failure: 6%  Regional failure: 6%  Distant failure: 19%  DFS at 2 years: 82.1%</td>
</tr>
</tbody>
</table>

Tekatli H, *in press* JTO 2017
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MR-guided radiotherapy: MRIdian (ViewRay®)

Split-core 0.35T MRI

Three cobalt-sources

Double-focussed collimator
MRI-guided SABR (daily adaptive plans)

- MR-guided tumor setup
- Adaptive planning
- Online guidance
- Gated delivery (markerless)

High-risk lung SABR
For some central tumors, oligometastases, re-irradiation,
MRI-guided radiotherapy (central lung tumor)

4DCT scan (uncoached)  Continuous MR during treatment

MR-guided tumor setup  Adaptive planning  Online guidance  Gated delivery (markerless)
Treat without a tissue diagnosis?

- “pre-treatment pathological diagnosis strongly recommended before any curative treatment for early stage NSCLC, unless a multidisciplinary tumour board (MDT) is of the opinion that the risk-benefit ratio of the procedure is unacceptable.

- Expert MDT’s may be best placed to assess the likelihood of benign disease in their own populations including, where available, algorithms that have been validated for the population in question [Herder G, Chest 2005]. In case of the latter, a likelihood of malignancy exceeding 85% may be preferred”.

ESMO Early stage NSCLC: consensus on diagnosis, treatment and follow-up [Vansteenkiste J, Ann Oncol 2014].
Dutch publications showed a ≤6% risk of **benign diagnosis** in resected lesions


1555 clinical stage I NSCLC cases operated 2013-2014; **0.8%** had a final diagnosis of benign disease

[Dutch Lung Surgery Audit, Heineman ATS 2016]
• High prevalence of granulomatous disease and other infectious causes of pulmonary nodules

• Diagnosis risk calculators developed in non-Asian patients may not be applicable

• Tuberculosis in Asia favors (i) lesser reliance on PET scanning, and (ii) greater use of non-surgical biopsy over surgical diagnosis or surveillance

Bai C, Chest 2016
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Stage I NSCLC: Follow-up after curative treatments

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

- 1294 surgical cases from MSKCC
  [Lou F, JTCVS 2012]
Follow-up after SABR

• 6 monthly CT scans for 3 years [III, B].

• Follow-up patients who are suitable for salvage treatment (e.g. surgery, local ablative therapy) [III, B]

• Selective use of FDG–PET is recommended when recurrence is suspected [III, B]

• Due to false-positive findings on FDG–PET, patients suitable for salvage should undergo a biopsy, whenever possible [III, B]

ESMO recommendations (Vansteenkiste J, Ann Oncol 2014)
**Suspicious radiological changes**

<table>
<thead>
<tr>
<th>High-Risk Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enlarging</strong> Opacity</td>
</tr>
<tr>
<td>Sequential <strong>Enlargement</strong></td>
</tr>
<tr>
<td><strong>Enlargement</strong> after 12 months</td>
</tr>
<tr>
<td>Bulging Margin</td>
</tr>
<tr>
<td>Linear Margin Disappearance</td>
</tr>
<tr>
<td>Loss of Air Bronchogram</td>
</tr>
<tr>
<td>Cranio-Caudal Growth</td>
</tr>
</tbody>
</table>

Huang K, Radiother Oncol 2012, 2013
Craniocaudal growth

Craniocaudal enlargement of opacity, (> 5 mm and >20% RECIST criteria). Most fibrosis after SABR is expected in axial plane.

Ronden M, *manuscript in preparation*
Loss of linear margins

A previously straight margin to the fibrotic area is replaced by a convex surface

Ronden M, manuscript in preparation
Recurrences after SABR

- Surgical salvage feasible for local recurrences after SABR
Overview

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SABR outcomes in operable patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Patients</th>
<th>2y OS (%)</th>
<th>3y OS (%)</th>
<th>5y OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARS and ROSEL (4)</td>
<td>Randomized</td>
<td>58</td>
<td></td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>National Defense Medical College, Tokozawa, Japan, Single Institution</td>
<td>Retrospective</td>
<td>29</td>
<td></td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>VU University, Single Institution [2012]</td>
<td>Retrospective</td>
<td>177</td>
<td></td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>JCOG 0403 [2015] (44,45)</td>
<td>Prospective phase II</td>
<td>64</td>
<td></td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>RTOG 0618 [2013] (46)</td>
<td>Prospective phase II</td>
<td>26</td>
<td>84</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Japanese Multi-Institutional [2011]</td>
<td>Retrospective</td>
<td>87</td>
<td></td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>Japanese Multi-Institutional [2015]</td>
<td>Retrospective</td>
<td>661</td>
<td></td>
<td>80 (IA); 77 (IB)</td>
<td></td>
</tr>
</tbody>
</table>

SBRT, stereotactic body radiotherapy; OS, overall survival; RTOG, Radiation Therapy Oncology Group.

Moghanaki D & Chang JY, TLCR 2016
Surgery vs. SABR in operable patients

4 unsuccessful attempts at performing prospective randomized trials

ROSEL  NCT00687986
STARS  NCT00840749
ACOSOG-4099/RTOG1021  NCT01336894
Mayo Clinic  NCT01622621


Figure 2: Overall survival (A) and recurrence-free survival (B)
One patient died and five had recurrences in the SABR group compared with six and six patients, respectively, in the surgery group. SABR = stereotactic ablative radiotherapy; HR = hazard ratio.
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 Rueh et al² 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 al⁶ (Hopitaux de Marseille), Cheung et al⁶ (Florida State Registries), He et al⁷ (Guangzhou), Haasbeek et al⁸ (Netherlands Registry), St Julien et al⁹ (Veterans Affairs), Damhuis et al¹⁰ (Rotterdam Registry), Powell et al¹¹ (English Registry), Landreneau et al¹² (University of Pittsburgh), and Samson et al¹³ (National Cancer Database).

Rusthoven CG, JCO 2017
National Cohort Analysis, England: Surgical outcomes

• 15,738 NSCLC patients in England (2006-2010) after a curative surgical resection

• 32% had stage I disease

• Mortality risk after 90 days was 3%

Moller H, EJC 2016
The changing legal landscape

Hilary Term [2015] UKSC 11
On appeal from: [2013] CSIH 3; [2010] CSIH 104

JUDGMENT

Montgomery (Appellant) v Lanarkshire Health Board (Respondent) (Scotland)

BMJ 2016;355:i5840 doi: 10.1136/bmj.i5840 (Published 1 November 2016)

Trusts risk litigation payouts by not adopting full consent process, warns college

Clare Dyer

Instead of leaving it to the doctors to decide what risks the patient should be told about, the Supreme Court ruled that any risks that would be significant to a reasonable person in the position of that particular patient should be outlined and possible alternatives explored. Doctors will have to get to know their patients well enough to understand their lifestyle, views, and values.
Comparative effectiveness research

PubMed-indexed publications associated with US National Cancer Data Base

NCDB lacks data on specific patient comorbidities, functional status, or pulmonary function, which may play a role in selecting the operative approach [Abdelsattar ZM, ATS 2017]

Blanchard P, JCO 2015
Overall survival in stage I nsclc (Duke Uni)

Post-surgical OS stratified by predicted DLCO

972 patients (1996-2012)

Berry MF, ATS 2015
Lung cancer–specific and noncancer-specific 5-year cumulative incidence of death (CID) by age-group

5,371 consecutive patients (2000-2011)

Fig 2. Lung cancer–specific and noncancer-specific 5-year cumulative incidence of death (CID) by age-group. (A) Up to approximately 1.5 years after surgery, noncancer-specific CID was higher than lung cancer–specific CID. After 1.5 years, lung cancer–specific CID surpassed noncancer-specific CID (N = 2,186). (B) The higher noncancer-specific CID observed in the early postoperative phase increased in patients ≥ 75 years of age, in whom noncancer-specific mortality was higher than lung cancer–specific mortality until approximately 2.5 years postsurgery (n = 638). (C) In patients 65 to 74 years of age, the difference between curves was similar to that for the total cohort (n = 894). (D) In patients < 65 years of age, lung cancer–specific mortality was higher than noncancer-specific mortality during most of the postoperative period (n = 654).
### New randomised trials

<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>Eligibility criteria</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>Primary Endpoint</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>Secondary end-points</td>
<td>QoL, patterns of failure, cause of death</td>
<td>OS, DFS, site-specific failure, Time to LR failure and DM</td>
<td>PFS, failure patterns, toxicity, and 5-year overall survival</td>
<td></td>
</tr>
<tr>
<td>Planned accrual</td>
<td>670</td>
<td>76</td>
<td>54 (feasibility phase)</td>
<td>258</td>
</tr>
</tbody>
</table>

**Late toxicity, 2\textsuperscript{nd} tumors, overall survival**

**Data on early deaths, toxicity, QoL**
Thank you for listening