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

Professor Suresh Senan, VU University Medical Center
Disclosures

Research grants: Varian Medical Systems, ViewRay Inc.
Advisory boards – Eli Lilly, AstraZeneca, Merck
SABR is a technique for delivering external beam radiotherapy to an extra-cranial target
- with a high degree of accuracy
- using high doses of irradiation
- 1-8 treatment fractions

Outline of talk

- Eligible patients
- Toxicity in peripheral tumors
- Post-treatment follow-up
- Higher risk tumors [central, ILD]
Imaging and delivery of SABR (typical examples)

- 4-Dimensional CT scan
- Cone-beam CT scan
- Linear accelerator
- Volumetric Modulated Arc Therapy (FFF delivery in <4 mins)

Doses should be $\geq \text{BED}_{10} 100 \text{ Gy}$
[Vansteenkiste J, ESMO guidelines 2014]

ESTRO ACROP consensus guidelines on implementation and practice of stereotactic body radiotherapy for peripherally located early stage NSCLC [Guckenberger M, Radioth Oncol 2017]
‘Risk-adapted’ SABR fractionation schemes

- **3 fractions of 18 Gy**: T1 lesions, not adjacent to chest wall
- **5 fractions of 11 Gy**: Broad chest wall contact, T2 lesions
- **8 fractions of 7.5 Gy**: Central lung lesion

**Single-fraction SABR (prospective clinical trials)**
- RTOG 0915, Videtic GM, IJROBP 2015: **34 Gy**
- Multi-institutional, Singh A, IJROBP 2017: **30 Gy**
- Yamamoto N, JTO 2016: \(\geq 36\) Gy (RBE, carbon ions)
**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>MD Anderson Hospital&lt;sup&gt;1&lt;/sup&gt;</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>
<tr>
<td>VU University Med Center&lt;sup&gt;2&lt;/sup&gt;</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>
</tbody>
</table>

<sup>1</sup> Brooks E, IJROBP 2017 and update at ASCO (Abstr 8501)

<sup>2</sup> Senthi S, Lancet Oncol 2012
SABR toxicity in peripheral tumors

• No decrease in quality of life - systematic review of 9 studies \(^1\)

• Chest wall pain, grade 3, or higher in between 1-19% of patients \(^2\)

• Radiation pneumonitis rates in 504 SABR patients:\(^3\)
  • Grade $\geq$ 3 pneumonitis in 2% of patients without interstitial lung disease (ILD)
  • Grade $\geq$ 3 pneumonitis in 32% of patients with ILD
  • Grade 5 pneumonitis in 21% of patients with ILD

\(^1\) Chen H, Clin Lung Cancer 2016; \(^2\) Shaik T, Cancer Treat Rev 2014; \(^3\) Bahig H, Prac Radiat Oncol 2016
SPACE trial [Nyman J, Radioth Oncol 2016]
102 stage I patients randomized between 2007-201
Primary endpoint: progression free survival at 3 years

Local control similar: SABR - 86% vs conventional - 86%
SABR had superior HRQL evaluation (EORTC QLQ 30, LC14 modules): After 3DCRT, worse dyspnea ($p = 0.01$), chest pain ($p = 0.02$) and cough (>10 points difference) observed

CHISEL trial [Ball D, WCLC 2017]
101 stage I patients randomized between 2009-2015
Primary endpoint: time to local failure

With SABR,
SABR led to superior freedom from local failure ($HR = 0.29$, 95% CI 0.130, 0.662, $P=0.002$)
SABR resulted in longer overall survival ($HR = 0.51$, 95% CI 0.51, 0.911, $P=0.020$)
SABR: Challenges in practice

- Establishing a tumor diagnosis in less fit patients
- Response assessment and salvage therapies (multi-disciplinary)
- Higher-risk populations for SABR
- Lack of reliable organ at risk tolerance data
**Guidelines on treatment without pathology**

MDT = multi-disciplinary team

<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>

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

Intraoperative diagnosis (IOD) in Dutch Cancer registry [Verhaegen A, 2017]

IOD rates of 55%, 39% and 23% after segmentectomy, lobectomy and bilobectomy, respectively
IOD rates highest in small tumors (cT1A - 59%)
IOD rates varied between hospitals (15% - 65%)

Post-SABR radiological changes

Serial images in a patient without recurrence

High-Risk Features (HRF)

- Enlarging Opacity
- Sequential Enlargement
- Enlargement after 12 months
- Bulging Margin
- Linear Margin Disappearance
- Loss of Air Bronchogram
- Cranio-Caudal Growth

Ronden M, IJROBP 2017

Huang K, Radioth Oncol 2014
Post-SABR radiological changes

Figure 1: DIFFUSE CONSOLIDATION

0-6 MONTHS POST-SABR

A consolidation measuring more than 5 cm in largest dimension. The involved region contains more consolidation than aerated lung.1

Figure 4: DIFFUSE GROUND GLASS OPACITY

0-6 MONTHS POST-SABR

A diffuse GGO is defined as a GGO of more than 5 cm, without consolidation. The involved region contains more GGO than normal lung.1 The diffuse GGO was seen at a more caudal aspect of the radiation field.

Figure 6: MODIFIED CONVENTIONAL PATTERN OF FIBROSIS

> 6 MONTHS POST-SABR

Consolidation, volume loss, and bronchectasis similar to, but usually less extensive than, conventional radiation fibrosis. Larger than the original tumor size. Occasionally with associated GGO.1

Figure 10: AIR BRONCHOGRAPHS

Planning CT – 10/10/10/10 300kV 26 months post-SABR

Visible air filled bronchi (low-attenuation), due to opacification of surrounding alveoli (high-attenuation). The branching, linear lucencies appear when normally aerated pulmonary parenchyma is replaced by non-aerated tissue, either fluid or cellular material.1 2 3

Figure 9: SUBPLEURAL RADIATION FIBROSIS

Planning CT – 10/10/10/10 300kV 30 months post-SABR

VMAT plans typically attempt to reduce chest wall doses, leading to opacities parallel to the treated chest wall region.2

Figure 8: MASS-LIKE FIBROSIS

> 6 MONTHS POST-SABR

Mass-like fibrosis is defined as a well-circumscribed consolidation that is limited to the area of high-dose irradiation.2

Ronden M, Pictorial atlas. JTO 2018
International Delphi consensus [Ngyuen T, Pract Rad Oncol 2017]

Suspicious of a local recurrence are: infiltration into adjacent structures, sustained growth, bulging margins, spherical growth, mass-like growth, cranio-caudal growth and a loss of air bronchograms

FDG-PET/CT scans recommended only when there was suspicion for a local recurrence
Due to a high number of false-positive findings on PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible [III, B].

ESMO Clinical Practice Guidelines
Postmus PE, Ann Oncol 2017
Post-SABR surgical salvage appears safe

- 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
Stage I NSCLC: New primary tumors

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

1294 surgical cases from MSKCC [Lou F, JTCVS 2012]

SEER database [Thakur MK, JTO 2018]: Rate of SPLC development is 1.10% per patient per year, with median time intervals between the IPLC and SPLC diagnoses of 59 and 62 months.
Central and ‘ultracentral’ tumors

Moderately central tumors

SABR is relatively safe
ASTRO guidelines [Videtic GMM, Prac Rad Onc 2017]

Ultracentral tumors

Toxicity with high-dose radiation
[Haseltine JM, PRO 2016, Tekatli H, JTO 2016; Lindberg K, WCLC 2016]
195 central tumors (585 bronchial structures) treated using ≤12 fractions between 2006-2015, at 2 Dutch centers

Doses recalculated to an equivalent dose of 2Gy with an α/β ratio of 3

**Radiographic toxicity** defined as:
- Airway stenosis
- Occlusion without atelectasis
- Occlusion with atelectasis

Tekatli, H, IJROBP 2017
Images of a patient treated with 12 fractions of 5 Gy. CT scans 12.7 months later show stenosis of the left main bronchus PLUS occlusion with atelectasis of the left lower lobe bronchus.

Tekatli, H, IJROBP 2017
Radiographic bronchial toxicity in 28% of patients
Clinical ≥G3 toxicity in 12%

Predictors for ≥G3 toxicity on multivariate analyses
(i) Tumor volume (PTV) overlapping trachea / main stem bronchus (p=0.005)
(ii) COPD (p=0.034)
(iii) total $V_{130Gy,EQD}$ (p=0.012)

Tekatli, H, IJROBP 2017
- Moderately central tumors [G5 toxicity possible or likely in 7.5% of patients, Tekatli H, Radioth Oncol 2015]
- Interstitial lung disease [G5 toxicity in 15%, Chen H, IJROBP 2017]
- Re-irradiation [G3 or higher toxicity in 5-30%, De Bari B, Ca Treat Rev 2015]
- Paramediastinal tumors, and lesions close to left hemi-diaphragm
MRI-guided adaptive SABR for high-risk SABR
MRI-guided SABR during breath-hold
**ESMO Guidelines** [Vansteenkiste J, Ann Oncol 2014]:
Surgery should be offered to patients who are willing to accept procedure-related risks.
SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.

**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 European Society for Radiotherapy & Oncology (ESTRO) and the IASLC.
4 previous unsuccessful attempts at performing prospective randomized trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSEL</td>
<td>NCT00687986</td>
</tr>
<tr>
<td>STARS</td>
<td>NCT00840749</td>
</tr>
<tr>
<td>ACOSOG-4099/RTOG1021</td>
<td>NCT01336894</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>NCT01622621</td>
</tr>
</tbody>
</table>
Local treatment for peripheral lung tumors

Table 1: 5-year survival rates after SABR in operable patients of 51-74%
Non-randomized comparisons of surgery vs SABR

National Cancer Database (NCDB): overall survival for stage IA NSCLC wedge resection vs SABR

Yerokun BA, JTCVS 2017
National Cancer Database does not capture data on pulmonary function, cardiac function, performance status. Data on cancer-specific or disease-free survival is unavailable [Rosen JE, Ann Thorac Surg 2014]

Post-surgical OS in 972 stage I patients operated at Duke Univ, stratified by predicted DLCO [Berry MF, ATS 2015]

Population study on COPD outcomes. [Lange P, AJRCCM 2012]
In the absence of completed clinical trials, propensity score studies have attempted to mimic clinical trials using non-randomized data.

We identified 16 studies comparing SABR and surgery

- In patients eligible for either treatment, better overall survivals were seen after surgery compared to SABR
- Similar lung cancer-specific survival for both treatments
- Propensity score-matching caliper distance and first author specialty were associated with survival endpoints on regression

Conclusions: Prospective clinical trials are preferred to propensity analyses in evaluating the nature of non-cancer related mortality post-SABR
Requirements of new studies in early-stage NSCLC

• Cause-specific outcome analysis
• Morbidity and mortality analysis for at least 1 year post-treatment
• Subgroup analysis for age, Charlson comorbidity index, and histologic subtypes
• Long-term pulmonary and cardiac function

Only such data can justify the rationalization to choose optimal curative-intent therapy for patients with stage I NSCLC.

T Eguchi, JCO 2017
Role of shared decision making (SDM)

SDM is a process in which patients and physicians discuss the current evidence on different treatment options and mutually arrive at a clinical management plan [Stacey D, CA Cancer J Clin 2008]

Dutch SDM website

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

UK Supreme Court ruling in 2015
Developments in the United Kingdom

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

Material risks for each option should be discussed with the patient. The test of materiality is twofold: whether, in the circumstances of the particular case, a reasonable person in the patient’s position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would likely attach significance to it.
Early-stage lung cancer: A preference sensitive disease?

**ESMO Guidelines** [Vansteenkiste J, Ann Oncol 2014]:

SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.

Preference-sensitive care describes a situation where the evidence for the superiority of one treatment over another is not available; there are therefore two or more valid approaches to care and the best choice depends on how a patient values the risks and benefits of the treatments available.


**Readmission rates**
- US - Stiles BM, ATS 2016

**90-day mortality after surgery and SABR**
- NCDB – Stokes WA, JCO 2018

**6 month mortality after adjuvant chemotherapy**
- NCDB - Morgensztern D, JTO 2018

**Survival from competing causes of death**
- Eguchi T, JCO 2017
- Soneji S, Chest 2017
90-day mortality for early-stage NSCLC (NCDB)

90-day mortality in Europe

- **English, lobectomy**
  - 70-80 years PS 0: 4%
  - 70-80 years PS 1: 6%

- **Dutch, lobectomy**
  - 70-79 years: 4.4%

---

**Surgery**
- n = 76,623

**SBRT**
- n = 8,216

Stokes WA, JCO 2018

---

1 O'Dowd EL, Lung Cancer 2016
2 iknl.nl
Trends in early-stage NSCLC [Netherlands]

Netherlands Cancer Registry (n = 21,032 patients) [Louie AV, Lung Cancer 2016]

<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>

71% of all lung cancer resections are performed by VATS [Detillon DE, ATS 2017]

49% of Dutch pulmonary physicians consider surgery and SABR to be equal treatment options [Hopmans W, Radioth Oncol 2015]
SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it [ESMO Guidelines 2017]

Early-stage lung cancer is a preference-sensitive disease

Growing data on SABR outcomes in patients fit to undergo surgery [Weder W, EJCTS 2018]. Results of prospective, randomized clinical trials are awaited

SABR-related toxicity is higher in patients who have centrally located tumors, and those with pre-existing interstitial lung disease
Thank you for your attention
Re-admission after surgery and discharge status

  - 20% and 45% were re-admitted as in-patients within 30 and 90 days, respectively

- State Inpatient Databases (Healthcare Cost and Utilization Project); all lobectomies from 2009 to 2011 in California, Florida, and New York [[Moller H, Eur J Cancer 2016]]
  - OL = open lobectomy; MIL = minimally invasive lobectomy

- 22,647 lobectomies identified (58.8% OL vs 41.2% MIL; median age, 68 years; median length of stay, 6 days)

- Most patients (59.8%) had routine discharge home
  - Other home health care, 29.4%; transfer to other facility, 8.8%; mortality, 1.9%
  - 90-day readmission rate was 19.8% (OL 21.1% vs MIL 17.9%, p < 0.001)
In patients $\geq 65$ years of age, noncancer-specific CID was higher than lung cancer-specific CID for up to 2.5 years after resection.

Higher noncancer-specific, early-phase mortality was enhanced in patients $\geq 75$ years of age than in those 65-74 years of age.

**Multivariable analysis**: the predicted postoperative (ppo) diffusing capacity of the lung for carbon monoxide a significant predictor of 1 year mortality, and noncancer specific deaths.
**NCDB: Surgical nodal sampling**

Treatment of stage I non–small cell lung cancer: What’s trending?

Timothy L. McMurry, PhD, a Puja M. Shah, MD, MS, b Pamela Samson, MD, MPH, c

<table>
<thead>
<tr>
<th>Year</th>
<th>Lobectomy</th>
<th>Sublobar resection</th>
<th>Pneumonectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>5 (3-9)</td>
<td>0 (0-2)</td>
<td>8 (5-14)</td>
</tr>
<tr>
<td>1999</td>
<td>6 (3-10)</td>
<td>0 (0-3)</td>
<td>9 (5-15)</td>
</tr>
<tr>
<td>2000</td>
<td>6 (3-10)</td>
<td>0 (0-3)</td>
<td>8 (5-13)</td>
</tr>
<tr>
<td>2001</td>
<td>6 (3-10)</td>
<td>0 (0-3)</td>
<td>10 (6-14)</td>
</tr>
<tr>
<td>2002</td>
<td>6 (3-10)</td>
<td>0 (0-3)</td>
<td>9 (6-15)</td>
</tr>
<tr>
<td>2003</td>
<td>6 (3-10)</td>
<td>1 (0-3)</td>
<td>9 (5-15)</td>
</tr>
<tr>
<td>2004</td>
<td>6 (3-10)</td>
<td>1 (0-3)</td>
<td>10 (6-15)</td>
</tr>
<tr>
<td>2005</td>
<td>7 (4-11)</td>
<td>1 (0-4)</td>
<td>10 (6-15)</td>
</tr>
<tr>
<td>2006</td>
<td>7 (4-11)</td>
<td>1 (0-4)</td>
<td>10 (6-15)</td>
</tr>
<tr>
<td>2007</td>
<td>7 (4-11)</td>
<td>1 (0-4)</td>
<td>10 (6-15)</td>
</tr>
<tr>
<td>2008</td>
<td>7 (4-11)</td>
<td>1 (0-4)</td>
<td>12 (7-17)</td>
</tr>
<tr>
<td>2009</td>
<td>7 (4-12)</td>
<td>1 (0-4)</td>
<td>11 (7-17)</td>
</tr>
<tr>
<td>2010</td>
<td>7 (4-12)</td>
<td>1 (0-4)</td>
<td>12 (7-17)</td>
</tr>
<tr>
<td>2011</td>
<td>8 (4-12)</td>
<td>1 (0-4)</td>
<td>11 (6-17)</td>
</tr>
<tr>
<td>2012</td>
<td>8 (5-12)</td>
<td>2 (0-5)</td>
<td>11 (8-17)</td>
</tr>
</tbody>
</table>

*P value <.001 <.001 <.001*
NCDB analysis of mortality within 6 months in 19,398 patients with Stage IB to IIIA NSCLC (2004-2012), and who received multiagent adjuvant chemotherapy starting within 120 days from resection with negative surgical margins.
Trust must pay £4.4m for failure to warn about risks of spinal surgery

BMJ 2018; 360 doi: https://doi.org/10.1136/bmj.k628 (Published 08 February 2018)
Cite this as: BMJ  2018;360:k628

Clare Dyer

Author affiliations

An NHS trust will have to pay £4.4m (£5m; $6.1m) in damages to a patient left permanently disabled by a spinal disc operation because the surgeon failed to explain the risk of spinal cord damage, even though he performed the operation competently.

A High Court judge has ruled that the patient would not have gone ahead with the operation if the risks had been properly explained and therefore that Hillingdon Hospitals NHS Foundation Trust must compensate her.¹

Tracy Hassell was a 41 year old mother of three and head of year at a secondary school in October 2011 when she underwent a C5/6 decompression and disc replacement operation, performed by Shaun Ridgeway, a consultant spinal orthopaedic surgeon at Hillingdon Hospital in north London. Her spinal cord injury has left her with tetraparesis, weakness in all four limbs.

To obtain the informed consent needed before an operation, doctors are under a duty to take reasonable care to ensure that patients are aware of any material risks and any reasonable alternative treatment.
<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>VALOR (USA)</th>
<th>POSTILV (China)</th>
<th>SABRTooth (UK)</th>
<th>STABLE-MATES (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor ≤5cm (peripheral and central)</td>
<td>Tumor ≤3 cm, fit for lobectomy or pneumonectomy</td>
<td>High-risk operable, peripheral tumors ≤5cm, patients pre-randomized</td>
<td></td>
<td></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>