Stereotactic ablative RT (SABR) for early stage NSCLC

Suresh Senan, Department of Radiation Oncology
Amsterdam University Medical Center
Disclosures

• **Departmental research grants:** Varian Medical Systems, AstraZeneca, ViewRay

• **Advisory boards:** AstraZeneca, Celgene, Varian Medical Systems, Merck
Stereotactic radiotherapy (SABR, SBRT)

A technique for delivering high-dose radiotherapy, with high precision, to an extra-cranial target

SABR is a guideline-recommended treatment for medically inoperable stage I NSCLC, and in patients who decline surgery

ESMO guidelines 2013; NCCN Guidelines [ver 7.2015]; Canadian CEPO guidelines [JTO 2015]; ASTRO guidelines [PRO 2017]; ESTRO guidelines [Radioth Oncol 2017]
Outline of talk

• Recommendations for setting up a SABR program (ESTRO-ACROP)

• Tumor control rates and toxicity

• Follow-up

• SABR in operable patients

• New techniques for high-risk cases, including central tumors and ILD patients
Route map for SABR

Multi-disciplinary tumor board
Establish diagnosis in accordance with guidelines

Linear accelerator
4-Dimensional CT scan
Cone-beam CT scan

Imaging before
Daily imaging on couch

ESTRO-ACROP guidelines, Guckenberger M, Radioth Oncol 2017
**ESTRO-ACROP guidelines**

- Equipment
- Staff training, credentialing
- Patient selection
- Treatment planning
- Dose-fractionation
- Image guidance
- Follow-up
- Quality assurance

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**Overview of all mandatory and recommended workflow and equipment of SBRT for early stage NSCLC (>90% agreement).**

<table>
<thead>
<tr>
<th>SBRT workflow or equipment items</th>
<th>MANDATORY (minimum) requirements</th>
<th>Recommended for best practice</th>
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</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>C-arm linear accelerator with volumetric in-room image guidance</td>
<td>Dedicated C-arm stereotactic linear accelerator (more advanced IGRT, more precise accuracy) High-resolution MLC &lt;10 mm</td>
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<tr>
<td></td>
<td>Respiration correlated 4D-CT</td>
<td>Participation in dedicated SBRT teaching course (e.g. ESTRO) Participation in Vendor-organized dedicated SBRT training Hands-on training at SBRT-experienced center Supervision of first SBRT treatments by SBRT-experienced colleague</td>
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<tr>
<td>Staff training, training and credentialing</td>
<td>Written departmental protocols Multi-disciplinary project team for SBRT implementation and application Structured follow-up for clinical outcome assessment</td>
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<tr>
<td></td>
<td>Biopsy confirmation of malignancy</td>
<td></td>
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<tr>
<td>Patient selection for SBRT</td>
<td>Discussion in interdisciplinary tumor board Minimum ECOG 3 Minimum life expectancy of 1 year</td>
<td>Dynamic IMRT planning (VMAT) Use of a fixed dose inhomogeneity in PTV</td>
</tr>
<tr>
<td></td>
<td>Risk adapted fractionation schemes for peripheral and central tumors, and for tumors with broad chest wall contact</td>
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<tr>
<td>Treatment planning</td>
<td>Daily pre-treatment volumetric image-guidance</td>
<td>Daily pre-treatment 4D volumetric image-guidance (in-room 4D-CT, 4D-CBCT) Routine biopsy confirmation of imaging-defined local failure only in patients who are likely to undergo salvage therapy</td>
</tr>
<tr>
<td>Dose and fractionation</td>
<td>Risk adapted fractionation schemes for peripheral and central tumors, and for tumors with broad chest wall contact</td>
<td>End-to-end testing in a moving 4D lung phantom</td>
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<tr>
<td>Inter- and intra-fraction image guidance</td>
<td>Daily pre-treatment volumetric image-guidance</td>
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<tr>
<td>Follow-up</td>
<td>Follow-up according to published guidelines</td>
<td></td>
</tr>
<tr>
<td>Quality assurance</td>
<td>Intensified quality assurance (mechanical accuracy of 1.25 mm and a dosimetric accuracy of 3% in a lung phantom inside the treatment field) Small field dosimetry detectors for commissioning End-to-end testing in a lung phantom Quality assurance of in-room image-guidance systems and of the 4D-CT scanner Weekly checks of the mechanical accuracy of the delivery system Daily quality checks of the alignment of the IGRT system with the MV treatment beam</td>
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</table>
SABR delivery schemes
‘Risk-adapted’ schedules

- **3 fractions of 18 Gy**: T1 lesions, away from chest wall
- **Single fraction of 30-34 Gy**
- **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

Doses refer to volumetric dose prescriptions to PTV
All schemes deliver biological doses ($\text{BED}_{10}$) >100 Gy

Hurkmans C, Rad Onc 2009; Yamamoto N, JTO 2016; Singh A, IJROBP 2017; RTOG 0915 - Videtic G IJROBP 2018
SABR versus conventional radiotherapy (RT) in NSCLC

National Cancer Database (2004-15)
Histologically-confirmed cT1-2aN0M0

SABR in 90% (20,802), conventional (CFRT) in 10% (2286)

Median overall survival (OS) was 38.8 months for SABR group versus 28.1 months for CFRT (p < 0.001)

Findings persist after propensity matching

Haque W, Radioth Oncol 2018
SABR vs. conventional RT
(CHISEL trial, pathology-proven)

Progression-free survival HR 0.32 (95% CI 0.13-0.77)

Overall survival, HR 0.53 (95% CI 0.30-0.94)

Ball D, Lancet Oncol 2019
**ESMO Guidelines [Vansteenkiste J, Ann Oncol 2014]**

A pre-treatment pathological diagnosis strongly recommended, unless a multidisciplinary tumour board (MDT) is of the opinion that the risk-benefit ratio of the procedure is unacceptable.

**ASTRO Guidelines [Videtic GMM, PRO 2017]**

SABR can be delivered in patients who refuse a biopsy, have a non-diagnostic biopsy, or who are thought to be at prohibitive risk of biopsy. Patients are recommended to be discussed in a multidisciplinary manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lesion based on tumor, patient, and environmental factors.

**Asian clinical practice consensus [Bai C, Chest 2016]**

Incidence of tuberculosis in Asia favors (i) a lesser reliance on PET scanning, and (ii) greater use of non-surgical biopsy over surgical diagnosis or surveillance.
Pathological diagnosis

All Dutch patients are presented at multidisciplinary tumor boards.

Dutch Lung Surgery Audit (2013-2014) of 1555 patients with clinical stage I NSCLC: a final post-operative diagnosis of benign disease was made in 0.8%\textsuperscript{1}

Netherlands Cancer Registry\textsuperscript{2}

<table>
<thead>
<tr>
<th>Pre-treatment pathology</th>
<th>cT1a</th>
<th>cT1b</th>
<th>cT2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>39%</td>
<td>56%</td>
<td>69%</td>
</tr>
<tr>
<td>Surgery</td>
<td>41%</td>
<td>57%</td>
<td>69%</td>
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\textsuperscript{1}Heineman D, \textsuperscript{2}Damhuis RAM, \textit{manuscript submitted}
### Post-SABR recurrences

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

2. Brooks E, IJROBP 2017, and updated at ASCO 2017 (Abstr 8501)
SABR related toxicity

- Chest wall pain (CWP) in 11.0% (95% CI, 8.0-14.4); fractures in 6.3% (95% CI, 3.7-9.7). Grade 3 CWP in 6.2% (95% CI, 3.88-8.93) ¹

- Pulmonary toxicity: Uncommon, except in preexisting interstitial lung disease ²

- Quality of life is maintained: Systematic review of 9 prospective studies ³

- Mortality rates from National Cancer Database: 0.7% at 30 days and 2.9% at 90 days ⁴

- Dutch cancer registry: For a ‘no-treatment group’, the 90-day mortality rate measured from date of diagnosis was 33.3% [Haasbeek CJ, Ann Oncol 2012]

¹ Ma J-T IJROBP 2019; ² Chen H, Int J Rad Onc Biol Phys 2017; ³ Chen H, Clin Lung Cancer 2016; ⁴ Stokes WA, JCO 2018
Chest-wall pain (CWP) and fracture developing 2 years after SABR, with pain resolving 3 months later

**Meta-analysis, 57 studies [Ma J-T, IJROBP 2019]**

Risk factors for CWP: sex, tumor to CW distance, maximum dose and dose to CW or ribs

Median time to onset of CWP was 9 months (range 6-30 months)

Median time to diagnosis of fracture was 20.6 months (range, 10.8-24 months)
Interstitial lung disease

- Chen H, IJROBP 2017, systematic review
  - SABR-related Grade 5 RP in 16% when co-existing ILD

- Bahig H, Prac Rad Oncol 2016
  - 504 SABR patients (6% preexisting ILD)
  - Grade ≥ 3 radiation pneumonitis (RP) in 2% of patients without ILD
  - Grade 5 RP in 21% of patients with ILD
ILD case: Grade 5 toxicity

Pre-treatment chest CT image

At 1 month follow-up
ILD workflow at Amsterdam UMC

Interstitial changes noted on chest CT scan ➔ Refer to ILD clinic ➔ ILD diagnosis and risk assessment ➔ SABR delivery ➔ SABR risk assessment and planning ➔ Follow-up at lung and ILD clinics

Figure 1. Estimated Relative Distribution of Specific Interstitial Lung Diseases (ILDs) in the United States.

Ronden M, submitted

Lederer DJ, NEJM 2018
Central lung tumors

Figure from RTOG0813 study protocol

**Moderately central** refers to tumors located within 2 cm of the proximal bronchial tree zone (black dotted line)

**Ultracentral lung** tumors defined as tumors with a planning target volume overlapping the trachea/main stem bronchi (red zone)

The nomenclature used for central tumors is less relevant than the true radiation tolerance doses of the proximal airways, heart, and esophagus

Tekatli H, Lung Cancer 2018
SABR - Bronchial stenosis in an ‘ultracentral tumor’

Right panel: Corresponding CT slices at 13 months. Stenosis of left upper lobe bronchus & atelectasis of lower lobe bronchus.

Tekatli H, J Thorac Oncol 2017
**SBRT: Higher risk patients**

Multiple primary lung cancers (MPLCs) can be difficult to differentiate from intrathoracic metastatic lung cancer and pose unique issues for parenchymal preservation; therefore, it is recommended that they are evaluated by a multidisciplinary team.

**Recommendation strength:** Strong  
**Quality of evidence:** Moderate  
**Consensus:** 100%

**Conditional recommendations** made when the balance between risks and benefits was more even or was uncertain.

In these cases, the task force believed “most informed people would choose the recommended course of action, but a substantial number would not”

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**ASTRO guidelines**  
(endorsed by ESTRO)

SBRT is an appropriate option for tumors >5 cm in diameter with an acceptable therapeutic ratio. Adherence to volumetric and maximum dose constraints may optimize the safety profile of this treatment.

**Recommendation strength:** Conditional  
**Quality of evidence:** Low  
**Consensus:** 89%

SBRT may be utilized in patients with cT3 disease due to chest wall invasion without clear evidence of reduced efficacy or increased toxicity compared to tumors abutting the chest wall.

**Recommendation strength:** Conditional  
**Quality of evidence:** Low  
**Consensus:** 88%

Videtic G, Prac Rad Oncol 2017
Radiological follow-up

• Surveillance 6 monthly for 2 years with preferably contrast-enhanced chest CT scan at least at 12 and 24 months recommended.

• Thereafter, an annual visit including history, physical examination and chest CT scan in order to detect second primary tumours [III, B]

• Due to a high number of false-positive findings on PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible [III, B]
Post-SABR fibrosis

88 patients without a local recurrence; 747 CT scans collected for ≥2 years post-SABR; none had a local recurrences; scoring by clinicians blinded to outcomes

High-risk radiological features scored by ≥3 clinicians on ≥1 follow-up scan: Enlarging opacity (64.8%), enlarging opacity after 12 months (50.0%), sequential enlargement (13.6%)
SABR: Radiological follow-up
High-risk radiological features (HRF’s)

Enlarging opacity

Cranio-caudal growth

Loss of air bronchograms

Bulging margins

Loss of linear margins

Ronden M, J Thoracic Oncol 2018
SABR: Follow-up

*High-risk CT features (HRF)

- Absence of HRF’s*
  - No recurrence
  - Continue regular CT follow-up

- Presence of 1 HRF*
  - Consider CT with shorter time FU
  - No changes
  - Continue regular CT follow-up

- Presence of > 2 HRF’s*
  - Discussion in multi-disciplinary team
  - High suspicion of recurrence
    - FDG-PET and biopsy
  - Low suspicion of recurrence
    - Continue regular CT follow-up

Ronden M, WCLC 2017
Post-SABR radiology: Awareness in radiology journals

Diagnostic and Interventional Imaging (2016) 97, 1037–1052

CONTINUING EDUCATION PROGRAM: FOCUS...

Imaging after radiation therapy of thoracic tumors

B. Ghaye, M. Wanet, M. El Hajjam

Stereotactic Body Radiation Therapy for Early-Stage Non–Small Cell Lung Cancer: A Primer for Radiologists

Jennifer A. Febbo, MD
Rana S. Gaddhuri, MD
Pam N. Shah, MD

The past 2 decades have seen a rapid growth in use of stereotactic body radiation therapy (SBRT) for the management of non–small cell lung cancer (NSCLC). Not only is SBRT the reference standard for treatment of early-stage node-negative NSCLC in medically inoperable patients, it is also currently challenging the role of surgery for early-stage operable disease. SBRT is also used to treat recurrent disease and has a role in the management of multiple synchronous lung cancers. Imaging changes after SBRT differ from...
Recurrences / second tumors

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

- 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

Patients undergoing a salvage therapy for an isolated local recurrence had a survival similar to those who did not experience a post-SABR recurrence  [Brooks ED, JAMA Network Open 2018]
The great debate flashes: Surgery versus stereotactic body radiotherapy as the primary treatment of early-stage lung cancer

Walter Weder a, Drew Moghanaki b, Brendon Stiles c, Shankar Siva d and Gaetano Rocco e,*
No completed randomized trials of surgery vs SABR

- Meta-analysis of propensity score studies in early-stage NSCLC

- In patients equally likely to receive surgery or SABR, lung cancer-specific mortality was similar, regardless of extent of surgery. However, all-cause mortality was higher for SABR compared with surgery

- In studies, survival endpoints were associated with the (i) propensity score-matching caliper distance and (ii) first-author specialty
Post-SABR survival: Impact of patient selection

Amsterdam Prognostic Model for SABR

Patient classes based on tumor diameter, age, WHO performance status and Charlson comorbidity index

Kann BH, Radioth Oncol 2019

SABR patients at 107 US community centers

Louie AV, IJROBP 2015
A patient’s right to be informed

Consent: Supported Decision-Making

A GUIDE TO GOOD PRACTICE

Common Law

Montgomery (Appellant) v Lanarkshire Health Board (Respondent) [2015] UKSC 11

The Supreme Court held that there was a duty for a doctor to warn a patient of a material risk inherent in the treatment and that there was a duty for the doctor to discuss this with the patient. The test for materiality was whether a reasonable person in the position of this particular patient would think the risk significant. In the claimant’s case it was found that

Doctors should not cherry pick what information to give patients, court rules

BMJ 2015; 350: h1414 doi:http://dx.doi.org/10.1136/bmj.h1414 (Published 13 March 2015)
Cite this as: BMJ 2015;350:h1414
Shared decision making

Data from England

National Cohort analysis 2016-2010
[Moller H, Eur J Cancer 2016]
Patterns of care: Clinical stage I NSCLC (jan 2015-Dec 2016)

Norway

Netherlands

England

Damhuis RAM, submitted
For the no-treatment group, the 90-day mortality rate measured from date of diagnosis was 33.3%.

For the radiotherapy group, the 90-day mortality rate measured from date of diagnosis was 3.3%.
Outline of talk

- Recommendations for setting up a SABR program (ESTRO-ACROP)
- Tumor control rates and toxicity
- Follow-up
- SABR in operable patients
- New techniques for high-risk cases, including central tumors and ILD patients
High-risk SABR cases

- Moderately central tumors [G5 toxicity in 7.5%, Tekatli H, Radioth Oncol 2015]
- Interstitial lung disease [G5 toxicity in 15%, Chen H, IJROBP 2017]
- Re-irradiation with SABR [≥G3 toxicity in 5-30%, DeBari B, Ca Treat Rev 2015]
- Tumors adjacent to heart / left hemi-diaphragm
- SABR and new drugs, immune checkpoint inhibitors
Hybrid MR-guided radiotherapy

Tekatli H, Lung Cancer 2018; Sornsen de Koste JR, IJROBP 2018; Finazzi T, ESTRO 2019
Unlike conventional SABR, patients can continuously visualize the tumor volume during treatment. SABR plans can also be adapted on-table each day.

Tekatli H, Lung Cancer 2018; Sornsen de Koste JR, IJROBP 2018; Finazzi T, ESTRO 2019
Conclusions

- SABR is superior to conventional radiotherapy for early-stage lung tumors
  Progression-free survival HR 0.32 (95% CI 0.13-0.77); overall survival, HR 0.53 (95% CI 0.30-0.94)

- In higher-risk patients (e.g. central tumors), newer techniques such as MR-guided SABR offer promise

- Areas of active research include the role of immune checkpoint blockade and more reliable estimates of organ at risk tolerance doses