Stereotactic Ablative Radiotherapy (SABR) for central lung tumors
• The Department of Radiation Oncology at VUMC has a research agreement with Varian Medical Systems.

• S Senan has received speakers honoraria from Varian Medical Systems.
SABR for stage I NSCLC (at VUMC)

SABR is image guided ablative radiotherapy delivered in 3-8 sessions

- 4-D imaging
- CT scan on treatment couch
- Delivery in <4 mins (Ong CL, 2012)

Dutch guidelines & quality assurance

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<thead>
<tr>
<th>Dutch guidelines &amp; quality assurance</th>
<th>References</th>
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<tbody>
<tr>
<td>ROSEL recommendations</td>
<td>Hurkmans C, Rad Oncol 2009</td>
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<td>EORTC recommendations</td>
<td>De Ruysscher D, JCO 2010</td>
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<tr>
<td>QA for 4DCT imaging</td>
<td>Hurkmans C, IJROBP 2011</td>
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<td>SABR Dosimetric audit</td>
<td>Cuijpers J, Proc ESTRO 2012</td>
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</table>
Generalizability of outcomes in populations

Dutch Cancer Registry data on 4605 patients aged ≥75 years

Haasbeek C, 2012

- SABR can be rapidly implemented at a national level
- Survival gains of 9.3 months attained in the unfit elderly
- No declines in quality of life after SABR \((\text{van der Voort van Zyp NC, 2010; Widder J, 2011; Lagerwaard F, 2012})\)
SABR in peripheral lung tumors

- Standard of care for unfit patients with peripheral lung tumors in Japan and The Netherlands


- NHS ‘radiotherapy implementation report’ 2011: *available to all* ..... *with early lung cancer and contraindications to surgery*

Three propensity score-matched analyses report similar loco-regional control following surgery and SABR, and also similar overall survivals [Robinson CG, JTO 2012; Verstegen N, Ann Oncol 2013; Varlatto J, Cancer 2013].
Overview of talk

• SABR use for central tumors is less widespread

• A systematic review of literature supports use of ‘risk-adapted’ SABR fractionation schemes

• Prospective studies are ongoing; new data on lung dose constraints; endoscopic nodal staging
SABR for central tumours

Timmerman R, JCO 2006
Used SABR dose of 60/66 Gy, delivered in three fractions

“Scheme should not be used for tumors near the central airways due to excessive toxicity”.
Dutch ‘risk-adapted’ SABR delivery

- T1 tumors (≤ 3 cm), without extensive contact with thoracic wall or mediastinum
  - 3 fractions x 18 Gy in 1 week

- Tumors adjacent to pericardium or hilus
  - 8 fractions x 7.5 Gy in 3 weeks

Doses prescribed acc. to ROSEL protocol: 95% prescription isodose to encompass PTV; 99% of PTV to receive a minimum of 90% of prescription dose.

Lagerwaard F, 2008; Hurkmans C, 2009
Risk-adapted SABR can be safe

Central tumors: 8 fractions of 7.5 Gy to the encompassing isodose

N = 63 patients

Median follow-up: 35 months
Median survival: 47 months

3-year local control: 92.6%
3-year overall survival: 64.3%

Haasbeek CJ, JTO 2011
Systematic review of SABR for central tumors

20 publications: 563 central lung tumours (315 were early-stage NSCLC)

Local control rates $\geq 85\%$ when prescribed dose ($\text{BED}_{10}$) was $\geq 100\text{ Gy}$.

Treatment-related mortality 2.7% overall versus 1.0% when normal tissue dose ($\text{BED}_3$) was $\leq 210\text{ Gy}$.

Grades 3-4 toxicities appear commoner following SABR for central tumours, but occurred in less than 9% of patients.

Senthi S, Radioth Oncol 2013
Risk adapted SABR schemes

• Fractionation schedules which may, or may closely, achieve a $\text{BED}_{10} \geq 100$ Gy and $\text{BED}_3 \leq 210$ Gy:
  
  – 50 Gy in 5 fractions
  – 54 Gy in 6 fractions
  – 56 Gy in 7 fractions
  – 60 Gy in 8 fractions

Prospective RTOG dose-escalation study evaluating a 5-fraction SABR scheme [RTOG 0813]

Senthi S, Radioth Oncol 2013
79 consecutive patients treated with either a PTV >100 cm$^3$ (n=69) or a prior pneumonectomy or bi-lobectomy (n=13).
Case report

Male, 78 yrs, diabetes, extensive cardiovascular history
T2N0M0 NSCLC, squamous cell carcinoma
• FDG positive tumor in left pulmonary hilum
• Bronchoscopy induration of upper / lower lobe carina

Tumor board:
1. Unfit to undergo a pneumonectomy
2. Referred for SABR to central lesion

Senthi S, *manuscript in preparation*
Case report

60Gy in 8 fractions

planningCT

3 months

6 months

12 months

Senthí S, *manuscript in preparation*
Case report

At 12 months, patient developed shortness of breath

Bronchoscopy: stenosis with scarring

Pathology: 8 biopsies showed no malignancy
Cytology of pleural fluid: no malignancy
No FDG-PET uptake: local or distant

Repeat FDG-PET at 24 months: no recurrence
Performance score: WHO 2

Senthi S, *manuscript in preparation*
Surgery for early-stage NSCLC

270 patients; median age: 62
72% had ECOG performance score 0

Chemotherapy for Early Stage Trial (CHEST)
• Phase III study – only 1 patient with N2 disease
• Randomized to either 3 cycles of chemotherapy followed by surgery, or surgery alone

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<tr>
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<th>Chemo + Surgery</th>
<th>Surgery</th>
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<tbody>
<tr>
<td>Perioperative mortality rate</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Complete resection rates</td>
<td>88%</td>
<td>84%</td>
</tr>
<tr>
<td>Failure at primary site</td>
<td>9.3%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Lymph node relapses</td>
<td>13.2%</td>
<td>6.4%</td>
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<tr>
<td><strong>Pneumonectomy</strong></td>
<td>17%</td>
<td>25%</td>
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</tbody>
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Scagliotti G, JCO 2012
Late radiological changes post-SBRT

Dahele M, JTO 2011
Fibrosis or recurrence after SABR?

Systematic review of literature on recurrences

**High-risk features (HRF):**

- enlargement of mass
- sequential enlargement on CT
- growing mass after 12 months
- bulging margin
- linear margin disappears
- air bronchograms disappear

Huang K, Radioth Oncol 2012
Fibrosis or recurrence after SABR?

Blinded scoring of 12 path. +ve recurrences matched with 24 non-recurrrences

A. No Recurrence

<table>
<thead>
<tr>
<th>Pre-SABR</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
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HRF: Enlarging Opacity

B. Recurrence

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<tr>
<th>Pre-SABR</th>
<th>6 months</th>
<th>12 months</th>
<th>21 months</th>
<th>21.5 months</th>
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HRFs: Enlarging Opacity
Craniocaudal Growth
Sequential Enlargement
Enlargement after 12 months
Linear Margin Disappearance
Bulging Margin
Loss of Air Bronchogram

Huang K, Senth S, submitted
• New HRF identified: cranio-caudal growth ($p<0.001$)

• All HRF’s associated with local recurrence ($p<0.01$). **Best individual predictor** of local recurrence was opacity enlargement after 12-months (100% sensitivity, 83% specificity, $p<0.001$)

• Odds of recurrence increased 4-fold for each additional HRF detected.

• Presence of $\geq 3$ HRFs highly sensitive and specific for recurrence (both $>90\%$).

Huang K, Senth S, submitted
Fibrosis or recurrence after SABR?

Huang K, Senth S, submitted
Routine EBUS-EUS staging

Any centrally located lung lesion

Any FDG cold lung lesion

Tournoy KG, Lancet Oncol 2012
Routine endoscopic nodal staging?

- ClinicalTrials.gov Identifier: NCT01786590, PI: K Yasufuku
- Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Lymph Node Staging in Patients With NSCLC Pursuing SBRT

- STAGE trial (in preparation) PI: JT Annema, S Senan
- STereotactic Ablative radiotherapy for lung cancer after staGING with Endosonography
Lung SABR paradigm (at VUMC)

Endobronchial treatment (if appropriate)

Hypofractionated radiotherapy (25x)

Patient refusal

Surgery ± chemo

Chemoradiation

Patient refusal

SABR: risk-adapted schemes

Senan S, unpublished
Conclusions

• SABR is an acceptable treatment option for patients with central tumors, who are ineligible for conventional radiotherapy or chemo-radiotherapy.

• Toxicity risks are higher with larger tumors, and a high contralateral mean lung dose.

• Other ‘risk adapted’ SABR schemes may be derived from ongoing prospective studies.