Stereotactic ablative radiotherapy in early NSCLC and metastases

Scheduled: 0810 - 0830 hrs, 10 March 2012

Professor Suresh Senan
Department of Radiation Oncology

SABR in stage I NSCLC

• A major treatment advance for high-risk groups (elderly, borderline operable)

• Current indications and reported toxicity

• Data available on operable patients

• Need for education & training needed for all members of thoracic oncology team (diagnosis, staging, quality assurance, follow-up schemes)
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

Some examples of treatment units
Some examples of treatment units

Treatment machines that permit CT scans of non-diagnostic quality to be made

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
Poorer outcomes after SABR have been reported [Bral S, 2007 and 2010; Nagata Y, 2010]

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, 3 chronic thoracic pain</td>
<td>0%</td>
</tr>
<tr>
<td>Koto et al.</td>
<td>31</td>
<td>1 grade 3 pneumonitis</td>
<td>0%</td>
</tr>
<tr>
<td>Fritz et al.</td>
<td>40</td>
<td>2 rib fractures</td>
<td>0%</td>
</tr>
<tr>
<td>Onishi et al.</td>
<td>257</td>
<td>14 pneumonitis, 3 grade 3-4 dermatitis, 4 rib fractures</td>
<td>0%</td>
</tr>
<tr>
<td>Zimmermann et al.</td>
<td>30</td>
<td>1 grade 3 pneumonitis, 1 fracture</td>
<td>0%</td>
</tr>
<tr>
<td>Baumann et al.</td>
<td>138</td>
<td>2 atelectasis, 2 rib fractures, 1 pneumonitis</td>
<td>0%</td>
</tr>
<tr>
<td>Ohnmaru et al.</td>
<td>41</td>
<td>2 grade 3 pneumonitis</td>
<td>0%</td>
</tr>
<tr>
<td>Beitler et al.</td>
<td>75</td>
<td>2 pleural effusions, 1 pneumothorax</td>
<td>0%</td>
</tr>
<tr>
<td>Gadenberger et al.</td>
<td>38</td>
<td>4 pneumonitis</td>
<td>0%</td>
</tr>
<tr>
<td>Nyman 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>1 grade 2-4 pneumonitis, pleural effusion, decline in pulmonary function test, skin reaction</td>
<td>6 (8.5%)</td>
</tr>
<tr>
<td>Riccardi et al.</td>
<td>43</td>
<td>3 grade 3 pneumonitis, 1 rib fracture</td>
<td>0%</td>
</tr>
<tr>
<td>Xia 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]
Eligibility for SABR

- SABR eligible
- Surgery +/- CT
- Concurrent CT-RT
- High-dose RT?
- SABR ??

Central tumors treated safely

Central tumors: 8 fractions of 7.5 Gy

- 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, 2011
SABR delivery (VUMC 2012)

- No rigid immobilization used
- Dose of 18 Gy in 4 mins [Ong CL, 2012]
- No implanted fiducials
- Setup using Cone Beam CT

New data on central tumors

- Pre-2009: excluded as too central or too large
- Since 2009, 12 fractions of 5 Gy delivered to >49 pts [Bongers E, submitted to ASTRO 2012]
What is the evidence to show that SABR is curative in stage I NSCLC?

- 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

Netherlands Cancer Registry

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2020 estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>6729</td>
<td>6700</td>
</tr>
<tr>
<td>Women</td>
<td>4047</td>
<td>8000</td>
</tr>
</tbody>
</table>

Current age at diagnosis of NSCLC:

- 46.3% > 70 years old
- 28% > 75 years
- 12% > 80 years

Van der Drift M, 2011

Netherlands Cancer Registry

Surgery in stage I NSCLC

<table>
<thead>
<tr>
<th>Age group</th>
<th>1989-3003</th>
<th>2004-2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 years</td>
<td>91% operated</td>
<td>91% operated</td>
</tr>
<tr>
<td>60-74 years</td>
<td>77% operated</td>
<td>82% operated (p&lt;0.001)</td>
</tr>
<tr>
<td>75 and older</td>
<td>35% operated</td>
<td>49% operated (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Van der Drijft M, 2012
Population vs registry based survivals

Detterbeck F, 2011

Dutch time-trends (2001-9)

- Netherlands Cancer Registry
- Dutch population -16 million (92 hospitals)
- 4605 patients with stage I NSCLC aged ≥75 years between 2001-2009

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

4605 stage I NSCLC patients aged ≥75 years

Haasbeek C, in press

* estimated SABR use in radiotherapy group was 75%,
North America: Population outcomes

- Nationwide Inpatient Sample, 1994 to 2003 (Finlayson E, 2006)

Table 1. Characteristics of Patients Undergoing Operations (Nationwide Inpatient Sample 1994–2003)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Age (y)</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>65–69</td>
<td>70,416</td>
<td>31.8</td>
<td>125,957</td>
<td>57.0</td>
<td>24,804</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Short-Term Outcomes by Age (Nationwide Inpatient Sample 1994–2003)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Age (y)</th>
<th>Operative mortality (%)</th>
<th>Length of stay (mean no. of days)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65–69</td>
<td>5.7</td>
<td>9.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>5.2</td>
<td>10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>80+</td>
<td>6.9</td>
<td>11.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Vulnerable group: severe COPD

N = 176 patients with severe COPD (GOLD III-IV)

- Median follow-up: 21 months
- Actuarial 3-yr local control: 89%
- Median overall surv (OS): 32 months.
- 1- and 3-year OS: 79% and 47%, resp.
- COPD severity correlated with OS (p = 0.01)

Palma D, 2011
Systematic review: surgery vs SABR in severe COPD

<table>
<thead>
<tr>
<th>First author</th>
<th>Institution</th>
<th>Publication year</th>
<th>Accrual period</th>
<th>( n )</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magdeleinat (26)</td>
<td>Hospital Hotel Dieu and Laminegge Surgical centre, Paris, France</td>
<td>2005</td>
<td>1983–2003</td>
<td>58</td>
<td>Segmentectomy or wedge (n = 14) Lobectomy or greater (n = 43) Open segmentectomy or VATS procedure (n = 43) Open lobectomy (n = 20)</td>
</tr>
<tr>
<td>Law (19)</td>
<td>Glenfield Hospital, Leicester, UK</td>
<td>2010</td>
<td>1997–2009</td>
<td>63</td>
<td>Segmentectomy or wedge (n = 43) Lobectomy or greater (n = 43) Open segmentectomy or VATS procedure (n = 43) Open lobectomy (n = 20)</td>
</tr>
<tr>
<td>SBRT</td>
<td>Henderson (27), Indiana University, USA</td>
<td>2008</td>
<td>2003–2004</td>
<td>33</td>
<td>60–66 Gy/3 fractions</td>
</tr>
<tr>
<td>Stephens (28), Cleveland Clinic, USA</td>
<td>2009</td>
<td>2004–2007</td>
<td>42</td>
<td>50 Gy/10 fractions to 60 Gy/3 fractions</td>
<td></td>
</tr>
<tr>
<td>Palma (current study)</td>
<td>VU University Medical centre, Netherlands</td>
<td>2010</td>
<td>2003–2010</td>
<td>176</td>
<td>60 Gy/3–8 fractions</td>
</tr>
</tbody>
</table>

Abbreviations: \( n \) = number of patients; RT = radiotherapy; SBRT = stereotactic body radiotherapy; VATS = video-assisted thoracoscopic surgery.

- Mean 30-day mortality: 0% post-SBRT and 10% post-surgery
- Local or locoregional control >89% after both treatments
- Survival at 1- and 3-years comparable between treatments

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 = wedge resection
- Limited follow-up – late recurrences may occur
- Anectodal (bronchial necrosis; ‘holes’ in esophagus)
Vulnerable group: patients ≥75 years

- Population-based registry in North Holland
- Matched-pair analysis of overall survival after surgery vs SBRT
- Patients matched by age, stage, gender, treatment year
- (but no data on co-morbidity; no VATS available)

![Graph showing survival analysis](image)

Fig. 1. Overall survival (OS) for 121 elderly patients (age ≥75) with stage I NOOC by treatment. There was no difference in OS between surgery and SBRT (log rank test, p = 0.22).

Palma D, 2011

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)
Local failure after complete resection of N0–1 NSCLC

Saynak M, 2011

Stage I NSCLC: Recurrence patterns

A propensity score-matched analysis of stage I-II NSCLC treated using either SABR or VATS-lobectomy

- 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

Verstegen N, submitted
Propensity score-matched analysis

Results under embargo

The clinical decision problem

Patients: unaware of treatment options and outcomes

Clinicians: unaware of patients’ preferences

Poor decision quality

www.informedmedicaldecisions.org
SABR in the future

Shared decision-making

A process in which clinicians and patients work together to select tests, treatments, management or support packages, based on clinical evidence and the patient’s informed preferences.

SABR for oligometastatic disease

Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET): A Randomized Phase II Trial

Principal Investigators
Dr. David Palma, MD, MSc, PhD, FRCPC
Radiation Oncologist
OICR Clinician Scientist
London Regional Cancer Program

Prof. Dr. Suresh Senan MRCP, FRCP, PhD
Professor of Clinical Experimental Radiotherapy
Department of Radiation Oncology
VU University Medical Center

Patients with up to 5 metastatic lesions from any primary tumor site, meeting inclusion criteria

RANDOMIZATION
(1:2 ratio of randomization to Arm 1 vs. Arm 2)

ARM 1: STANDARD OF CARE
Palilative RT to any symptomatic sites
Further chemotherapy at discretion of medical oncologist

ARM 2: STANDARD OF CARE + SABR
SABR to all sites of known disease
Further chemotherapy at discretion of medical oncologist

FOLLOW-UP

Primary Endpoint
- Overall Survival
  - Defined as time from randomization to death from any cause

Secondary endpoints:
- Quality of life
  - Assessed with the Functional Assessment of Cancer Therapy: General (FACT-G)
- Toxicity
  - Assessed by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4 for each organ treated (e.g. liver, lung, bone)
- Progression-free survival
  - Time from randomization to disease progression at any site or death
- Lesional control rate
- Number of cycles of further chemotherapy/systemic therapy

Required Sample Size: 99 Patients
Conclusions

• SABR achieves local control rates of >90%; and has led to improvement in population-based survivals in the elderly [Palma D, 2010; Haasbeek C, in press]

• Since 2007, SABR has accepted as the standard of care in less fit Dutch patients presenting with a stage I NSCLC.

• SABR undergoing evaluation in patients with 1-5 metastases (‘oligometastases’).