SABR after surgical treatment for NSCLC

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• The Department of Radiation Oncology, VUMC has a research agreement with Varian Medical Systems

• Speakers honoraria Varian Medical Systems
SABR (or SBRT) is a technique for delivering external beam radiotherapy to an extra-cranial target

- with high degree of accuracy
- using high doses of irradiation
- delivered in 1-8 treatment fractions

IASLC textbook: Multidisciplinary Approach to Thoracic Oncology 2014
SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it. 


Comparative effectiveness research suggests that survival is similar after either surgery or SABR for early-stage NSCLC

[reviewed in Louie AV, Radiotherapy Oncol 2015]
• Recurrences after surgery
• Synchronous 2nd primary lung cancer
• Metachronous 2nd primary lung cancer
• Changes in diagnostic approaches
Recurrences after surgery (n=1294 pts)

Risk of recurrence in years 1-4 post-surgery ranged from 6-10% per person-year, decreasing thereafter to 2%.

Risk of 2\textsuperscript{nd} primary lung cancer of 3-6% per person-year, undiminished over time.

Lou F, JTCVS 2012
Recurrences after surgery (n=271 pts)

- Surveillance using minimal dose CT or CXR (2007-2012)
- 271 patients analyzed (80% stage I, 12.5% stage II),
- 80% lobectomy, 18% sub-lobar resections
- New or recurrent lung cancer was confirmed in 23.2%
- 78% of recurrences were asymptomatic

**FIGURE 2.** Distribution over time (in months) of the recurrences or new cancers diagnosed by MnDCT.
• Recurrences after surgery
• **Synchronous** 2nd primary lung cancer
• **Metachronous** 2nd primary lung cancer
• Changes in diagnostic approaches
Treatment of multiple primary lung cancers using stereotactic radiotherapy, either with or without surgery

Gwendolyn H.M.J. Griffioen\textsuperscript{a}, Frank J. Lagerwaard\textsuperscript{a,*}, Cornelis J.A. Haasbeek\textsuperscript{a}, Egbert F. Smit\textsuperscript{b}, Ben J. Slotman\textsuperscript{a}, Suresh Senan\textsuperscript{a}

- 62 patients (7\% of our SABR population)
- SABR to both lesions (n = 56)
- Surgery for one lesion plus SABR (n = 6)

- 31 patients with bilateral lesions (M1a, 7th TNM)
- 31 patients with second lesion in ipsilateral lung (T3-T4)

- Local control rates (per lesion) of 84\% at 2 years, and 78\% at 3 years
- Two-year actuarial regional control rate was 87\%
Toxicity

- Fatigue (31%), cough & dyspnea (16%), local pain (8%)

- Late side effects observed in 25 patients: Grade 3 in 5% with local pain (2 patients) and pneumonitis (1 patient).

- 6 patients underwent surgery and 2 developed high-grade toxicity (septicaemic shock requiring resuscitation in one, and empyema and broncho-pleural fistula in another)
Stereotactic Ablative Radiotherapy
A Potentially Curable Approach to Early Stage Multiple Primary Lung Cancer

Joe Y. Chang, MD, PhD; Yung-Hsien Liu, MD; Zhengfei Zhu, MD, PhD; James W. Welsh, MD; Daniel R. Gomez, MD; Ritsuko Komaki, MD; Jack A. Roth, MD; and Stephen G. Swisher, MD

<table>
<thead>
<tr>
<th>TABLE 1. Criteria for Diagnosis of Second Primary Lung Tumor&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td>Synchronous tumors (diagnosed within 6 mo)</td>
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<tr>
<td>Different histology</td>
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<tr>
<td>Same histology; second tumor in different lobe or lung&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metachronous tumors (diagnosed &gt;6 mo apart)</td>
</tr>
<tr>
<td>Different histology</td>
</tr>
<tr>
<td>Same histology&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>1. Second tumor in different lobe or lung</td>
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<td>2. Tumor-free interval of at least 4 y</td>
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<sup>a</sup> Table reproduced, with modifications, from Martini N, Melamed M. Multiple primary lung cancers. J Thorac Cardiovasc Surg. 1975;70:606-612.

<sup>b</sup> No patient had extrapulmonary or common lymphatic carcinoma at the time of diagnosis.
101 patients post-SABR had a median OS of 46 months
2-year and 4-year in-field local control rates: 97% and 96%

Metachronous tumors had better OS and PFS, than those with synchronous tumors

After either surgery or SABR for index tumor, the incidence of grade ≥3 pneumonitis was 3%
Other grade ≥3 toxicities included chest wall pain (3%) and grade 3 skin toxicity (1%)
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%) or Median (Range)</th>
</tr>
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<tbody>
<tr>
<td>Male gender</td>
<td>73 (68%)</td>
</tr>
<tr>
<td>Age at SPLC (years)</td>
<td>72 (50–90)</td>
</tr>
<tr>
<td>Treatment interval (months)</td>
<td>48 (6–349)</td>
</tr>
<tr>
<td>COPD</td>
<td>85 (79.4%)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3 (0–10)</td>
</tr>
<tr>
<td>WHO Performance Score (PS)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td><strong>Stage initial lung cancer (7th TNM)</strong></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>67 (62.6%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>18 (16.8%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>17 (15.9%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td><strong>Treatment initial lung cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Lobectomy/bilobectomy/trimodality</td>
<td>78 (72.9%)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>17 (15.9%)</td>
</tr>
<tr>
<td>Wedge/segmentectomy</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>CRT</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Palliative (chemo or RT)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td><strong>Histology initial lung cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>50 (46.7%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>39 (36.4%)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>11 (10.3%)</td>
</tr>
<tr>
<td>SCLC</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (3.7%)</td>
</tr>
<tr>
<td>Double tumor—different histology</td>
<td>2 (1.9%)</td>
</tr>
</tbody>
</table>
• Acute grade $\geq 3$ toxicity: 1 grade 3 brachial plexopathy 2 months after SABR to an apical lung tumor

• Late radiation-pneumonitis in 7% of patients (steroids)
• Late grade $\geq 3$ toxicity in 3.7% of patients, including one case of grade 3 hemoptysis (blood transfusion)
• Grade 5 toxicity in 2 cases: bleeding into cavity due to aspergillus infection & a bronchial stricture leading hemoptysis and respiratory failure

• 3-year OS of 60% and local control rates of 89%

Griffioen G, JTO 2014
Meta-Analysis of Resected Metachronous Second NSCLC

- Sublobar resections in 51.4%; Lobectomy in 34.7%
- Pooled operative mortality rate: 7% (95% CI: 3% to 11%)
- Pooled operative morbidity: 32% (95% CI: 28% to 36%)
- Pooled rate of 5-year OS: 46% (95% CI: 36% to 56%)

Hamaji M, Ann Thorac Surg 2015
“pre-treatment pathological diagnosis strongly recommended for all patients 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].
• Recurrences after surgery
• Synchronous 2nd primary lung cancer
• Metachronous 2nd primary lung cancer
• Changes in diagnostic approaches

Griffioen G, JTO 2014: 12 patients with a SPLC developed a third (or fourth) primary lung tumor at a median of 20 months after SABR (range, 7–36 months)
2006, 2008: Floor-of-mouth carcinoma

2009: Right lower lobectomy for a pT2N0M0 squamous cell cancer. Post-operative complications leading to refusal to undergo further surgery.

2010: Synchronous 2\textsuperscript{nd} lung tumor in left upper lobe (clinical diagnosis). SABR in 5 fractions (55 Gy) for clinical stadium I NSCLC.
Patient W, current age 60 years

- 2009-2010: Right lower lobectomy and SABR left upper lobe

- 2013: New subpleural abnormality in left upper lobe. CT and FDG-PET-scan showed abnormality in the left hilus;
Patient W, current age 60 years

- 2013: CT thorax and FDG-PET showed abnormality in left hilus

- 2013: **Open thoracotomy** revealed **small cell lung carcinoma** (T2N1M0) in the hilar region. Treated using concurrent thoracic chemoradiotherapy and PCI

End-2014: growing PET-positive sub-pleurale lesion in left upper lobe, with no FDG uptake elsewhere. Treated with stereotactic radiotherapy
• Recurrences after surgery
• Synchronous 2nd primary lung cancer
• Metachronous 2nd primary lung cancer
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Patient V, current age 68 years

1995: larynx carcinoma treated with radiotherapie.

2008: Growing FDG-PET nodule in left lower lobe; moderate FDG uptake in mediastinal and hilar lymph nodes

Cervical mediastinoscopy: no nodal metastases

Treated in randomised trial of surgery versus SABR (ROSEL study)
Transthoracic needle biopsy: squamous cell malignancy (primary)

EBUS showed reactive nodes at locations 4R, 7, 4 left and 11L
Patient V, current age 68 years

July 2013

November 2013
Patient V, current age 68 years

November 2013

- Transthoracic needle biopsy: squamous carcinoma

- Array CGH analysis: clonal relationship unlikely. Differences as well from the previous larynx carcinoma (1995)

- November 2013: SABR to right lower-lobe

- November 2014: No evidence of disease
Patient V, current age 68 years

Nov 2013

Jan 2015

CT: Series: 2 / Slice: 85
PT: Series: 539210 / Slice: 120
2015: SABR (55 Gy) to 4th lung tumor

Pneumothorax complicating needle biopsy – ‘malignant cells’
Patient V, current age 68 years

Pathology attempted

2008

Pathology+

2013 - July

Pathology+

2013 - Nov

Cytology suspicious

2015 - Jan
SABR after surgery for early-stage NSCLC

- High incidence of second primaries / recurrences after surgery

- SABR offers curative treatment with limited toxicity, and no significant reduction in quality of life [Louie AV, 2015]

- Guideline-recommended CT follow-up, and efforts to obtain a pathological diagnosis, are important