CURRENT ADVANCES IN RADIATION THERAPY

ESMO Summit Africa 2018

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CONFLICT OF INTEREST DISCLOSURE

Research grants: Varian Medical Systems, ViewRay Inc

Advisory boards: Eli Lilly, AstraZeneca, Merck
CURRENT ADVANCES IN RADIATION THERAPY

- Stereotactic ablative radiotherapy (SABR, SBRT)
- Stereotactic radiosurgery (SRS) for brain metastases
- Intensity modulated radiotherapy (IMRT)
- Adaptive radiotherapy
RADIOTHERAPY WORKFLOW

Treatment planning
(use staging information)

Treatment delivery

Treatment verification

CT scan
4-D CT scans
FDG-PET
MRI scans

2-Dimensional RT
3-D conformal RT
Intensity-modulated RT
Particle therapy

kV radiographs
Cone-beam CT
Continuous MRI
MODERN RADIOTHERAPY WORKFLOW

Positioning using a cone-beam

Intensity modulated radiotherapy (IMRT)
CURRENT ADVANCES IN RADIATION THERAPY

Intensity-modulated radiotherapy (IMRT); image guided radiotherapy (IGRT)

- Breast IMRT
- Lung IMRT
- Prostate IGRT

Citrin DE, NEJM 2017
WHAT DOES THE TUMOR BOARD EXPECT?

Brain metastases: stereotactic radiosurgery (SRS) for 1-3 lesions

Lung tumors: stereotactic ablative radiotherapy (SABR)

Curative chemo-radiotherapy delivery using CT planning
(minimal standard is 3D conformal radiotherapy, contour target volumes and organs at risk, use published organ at risk tolerance doses)
RADIOThERAPY: INDICATIONS and IMPLEMENTATION

INDICATIONS


IMPLEMENTATION

- European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. De Ruysscher D, et. al. Radioth Oncol 2017

- ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Guckenberger M, et. al. Radioth Oncol 2017

- Gamma Knife Surgery Compared with Linac-Based Radiosurgery Systems in the Treatment of Intracranial Lesions or Tumours and Functional Neurosurgery: A Review of the Precision, Accuracy, Clinical Effectiveness, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Mar 11. PMID: 25590125
STEREOTACTIC RADIOTHERAPY FOR BRAIN METS

For a single metastasis, stereotactic radiosurgery (SRS) or resection is the recommended treatment [II, B]

For two to three metastases, SRS is recommended in patients with RPA class I–II [II, B]

There is no evidence that adding upfront whole brain radiotherapy (WBRT) to surgery or to SRS has an impact on OS [I, A]

<table>
<thead>
<tr>
<th>Topic and author</th>
<th>Design</th>
<th>Study name / trials number</th>
<th>Patients enrolled</th>
<th>Completed accrual: Y/N</th>
<th>Results: primary endpoint</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV cancer with a resected brain metastasis</td>
<td>Ph 3 RCT of post-op SRS to surgical cavity vs observation</td>
<td>NCT00950001</td>
<td>132</td>
<td>Y</td>
<td>12-month freedom from local recurrence 72% (SRS) vs 41% (obs)</td>
<td>20% NSCLC. SRS was single-fraction, volume-based dosing median 16 Gy (range 12-18)</td>
</tr>
<tr>
<td>(Mahajan A)</td>
<td>Superiority design.</td>
<td></td>
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<tr>
<td></td>
<td>Primary endpoint: local control in resection cavity</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Ph 3 RCT, comparing postoperative SRS to cavity vs WBRT. (Additional</td>
<td>NCCTG N017C/CEC-3</td>
<td>194</td>
<td>Y</td>
<td>Cognitive deterioration-free</td>
<td>59% NSCLC. SRS was single-fraction, volume-based dosing (range 12-20 Gy).</td>
</tr>
<tr>
<td>Stage IV cancer with a resected brain metastasis</td>
<td>brain mets received SRS in both arms) Superiority design.</td>
<td>NCT01372774</td>
<td></td>
<td></td>
<td>survival 3.7 (SRS) vs 3.0 mo (WBRT) (HR 0.47). OS 12.2 vs 11.6 mo (NS)</td>
<td></td>
</tr>
<tr>
<td>(Brown P)</td>
<td>Primary endpoint: cognitive deterioration free survival.</td>
<td></td>
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<tr>
<td></td>
<td>Co-primary endpoint of OS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EGFR NSCLC with ≥3 brain metastases</td>
<td>Ph 3 RCT, comparing icotinib vs WBRT plus chemotherapy Superiority</td>
<td>BRAIN NCT01724801</td>
<td>158</td>
<td>Y</td>
<td>Intracranial PFS 10.0 (icotinib)</td>
<td>Higher intracranial objective response rates with icotinib. No differences in OS.</td>
</tr>
<tr>
<td>(Yang JJ)</td>
<td>design.</td>
<td></td>
<td></td>
<td></td>
<td>vs 4.8 mo (WBRT) (HR 0.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary endpoint: Intracranial PFS</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Senan S, JTO 2017
SABR PRACTICE AT VUMC, Amsterdam

4-Dimensional CT scan

Cone-beam CT scan

Linear accelerator

Volumetric Modulated Arc Therapy (FFF mode in <4 mins)

Doses delivered to $\geq \text{BED}_{10} 100$ Gy [ESMO guidelines 2014]
## Stage I NSCLC: SABR OUTCOMES

<table>
<thead>
<tr>
<th>Recurrences</th>
<th>Local</th>
<th>Regional</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MD Anderson Hospital</strong>&lt;sup&gt;1&lt;/sup&gt; 912 patients; median follow-up of 59 months</td>
<td>11%</td>
<td>12%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>VU University Med Ctr</strong>&lt;sup&gt;2&lt;/sup&gt; 676 patients; median follow-up of 33 months</td>
<td>10.5%</td>
<td>12.7%</td>
<td>20%</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

Doses delivered to $\geq$BED$_{10}$ 100 Gy [ESMO guidelines 2014]
Stage I NSCLC: **SABR vs conventional radiotherapy**

**SPACE trial** [Nyman J, Radioth Oncol 2016]
102 stage I patients were randomized (2007-2011)
Primary endpoint: progression free survival at 3 years

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

**CHISEL trial** [Ball D, WCLC 2017]
101 stage I patients were enrolled (2009-2015)
Primary objective: time to local failure: randomized 2:1 for SABR vs conventional

With SABR,
SABR led to superior freedom from local failure (**HR = 0.29**, 95% CI 0.130, 0.662, $P=0.002$)
Longer overall survival (**HR = 0.51**, 95% CI 0.51, 0.911, $P=0.020$)
SYNCHRONOUS OLIGOMETASTASES
Patients with 1-3 *synchronous* metastases at diagnosis may experience long-term disease-free survival (DFS) following systemic therapy and radical local treatment (high-dose radiotherapy or surgery) [III, B]

Stage IV patients with limited *metachronous* metastases may be treated with a radical local treatment as some may experience long-term DFS [III, B]

Limited evidence available; inclusion in *clinical trials* is preferred
# SYNCHRONOUS OLIGOMETASTASES

## Prospective clinical trials in NSCLC

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>48</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>PFS</td>
<td><strong>11.9</strong> months (5.7–20.9) vs 3.9 months (2.3 – 6.6)</td>
<td><strong>9.7</strong> months vs 3.5 months</td>
<td><strong>11.2</strong> months (8.1-17.1)</td>
</tr>
<tr>
<td>Median OS</td>
<td></td>
<td></td>
<td>22.2 months (13.3-45.8)</td>
</tr>
</tbody>
</table>

Brackets indicate 95% Confidential Intervals
OLIGOMETASTASES

Individual NSCLC Patient Meta-Analysis

757 NSCLC patients with 1-5 synchronous or metachronous mets

Median OS **26 months**, 1-year OS 70.2%, and 5-year **OS 29.4%**

*Surgery* was the commonest treatment modality for both the primary (n=635, 83.9%) and for metastases (n=339, **62.3%**)

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**Recursive Partitioning Analysis for risk groups:**

- **Low-risk:** metachronous metastase (5-year OS 48%)
- **Intermediate risk:** synchronous metastases, N0 disease (5-year OS 36%)
- **High-risk:** synchronous metastases, N1/N2 disease (5-year OS 14%)

Ashworth A, Clin Lung Cancer 2014
SYNCHRONOUS BRAIN METASTASES

NSCLC – data from NCDB (United States)

561 patients with brain metastases AND T1/T2 and N0/N1 stage AND underwent surgery to the primary site

Median OS of 21.4 months; OS rates at 1, 2 and 3 years being 69.2%, 45.5% and 36.2% respectively

Within this subset, 237 patients (42%) also had resection of a distant site.

Median, 1, 2 and 3-year OS were 26.5 months, 79.1%, 53.2% and 48.6% respectively

Waqar SN, Clin Lung Cancer 2018
OLIGO-RECURRENTE
SABR-COMET TRIAL
NCT01446744

Eligibility: Controlled primary malignancy with 1-5 metastatic lesions, all of which were amenable to SABR
Good performance status and life expectancy >6 months

Stratification: number of metastases (1-3 vs. 4-5)

Randomization: 1:2 ratio between palliative standard of care (SOC) treatments [Arm 1] vs. SOC plus SABR to all metastatic lesions [Arm 2]

Primary endpoint: Overall survival (OS)

A randomized phase II screening design with a two-sided alpha of 0.20 (wherein a p-value <0.20 designates a positive trial) to provide an initial comparison of the 2 treatment strategies.

Enrolled 99 patients between 2012-2016

Palma D, BMC Cancer 2012
OLIGO-RECURRENT
Head and neck cancer

- 74 year-old man

- December 2015: Base of tongue squamous cell cancer (HPV type 16) stage cT4N2M0. Treatment to 70 Gy (2 Gy/fraction with cetuximab)

- May 2016: 2 new FDG-avid sub-pleural lung lesions. Biopsy - squamous cell cancer
OLIGO-RECURRENCE
Head and neck cancer

- 74 year-old man
- December 2015: Base of tongue squamous cell cancer (HPV 16)
- May 2016: Biopsy-proven lung metastases (P16 positive)
- Which treatment option?
OLIGO-RECURRENT
Head and neck cancer

- 74 year-old man

- December 2015: Base of tongue cancer (HPV type 16 positive squamous cell cancer, stage cT4N2M0. Treatment 35 x 2 Gy with cetuximab (end Jan 2016)

- May 2016: p16-over expressing lung metastases
- Advice of tumor board: SABR

HPV status correlates with survival in patients with recurrent or metastatic disease. NCCN Guidelines, Adelstein JNCCN 2017 2017
OLIGO-RECURRENCE
Head and neck cancer

May 2016

SABR in 5 fractions (55 Gy)

SABR in 8 fractions (60 Gy)
OLIGO-RECURRENTE
Head and neck cancer

December 2015: Oropharynx cancer – radiotherapy and cetuximab

May 2016: 2 new FDG-avid lung metastases – SABR

September 2016: 3rd right-sided lung metastasis - SABR

SABR in 5 fractions (55 Gy)
OLIGO-RECURRENCE
Head and neck cancer

May 2016: 2 new FDG-avid lung metastases - SABR

September 2016: 3rd new lung lesion – SABR

February 2018: New PET-positive lung nodule in left lower lobe – SABR
CHANGING INDICATIONS FOR SABR: CENTRAL TUMORS, ILD

Moderately central tumors

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

Ultracentral tumors

Toxicity with high-dose radiation
[Haseltine JM, PRO 2016, Tekatli H, JTO 2016; Lindberg K, WCLC 2016]

In early-stage NSCLC and coexisting interstitial lung disease (ILD), the treatment-related mortality in medically inoperable patients following SABR is 16% [Systematic review. Chen H, IJROBP 2017]
SABR AND SYSTEMIC THERAPY

Clinical challenges in implementation

Limited safety data on combining/sequencing new and old systemic agents with radiotherapy
  - Antiangiogenic agents
  - BRAF inhibitors
  - Gemcitabine

SABR for multiple lung lesions

Response evaluation

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ANTI-PD-1/L1 COMBINATION TRIALS

Size of bubble correlates with number of trials

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42

Tang J, Ann Oncol 2017
Symptomatic radiation necrosis defined as an enlarging lesion after SRS causing neurologic symptomatology that displayed a pathology specimen showing only necrosis or changes consistent with necrosis on dual-phase PET-CT or serial MRI.

Martin AM, JAMA Oncol 2018
CURRENT ADVANCES IN RADIATION THERAPY

Intensity-modulated radiotherapy (IMRT); image guided radiotherapy (IGRT)

- Breast IMRT
- Lung IMRT
- Prostate IGRT
IMRT FOR BREAST CANCER

Breast irradiation (lumpectomy)

Randomized clinical trial of breast IMRT versus standard wedge-field technique [Pignol J-P, JCO 2008]

**Primary end point:** chronic breast pain

**Secondary endpoints:** breast cosmesis, quality of life, and local recurrence-free, disease-free, and overall survival

**Results:** IMRT reduced incidence of moist desquamation, which correlated with increased pain and reduction in the quality of life

10-year update [Pignol J-P, Radioth Oncol 2016]

No significant differences in chronic pain
No differences for secondary endpoints

Acute moist desquamation associated with late subcutaneous fibrosis (p = 0.003) and telangiectasia (p = 0.039)

Late toxicities correlated significantly with acute side effects, which in turn were increased when dose distribution was poor
## IMRT FOR LUNG CANCER

<table>
<thead>
<tr>
<th>Randomised Trials</th>
<th>Pneumonitis ≥G3</th>
<th>Esophagitis ≥G3</th>
<th>* IMRT use</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 0617 (60 Gy)</td>
<td>7%</td>
<td>7%</td>
<td>48%</td>
</tr>
<tr>
<td>PROCLAIM</td>
<td>2.5-1.8%</td>
<td>16-21%</td>
<td>25%</td>
</tr>
<tr>
<td>KCSG-LU05-04</td>
<td>1.2%</td>
<td>10%</td>
<td>Not reported</td>
</tr>
<tr>
<td>CONVERT (LD-SCLC)</td>
<td>2-2.4 % (OD vs BID)</td>
<td>19%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Cumulative incidence of severe radiation pneumonitis (RP) and local failure (LF) among NSCLC patients randomly assigned and treated according to random assignment

(A) Cumulative incidence of RP and LF for patients treated with intensity-modulated radiation therapy (IMRT) or protons (PSPT)

(B) Cumulative incidence of $\geq$ grade 3 RP

(C) Cumulative incidence of LF

Liao Z, JCO 2018
Phase 3 trial in intermediate or high-risk adenocarcinoma of the prostate

**Randomization:** 78 Gy guided either by weekly offline orthogonal portal imaging (15 mm margins to PTV) or by daily online CBCT IGRT (7 mm margins to PTV)

**Primary outcome:** acute rectal toxicity at end of radiation as evaluated using patient reported side effects (PRO’s)

**Results:** No difference between groups in rectal toxicity
No significant differences between groups for any other gastrointestinal or urinary symptom. Similar health related quality of life analyses (EORTC QLQ 30)

Tondel H, Radioth Oncol 2018
**Interpretation:** Daily CBCT IGRT with reduced PTV margins demonstrated no advantage with respect to patient reported side effects at end of RT as compared to weekly orthogonal offline portal imaging with standard PTV margins.

<table>
<thead>
<tr>
<th>Irradiated volumes</th>
<th>2D-IGRT (arm A)</th>
<th>3D-IGRT (arm B)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rectum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V50 (cm³)</td>
<td>44.9 (40.8–49.0)</td>
<td>29.8 (26.9–32.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V60 (cm³)</td>
<td>36.2 (32.7–39.7)</td>
<td>22.6 (20.4–24.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V70 (cm³)</td>
<td>18.5 (16.3–20.62)</td>
<td>11.5 (10.3–12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V50 (cm³)</td>
<td>83.6 (78.6–88.5)</td>
<td>53.8 (50.0–57.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V60 (cm³)</td>
<td>74.0 (69.5–78.6)</td>
<td>45.1 (41.6–48.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V70 (cm³)</td>
<td>46.3 (42.5–50.0)</td>
<td>30.4 (27.5–33.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CTV2 (0–70)</strong></td>
<td></td>
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</tr>
<tr>
<td>Total volume (cm³)</td>
<td>49.2 (45.5–52.9)</td>
<td>49.2 (45.8–52.6)</td>
<td>0.687</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>77.59 (77.21–77.78)</td>
<td>77.65 (77.58–77.72)</td>
<td>0.449</td>
</tr>
<tr>
<td><strong>PTV2 (0–70)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total volume (cm³)</td>
<td>279.7 (269.1–290.3)</td>
<td>131.9 (125.7–138.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V66.5 (cm²)</td>
<td>270.1 (259.8–280.3)</td>
<td>131.0 (124.8–137.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>74.5 (74.1–74.8)</td>
<td>76.2 (76.1–76.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Due to non-normally distributed data, p-values are from Mann-Whitney’s test, and confidence intervals are Bias corrected and accelerated (BCa) Bootstrap confidence intervals with B = 10,000 bootstrap samples.

* Student’s t-test assuming unequal variances.

Tondel H, Radioth Oncol 2018
MRI-GUIDED RADIOTHERAPY DELIVERY

Stereotactic
MRI-guided
Adaptive
RadioTherapy

MR-guided tumor setup
Adaptive planning
Online guidance
Gated delivery (markerless)

Bohoudi O, Radioth Oncol 2017
MRI-GUIDED RADIOTHERAPY DELIVERY

Current standard of care
Cone-beam CT scan before treatment

MRI-images during SABR for patient video-controlled breath-hold delivery

Bohoudi O, Radioth Oncol 2017
Palacios M, Proc ASTRO 2017
TAKE-HOME MESSAGES

Expectations of tumor board can differ from that of the radiation oncology department
(IGRT, IMRT, MR-guided RT, etc. versus …access to SRS for brain metastases, SABR for extracranial metastases, quick start of CT-RT)

Ensure access to safe high-dose radiotherapy
The perfect is the enemy of the good. Voltaire 1694-1778
THANK YOU FOR LISTENING

http://www.x-rays.nl/