Current advances in radiation therapy

Professor Suresh Senan
VU University Medical Center, Amsterdam, The Netherlands
Disclosures

Varian Medical Systems: Research grants, speaker honoraria

Lilly Oncology: Advisory board
~3,500 new patients / year
Current advances in radiation therapy

- Intensity modulated radiotherapy (IMRT)
- Hypofractionation, SBRT or SABR
- MR-guided radiotherapy
- Adaptive radiotherapy
- Particle therapy
Radiotherapy workflow

Treatment planning (staging info)
- CT scan
- 4-D CT scans
- FDG-PET
- MRI scans

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

Treatment verification
- kV radiographs
- Cone-beam CT
- Continuous MRI
Imaging for radiotherapy planning

CT scan
4-D CT scans
FDG-PET
MRI scans
Positional verification during treatment

On-table cone-beam CT scans

Kilovoltage X-ray source
Pancreatic tumor: Imaging for planning and on-table delivery

Planning CT scan

Cone-beam CT scan

0.35T MR image

Real-time MR-gated delivery
Current advances in radiation therapy

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Intensity Modulated Radiotherapy (IMRT)

- Vary dose across radiation field to achieve a specifically designed intensity pattern
- Sum of all fields in 3D space delivers high doses to irregularly shaped volumes
Randomized clinical trial [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*

IMRT reduced incidence of moist desquamation (vs standard wedge-field technique)
Moist desquamation correlated with increased pain and reduction in the quality of life
IMRT for breast cancer

Phase III randomised trial
Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial

- 241 patients available for assessment
- No significant differences in chronic pain between treatment arms
- No differences for the 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 in patients having poor dose distribution

- Breast IMRT may be useful for selected patients

Pignol J-P, Radioth Oncol 2016
Breast radiotherapy: late toxicities

Risk of **congestive heart failure** by treatment group (Cox model), adjusted for age and for patients treated since 1980

Hooning MJ JNCI 2007
Breast IMRT using breath-hold delivery

Colour-wash images of cumulative dose distributions (as % of prescribed dose)

Hypofractionated radiotherapy (16 fractions) using a Simultaneous Integrated Boost, and delivered during breath-hold
IMRT for lung cancer

63-year old non-smoking East Asian lady, who presented in 2008 with an adenocarcinoma. Planning Target Volume = 735.6 cm$^3$
After concurrent chemo-radiotherapy,

- Severe dyspnea or radiation pneumonitis in 15%-30% of cases
- Acute grade 3-4 radiation esophagitis in 20%-30% of cases

De Ruysscher D, Clinical controversies: proton therapy for thoracic tumors. Sem Rad Onc 2013
<table>
<thead>
<tr>
<th>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>

* IMRT = intensity-modulated radiotherapy

Locally advanced lung cancer: Toxicity of CT-RT

Faivre-Finn C, pASCO 2016
### Table 4. CTCAE Grade 3 Radiation-Related Adverse Events of 3D-CRT and IMRT

<table>
<thead>
<tr>
<th>≥ Grade 3 Toxity</th>
<th>3D-CRT, % (No.)</th>
<th>IMRT, % (No.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>254</td>
<td>228</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>7.9 (20)</td>
<td>3.5 (8)</td>
<td>.039</td>
</tr>
<tr>
<td>Esophagitis/dysphagia</td>
<td>15.4 (39)</td>
<td>13.2 (30)</td>
<td>.534</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.8 (7)</td>
<td>3.9 (9)</td>
<td>.419</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8.3 (21)</td>
<td>4.8 (11)</td>
<td>.131</td>
</tr>
</tbody>
</table>

NOTE. P values from a Cochran-Mantel-Haenszel test stratified by radiation therapy dose level (60 vs 74 Gy) and cetuximab random assignment. Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; CTCAE, Common Terminology Criteria for Adverse Events (version 3); IMRT, intensity-modulated radiation therapy.
# RTOG 0617: Outcomes of IMRT and 3D-Conformal RT

## Locally advanced NSCLC

### Table 3. Outcomes at 2 Years by Radiation Therapy Technique

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3D-CRT, % (95% CI)</th>
<th>IMRT, % (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>49.4 (42.9 to 55.5)</td>
<td>53.2 (46.4 to 59.6)</td>
<td>.597</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>27.0 (21.5 to 32.7)</td>
<td>25.2 (19.7 to 31.1)</td>
<td>.595</td>
</tr>
<tr>
<td>Local failure</td>
<td>37.1 (31.0 to 43.1)</td>
<td>30.8 (24.8 to 36.9)</td>
<td>.498</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>49.6 (43.2 to 55.8)</td>
<td>45.9 (39.2 to 52.3)</td>
<td>.661</td>
</tr>
</tbody>
</table>

NOTE. P values from a two-sided log-rank test stratified by radiation therapy dose level (60 v 74 Gy). Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; IMRT, intensity-modulated radiation therapy.

Chun G, JCO 2016
Can protons improve outcomes in NSCLC?

Skinner HD, Translational Cancer Res 2013
Protons vs. IMRT in stage III NSCLC

• Bayesian randomized trial comparing IMRT versus passively scattered proton therapy NSCLC

• End-point: Rates of, and time to, treatment failure (TF), defined as either ≥ G3 radiation pneumonitis (RP) or local recurrence (LR) within 12 months

• IMRT treatment failure rates of 30% at 6 months and 40% at 12 months; Protons would reduce the treatment failure rate by 10%.

Liao ZX, J Clin Oncol 34, 2016 (suppl; abstr 8500)
• 149 randomly allocated to IMRT (n = 92) or protons (n = 57)

• Treatment failure rates at 12 months were 20.7% in all patients, 15.6% in IMRT, 24.6% in proton groups

• **Conclusions:** No differences between IMRT vs. protons on treatment failures in this randomized trial.

Liao ZX, J Clin Oncol 34, 2016 (suppl; abstr 8500)
New versus old proton delivery techniques

Passive scatter proton therapy

Intensity-modulated proton therapy

Giap H, Translational Cancer Res 2015
Current advances in radiation therapy

- Intensity modulated radiotherapy (IMRT)
- Hypofractionation, SBRT or SABR
- MR-guided radiotherapy
- Adaptive radiotherapy
- Particle therapy
SABR is a technique for delivering high-dose external beam radiotherapy, with high precision, to an extra-cranial target

- Tumors up to 5 cm; minimal dose $\text{BED}_{10} \geq 100 \text{ Gy}$
- $\text{BED}_{10} \geq 100 \text{ Gy}$ delivered in 3-8 once-daily fractions

When SABR is unavailable, a hypofractionated radiotherapy schedule with a high biologically equivalent dose is advised in patients with early-stage NSCLC who are unfit for surgery

ESMO Clinical Practice Guidelines, Vansteenkiste J, Ann Oncol 2013
SABR versus non-SABR radiotherapy in NSCLC

- **SPACE trial** (NTC01920789)
- **CHISEL - TROG 09.02** (NCT01014130)
- Canadian SBRT vs hypofractionated RT (NCT01014130)

**SPACE trial [Nyman J, Radioth Oncol 2016]**

102 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)
Stage I NSCLC: SBRT vs no treatment (NCDB)

3147 pathology proven patients >70 years (2003-2006)
No treatment = 2889 patients (91.8%); **SBRT** = 258 patients (8.2%)
No significant differences in Charlson/Deyo comorbidity index scores

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**Median survival:**
- Observation: 10.1 months
- SABR: 29 months

Nanda RH, Cancer 2015
Patterns of care in the SABR-era

Treatment utilization for stage IA NSCLC (SEER 2004-2012)

Haque W, AJCO 2016
• Conventional C-arm linacs equipped only with an Electronic Portal Imaging Device (EPID) and 10mm MLC are considered as insufficient for lung SBRT (5/8).

• C-arm linacs equipped with image-guidance technology with improved image-contrast compared to an EPID, are considered as mandatory (6/8),

• Dedicated stereotactic C-arm linacs equipped with more advanced image guidance, a high resolution MLC of <10mm and improved mechanical accuracy are recommended for best SBRT practice (6/8).

Role of radiotherapy in early-stage NSCLC

Planning 4DCT scan

Cone-beam CT

Fast delivery in <4 minutes

Risk adapted fractionation schemes [Hurkmans C, Rad Onc 2009]

- **3 fractions of 18Gy**: T1 lesions, not adjacent to chest wall
- **5 fractions of 11Gy**: T1 lesions with broad chest wall contact, and T2 lesions
- **8 fractions of 7.5Gy**: central lesions - limited overlap with mediastinal structures
• High prevalence of granulomatous disease and other infectious causes of pulmonary nodules

• Diagnosis risk calculators developed in non-Asian patients may not be applicable

• Tuberculosis in Asia favors (i) lesser reliance on PET scanning, and (ii) greater use of non-surgical biopsy over surgical diagnosis or surveillance
Radiation pneumonitis (RP) after SABR

• Bahig H, Prac Rad Oncol 2016
  • 504 SABR patients (6% had preexisting Interstitial Lung Disease)
  • Grade ≥ 3RP of 4% in entire cohort
  • Grade ≥ 3 RP in 2% of patients without ILD
  • Grade ≥ 3 RP in 32% of patients with ILD
  • Grade 5 RP in 21% of patients with ILD

• Chen H, Proceedings WCLC 2016 (P1.05-061)
  • Systematic literature review: SABR-related mortality rate in IPF of 16%
Usual interstitial pneumonitis (UIP)

Fig 1—71-year-old man with shortness of breath and crackles on auscultation.

A–D, Axial high-resolution CT images show peripheral and basilar-predominant pulmonary fibrosis and clustered honeycombing (arrows, B–D) in subpleural lung in this patient with usual interstitial pneumonitis pattern of pulmonary fibrosis.

Chung JH, AJR 2016
Moderately central vs ‘ultracentral’ tumors

**Moderately central tumors**

SABR appears feasible

**Ultracentral tumors**

Higher toxicity with any RT
[Data MSKCC, Stanford, VUMC, Tekatli H, JTO 2016; HILUS study Lindberg K, WCLC 21016]
Post SABR radiological follow-up

- Recognize ‘expected’ patterns of fibrosis  
  (avoid patient anxiety, risky interventions)
- Toxicity (rib fractures, pneumonitis)
- Identify recurrences (high-risk features)
- Detect and treat second tumors
Acute: ≤6 months

Dahele M, JTO 2011

Late: >6 months

Common post-SABR lung changes (fixed beam SABR)
Radiological changes post-SABR

<table>
<thead>
<tr>
<th>High-Risk Features</th>
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<tbody>
<tr>
<td>Enlarging Opacity</td>
</tr>
<tr>
<td>Sequential Enlargement</td>
</tr>
<tr>
<td>Enlargement after 12 months</td>
</tr>
<tr>
<td>Bulging Margin</td>
</tr>
<tr>
<td>Linear Margin Disappearance</td>
</tr>
<tr>
<td>Loss of Air Bronchogram</td>
</tr>
<tr>
<td>Cranio-Caudal Growth</td>
</tr>
</tbody>
</table>

Huang K, Radiother Oncol 2012, 2013
High-risk radiological feature

Enlarging opacity

An enlarging lung abnormality with an increased density in the irradiated area

Ronden M, *manuscript in preparation*
Craniocaudal growth

Craniocaudal enlargement of opacity, (> 5 mm and >20% RECIST criteria).
Most fibrosis after SABR is expected in axial plane.

Ronden M, *manuscript in preparation*
Loss of linear margins

A previously straight margin to the fibrotic area is replaced by a convex surface

Ronden M, manuscript in preparation
Changing paradigms: metastatic disease

clinical practice guidelines

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

S. Novello1, F. Barlesi2, R. Califano3,4, T. Cufer5, S. Ekman6, M. Giaj Levra7, K. Kerr8, S. Popat9, M. Reck10, S. Senan11, G. V. Simo12, J. Vansteenkiste13 & S. Peters14 on behalf of the ESMO Guidelines Committee†
Oligometastatic paradigm

Patients developing a small number of metastatic lesions might achieve long-term survival if all these lesions are ablated

Hellman and Weichselbaum, JCO 1995
Oligometastatic NSCLC without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study

Progression-free survival

11.9 months (90% CI 5.72–20.90) versus 3.9 months (2.30–6.64) in the maintenance treatment group (HR 0.35 [90% CI 0.18–0.66]; log-rank p=0.0054).

Gomez D, Lancet Oncol 2016
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MR-guided radiotherapy: MRIdian (ViewRay)

Split-core 0.35T MRI

Three cobalt-sources

Double-focussed collimator
Challenge of adrenal metastases

79 year-old man with a solitary adrenal metastasis, 3 months after completing chemo-radiotherapy to the thorax
MR-guided treatment delivery (SMART)

Stereotactic
MRI-guided
Adaptive
RadioTherapy

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

- **Simulation**: Light meal. Breath-hold CT during shallow inspiration, and 0.35 Tesla MR on MRIdian during 17 sec breath-hold.

- **Pre-fraction**: MR during 17 sec breath-hold

- Setup by aligning GTV; after contour propagation and deformation, OAR contours are manually adjusted within 3 cm of PTV

- **Re-optimize** step-and-shoot IMRT plan (MRIdian TPS), which is available at treatment console, using a Monte Carlo dose calculation algorithm to generate “plan of the day”

- **Breath-hold delivery** under MR-guidance: 3mm GTV-PTV margin

- **Patient’s** observe sagittal tracking view from MRIdian console
Contouring for plan-of-the-day

5 fractions of 10 Gy (to encompassing isodose)
Patient-controlled breath-hold gated RT
Patients can receive copies of their real-time movies
MRIdian: Image quality with 0.35 Tesla

More than sufficient for RTH purposes, i.e. contouring
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Thank you for your attention