# Current advances in radiation therapy

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# Disclosures

Varian Medical Systems: Research grants, speaker honoraria

Lilly Oncology: Advisory board

# VU University medical center



~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

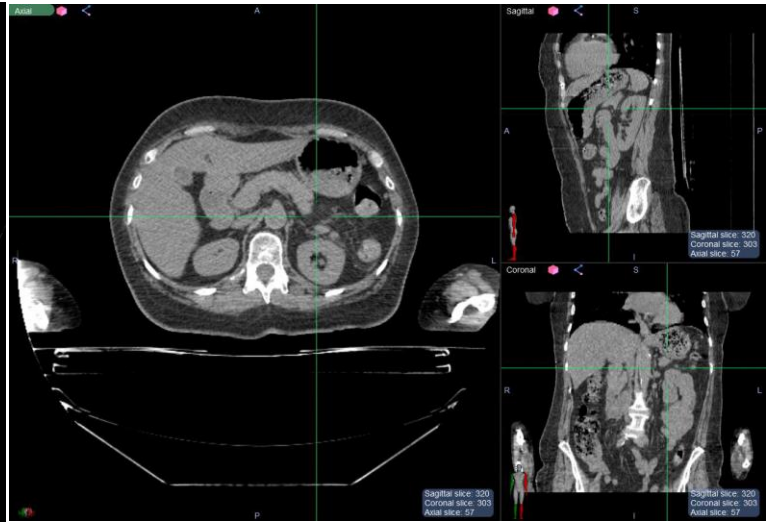
# Radiotherapy workflow

Treatment planning (staging info) → Treatment delivery → Treatment verification

| Treatment planning | Treatment delivery | Treatment verification |
|---|---|---|
| CT scan | 2-Dimensional RT | kV radiographs |
| 4-D CT scans | 3-D conformal RT | Cone-beam CT |
| FDG-PET | Intensity-modulated RT | Continuous MRI |
| MRI scans | Particle therapy | |

# Imaging for radiotherapy planning

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

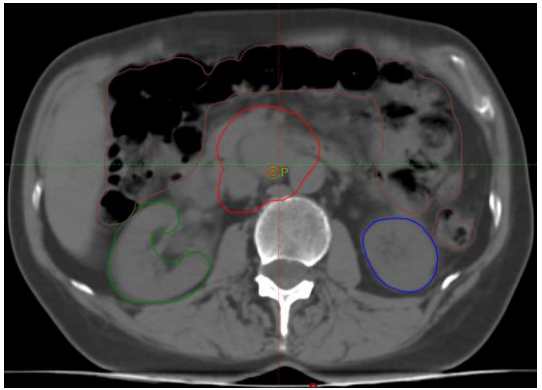
# Positional verification during treatment

## On-table cone-beam CT scans

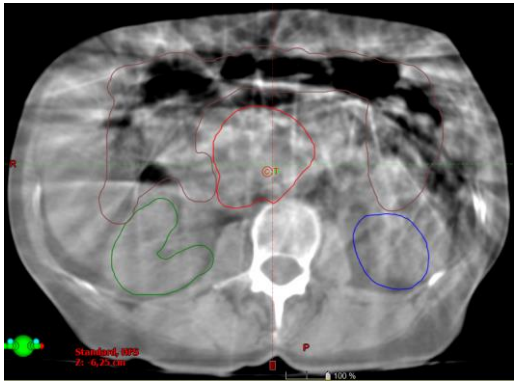
Kilovoltage X-ray source

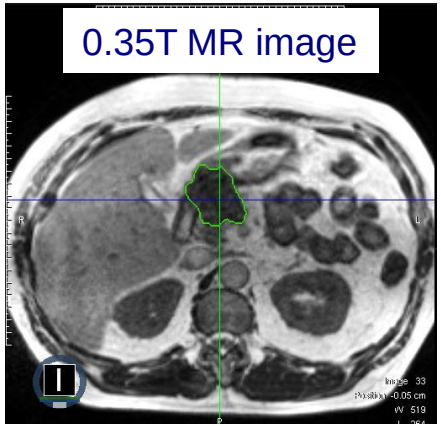
# Pancreatic tumor: Imaging for planning and on-table

Planning CT scan



Cone-beam CT scan






Real-time MR-gated delivery

# Current advances in radiation therapy

- Intensity modulated radiotherapy (IMRT)
- Hypofractionation, SBRT or SABR
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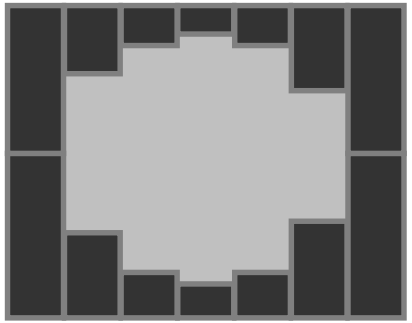
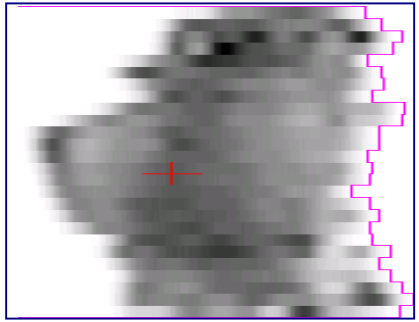
- Adaptive radiotherapy
- Particle therapy

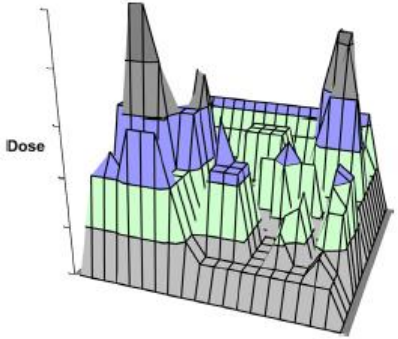
# Intensity Modulated Radiotherapy (IMRT)

Uniform field

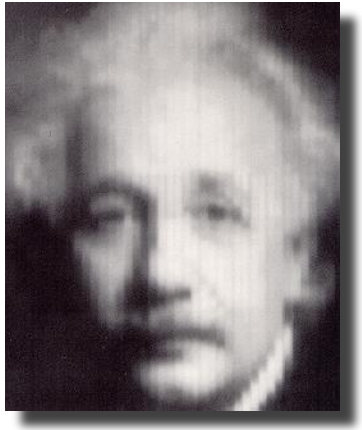


Non-uniform field






- 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



# IMRT for breast cancer

**Breast irradiation (lumpectomy)**

**Chest wall RT (mastectomy)**

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

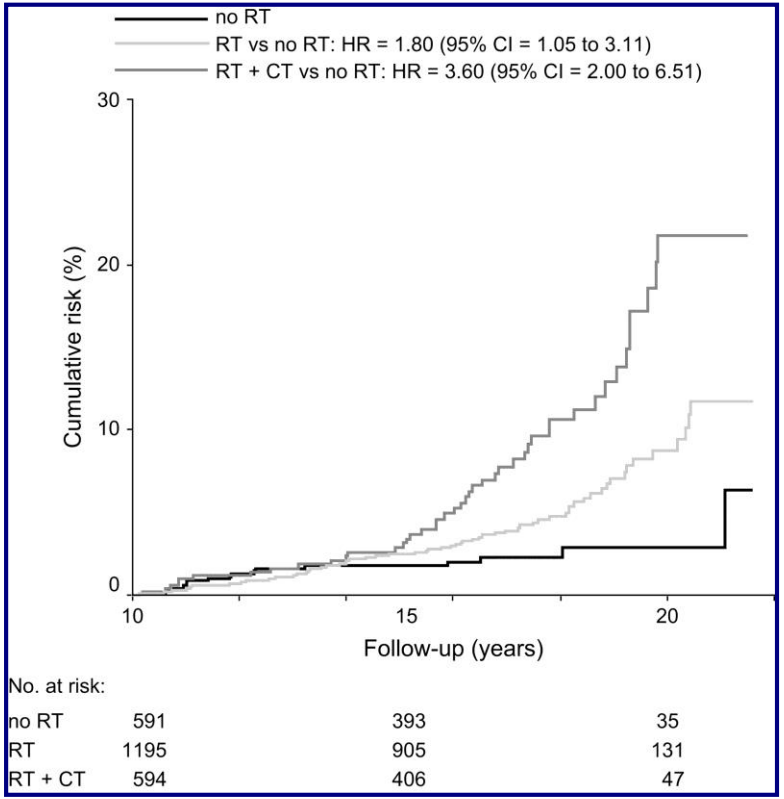
- 241 patients available for assessment
- No significant differences in chronic pain between treatment arms
- No differences for the secondary endpoints

- 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

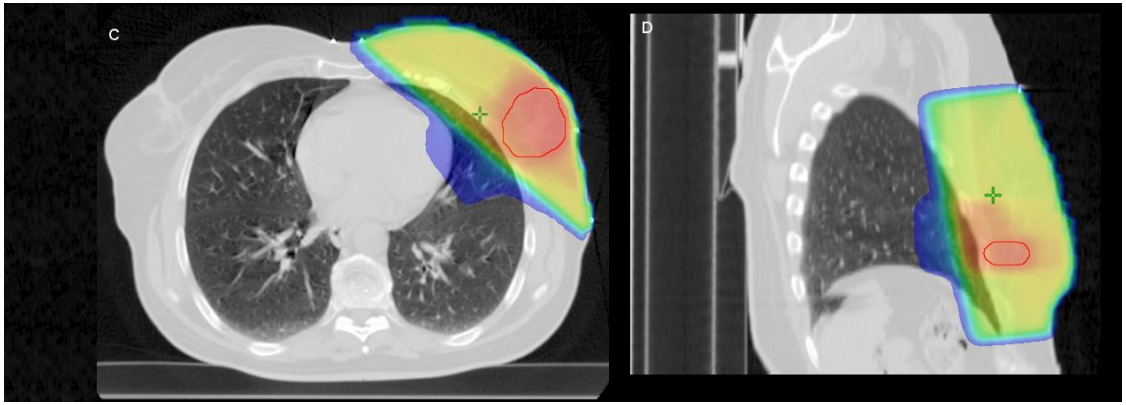
# Breast radiotherapy: late toxicities




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

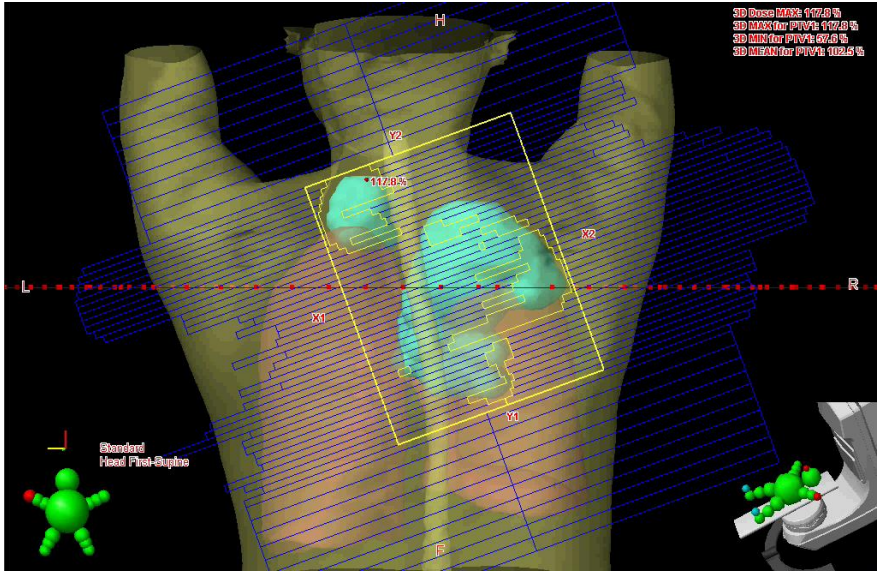


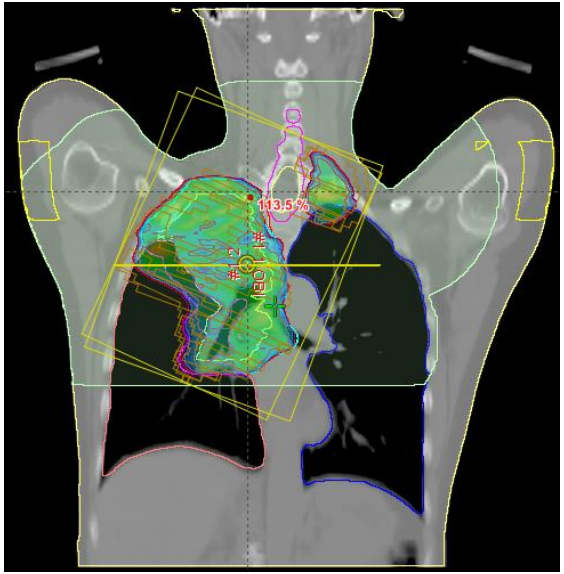

Colour-wash images of cumulative dose distributions
(as % of prescribed dose)

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 $cm^3$




Volumetric modulated radiotherapy (RapidArc™)

# Locally-advanced lung cancer

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

# Locally advanced lung cancer: Toxicity of CT-RT

* IMRT = intensity-modulated radiotherapy

| Trials | Pneumonitis ≥G3 | Esophagitis ≥G3 | * IMRT use |
|---|---|---|---|
| RTOG 0617 (60 Gy) | 7% | 7% | 48% |
| PROCLAIM | 2.5-1.8% | 16-21% | 25% |
| KCSG-LU05-04 | 1.2% | 10% | Not reported |
| CONVERT (LD-SCLC) | 2-2.4 % (OD vs BID) | 19 % | 17 % |

Bradley J, Lancet Oncol 2015, Ahm JS, J Clin Oncol 2015, Senan S, J Clin Oncol 2016
Faivre-Finn C, pASCO 2016

# Locally advanced NSCLC

## RTOG 0617: Outcomes of IMRT and 3D-Conformal RT

**Table 4.** CTCAE ≥ Grade 3 Radiation-Related Adverse Events of 3D-CRT and IMRT

| ≥ Grade 3 Toxicity | 3D-CRT, % (No.) | IMRT, % (No.) | *P* |
|---|---|---|---|
| No. of patients | 254 | 228 | |
| Pneumonitis | 7.9 (20) | 3.5 (8) | .039 |
| Esophagitis/dysphagia | 15.4 (39) | 13.2 (30) | .534 |
| Weight loss | 2.8 (7) | 3.9 (9) | .419 |
| Cardiovascular | 8.3 (21) | 4.8 (11) | .131 |

NOTE. *P* values from a Cochran-Mantel-Haenszel test stratified by radiation therapy dose level (60 *v* 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.

Chun G, JCO 2016

# Locally advanced NSCLC

## RTOG 0617: Outcomes of IMRT and 3D-Conformal RT

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

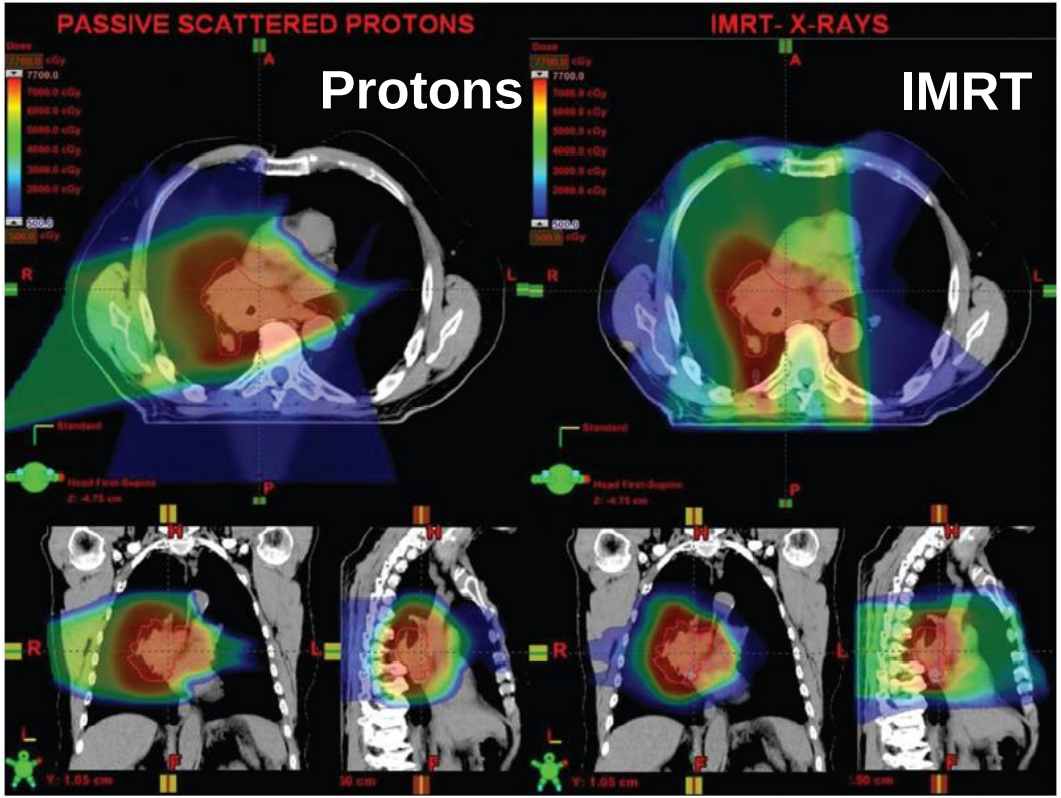
| Outcome | 3D-CRT, % (95% CI) | IMRT, % (95% CI) | *P* |
|---|---|---|---|
| Overall survival | 49.4 (42.9 to 55.5) | 53.2 (46.4 to 59.6) | .597 |
| Progression-free survival | 27.0 (21.5 to 32.7) | 25.2 (19.7 to 31.1) | .595 |
| Local failure | 37.1 (31.0 to 43.1) | 30.8 (24.8 to 36.9) | .498 |
| Distant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

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)

# Protons vs. IMRT in stage III NSCLC

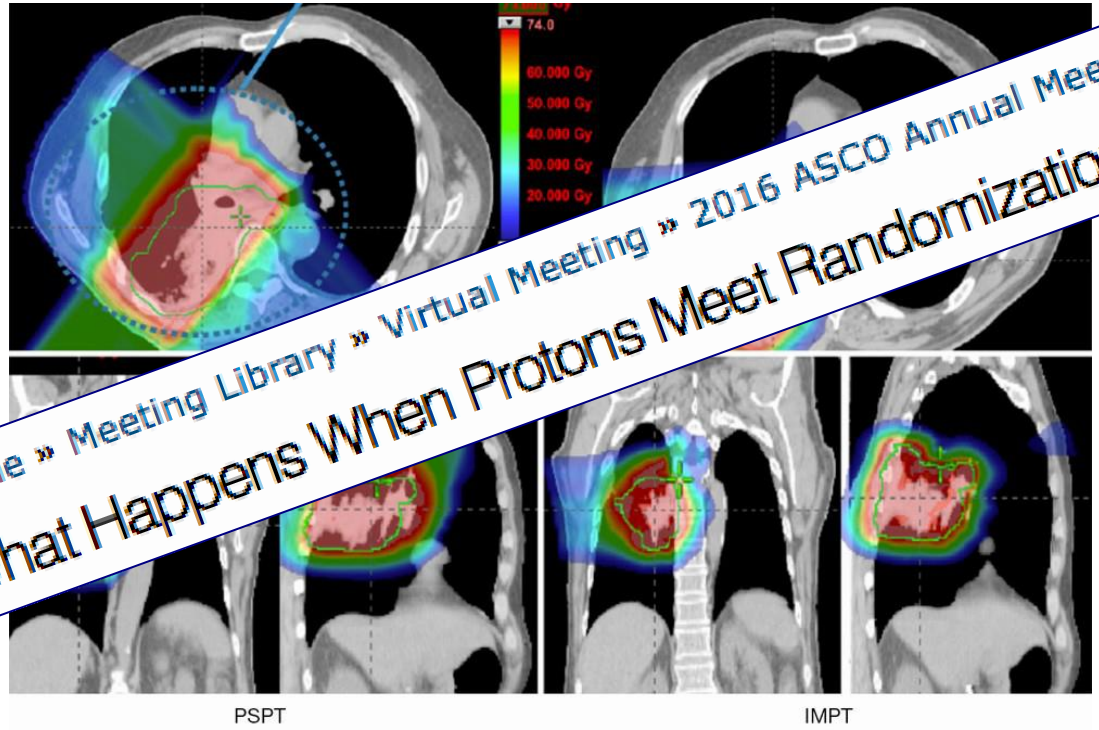
- 149 randomly allocated to IMRT (n = 92) or protons (n = 57)
- Treatment failure rates at 12 months were **20.7**% in all patients, **15.6%** in IMRT, **24.6%** in proton groups
- **Conclusions:** No differences between IMRT vs. protons on treatment failures in this randomized trial.

Liao ZX, J Clin Oncol 34, 2016 (suppl; abstr 8500)

# New versus old proton delivery techniques

**Passive scatter** proton therapy

**Intensity-modulated** proton therapy




Home » Meeting Library » Virtual Meeting » 2016 ASCO Annual Meeting

What Happens When Protons Meet Randomization?

Giap H, Translational Cancer Res 2015

# Current advances in radiation therapy

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- Hypofractionation, SBRT or SABR
- MR-guided radiotherapy
- Adaptive radiotherapy
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# Stereotactic ablative radiotherapy (SABR, SBRT)

- 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 $BED_{10}$ ≥100 Gy
  - $BED_{10}$ ≥100 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%

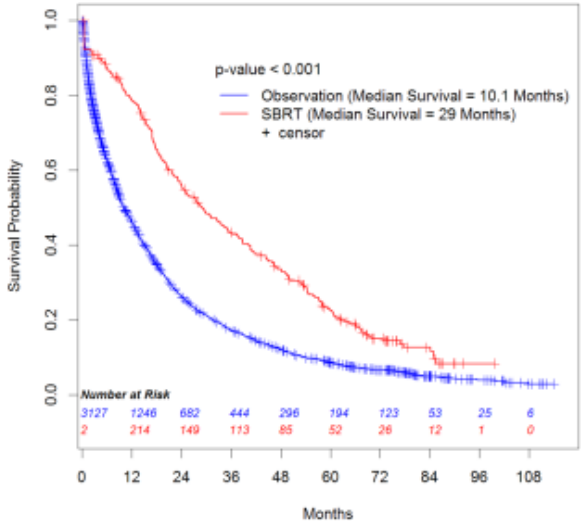
HRQL evaluation (EORTC QLQ 30, LC14 modules): 3DCRT patients had **worse dyspnea** ($p$ = 0.01), **chest pain** ($p$ = 0.02) and **cough** (>10 points difference)

# 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

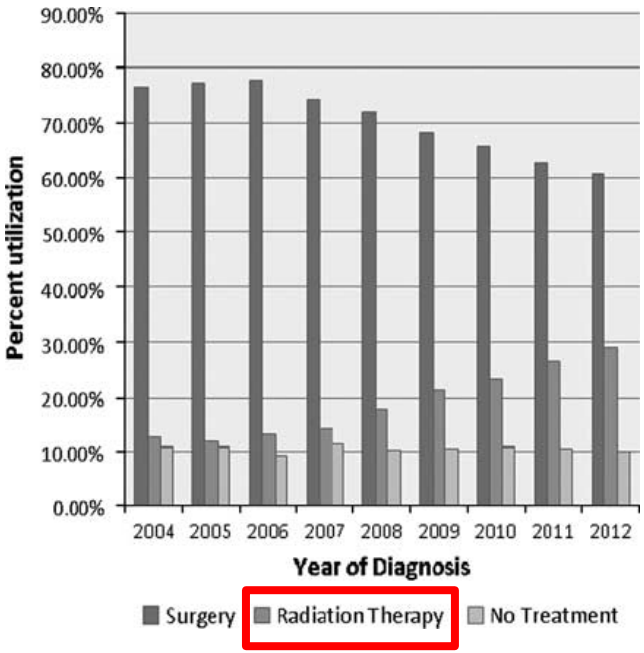



**Median survival**:
Observation: 10.1 months
SABR: 29 months

Nanda RH, Cancer 2015

# Patterns of care in the SABR-era

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




Haque W, AJCO 2016

# Requirements for lung SABR (ESTRO ACROP)

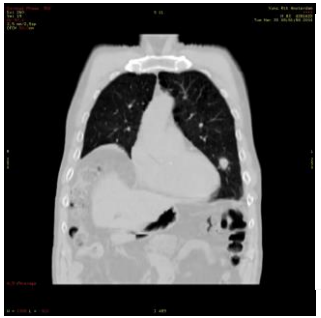
- Conventional C-arm linacs equipped only with an Electronic Portal Imaging Device (EPID) and 10mm MLC are considered as insufficient for lung SBRT (5/8).

- 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).

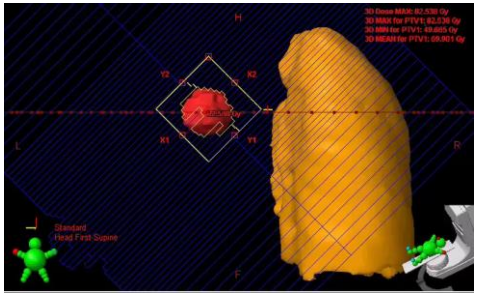
*ESTRO ACROP Guideline on implementation and practice of SBRT for early stage NSCLC [Guckenberger M, et al, **in preparation**]*

# SABR at VU University medical center

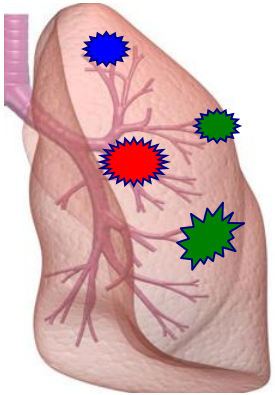


Planning 4DCT scan

Cone-beam CT



Fast delivery in <4 minutes



**<u>Risk adapted</u>** <u>fractionation schemes [Hurkmans C, Rad Onc 2009]</u>

- **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

# SPN: Asian clinical practice consensus


- High prevalence of granulomatous disease and other infectious causes of pulmonary nodules
- Diagnosis risk calculators developed in non-Asian patients <u>may not be applicable</u>
- Tuberculosis in Asia favors (i) lesser reliance on PET scanning, and (ii) greater use of non-surgical biopsy over surgical diagnosis or surveillance

Bai C, Chest 2016

# 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)

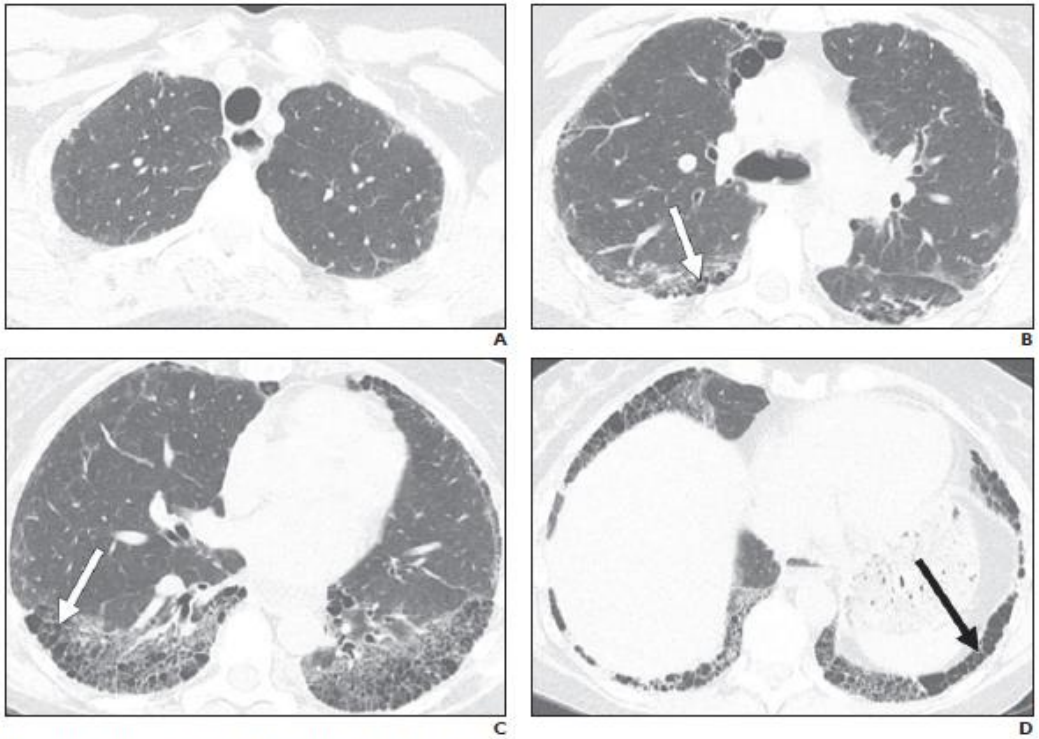
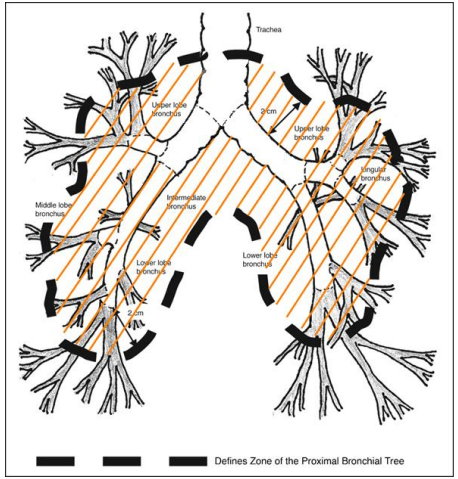



**Fig. 1**—71-year-old man with shortness of breath and crackles on auscultation.
**A–D**, Axial high-resolution CT images show peripheral and basilar-predominant pulmonary fibrosis and clustered honeycombing (*arrows*, **B–D**) in subpleural lung in this patient with usual interstitial pneumonitis pattern of pulmonary fibrosis.

Chung JH, AJR 2016

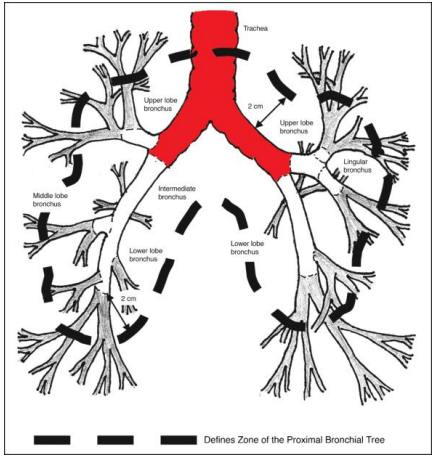
# Moderately central vs ‘ultracentral’ tumors

## Moderately central tumors




**SABR appears feasible**
RTOG 0813 [Bezjak A, WCLC 2016]. Update [Tekatli H, Rad Onc 2015]

## 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

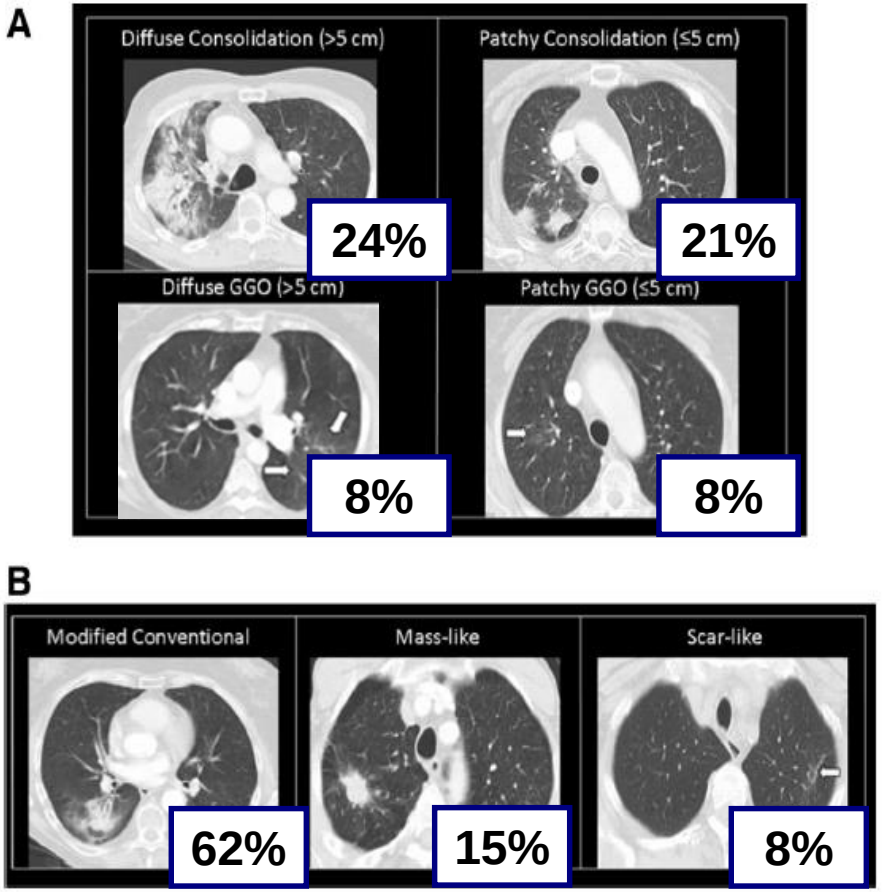
- Recognize ‘expected’ patterns of fibrosis

  (avoid patient anxiety, risky interventions)
- Toxicity (rib fractures, pneumonitis)
- Identify  recurrences (high-risk features)
- Detect and treat second tumors

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

**Acute:**
**≤6 months**

**Late:**
**>6 months**




Dahele M, JTO 2011

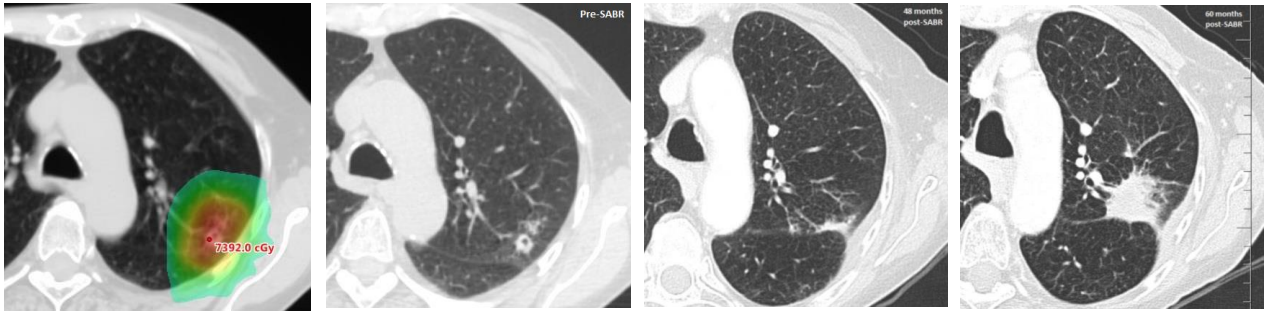
# Radiological changes post-SABR

| High-Risk Features |
| --- |
| Enlarging Opacity |
| Sequential Enlargement |
| Enlargement after 12 months |
| Bulging Margin |
| Linear Margin Disappearance |
| Loss of Air Bronchogram |
| Cranio-Caudal Growth |

Huang K, Radiother Oncol 2012, 2013

# High-risk radiological feature

## Enlarging opacity




Planning CT
Isodose colorwash 30Gy

36 months post-SABR

48 months post-SABR

60 months post-SABR

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

Ronden M, *manuscript in preparation*

# High-risk radiological feature

## Craniocaudal growth

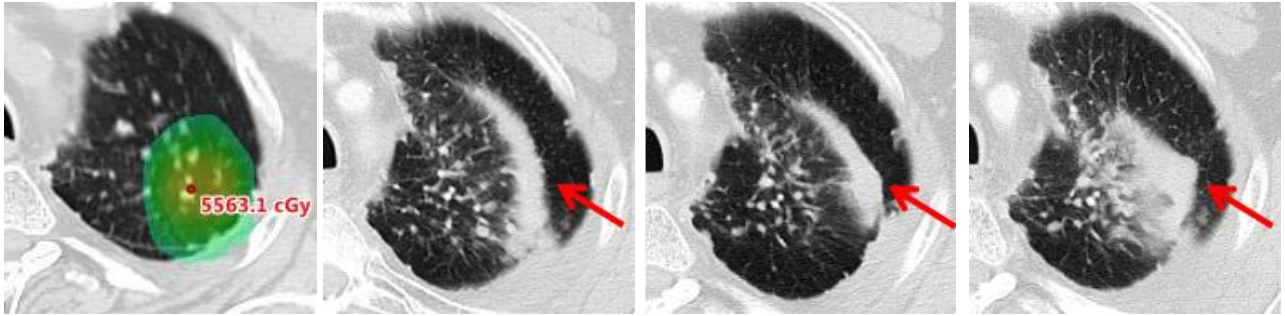

Planning CT – Isodose colorwash 30Gy | 10 months post-SABR | 16 months post-SABR

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

Ronden M, *manuscript in preparation*

# High-risk radiological feature

## Loss of linear margins




Planning CT
Isodose colorwash 30Gy

22 months post-SABR

25 months post-SABR

28 months post-SABR

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

Ronden M, *manuscript in preparation*

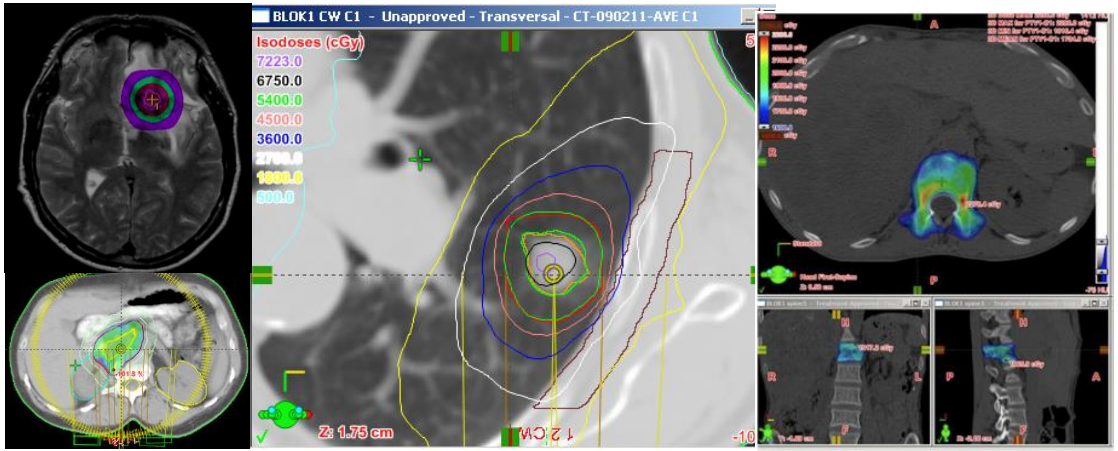
# Changing paradigms: metastatic disease

clinical practice guidelines

*Annals of Oncology* 27 (Supplement 5): v1–v27, 2016
doi:10.1093/annonc/mdw326

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

S. Novello[1], F. Barlesi[2], R. Califano[3,4], T. Cufer[5], S. Ekman[6], M. Giaj Levra[7], K. Kerr[8], S. Popat[9], M. Reck[10], S. Senan[11], G. V. Simo[12], J. Vansteenkiste[13] & S. Peters[14] on behalf of the ESMO Guidelines Committee*



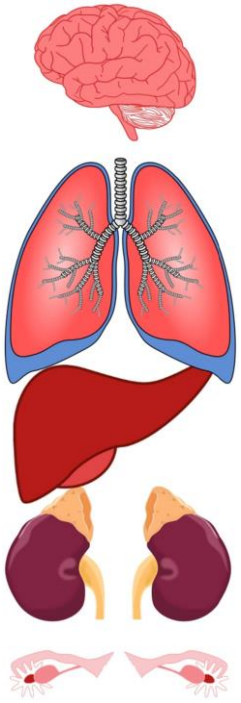
# Oligometastatic paradigm

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

Hellman and Weichselbaum, JCO 1995

Imaging (PET-CT, brain MRI) → SABR/SBRT

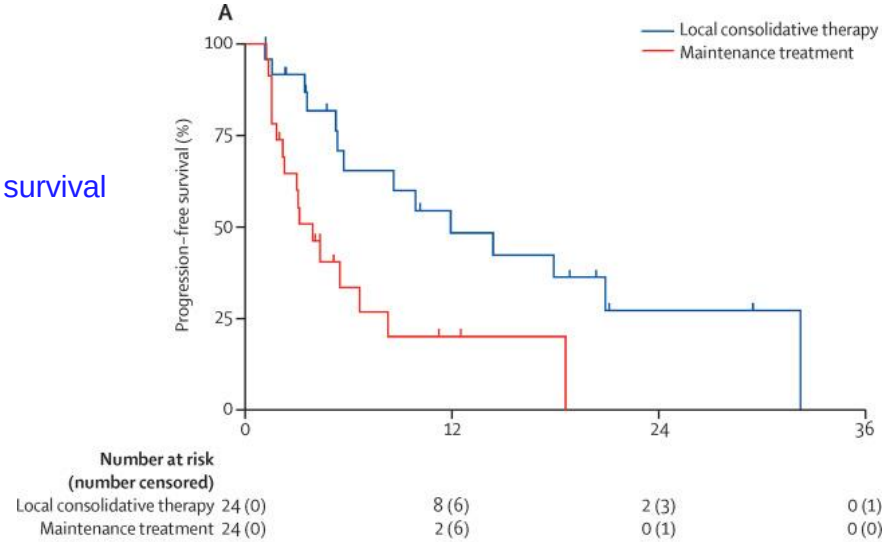
Sites of treatable oligometastases



Westover KD, Lung Cancer 2015

# 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

# Current advances in radiation therapy

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- Hypofractionation – SBRT
- MR-guided radiotherapy
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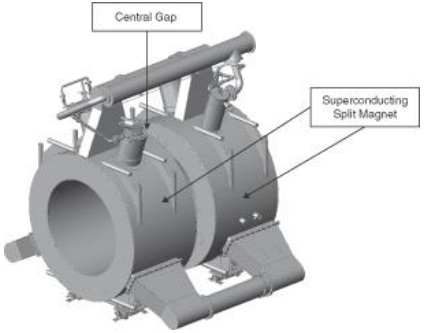
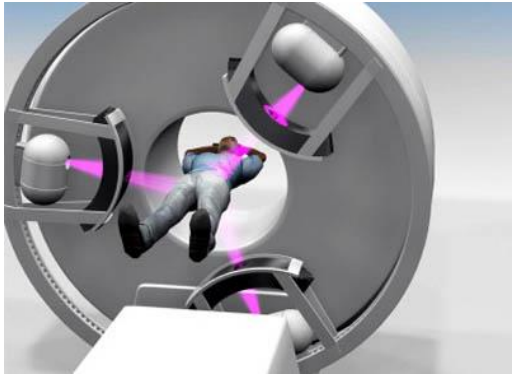
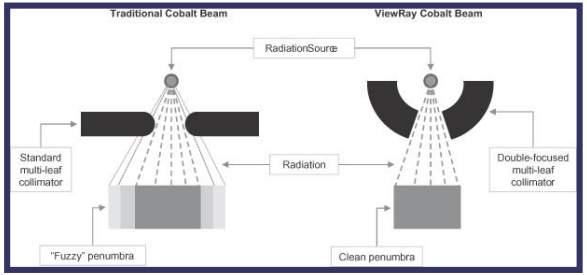
# MR-guided radiotherapy: MRIdian (ViewRay)


***Split-core 0.35T MRI***



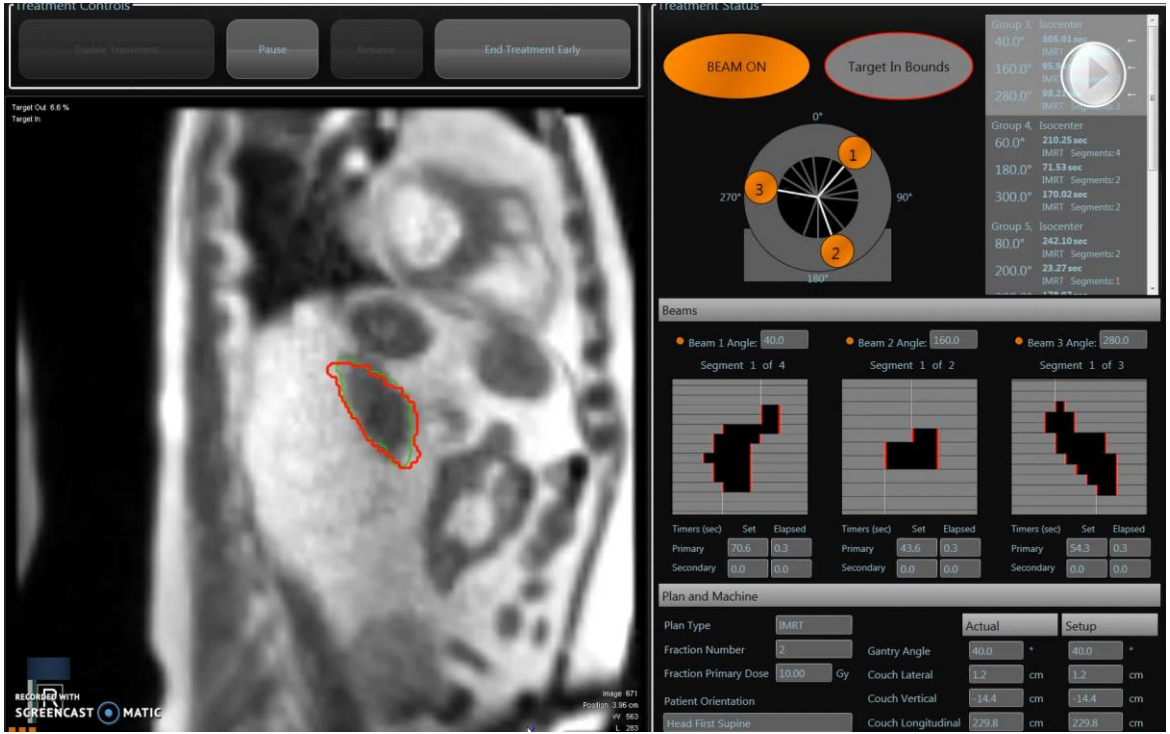
***Three cobalt-sources***




***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



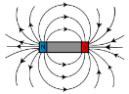
# MR-guided treatment delivery (SMART)

**S**tereotactic

**M**RI-guided

**A**daptive

**R**adio**T**herapy

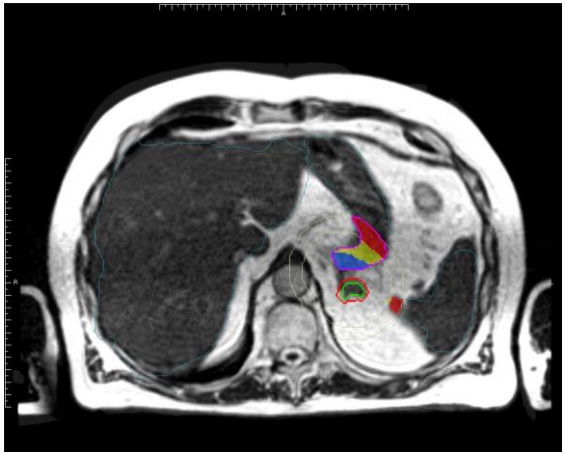


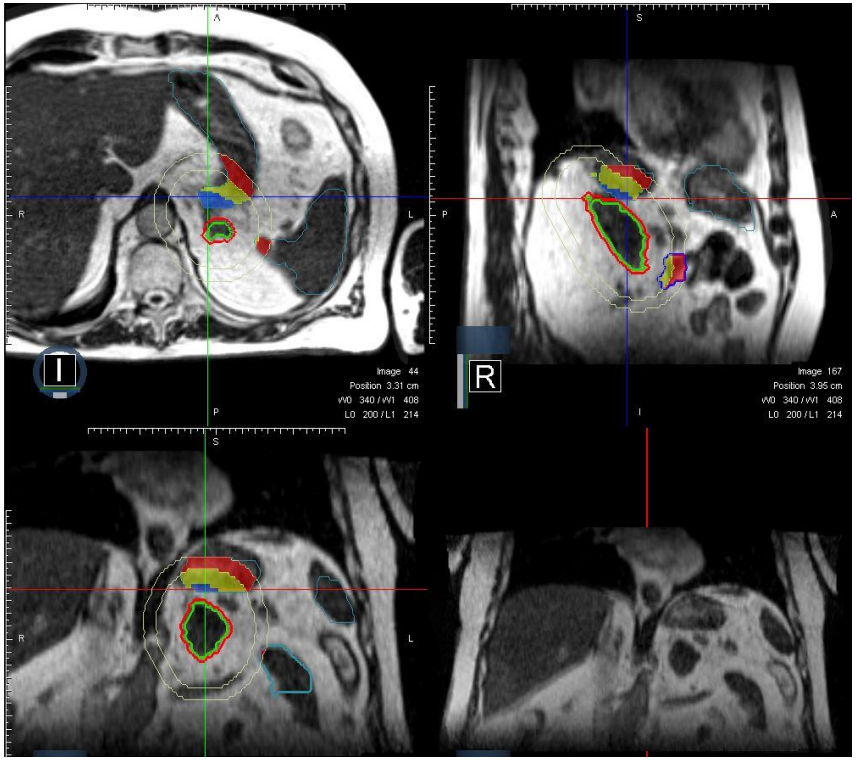

| MR-guided tumor setup | Adaptive planning | Online guidance | Gated delivery (markerless) |
|---|---|---|---|

# 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

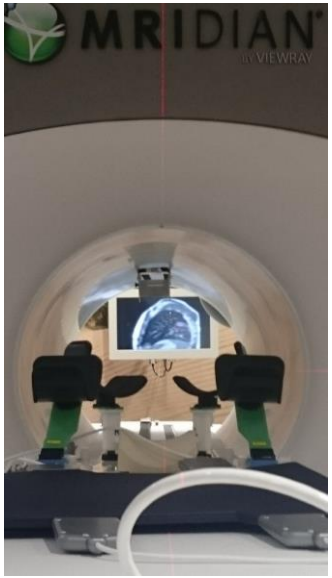
# Contouring for plan-of-the-day

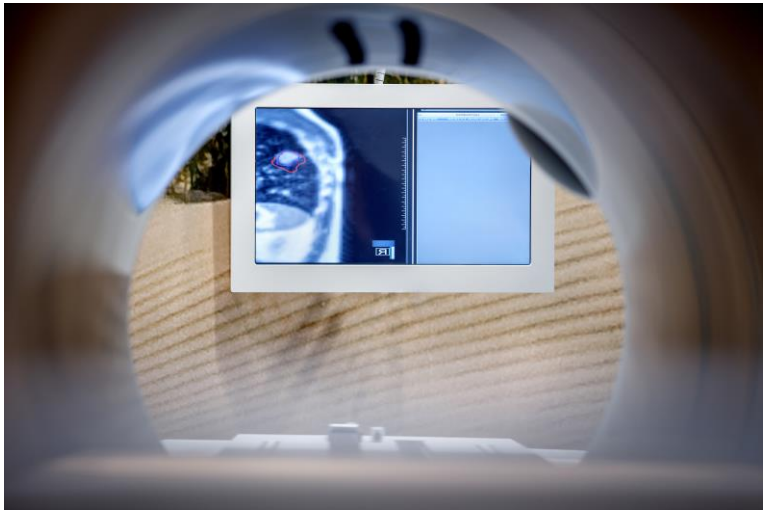




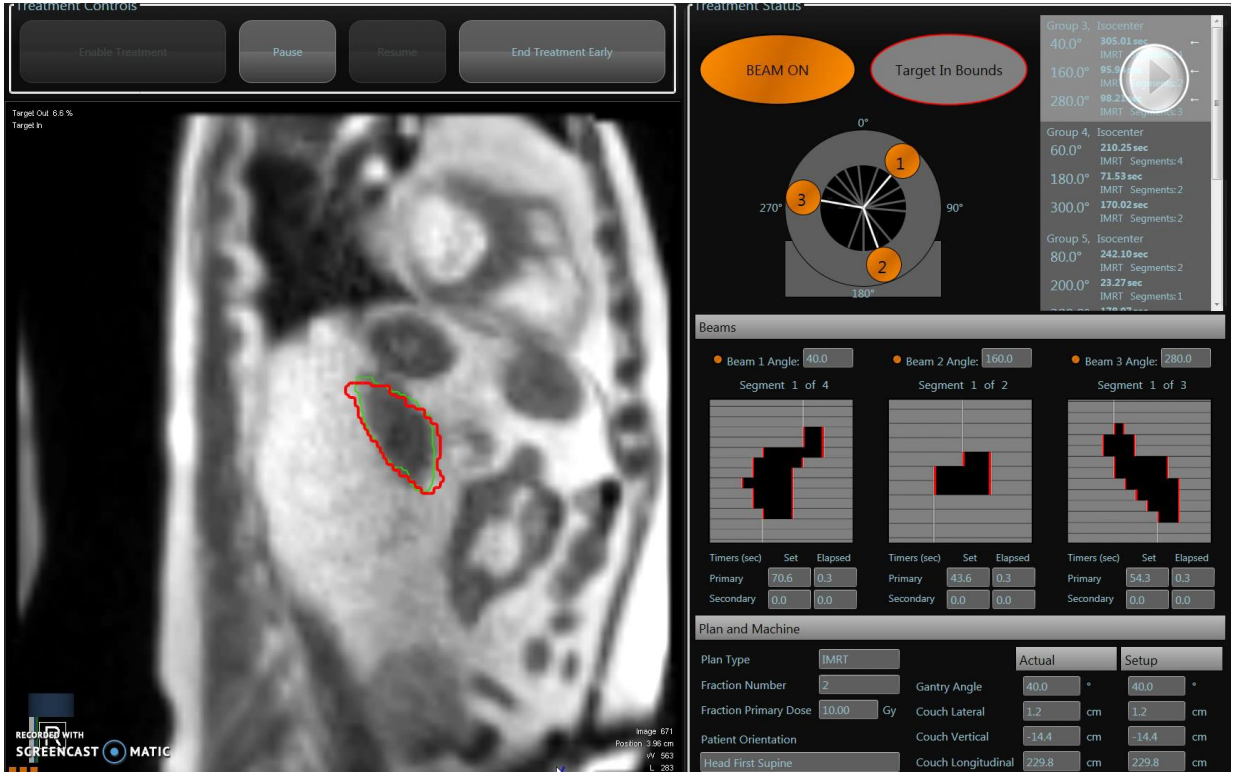

5 fractions of 10 Gy (to encompassing isodose)

# Patient-controlled breath-hold gated RT



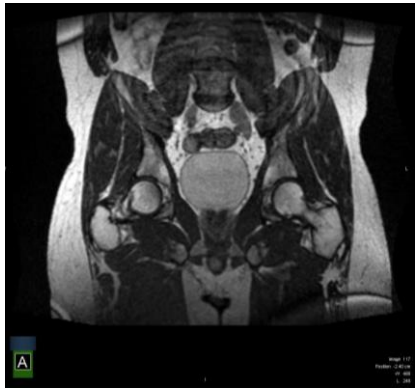



# SMART gated breath-hold delivery

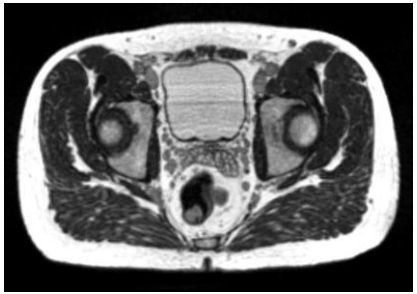
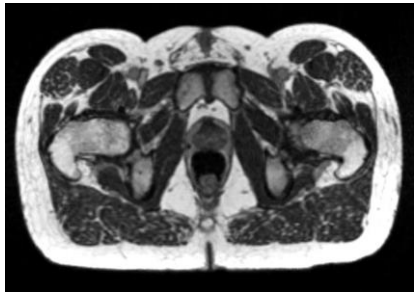
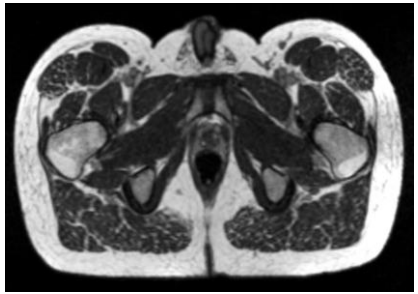



Patients can receive copies of their real-time movies

# MRIdian: Image quality with 0.35 Tesla



**More than sufficient for RTH purposes, i.e. contouring**

# Radiotherapy workflow

Treatment planning (staging info) → Treatment delivery → Treatment verification

| Treatment planning | Treatment delivery | Treatment verification |
|---|---|---|
| CT scan | 2-Dimensional RT | kV radiographs |
| 4-D CT scans | 3-D conformal RT | Cone-beam CT |
| FDG-PET | Intensity-modulated RT | Continuous MRI |
| MRI scans | Particle therapy | |

# Current advances in radiation therapy

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

Thank you for your attention