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DEPARTMENT OF RADIATION ONCOLOGY

Radiation Treatment Techniques: Where to find rooms for improvement?

Cedric Yu, D.Sc.

Carl M. Mansfield, M.D. Professor

University of Maryland School of Medicine

Founder and CEO, Xcision Medical Systems, LLC

"The Age of Gizmos"

MLC (1990)
Cyber Knife (1992)
IMRT (1993)
Tomotherapy (1993)
IMAT/VMAT (1995)
CBCT (2000)
SBRT (2004)
IGRT (2004)

GammaPod (2007)
Protons (1990 -)
ViewRay (2007)
Elekta Unity (2015)
Adaptive RT
AI …

Are We Hitting a Limit?

VISION 20/20: Planning and delivery of intensity-modulated radiation therapy

Cedric X. Yu, Christopher J. Amies, and Michelle Svatos

Med. Phys. **35**, 5233 (2008);

Based on 10 years of experience with IMRT, we have learned that the opportunities in improving plan quality are limited within the constraint of present linac/MLC delivery. To improve the quality of IMRT treatment plans, we must inject new degrees of freedom. This may require an overhaul of existing technologies.

Rooms for Improvement

- New Physics – Protons, Carbon ion
- New Degrees of Freedom
- Site Specific Solutions
- New Biology

Rooms for Improvement

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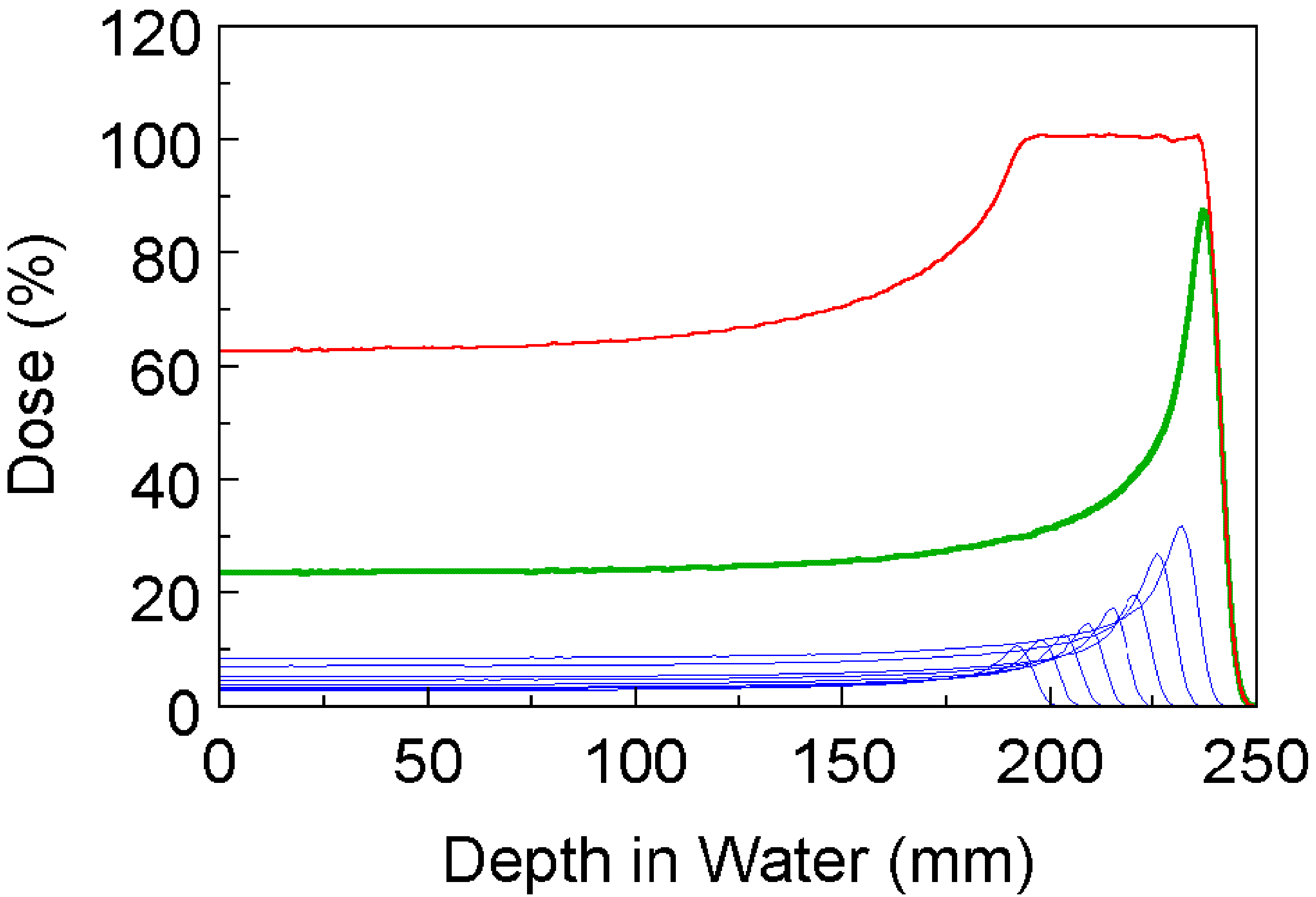
- Site Specific Solutions
- New Biology

Ideal Depth Dose with SOBP



Why not Protons?

- Technology
  - More complicated, therefore harder to advance
- Physics
  - Penumbra, Bragg Peak uncertainty
  - Sensitive to anatomical variations
  - Interplay effects with organ motion
- Biology
  - RBE uncertainty
- Economy

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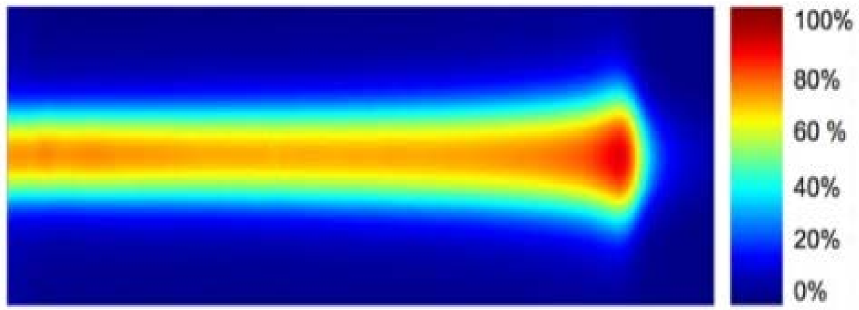
Lateral Penumbra

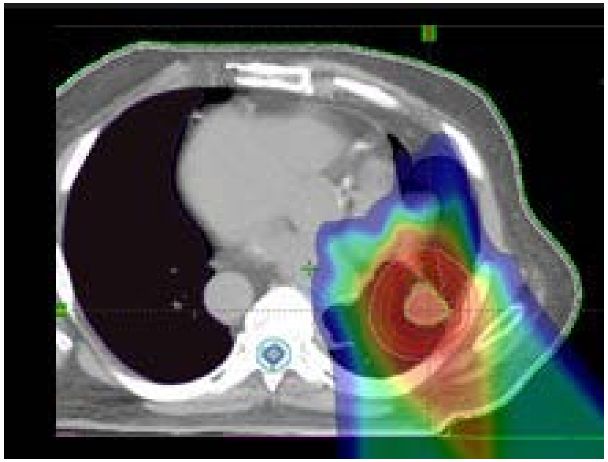
The dose penumbra at deeper depth is less steep for Proton beam (6-10mm) than for photon beams



Med Phys. 2013 Apr;40(4):041723

Effects of large penumbra

Protons



S.J. Gandhi et al: Practical Rad Oncol. 2015 1-10.

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Why not Protons?

- Technology
  - More complicated, therefore harder to advance
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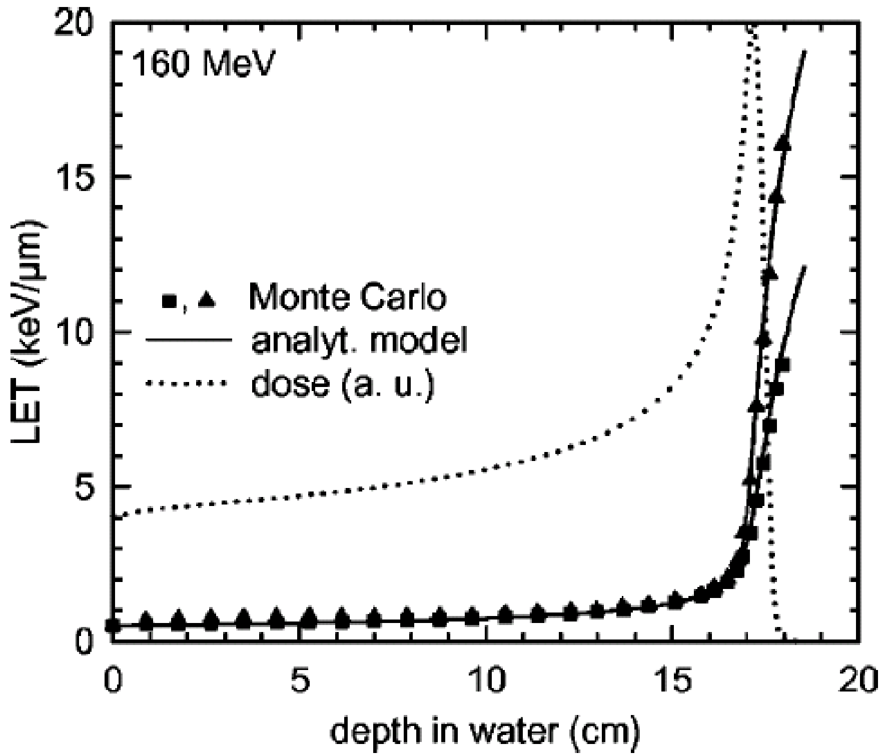
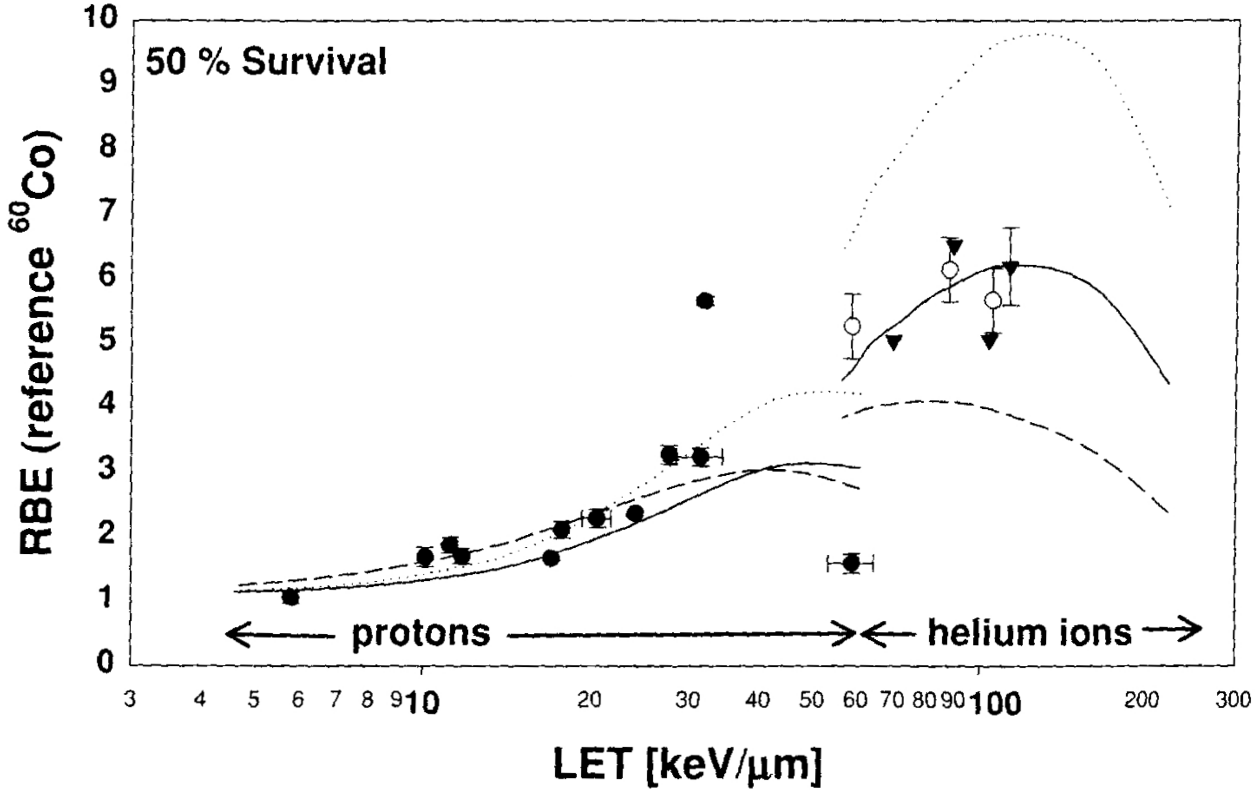
  - Penumbra, Bragg Peak uncertainty
  - Sensitive to anatomical variations
  - Interplay effects with organ motion
- Biology
  - RBE（radiobiological effectiveness）uncertainty

LET



160 MeV
■, ▲ Monte Carlo
analyt. model
dose (a. u.)
LET (keV/µm)
depth in water (cm)
0
5
10
15
20

Published RBE Proximal to SOBP



From H Paganetti PMB 47(5)

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Higher RBE for Lower Doses

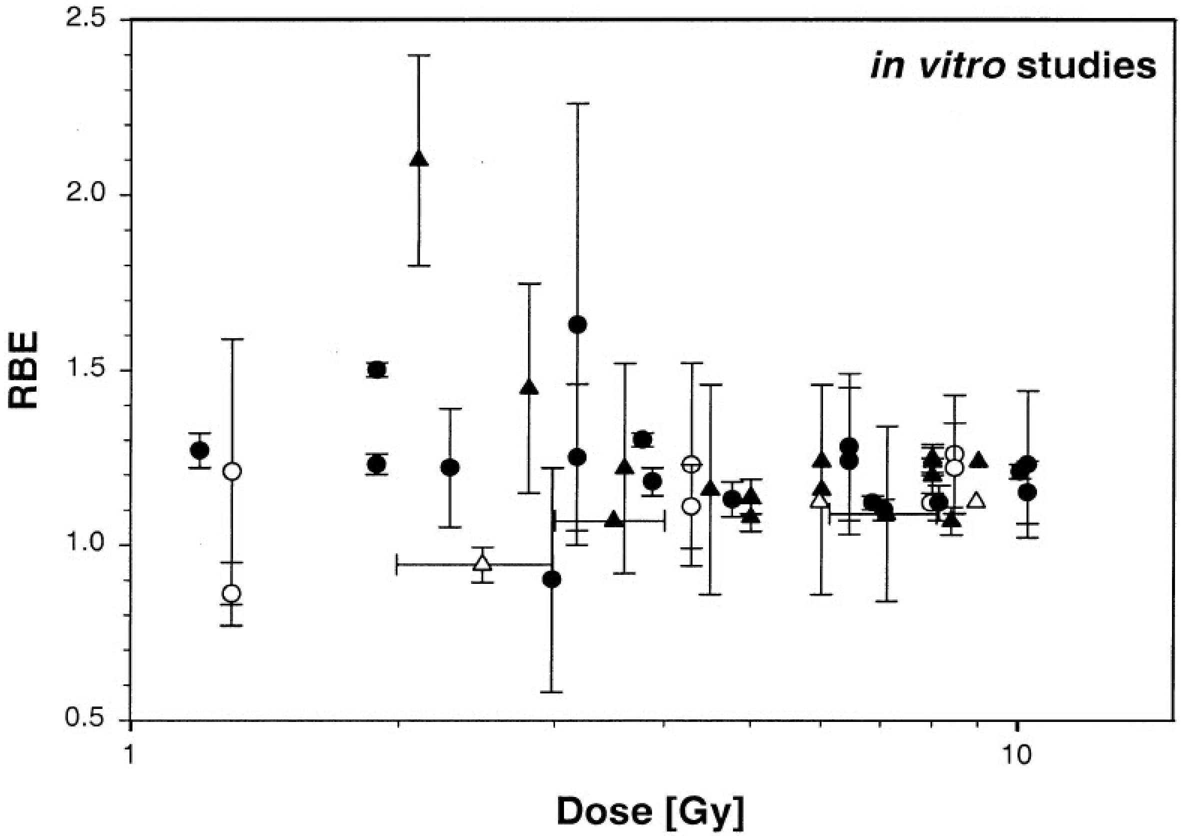

Fig. 1. Experimental proton RBE values (relative to ^{60}Co) as a function of dose/fraction for cell inactivation measured *in vitro* in the center of a SOBP. Closed symbols show measurements using Chinese Hamster cell lines; open symbols stand for other cell lines. Circles represent RBEs for <100-MeV beams and triangles for >100-MeV beams.

From H Paganetti PMB 47(5)

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Assumption: $RBE_{Co-60}^{Proton} = 1.1$

- Higher RBE near BP is good for target cell killing
- It is also the area with the largest penumbra. Dose is lower in surrounding tissue and the goals are different (Kill v.s. Injury)
- In radiation protection, we have been using a quality factor of Q = 20!
- If we use a RBE of 1.5 for normal tissue dose, the physics advantage of protons v.s. photons will be reversed!

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Rooms for Improvement

- New Physics – Protons, Carbon ion
- New Degrees of Freedom
- Site Specific Solutions
- New Biology

How to Improve Photon Plan Quality?

Intensity-modulated arc therapy with dynamic multileaf collimation: an alternative to tomotherapy

Cedric X Yu
William Beaumont Hospital, Royal Oak, MI, USA

Received 9 February 1995, in final form 20 April 1995

“The DVHs or subsequently derived biological scores depend on the total number of strata, ...”

In coplanar IMRT and VMAT, we are only using 20-30 independent apertures!

Is it true that increasing the number of independent apertures will improve plan quality?

Dyconic CRT

Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 1, pp. 287–295, 2003
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0360-3016/03/$–see front matter

ELSEVIER

doi:10.1016/S0360-3016(03)00087-7

3D-CRT

DYNAMIC CONICAL CONFORMAL RADIOTHERAPY USING A C-ARM–MOUNTED ACCELERATOR: DOSE DISTRIBUTION AND CLINICAL APPLICATION

Keiichi Nakagawa, M.D., Ph.D., Yukimasa Aoki, M.D., Ph.D., Masao Tago, M.D., Ph.D., and Kuni Ohtomo, M.D., Ph.D.

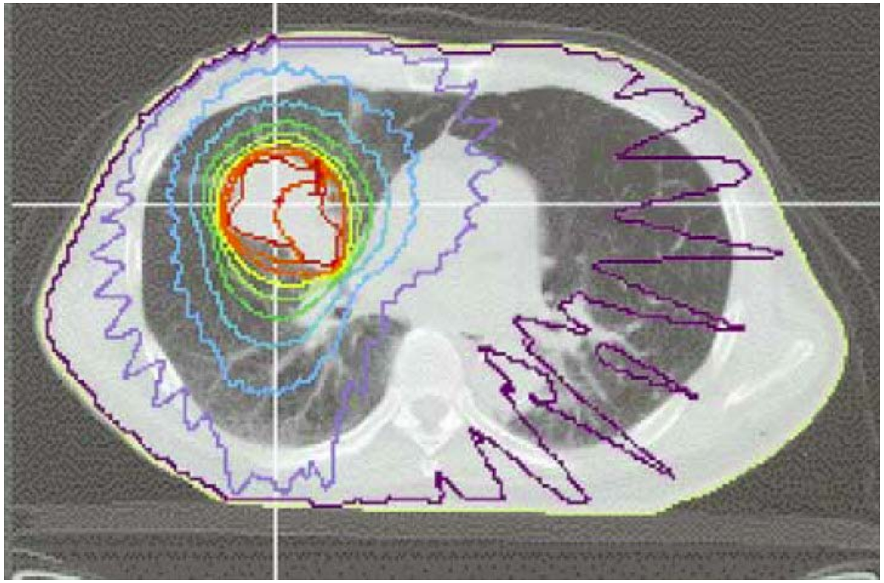
Department of Radiology, University of Tokyo Hospital, Tokyo, Japan

University *of* Maryland
School of Medicine

Dyconic CRT for NSCLC

Rotational CRT

Dyconic CRT



— 10%

— 20%

Can protons create such dose distribution?

4π RT

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Physics Contribution

4π Non-Coplanar Liver SBRT: A Novel Delivery Technique

Peng Dong, PhD,* Percy Lee, MD,* Dan Ruan, PhD,* Troy Long, BS,† Edwin Romeijn, PhD,† Yingli Yang, PhD,* Daniel Low, PhD,* Patrick Kupelian, MD,* and Ke Sheng, PhD*

*Department of Radiation Oncology, University of California, Los Angeles, California; and †Department of Industrial and Operations Engineering, University of Michigan, Ann Arbor, Michigan

Received Jun 8, 2012, and in revised form Aug 17, 2012. Accepted for publication Sep 24, 2012

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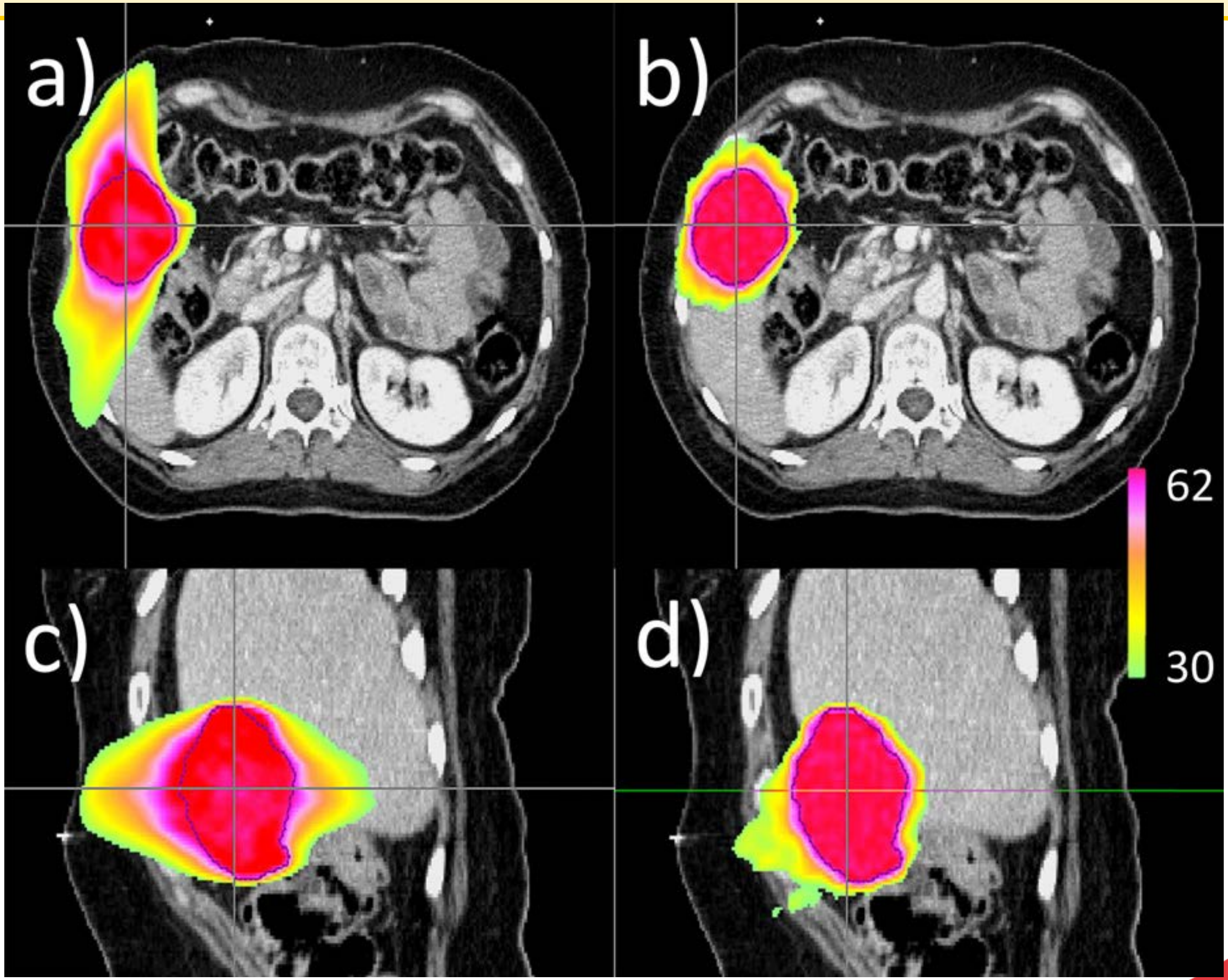
4π RT for Liver Cancer



Peng Dong et al: Int J Rad Oncol Biol Phys. 85(5), 2013

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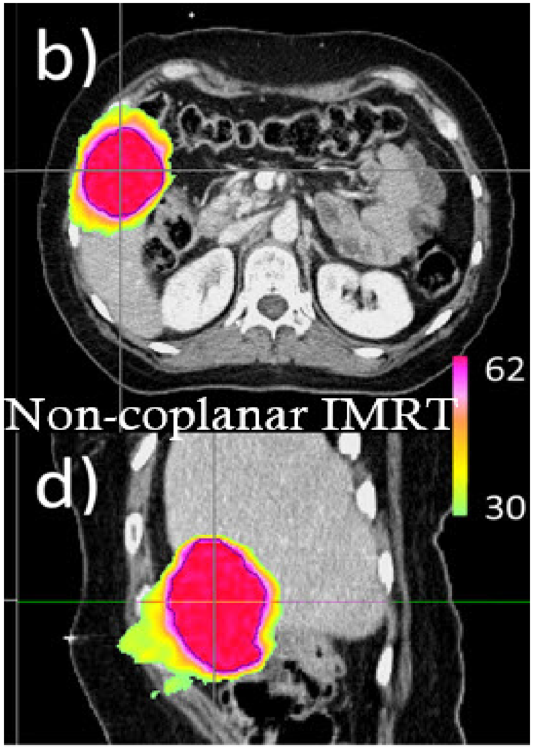
Compared with 4π RT

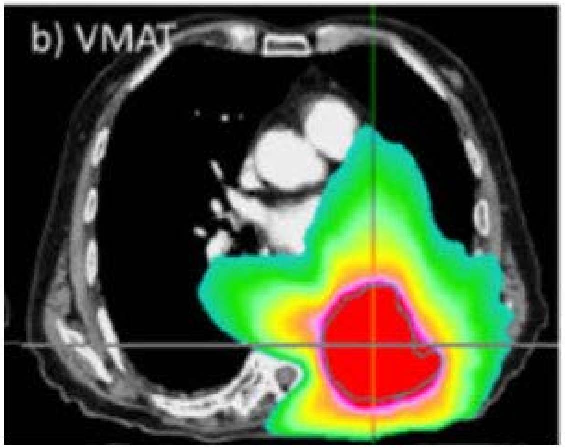
S.J. Gandhi et al: Practical Rad Oncol. 2015 1-10.

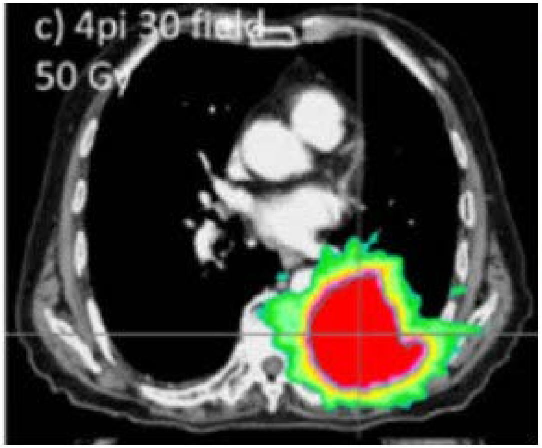


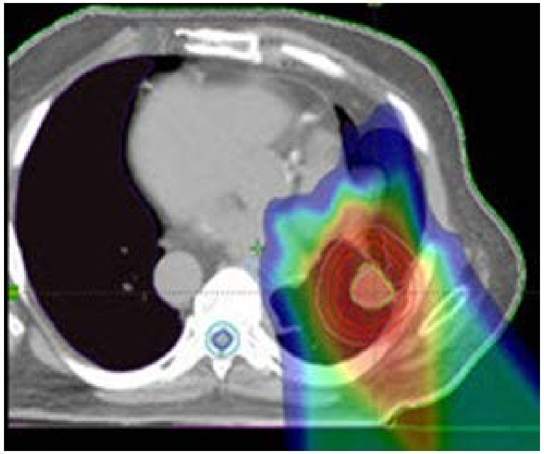
Dong P, Int J Radiat Oncol Biol Phys 2013; 85:1360-6

Uniform dose, non-uniform LET

Compared with 4π RT for Lung Cancer







Dong P, et al. Int J Radiat Oncol Biol Phys 2013; 86(3):pp.407-413

Question 1

1) What makes IMRT dose distribution better than 3D conformal therapy?

a) intensity of a field is allowed to change

b) more independent apertures are used

c) Inverse planning

d) all of the above

Answer 1

Answer is **d).**

1. A Brahme, “Optimization of stationary and moving beam radiation therapy techniques,” Radiother Oncol. **12**, 129-140 (1988).
2. C.X. Yu, M.J. Symons, M.N. Du “et al : A method for implementing dynamic photon beam intensity modulation using independent jaws and multileaf collimator,” Phys. Med. Biol. 40, 769-787 (1995).

Rooms for Improvement

- New Degrees of Freedom
- Site Specific Solutions
  - ✓ GammaPod for Breast Cancer
- New Biology

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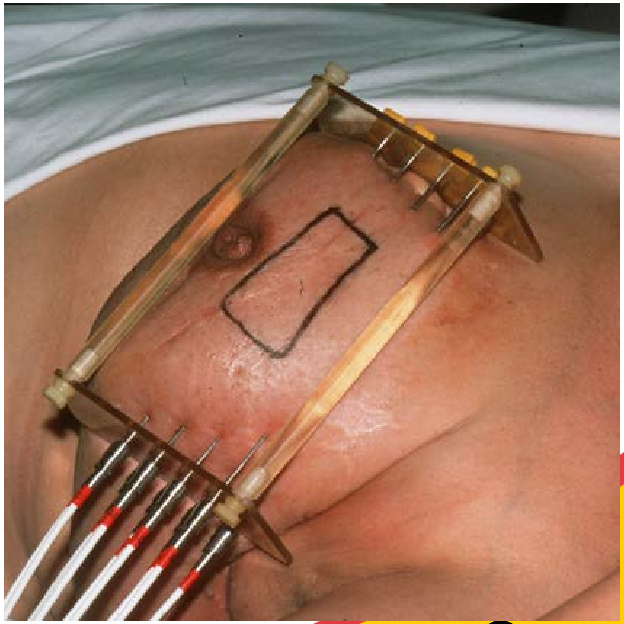
Brachytherapy

LDR

- I-125 implants

HDR

- Breast HDR template



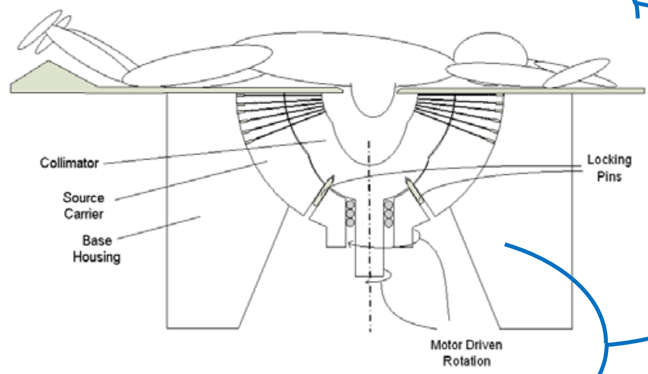
"hot spots", V_{150} & V_{200} , predicts Skin toxicity & fat necrosis

Antonucci JV et al: Int J Rad Oncol Biol Phys. 2009, 74(2):447-52.

1996 NIH proposal

"Stereotactic conformal therapy of breast cancer"

More convenient, consistent, noninvasive, less toxic



1996 NIH proposal: “Stereotactic conformal therapy of breast cancer”

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GammaPod

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GammaPod™ workflow for each treatment fraction

Cup Fitting → CT Scanning → Treatment Planning → Treatment Delivery

Cup Fitting

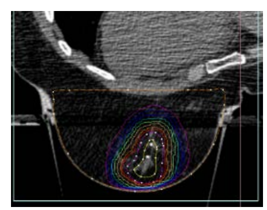
Fit cup to patient
Establish suction

CT Scanning

Load patient
Acquire images

Treatment Planning

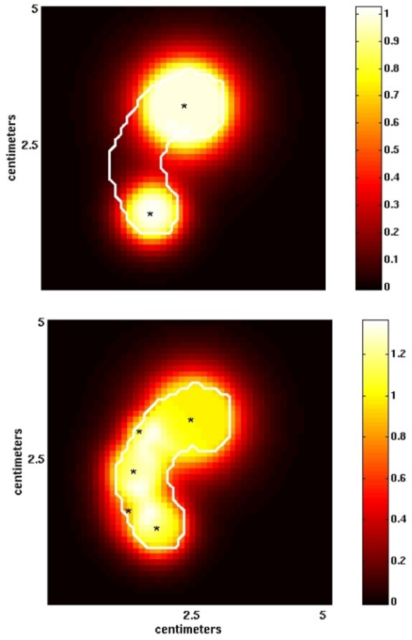
Contour images
Optimize plan



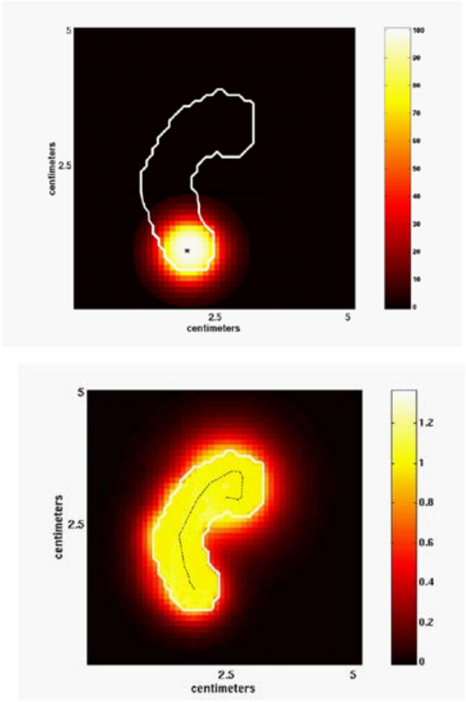
Treatment Delivery

Load patient
Deliver treatment

“Ball packing” v.s. “Dose painting”

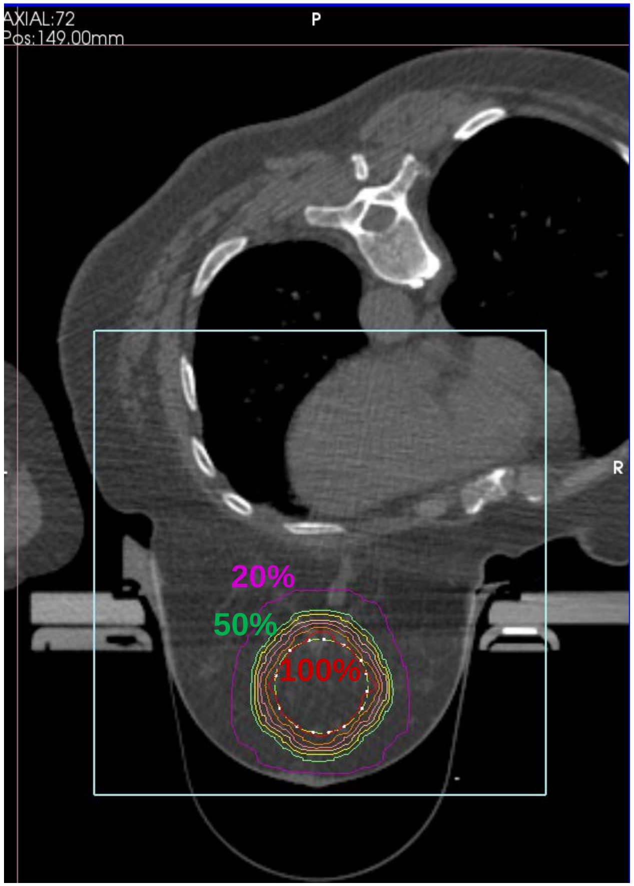


V.S.

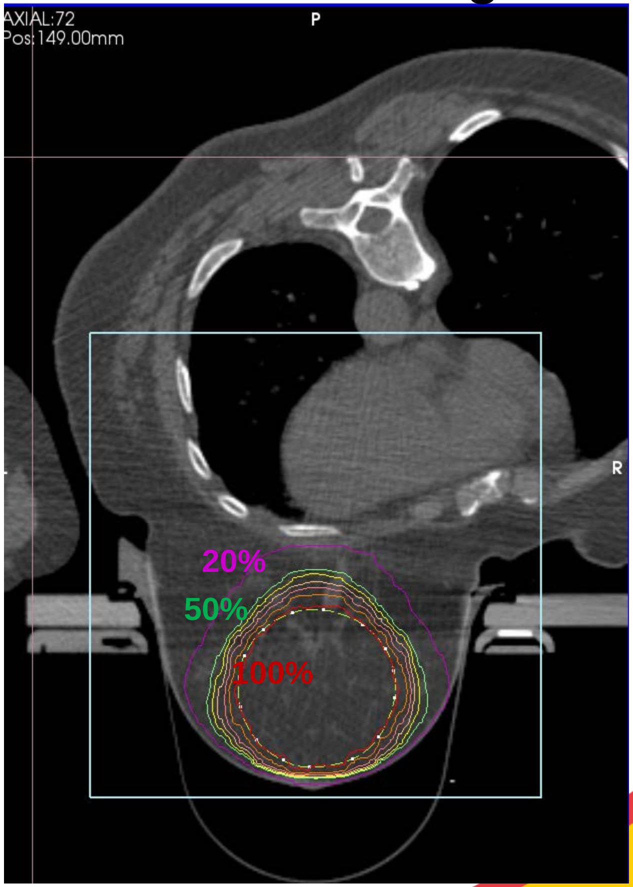


Example Dose Distributions

45 cc target



215 cc target



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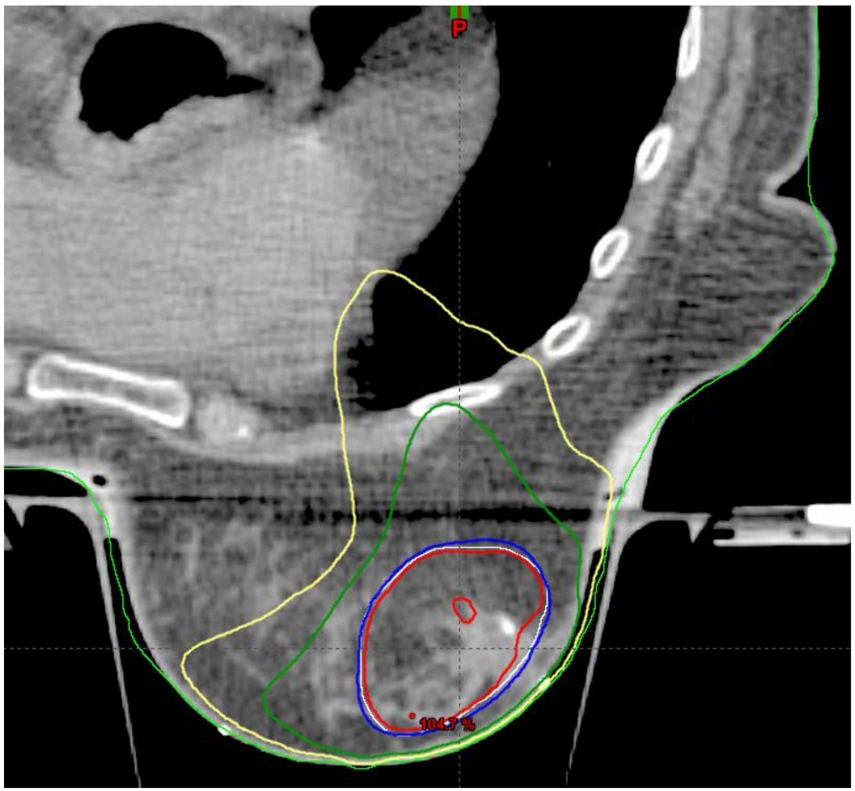
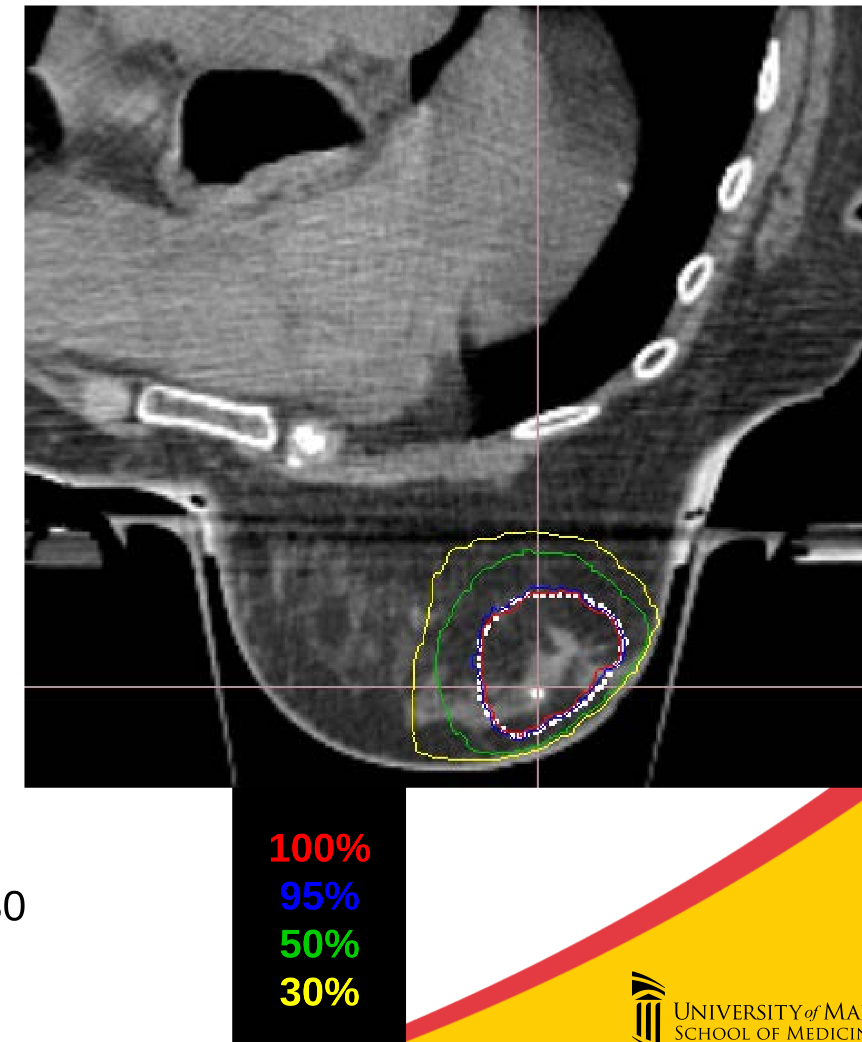
Benefits of GammaPod





J.W. Snyder et al, Oncology 92, p.21-30

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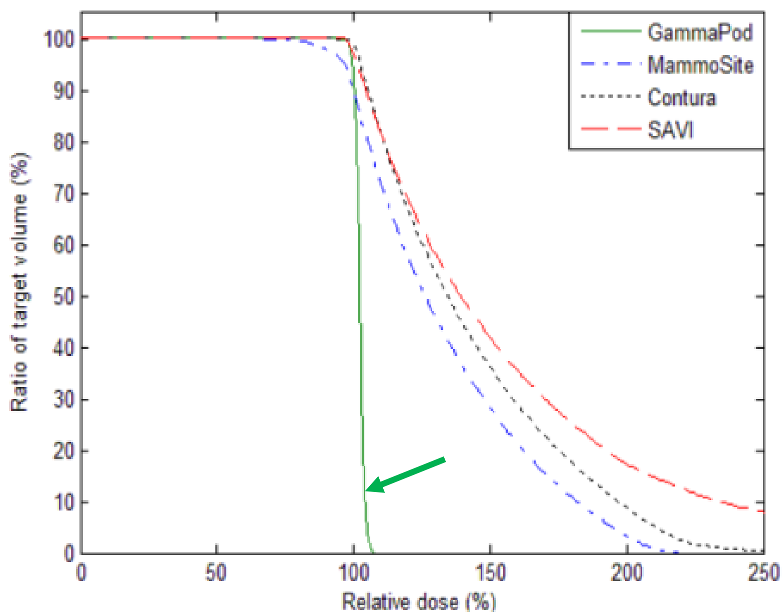
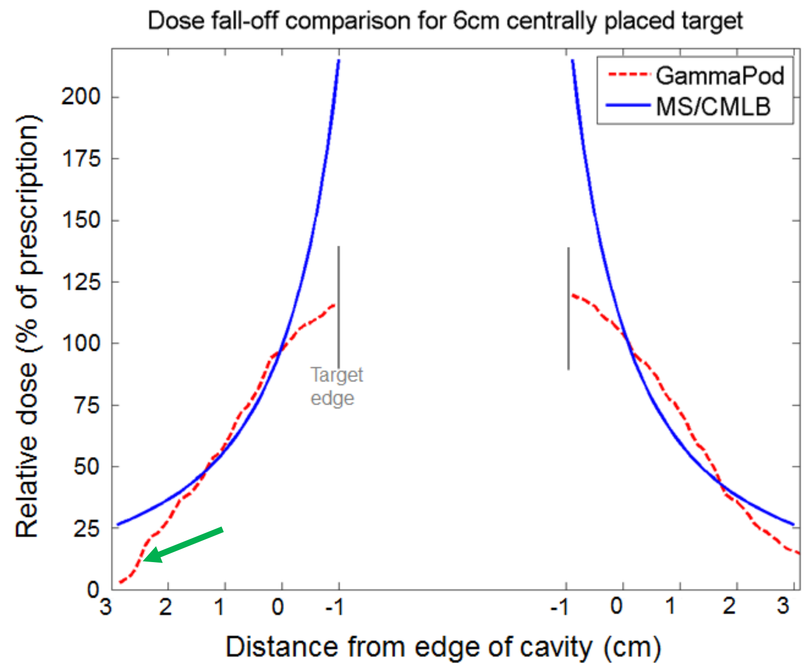
GammaPod vs Balloon Brachytherapy

Phys Med Biol. 2013 Jul 7;58(13)

Dosimetric comparison between intra-cavitary breast brachytherapy techniques for accelerated partial breast irradiation and a novel stereotactic radiotherapy device for breast cancer: GammaPod™.

Ödén J, Toma-Dasu I, Yu CX, Feigenberg SJ, Regine WF, Mutaf YD.





Phase III trial points to omitting radiation

IH Kunkler, LJ Williams, WJL Jack, DA Cameron, J M Dixon on behalf of the PRIME II investigators: **Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial**
Lancet Oncology 16(3), 266-237, 2015

T1-2, ≤3cm, ER+, 65yo+, 1326 patients

With radiation 5yr IBR = 1.3%

Without radiation, 5yr IRB = 4.1%

“5-year rate of ipsilateral breast tumour recurrence is probably low enough for omission of radiotherapy”

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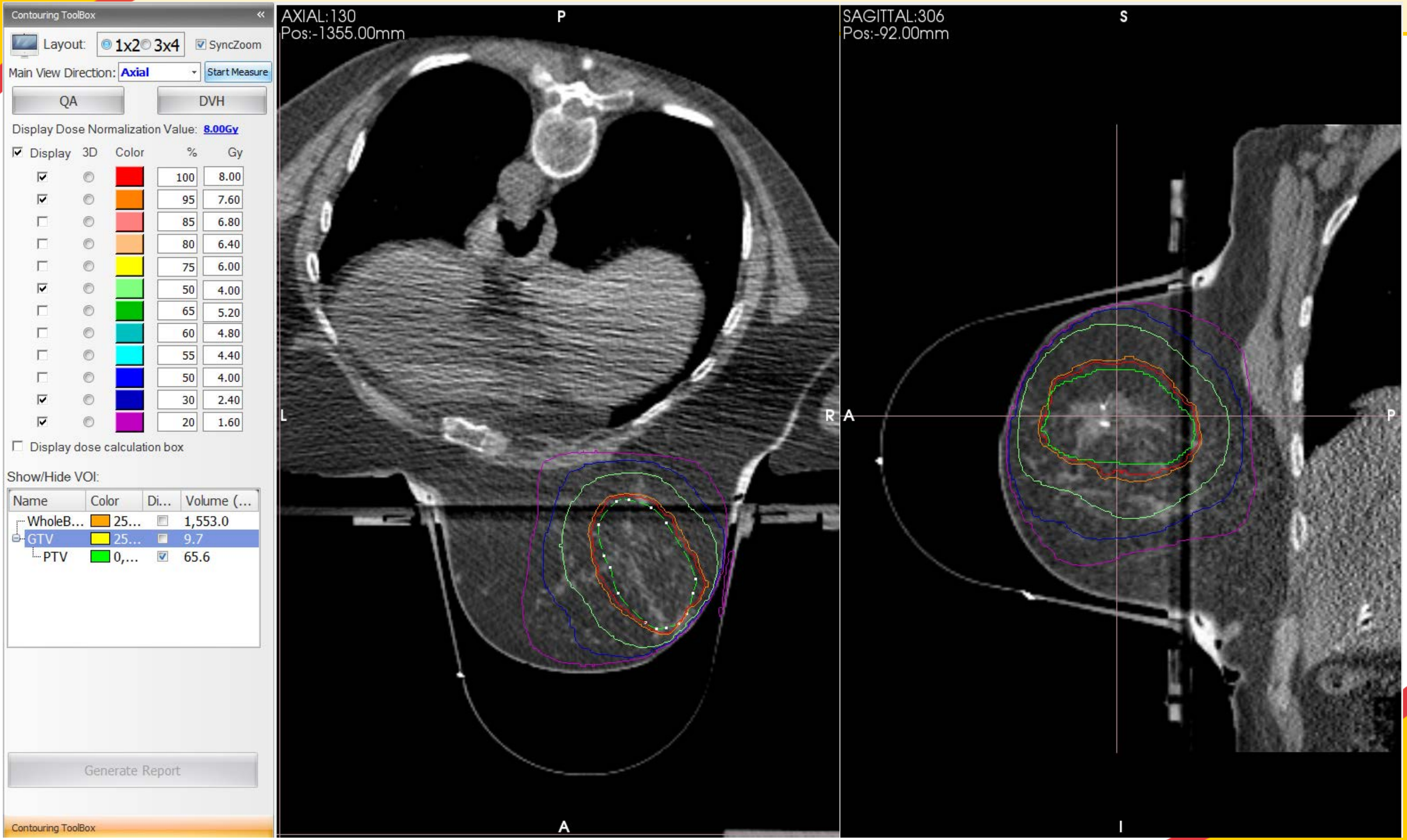
Why not Omitting Surgery?

Nichols E et al IJROBP 2010 May 1;77(1)197-202
Nichols E et al AJCO 2013 June; 36(3) 32-38

Patient 2



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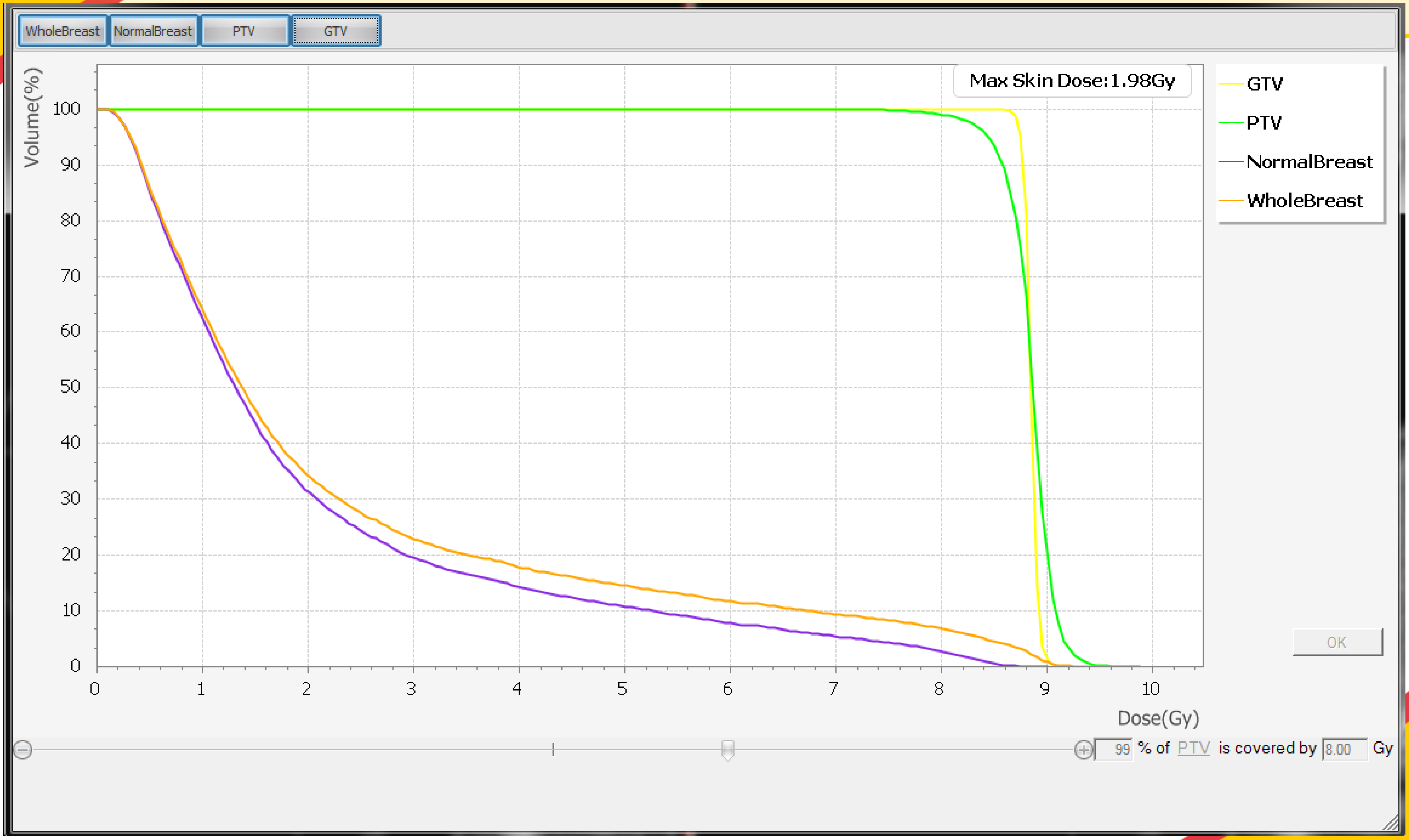
Patient 2 DVH



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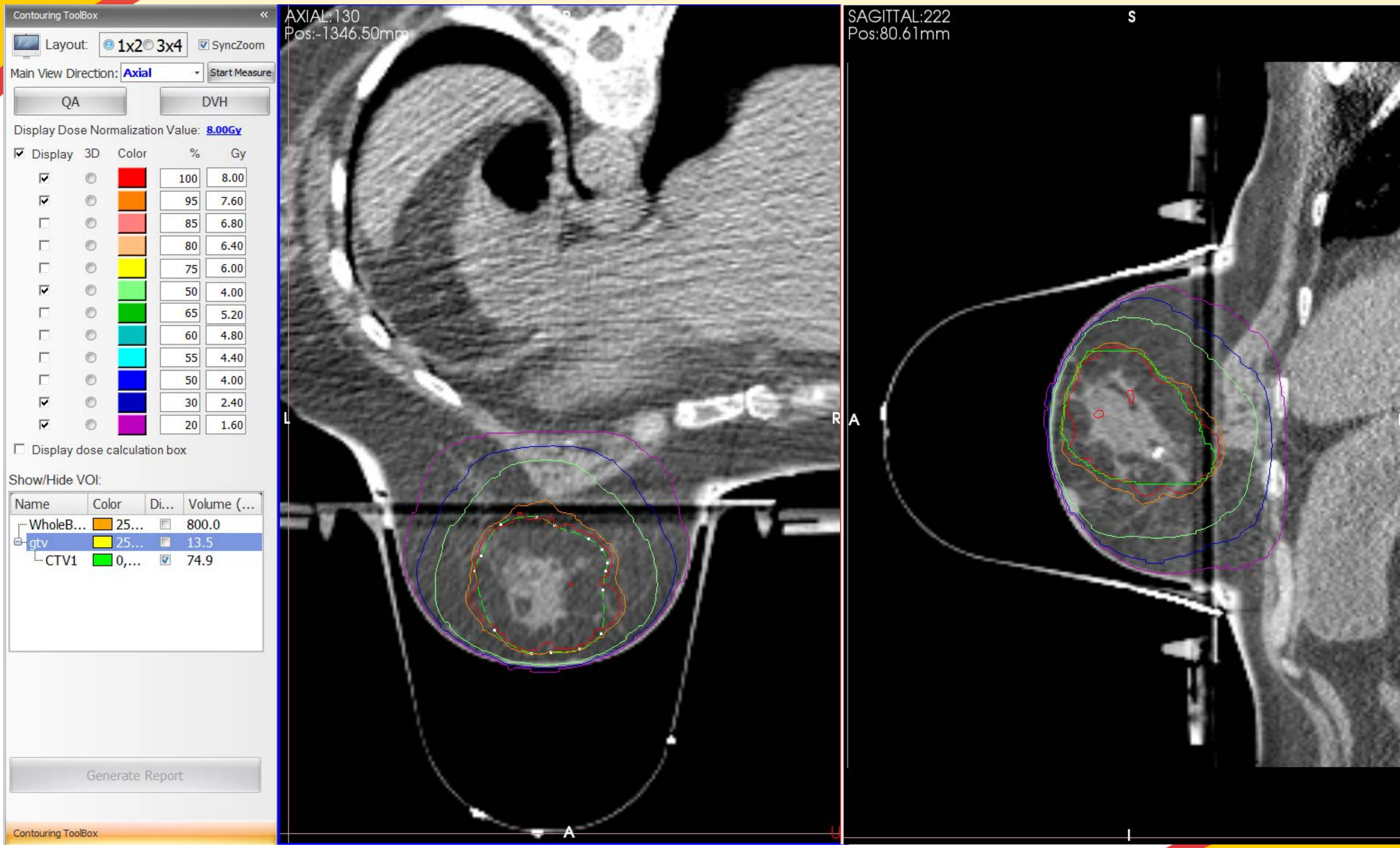
Patient 3



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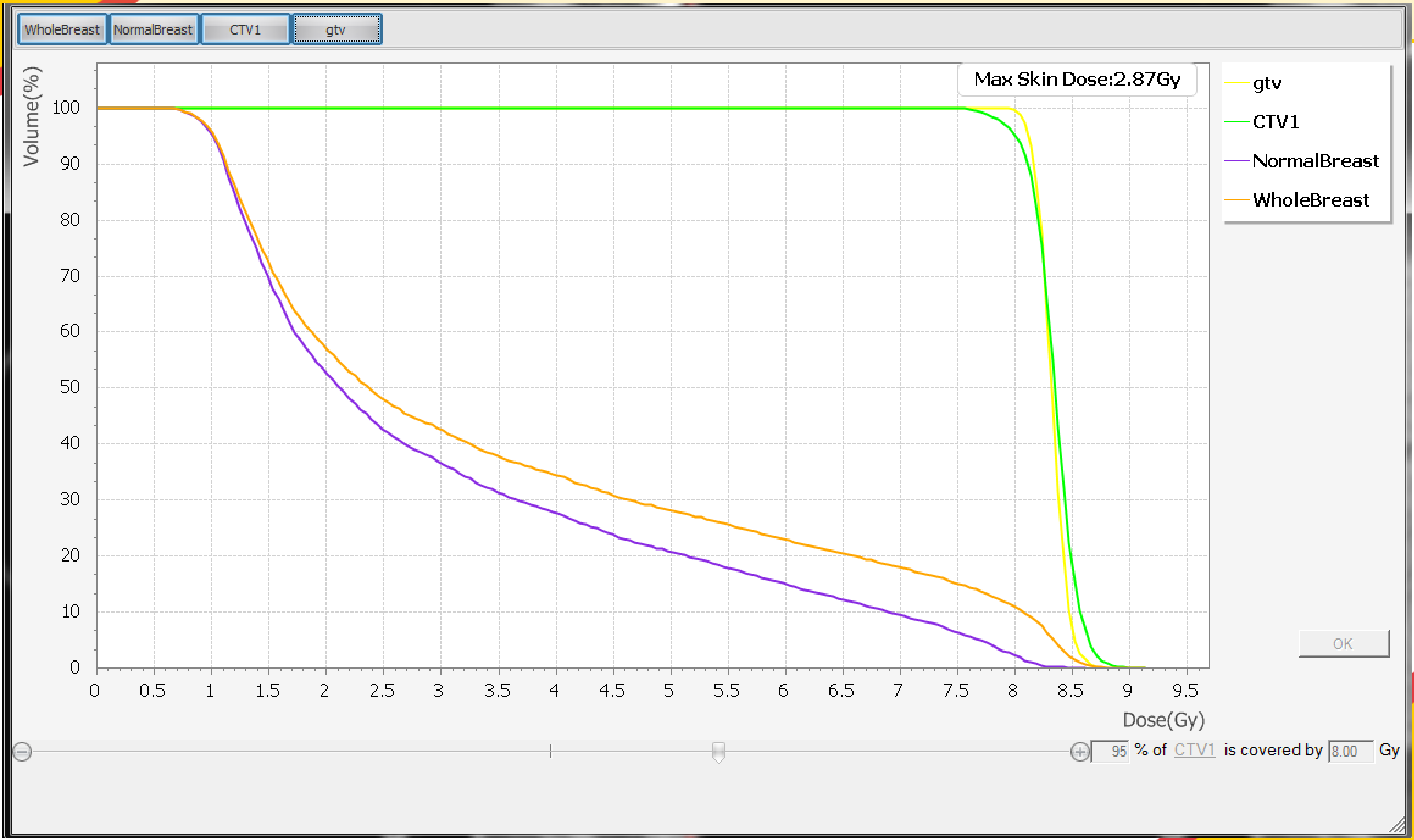
Patient 3 DVH



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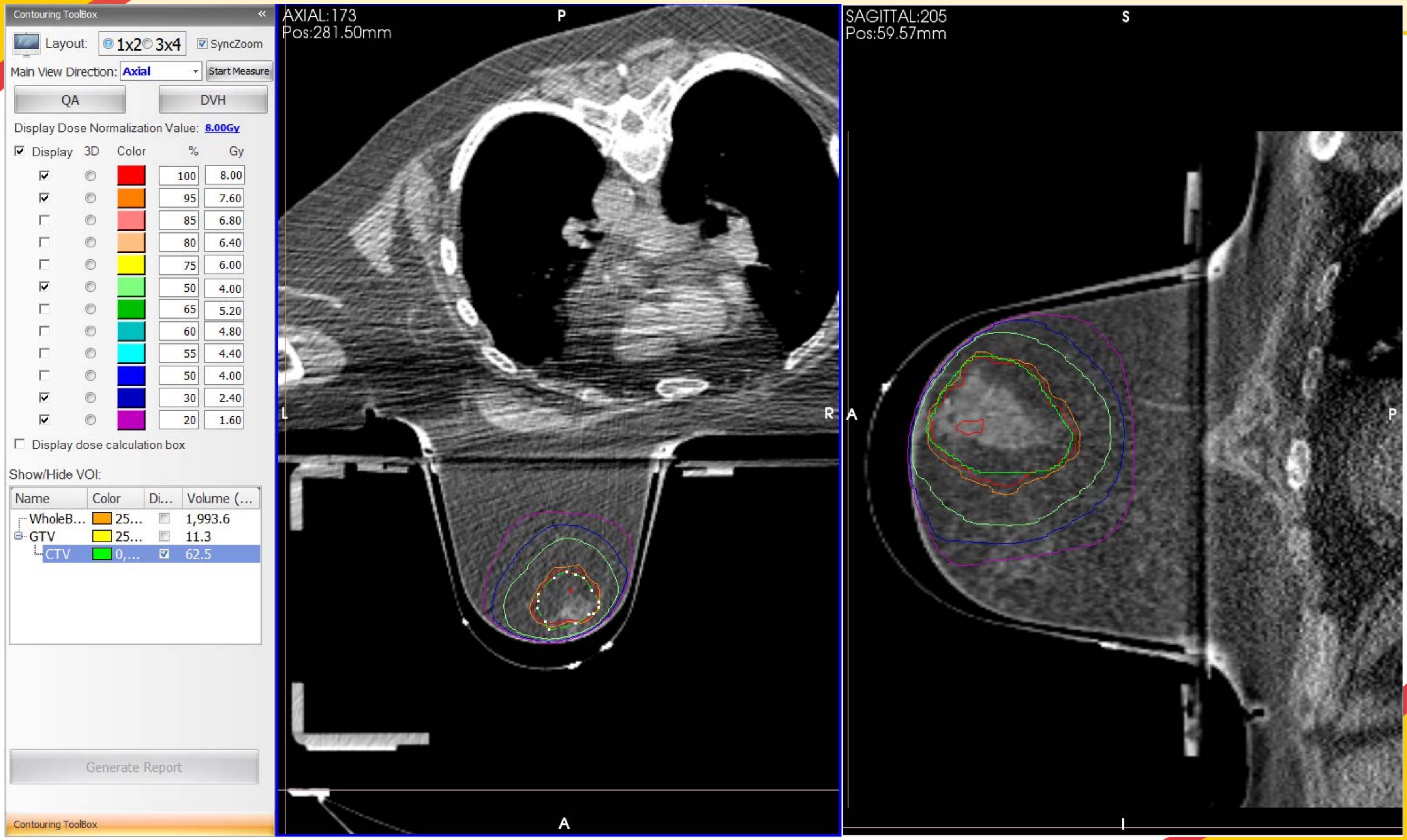
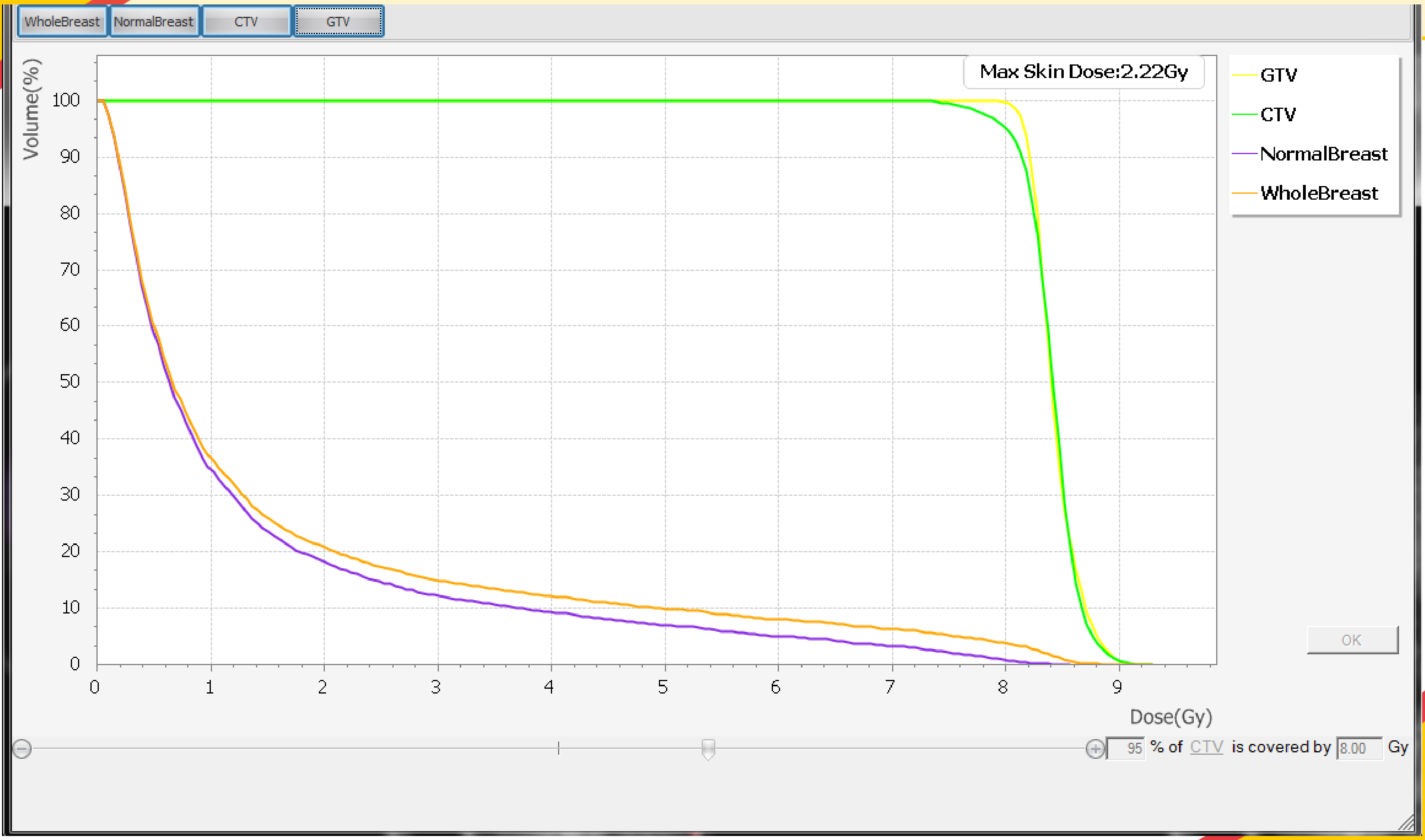
Patient 4



Contouring ToolBox
Layout: 1x2 3x4 SyncZoom
Main View Direction: Axial
Start Measure
QA
DVH
Display Dose Normalization Value: 8.00Gy
Display 3D Color % Gy
100 8.00
95 7.60
85 6.80
80 6.40
75 6.00
50 4.00
65 5.20
60 4.80
55 4.40
50 4.00
30 2.40
20 1.60
Display dose calculation box
Show/Hide VOI:
Name Color Di... Volume (...
WholeB... 25... 1,993.6
GTV 25... 11.3
CTV 0,... 62.5
Generate Report
Contouring ToolBox
AXIAL:173
Pos:281.50mm
P
L
R
A
SAGITTAL:205
Pos:59.57mm
S
A
P
I

Patient 4 DVH



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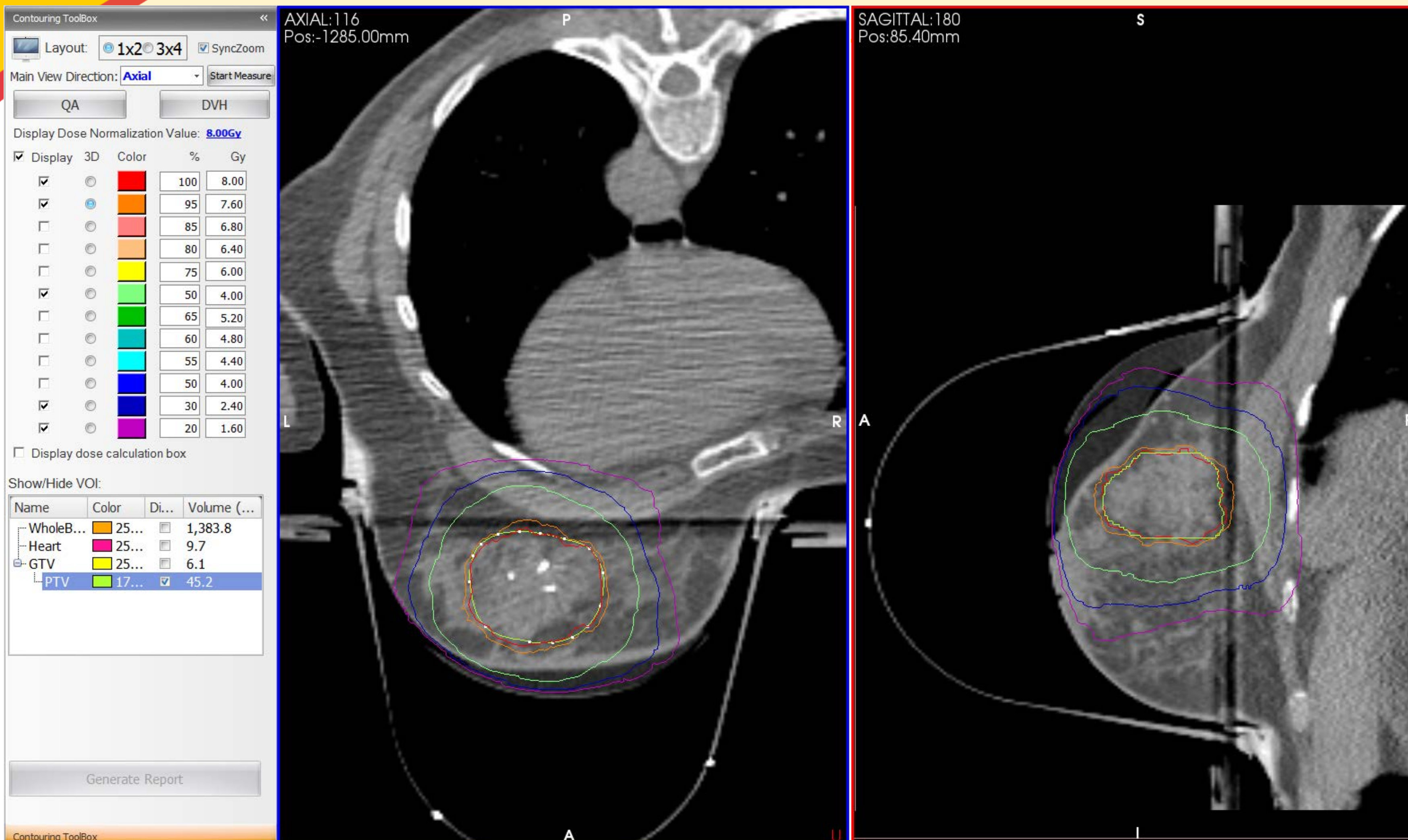
Patient 5



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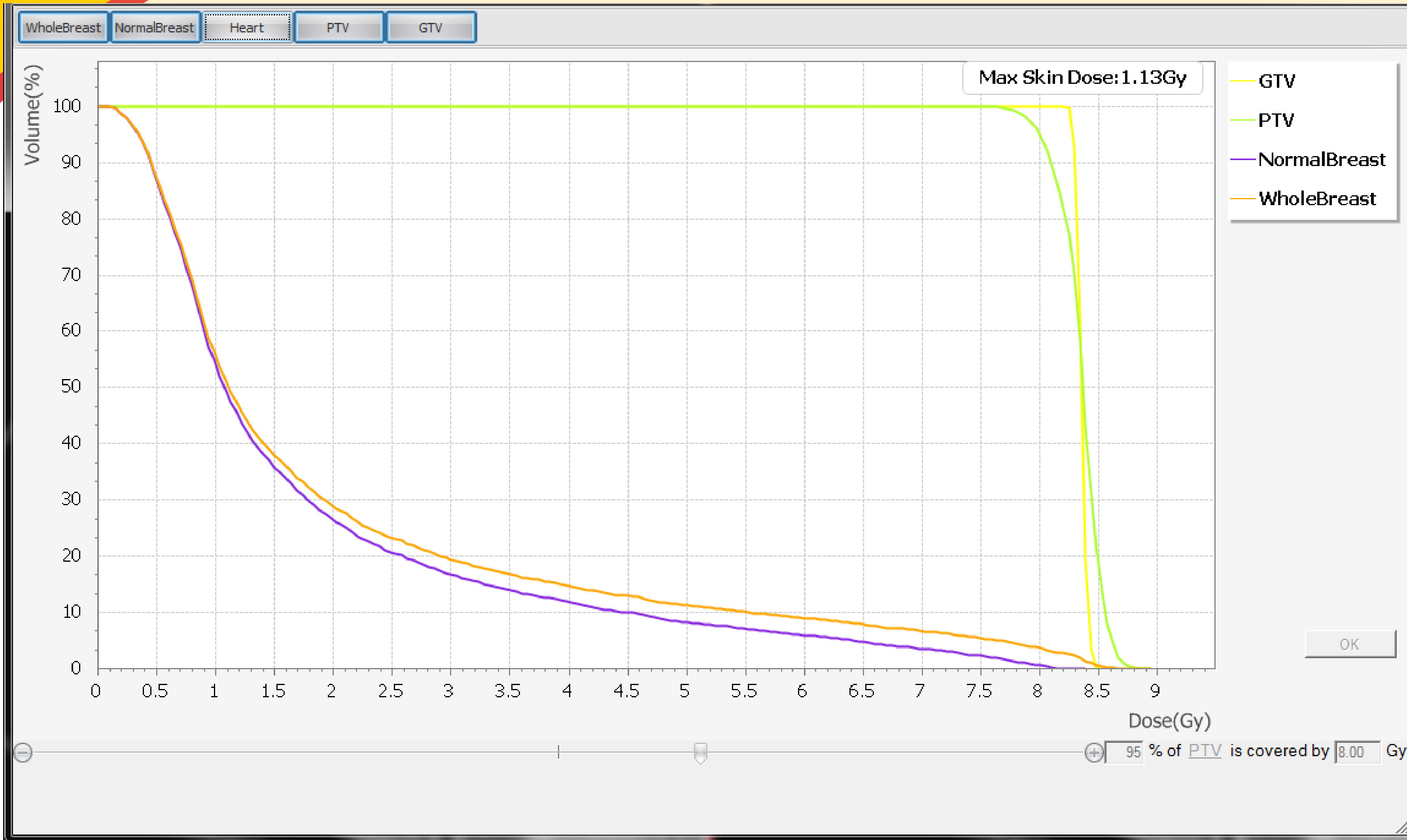
Patient 5 DVH



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Trial Observation

Breast size: 728cc to 2005 cc, average 1274cc

PTV size: Average 66.4cc

Equivalent to: Diameter = 5.03cm

2cm GTV + 1.5cm margin

Prescription Dose: 8Gy

Mean Heart Dose (Left breast) : 18.9 cGy

If mean heart dose < 1Gy, we can deliver 40Gy to PTV

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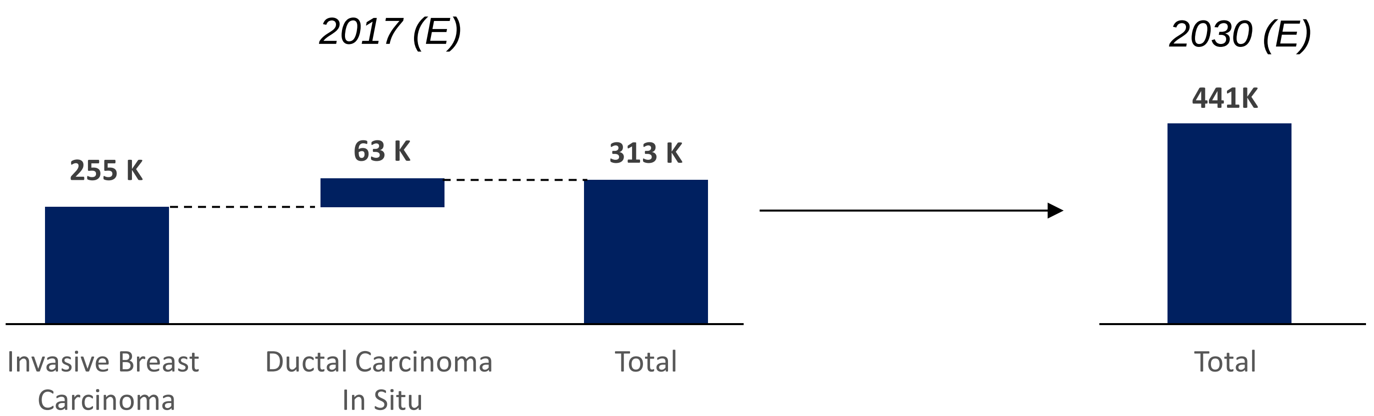
Early-Stage Breast Cancer by the Numbers

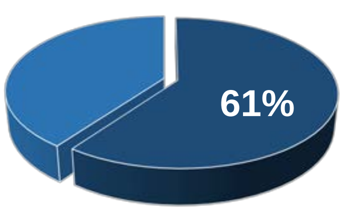
US New Breast Cancer Cases



In 2017, breast cancer accounts for ~1 of 3 newly diagnosed cancer cases in US women (and ~1 in 7 of all cancer cases)

Stage I Disease

Tumor size < 2cm



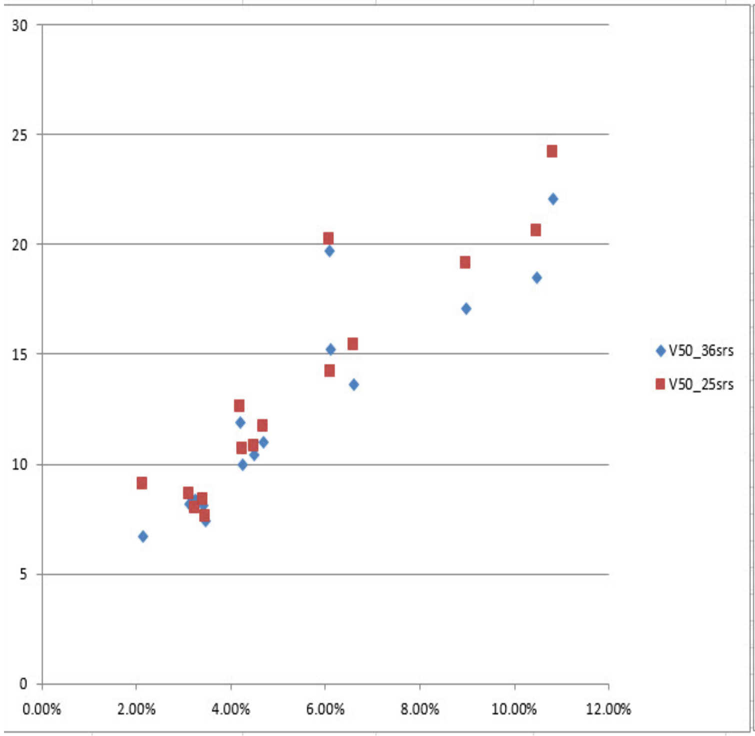
Source: Smith R. *CA: A Cancer Journal for Clinicians.* (2017): 67: 7-30.; Rosenberg, Philip S. et al. Estrogen receptor status and the future burden of invasive and in-situ breast cancers in the United States." AACR Annual Meeting, Abstract 3699. 2015.; National Cancer Instiute, SEER Cancer Statistics Review 1975-2013.

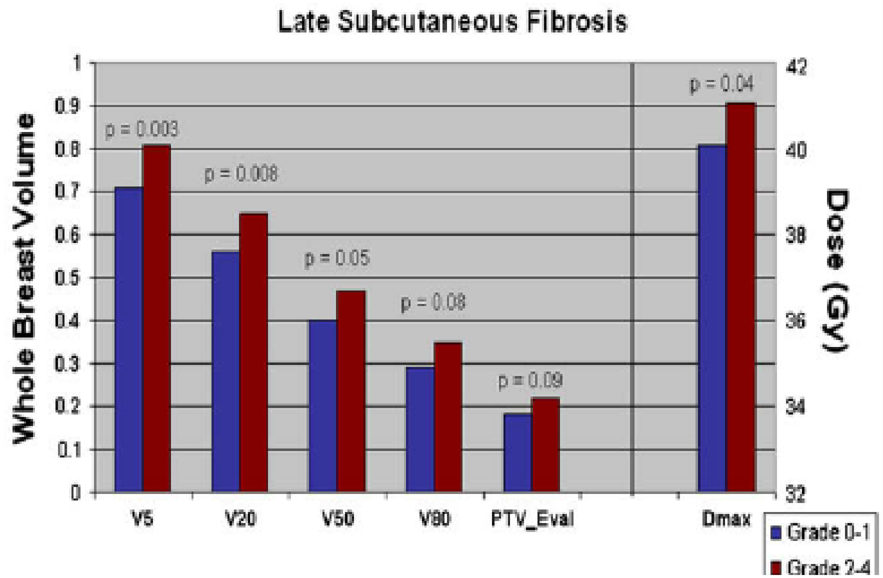
Trial Extrapolations

For 61% of breast cancer patients (GTV<2cm), we could use GammaPod to deliver 40Gy to GTV plus 15mm margin, still keeping heart dose <1Gy

heart dose may not be a limiting factor for SRS

Trial Observations: Normal Breast Dose





Jaroslaw Hepel et al. "Toxicity of Three Dimensional Conformal Radiotherapy for Accelerated Partial Breast Irradiation".Int. J. Radiation Biol. Phys. Vol. ,No. pp 2009

Average V50 = 13.4%
Maximum V50 = 24.1%

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Trial Extrapolation

$$BED = nd(1 + d/[\alpha/\beta]) - \log_e 2(T - Tk)/\alpha Tp$$

Take: $\alpha = 0.35$, $\alpha/\beta = 4$, Tk = 28 days, Tp = 100days

3.85Gy B.I.D. x 10 Fx ≈ 6 Gy x 5 fx (BED < 80Gy)

Using GammaPod, we could deliver:

6Gy/(40/24.1) = 10Gy per fraction for 5 fractions while keeping the equivalent V50 < 40% (No Grade II toxicity)

For a higher BED of ~100Gy, we can deliver:

10Gy x 3Fx, or 12.5Gy x 2Fx, or 18.5Gy x 1Fx

Much higher effective dose, less time, less toxicity

GammaPod Opportunity

1. Single ablative dose (breast SRS)

2. Ultra-accelerated pre-op or post-op PBI (1 to 3 Fx)

Question 2

Directions to improve photon dose distribution from this point forward include (Select all right ones)

a) increase the number of apertures in an arc;

b) try to make the apertures within an arc truly independent;

c) adding independent apertures from non-coplanar beam angles;

d) developing site-specific solutions.

Question 2

Directions to improve photon dose distribution from this point forward include (Select all right ones)

a) increase the number of apertures in an arc;

b) try to make the apertures within an arc truly independent;

c) adding independent apertures from non-coplanar beam angles;

d) developing site-specific solutions.

Answer: C & d.

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Question 3

What is the key mechanism of radiation delivery in SRS and SBRT?

a) Intensity modulation

b) stereotactic localization

c) geometric focusing

d) employing arcs

Question 3

What is the dominant mechanism of radiation delivery in SRS and SBRT?

a) Intensity modulation

b) stereotactic localization

c) geometric focusing

d) employing arcs

Answer: **c)**

AAPM TG 42 report: Stereotactic Radiosurgery

Question 4

Protons and heavy ions will be the primary tool for radiation therapy.

True or False?

Question 4

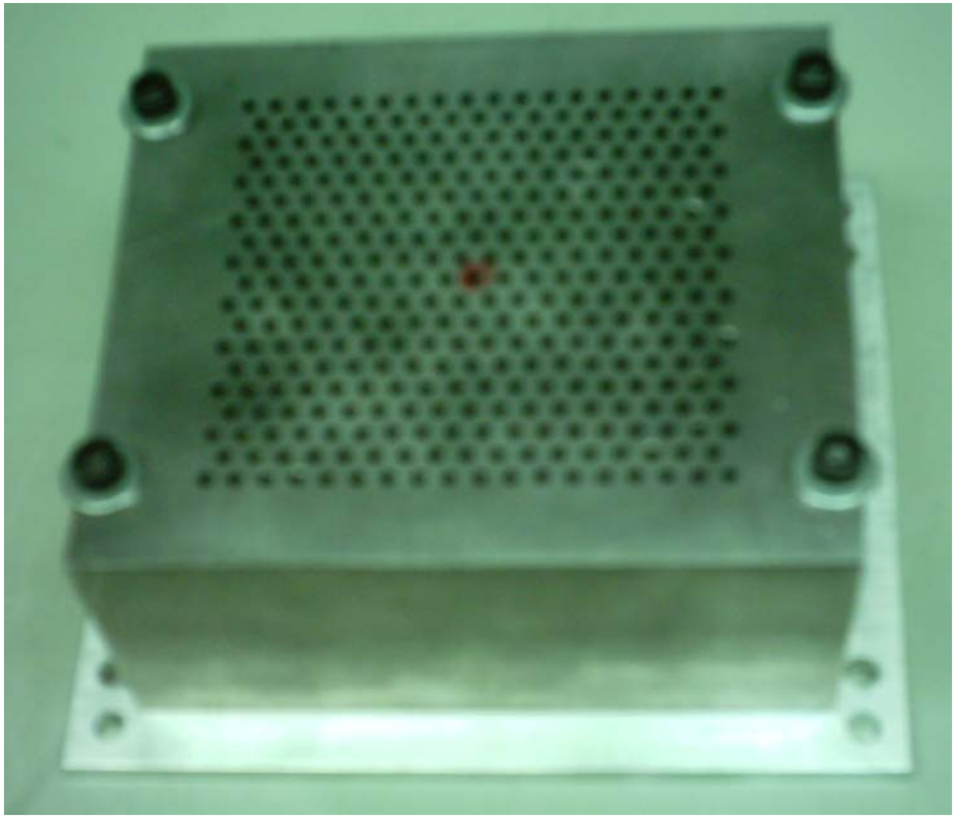
Protons and heavy ions will be the primary tool for radiation therapy.

True or False?

Rooms for Improvement

- New Degrees of Freedom
- Site Specific Solutions
- New Biology
  - Spatial Fractionation?

Grid Therapy



- Open-to-Closed Ratio

  = 1:3 (~25% open)
- Typical Dose 15 – 20 Gy

Courtesy of
the University of Kentucky

Clinical Study of Grid Therapy Conducted by University of Kentucky

- 71 Patients were admitted in the clinical trial;
- 16% show a complete clinical response;
- 62% show at least a partial clinical response;
- Head and Neck has the most successful rate.

Int. J. Radiation Biol. Phys., Vol. 45, pp. 721-727, 1999.

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What makes it work?

No explanation on the lack of normal tissue damage.

- Different apoptotic pathway with single high dose?
- Different mechanisms exist between tumor and normal structure in the repair of small regions of damage.
- Cell mobility and “system control” may play a role.
- By-stander effect (not just to signal the by-stander to die, but to single them to help).

Work published in 1950s

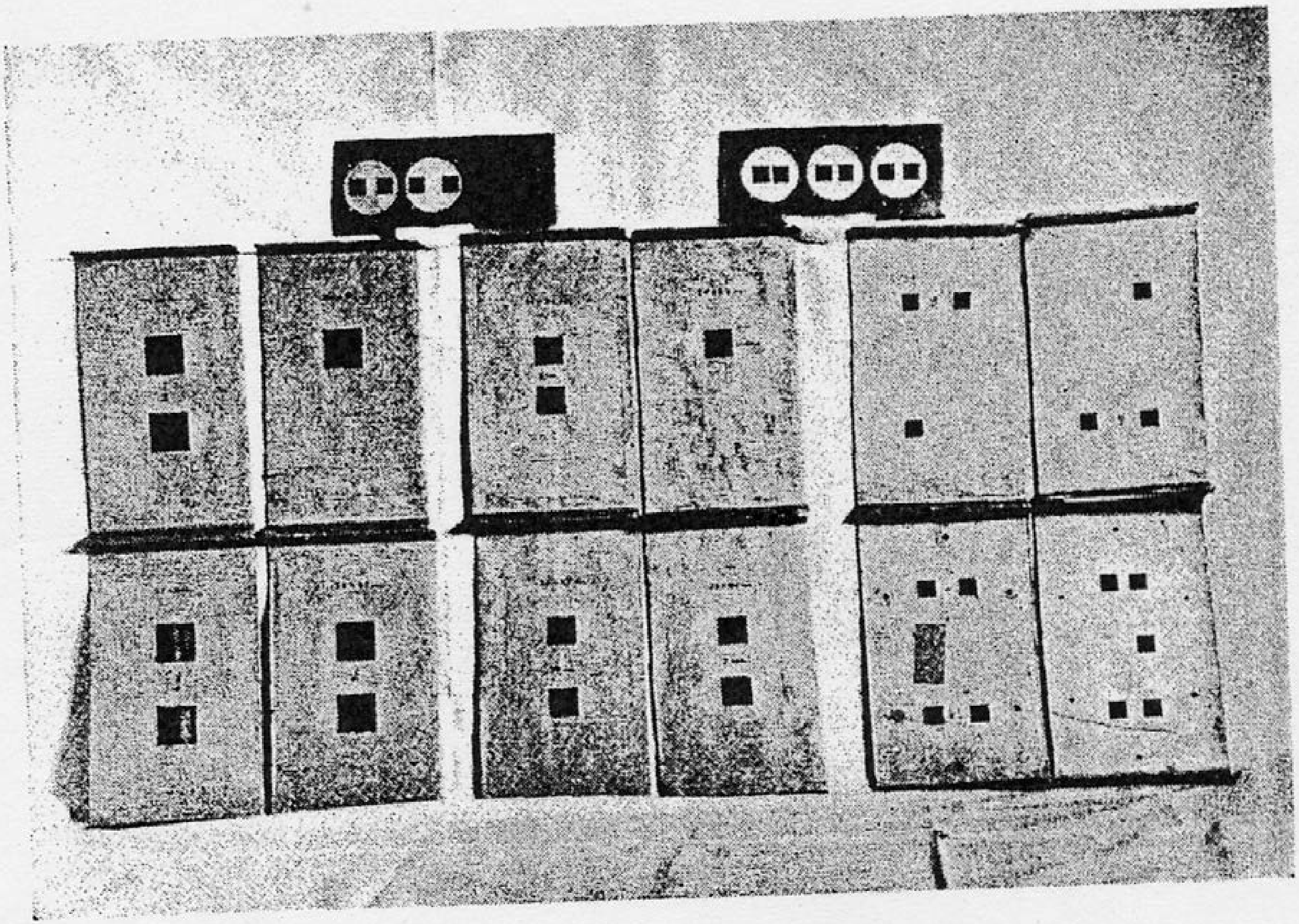

FIG. 1.

... panels with exposure windows. The separations

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Effect of Separation

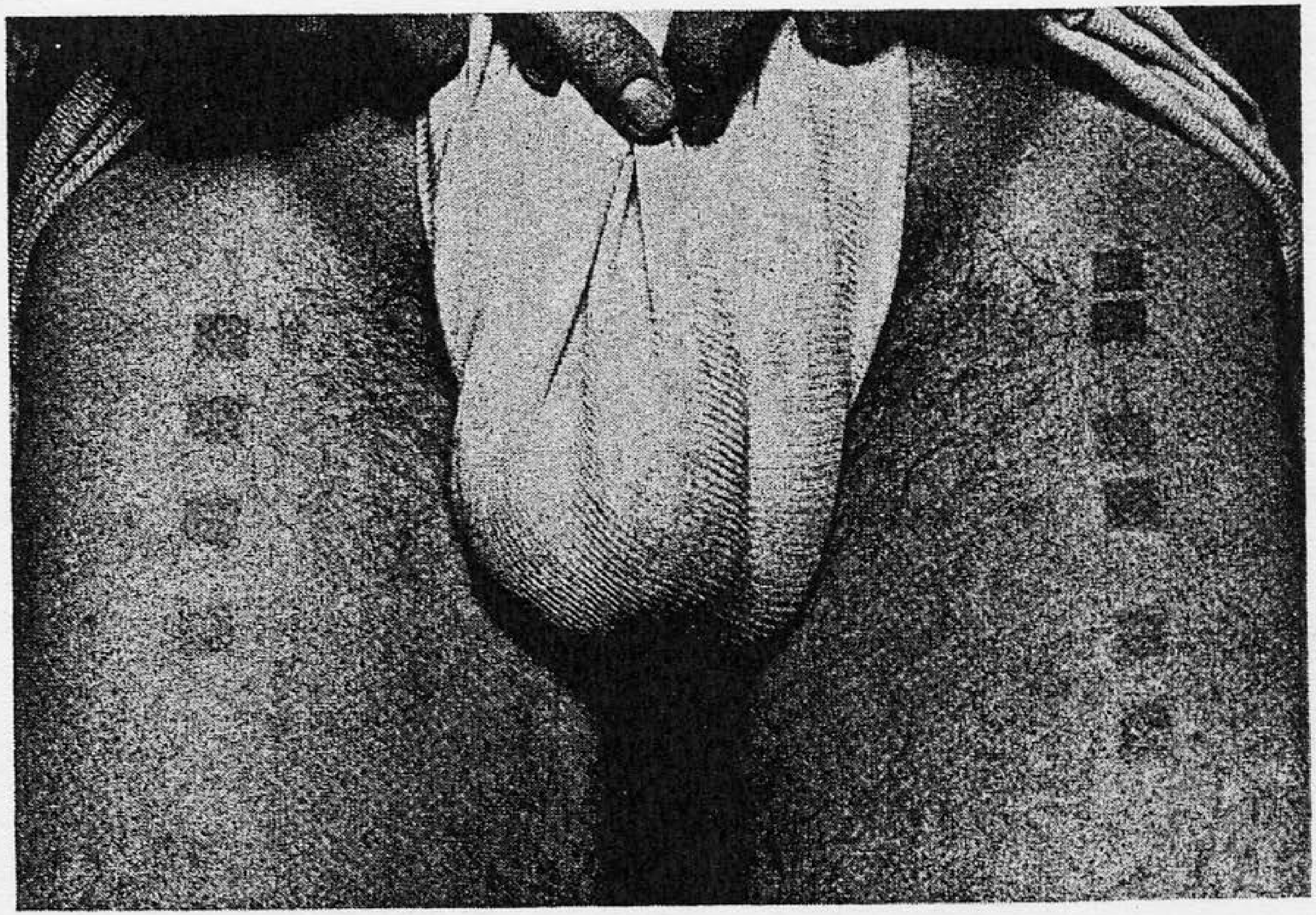

Fig. 2.

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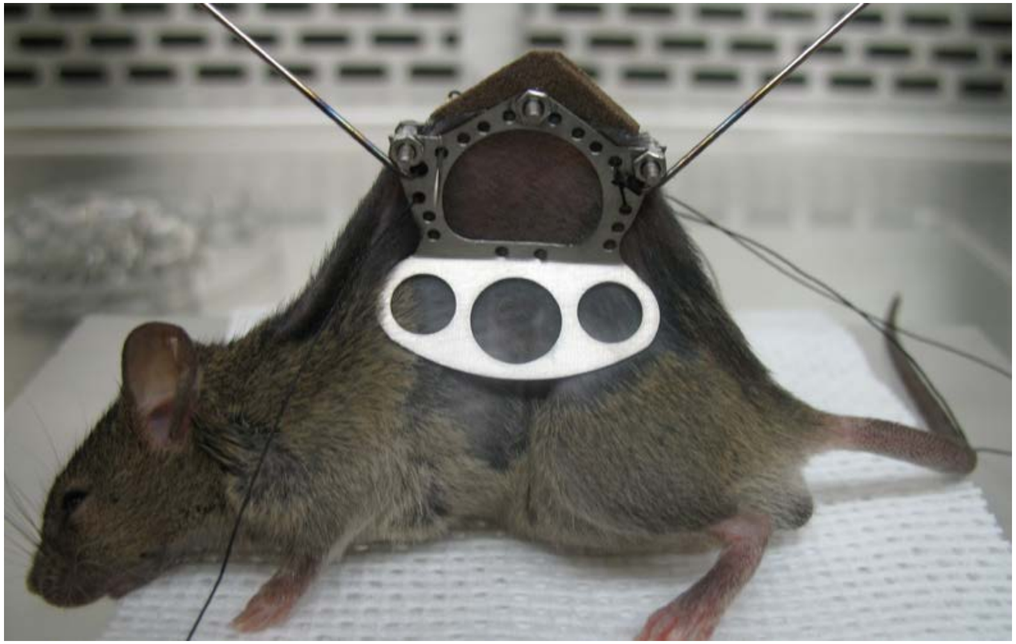
Animal Experiment: SF vs. TF

- Space Fractionation (SF): Irradiating the target volume partially in each fraction, but with larger doses

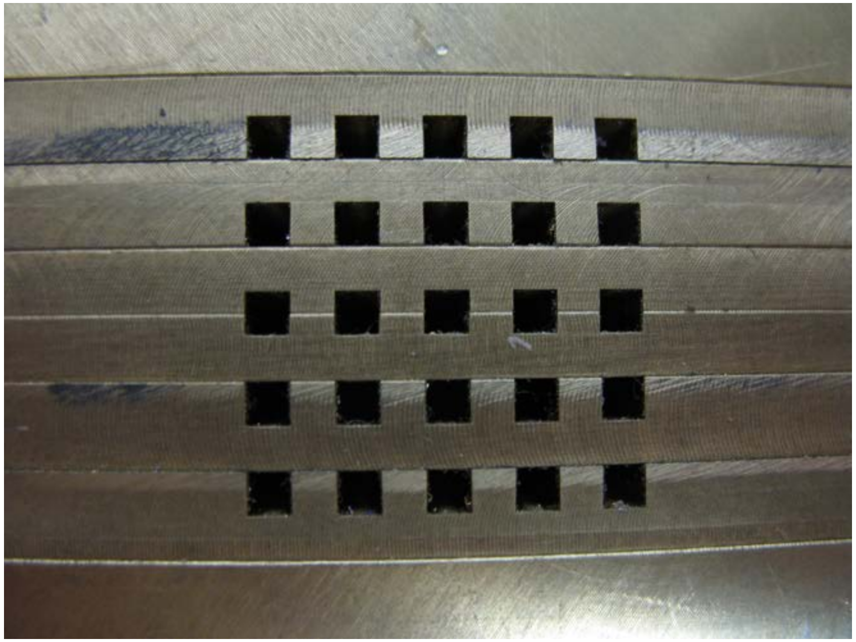
- Time Fractionation (TF): Irradiating the whole target volume with small doses in each fraction, similar to conventional radiation therapy

Experimental Setup



Tumor cells are implanted in the window fixed in space with Titanium fixtures, let it grow to 6-8mm in diameter before randomize to time or space fractionated radiation.

Experimental Setup



Home-made grid of 2.2mm x 2.2mm. All grid openings are double focused. Space Fractionated (SF) irradiation is delivered through this grid.

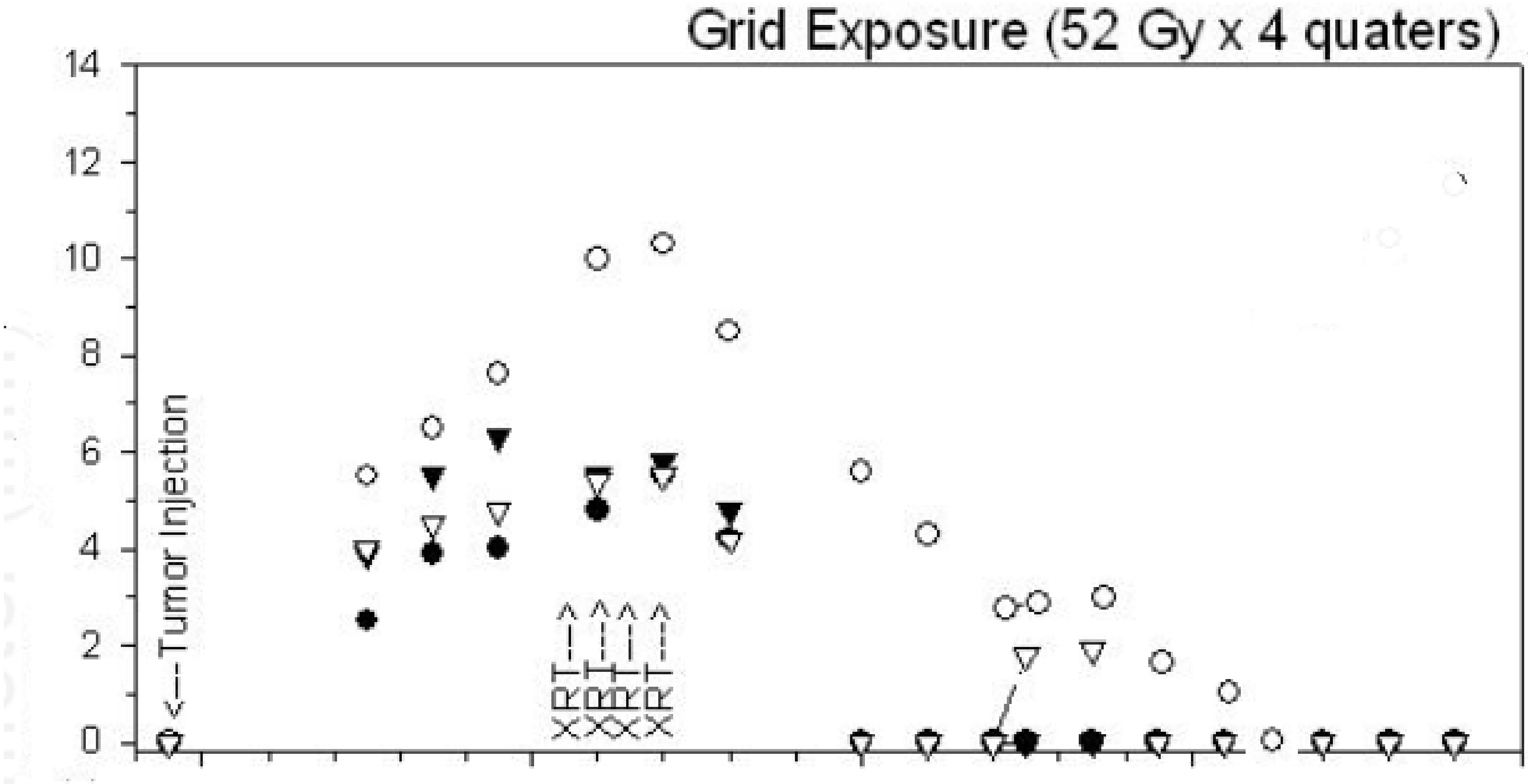
Two Groups

Group1: Open irradiation of 13Gy x 4 days, irradiating the entire window. 17 mice.

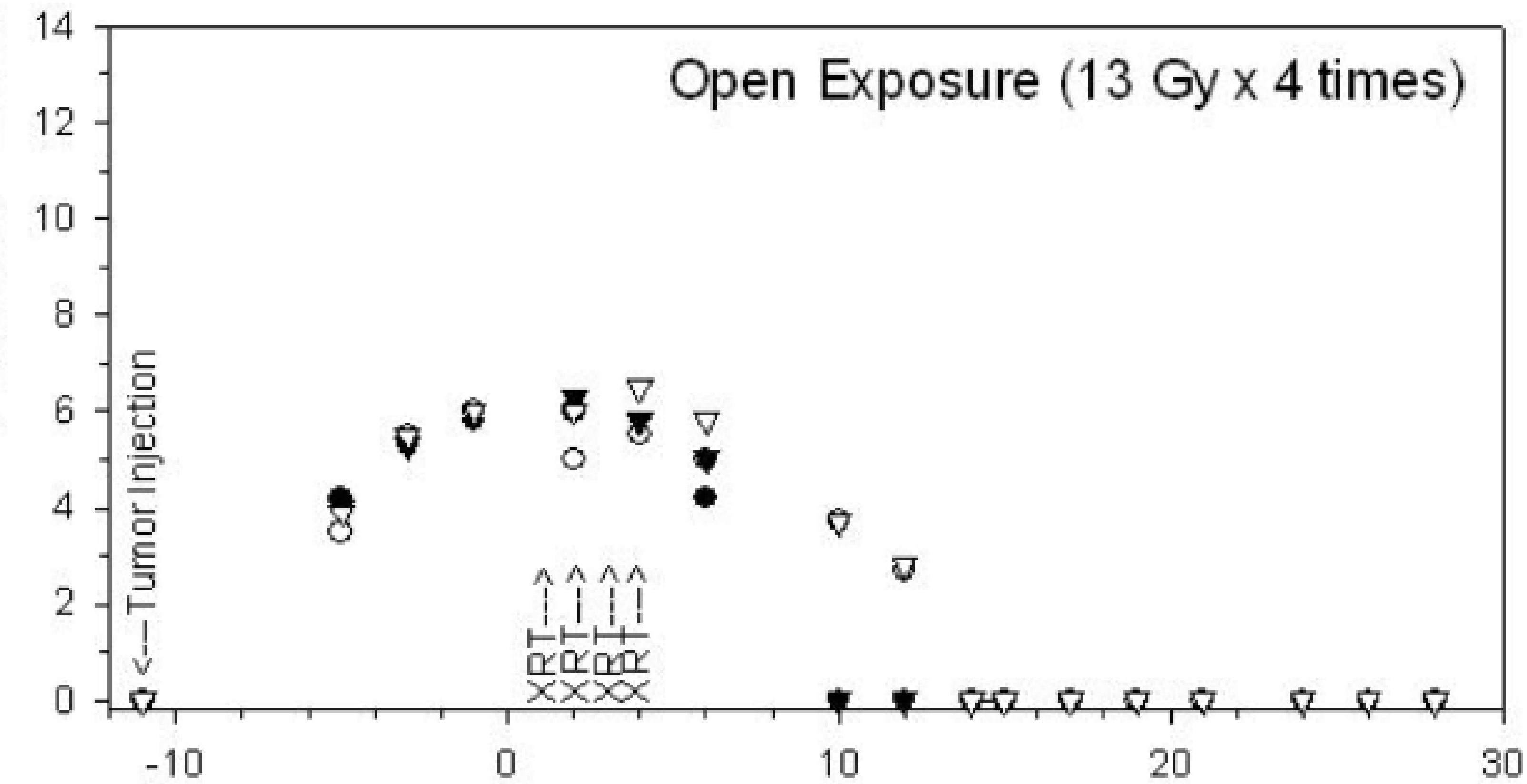
Group 2: Grid irradiation of 52Gy, shifting 4 times to un-irradiated areas in 4 days. At the end of the 4 days, the entire window is treated in confluence. 12 mice.

The total dose to the window are the same (52 Gy) for the two groups.

Tumor Regression - Grid



Tumor Regression - Open



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Late Recovery

Observation 3:

Grid Has Far Less Late Toxicity

Quantified by hair counts

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School of Medicine

To Count Hair: (1)Close Shave and select a fixed area

Count Hair within the selected area

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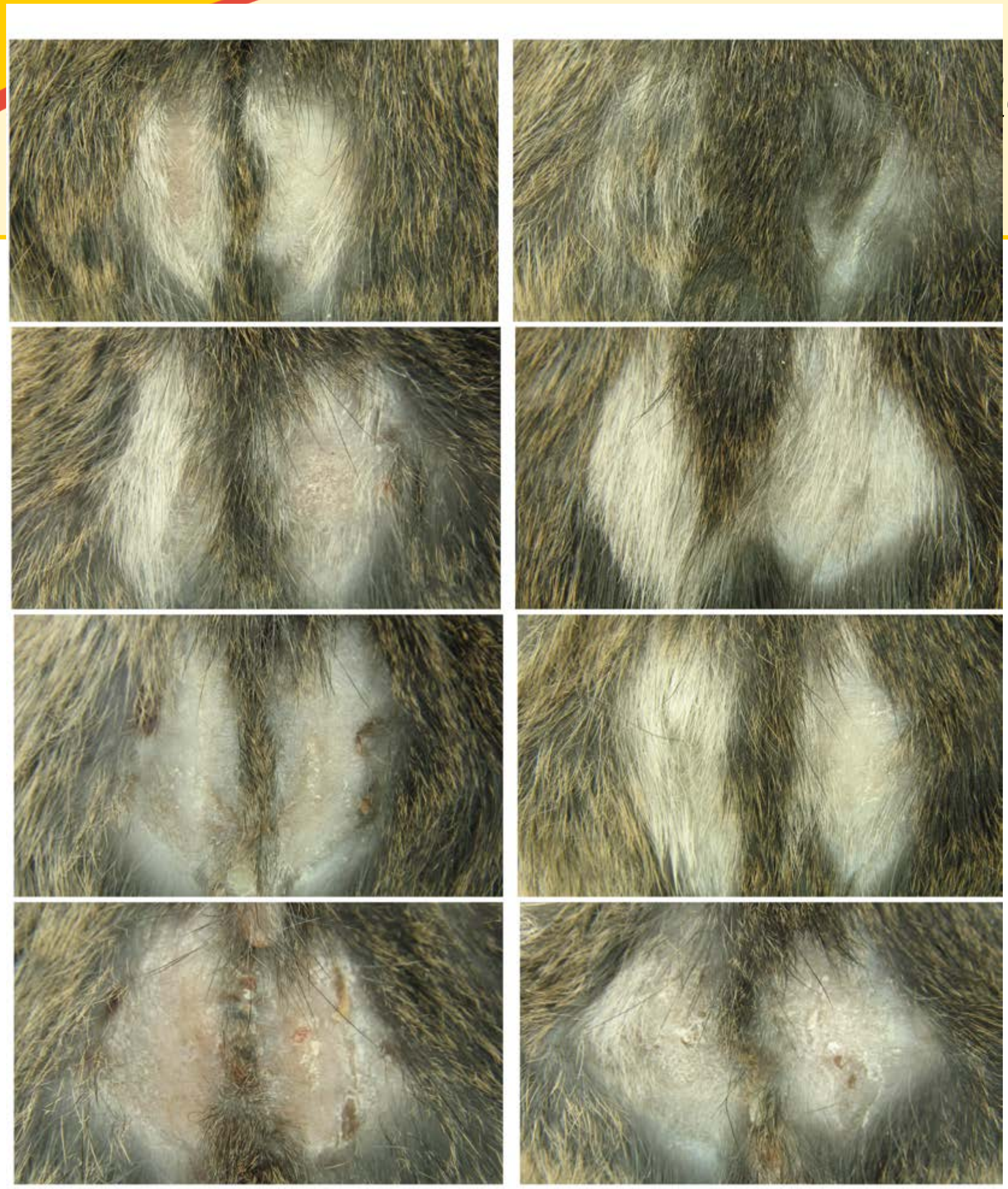
Hair Counts

	Open	Grid	p-value
Entry side	452	860	0.0003
Exit side	223	730	0.0001

Spatial fractionation through grid resulted in fuller skin and hair recovery than open field time fractionation on both the beam entrance and beam exit sides, while both achieved tumor control.

esults



Entry Exit Entry Exit

TF:

Tumor gone.

Poor fir recovery.

More visible bare skin.

SF:

Tumor gone.

Better fir recovery.

Less visible bare skin.

Possible Clinical Translation

- SBRT has shown effective for lung, liver, spine, pancreas, kidney **if the tumor is small** (*Robert D. Timmerman,et al,* SBRT in Multiple Organ Sites, *J Clin. Oncol 25(8), 2007)*
- Large tumors are not eligible for SBRT due to normal organ toxicity
- SF may circumvent this limitation

Question 5

Why radiobiology results obtained by irradiating cells in a dish fail to predict radiation responses in humans?

i) there is a lack of circulating stem cells

ii) there is a lack of the micro-environment

iii) There is a lack of the macro-environment

iv) There is a lack of bystander effect

a) All of the above;

b) iii) is the only correct answer;

c) iv) is the only wrong answer;

d) i) and ii) are correct.

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c) iv) is the only wrong answer;

d) i) and ii) are correct.

The correct answer is b), i) the lack of circulating stem cell is true, but not the reason to our question. ii) is wrong because there is communication between cells through the micro-environment; iv) is wrong because the "bystander effect" was discovered through irradiating cells in a dish.

Summary

- EXRT treatment with linacs is facing a crisis and presents exciting opportunities
- IMPT is dosimetrically better than IMRT but it has its own problems and limitations
- Site-specific solutions is one of the ways to enhance our ability to improve therapeutic ratio
- New understandings of radiation biology may give birth to new treatment delivery methods