Application of advanced patient-specific Monte Carlo dose calculations for brachytherapy

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Ottawa Medical Physics Institute

Carleton UNIVERSITY

Radiotherapy

Radiotherapy used for > 50% of cancer treatments

- "the majority of our radiotherapy strategies were derived by empirical optimization of clinical experience performed with inferior technologies." Chapman & Nahum, 2015

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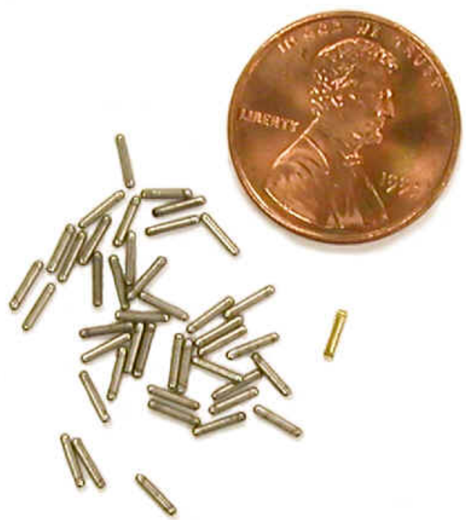
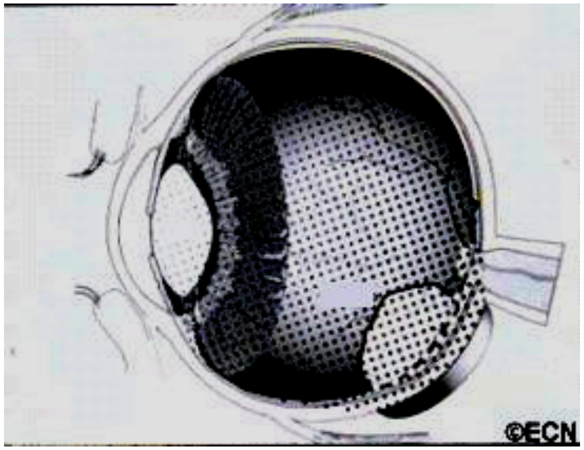
- Development of new technologies; quantitative assessment of treatments → Collaborations
- Innovate…
  - Equally good or better treatment outcomes with less normal tissue trauma
  - Improve "Therapeutic Ratio" = efficiency of tumour cell kill relative to normal tissue complications

Today

- Brachytherapy & dose calculations approaches
- Advanced model-based dose calculations:
  patient/treatment model → calculation
- Applications of advanced dose calculations for brachytherapy: breast, eye, prostate
  - Dose differences
  - Clinical implications, outcomes modelling
- Ongoing and future research

Brachytherapy: 'up close' radiotherapy





- Goal: deliver high doses to target; minimizing dose to normal tissues
- Evaluation of radiation doses is critical

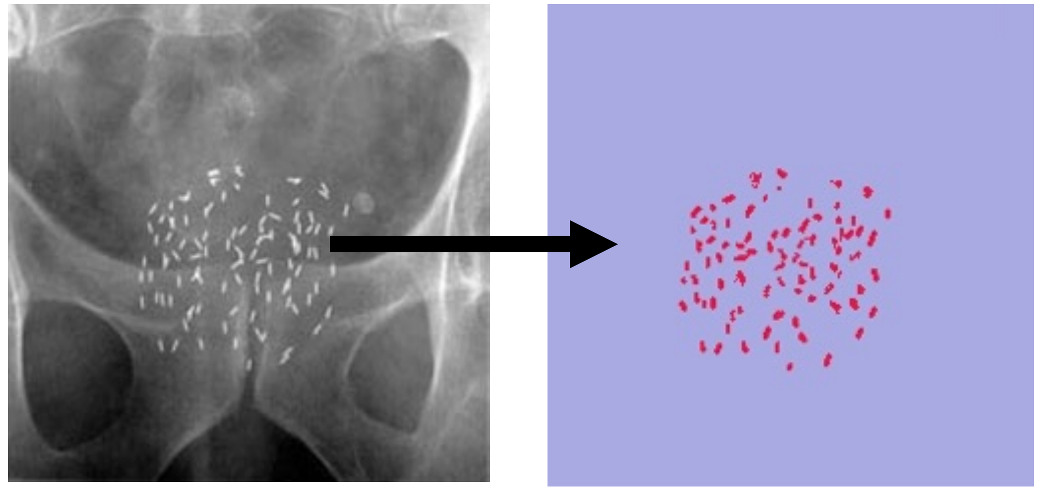
www.brachytherapy.com

Current clinical approach: TG-43

$$D_{TG43}(x,y,z) = \Sigma\ D_{1,w}(x,y,z)$$

Sum over all seeds

Dose for 1 seed in water



Patient and sources   TG-43 formalism

Formalism developed by Task Group 43 (TG-43) of the American Associate of Physicists in Medicine (AAPM)

TG-43 is inaccurate

$$D_{TG43}(x,y,z) = \Sigma\, D_{1,w}(x,y,z)$$

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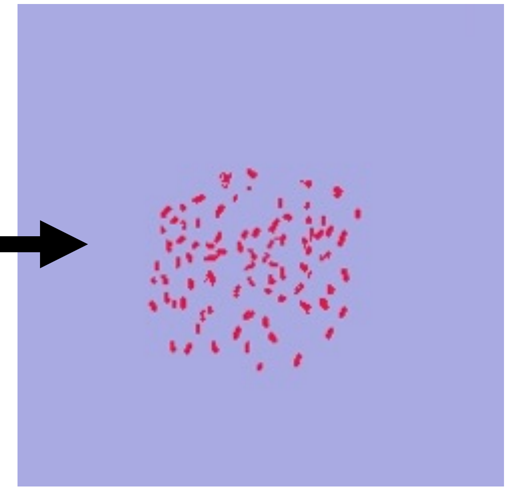
Patient and sources



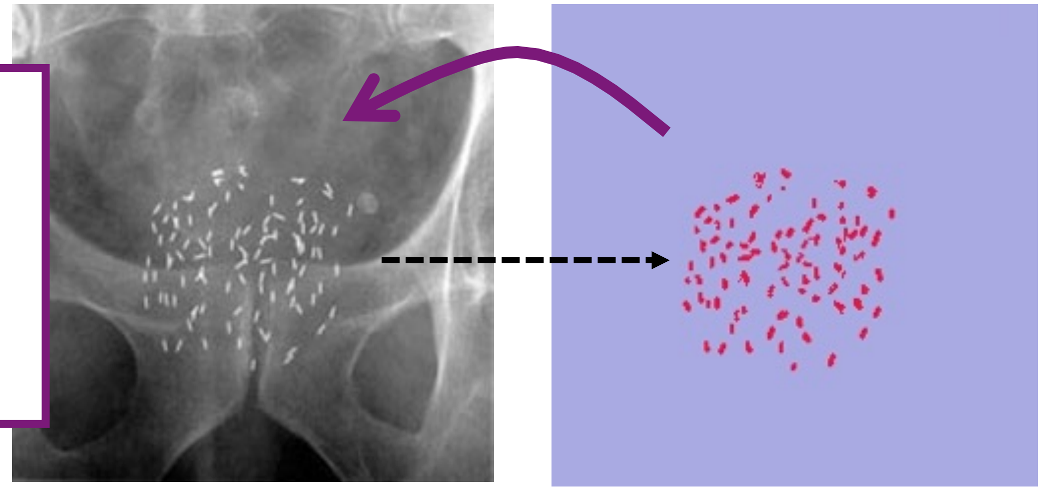
TG-43 formalism

- Effects of non-water tissues, sources, shielding neglected
- Calculated doses inaccurate

  Beaulieu et al (TG-186), Med Phys **39** (2012)

If not TG-43, then what?

"**TG-186**" Model-based dose calculation: detailed virtual patient model, sources



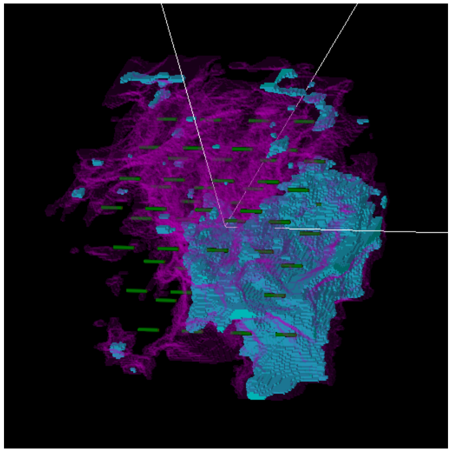
Patient and sources   TG-43 formalism

Model-based dose calculation algorithms (MBDCAs)

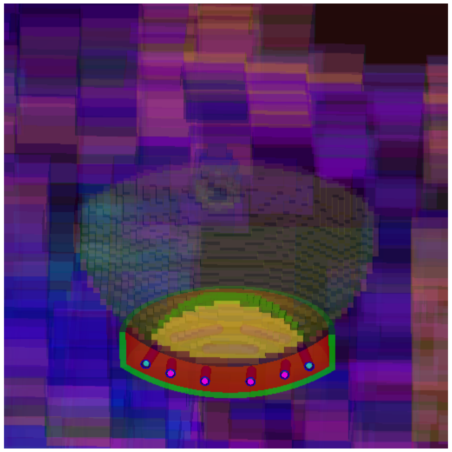
- e.g. Monte Carlo (MC) simulations
- Clinical adoption recommended (AAPM/ESTRO/ABG TG-186)

Monte Carlo (MC) dose calculations

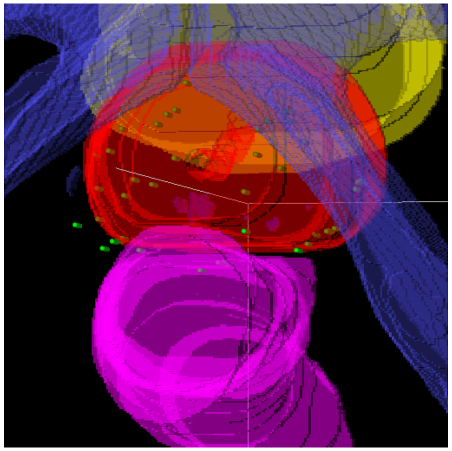
- BrachyDose, egs_brachy (Carleton Laboratory for Radiotherapy Physics: CLRP)
- Simulation of transport of radiation quanta through matter (EGSnrc)
- Flexible, accurate, & fast: promising tool wide range of applications



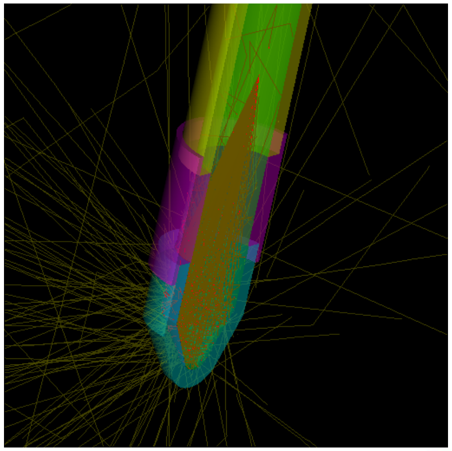
^{103}Pd breast implant



^{125}I eye plaque



^{125}I prostate implant



Electronic brachytherapy

IOP Publishing | Institute of Physics and Engineering in Medicine — Physics in Medicine & Biology

Phys. Med. Biol. **61** (2016) 8214–8231 — doi:10.1088/0031-9155/61/23/8214

egs_brachy: a versatile and fast Monte Carlo code for brachytherapy

Marc J P Chamberland, Randle E P Taylor, D W O Rogers and Rowan M Thomson

Carleton Laboratory for Radiotherapy Physics, Department of Physics, Carleton

- egs_brachy to be released as free, open source software to research community (2017)
- Sub-30 s calculation times on a single CPU for clinical scenarios (even shorter times by running in parallel)

Overview: Patient data → MC calculations

For model-based (MC) dose calculations, need model of patient and treatment: How to develop model?

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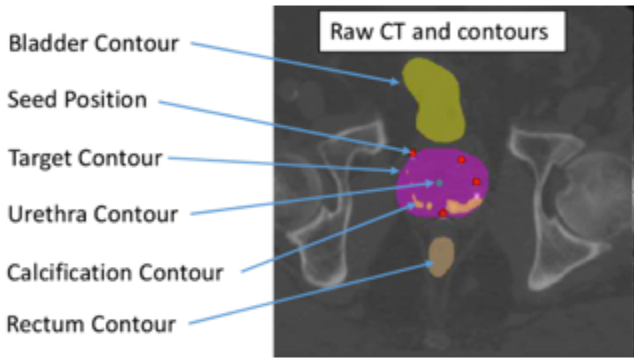

e.g. ^{125}I prostate brachytherapy post-implant CT images, physician contours

→ Correct artifacts in CT images → Assign tissues → Virtual patient model including non-water tissues: use in MC calculations

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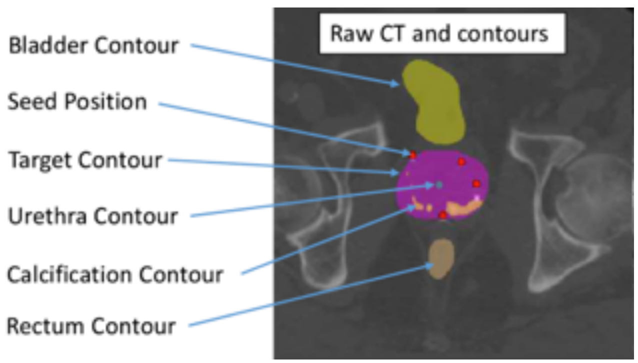

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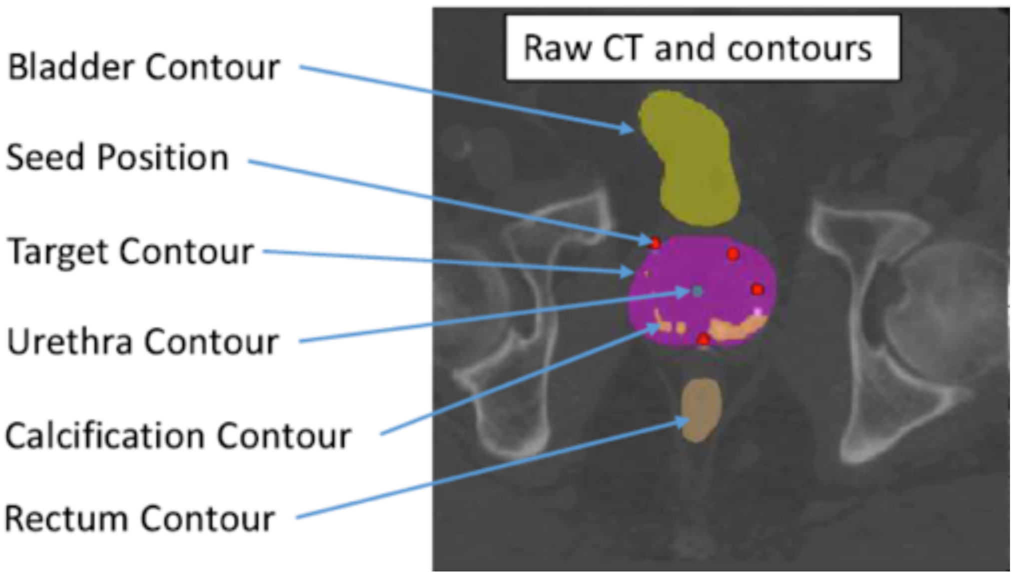
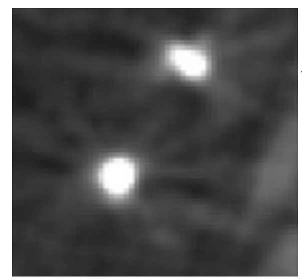
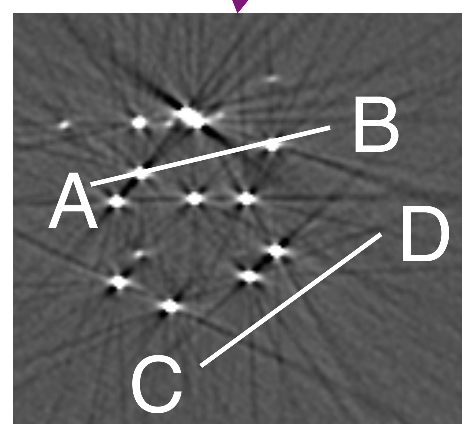
CT artifacts

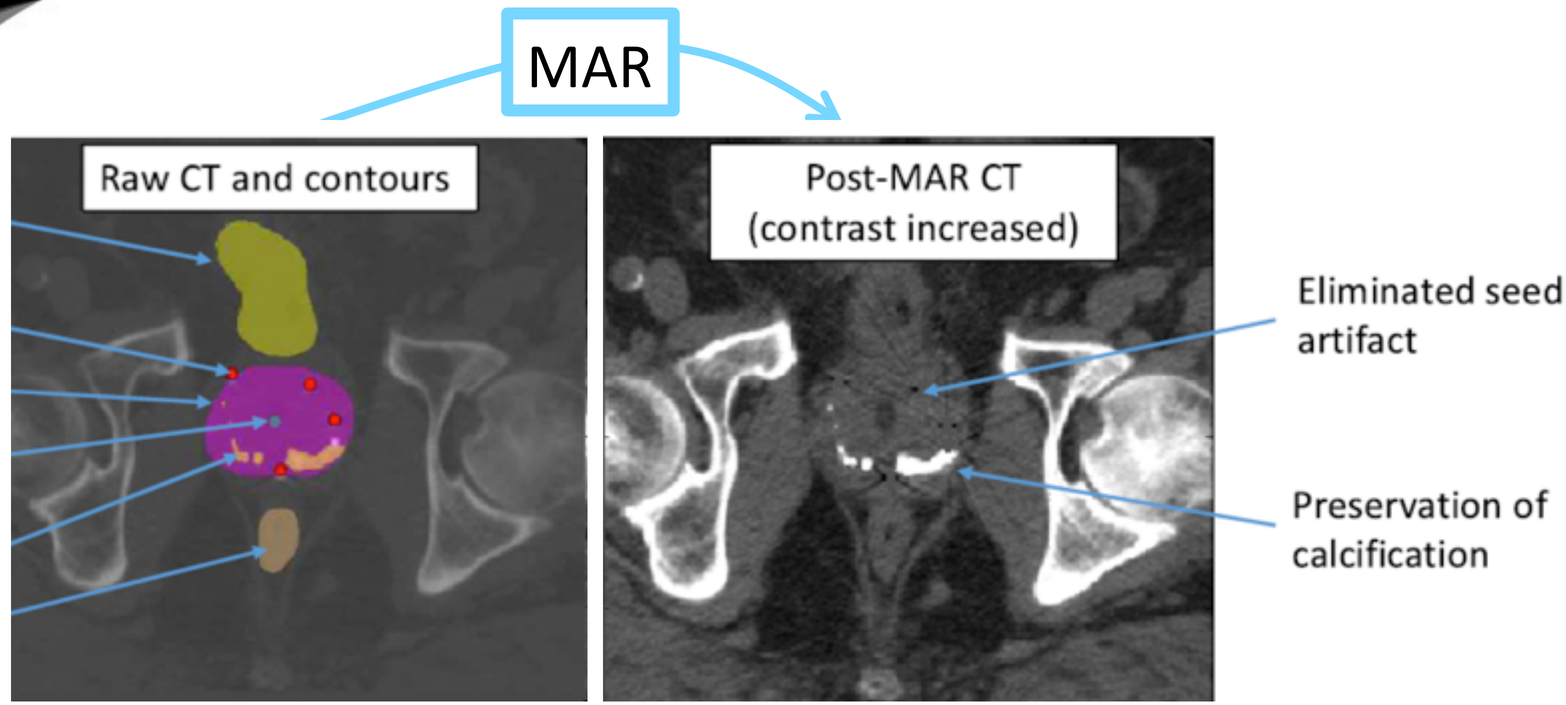


Artifacts: bright spots larger than seed dimensions, streaks.





CT artifacts: mitigate



- Use Metallic Artifact Reduction (MAR) technique*
- Bright spot artifacts are eliminated
- Retain important anatomical features

*Miksys et al. Phys Med Biol 2015;60:6039-6062.

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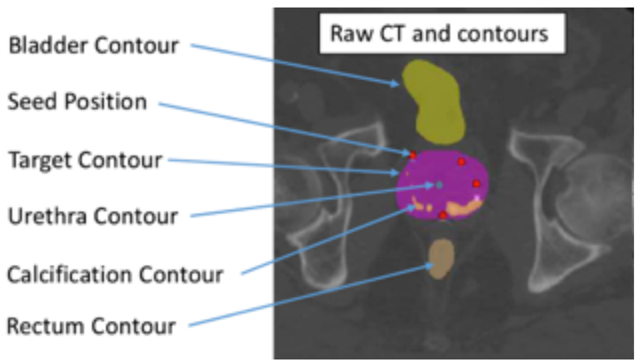

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→ ✔ Correct artifacts in CT images

→ Assign tissues

↓ Virtual patient model including non-water tissues: use in MC calculations

Assign tissues

- Assign mass density to each voxel: CT number → density calibration curve

CT number (HU)	mass density (g/cm^3)
-832	0.217
-522.8	0.508
-74.2	0.967
-34.7	0.99
6.2	1.018
47.8	1.061
56.5	1.071
244.2	1.159
999	1.575

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- Use physician-drawn contours and tissue assignment scheme to assign elemental composition to each voxel

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Reference MC model **MCref**

Region	Tissue	Mass density range
Target	*Prostate* (18)	$\leq$1.14 g/cm^3
	50P50C	1.14-1.27 g/cm^3
	Calcification(breast)	>1.27 g/cm^3
Urethra	*Prostate*	All
Rectum	*Rectum* (19)	All
Bladder	*Urinary bladder(empty)* (18)	All
Remainder	*Mean male soft tissue* (17)	$\leq$1.14 g/cm^3
	Cortical bone (18)	>1.14 g/cm^3

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Tissue elemental compositions are quite uncertain!

- One or a few samples, > 30 years ago
- Variations over population

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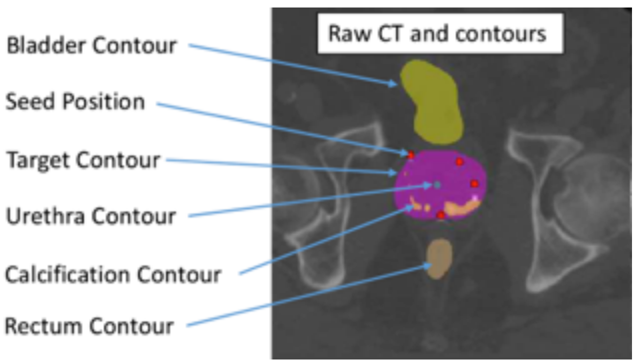


e.g. ^{125}I prostate brachytherapy post-implant CT images, physician contours

→ Correct artifacts in CT images ✔

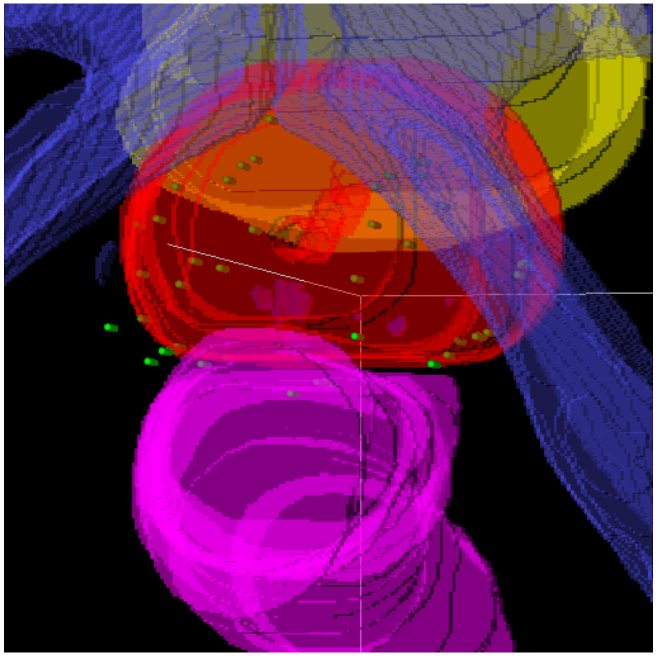
→ Assign tissues ✔

↓

Virtual patient model including non-water tissues: use in MC calculations

MC dose calculations

- Voxelized patient models with detailed source/applicator models superimposed = Model-based dose calculation (TG-186)
- TG-43 or "TG43sim" calculations carried out (consistency): sources in water, no interseed effects



^{125}I prostate implant

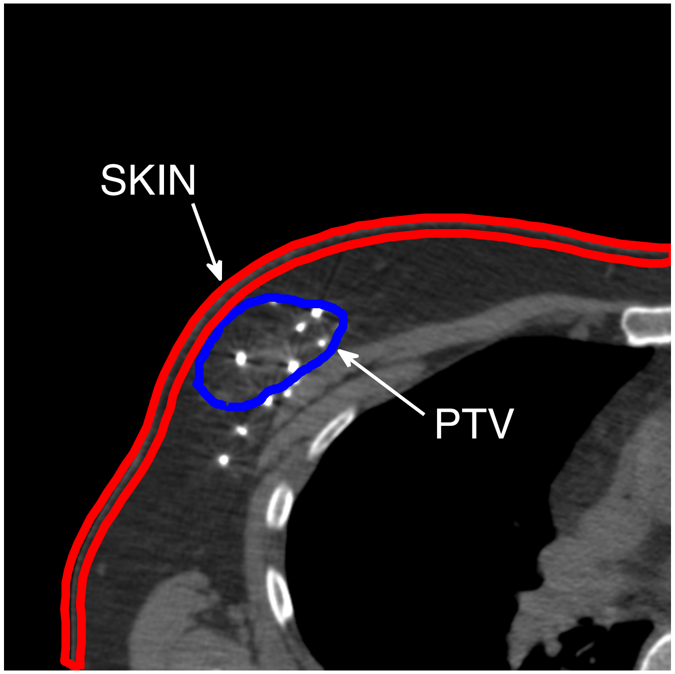
Applications

Application of MC dose calculations to breast, eye, prostate brachytherapy treatments

- What are dose differences between MBDCA/MC and TG43?

- Know doses more accurately – so what?
  - Clinical implications
  - Biological outcomes modelling
  - Connections with patient outcomes

Breast: ^{103}Pd brachytherapy

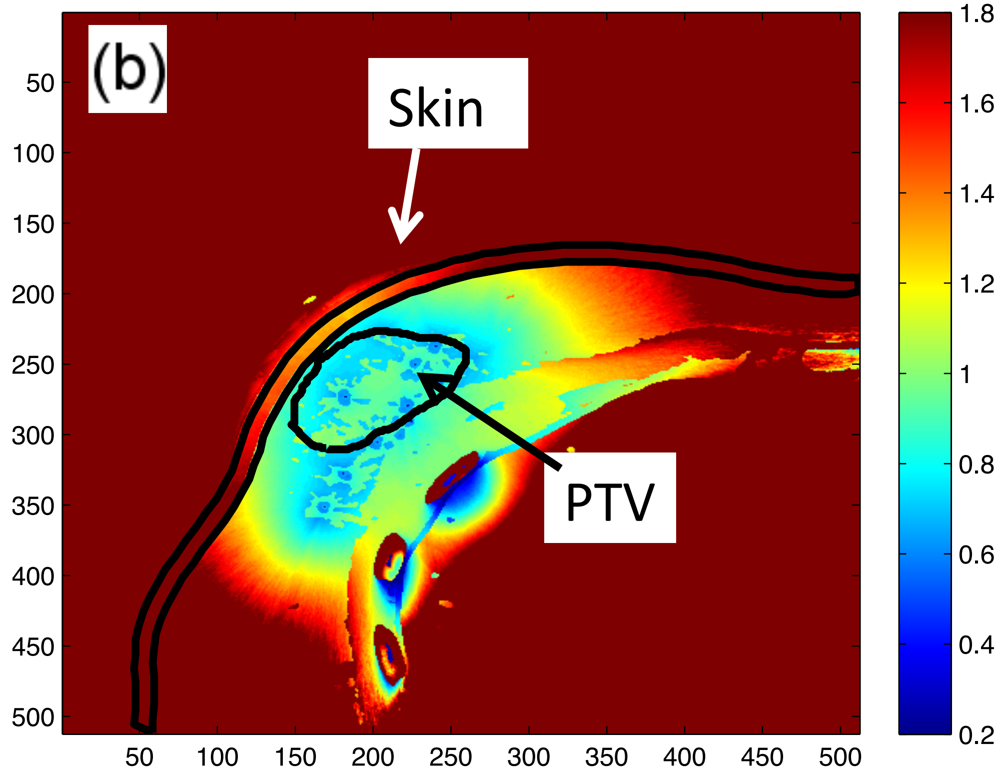


Miksys et al, PMB **61** (2016)

- Permanent breast seed implant (PBSI) is a form of accelerated partial breast irradiation
- Treat common form of breast cancer (Ductal Carcinoma In-Situ), following breast-conserving surgery (lumpectomy)
- Pioneered 10 years ago at Sunnybrook - Pignol et al, IJROBP **64** (2006)
- ^{103}Pd seeds

Breast: MC, TG43 comparison

Colour wash gives ratio of doses: detailed tissue MC / TG43



- Target: doses overestimated with TG43 (D_{90}: 10-30%), possibility of "cold spots"
- Skin (OAR): doses underestimated with TG43 (D_{1cm3}: 10-48%)

Miksys et al, PMB **61** (2016)
Afsharpour et al, PMB 55 (2010)

Breast: Clinical implications

- Retrospective study of 140 PBSI patients treated at Sunnybrook – Mashouf et al, IJROBP **94** (2016)
- "Inhomogeneity Correction Factor" (ICF) applied to TG43 (some tissue effects, no interseed attenution)
- Target volume V_{100} is 19% lower with ICF than TG43: possible recurrence risk, underdose (need more data)
- Skin complications (desquamation, erythema, telangiectasia) – better predictions with ICF than TG43

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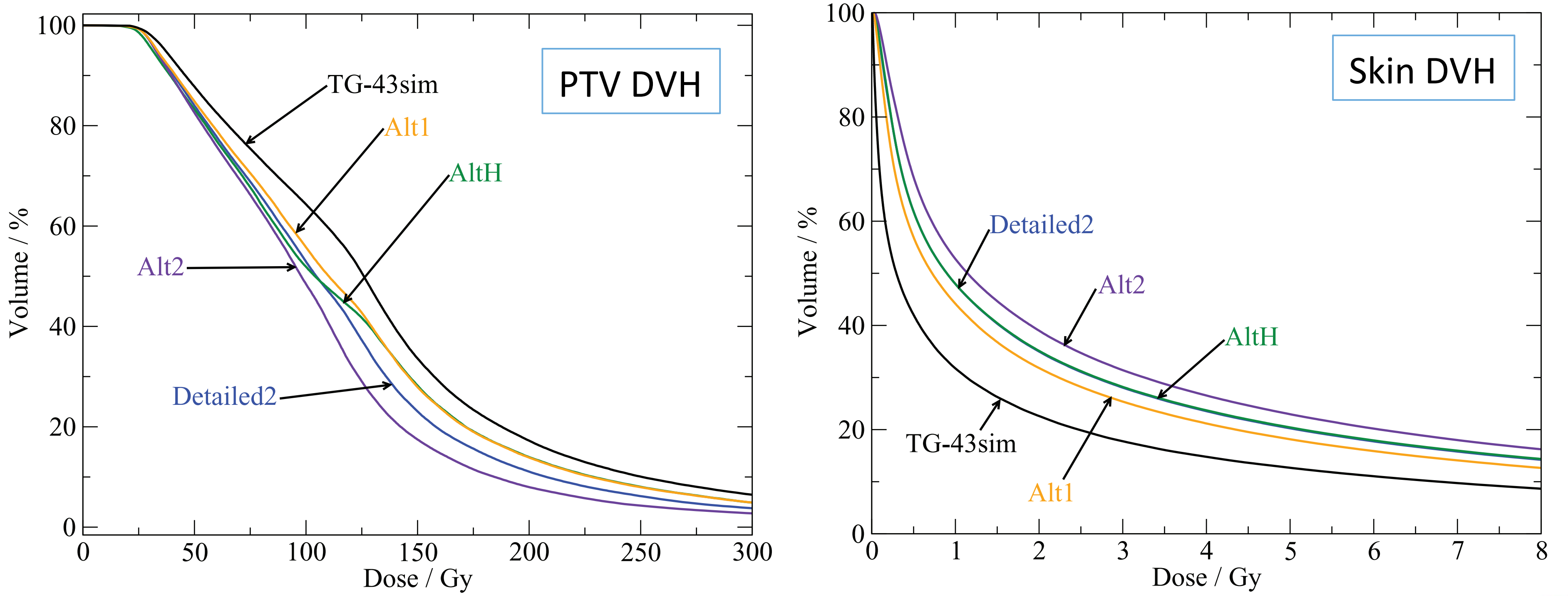
→ Promise of MBDCAs: identify/distinguish inadequate dose coverage of target (may be missed with TG43); improve prediction of skin toxicity

- More research: full MBDCA, prescription dose revision, skin toxicity thresholds

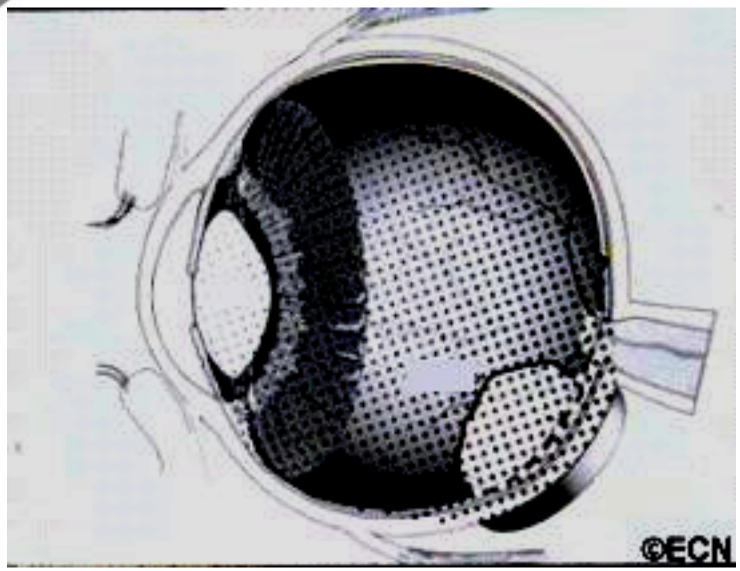
Breast: tissue composition uncertainty

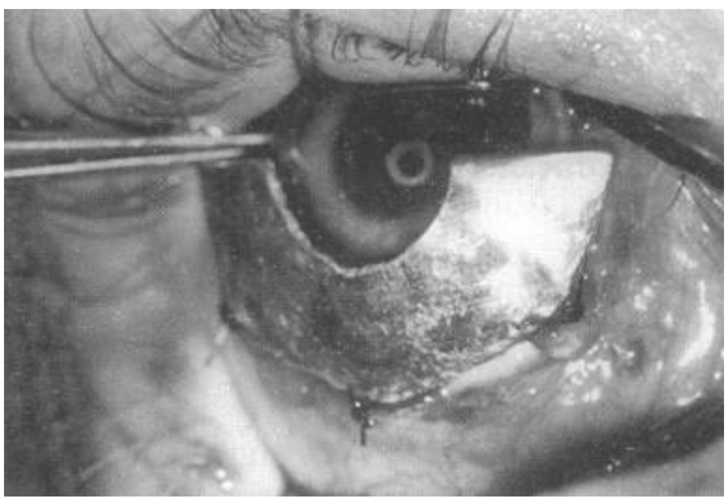
Possible confounding factor in analyses – uncertainty in tissue compositions



Miksys et al, PMB **61** (2016)

Eye plaque brachytherapy





- Plaque containing radiocative sources (^{103}Pd, ^{125}I) is temporarily implanted adjacent to tumor; removed 3-7 days later
- Posterior (choroidal melanoma) and anterior (iris melanoma)

www.eyecancer.com

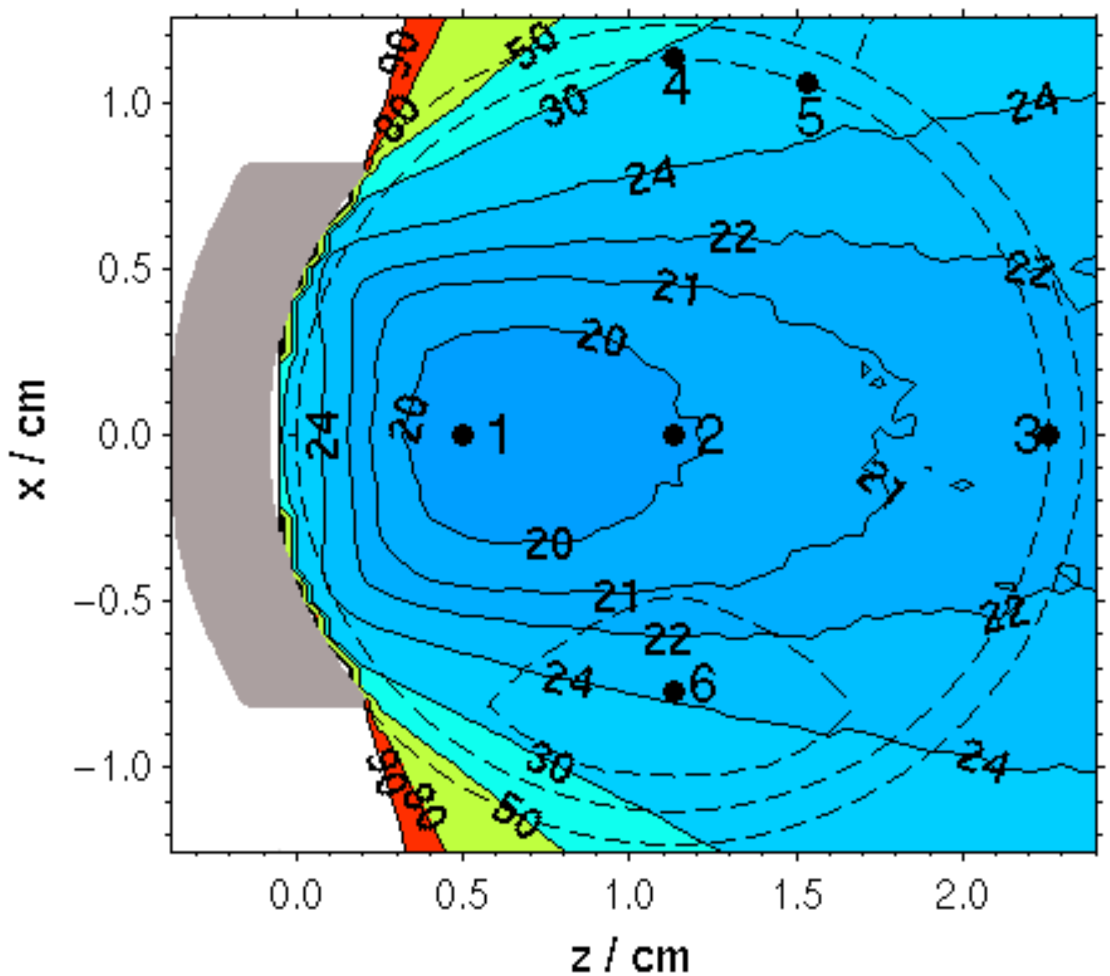
Shields *et al*, Br J Ophthalmol **79** (1995).

Eye: Plaque in water

Contours give percent difference in dose for plaque in water versus TG43:

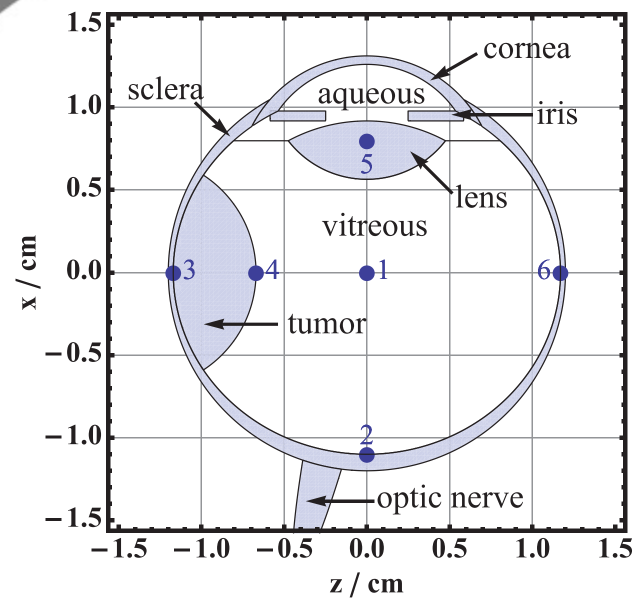
- Differences >20% in tumour and normal ocular structures
- 90% differences possible at optic nerve

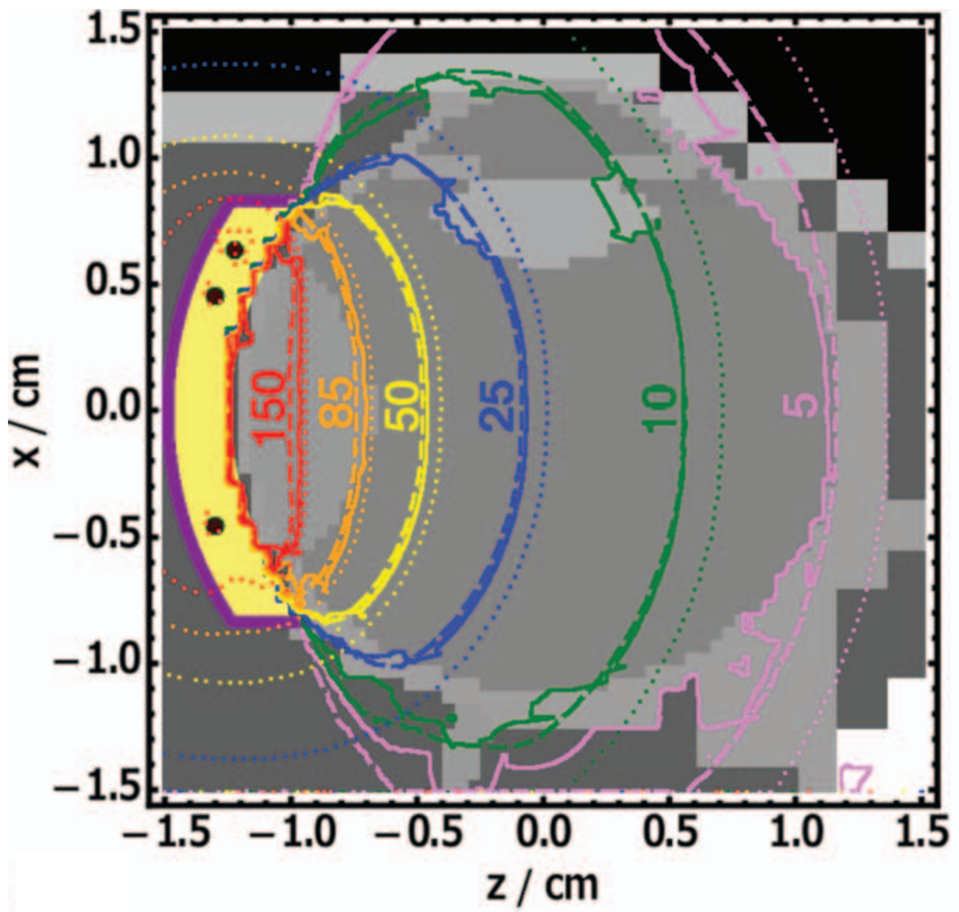
^{103}Pd



Rivard et al, Med Phys **38** (2011); Thomson et al Med Phys **35** (2008)

Eye: Plaque and patient models





Colour isodose lines:

-Dotted: TG43

-Dashed: plaque in water

-Solid: plaque and patient models

→ Considerable dose differences between full model and TG43

Lesperance et al, Med Phys **41** (2014)

Eye: Clinical implications

- Plaque therapy effective − local control in 90% of patients
- Radiation-induced injury not uncommon:
  - Necessitated enucleation in 5% of cases
  - 3 years after brachytherapy, 49% of patients had lost 6 or more lines of visual acuity from baseline (radiation toxicity to retina or optic nerve)

Collaborative Ocular Melanoma Study (COMS) Group, Arch Ophthalmol **124** (2006); Melia et al, Ophthalmology **108** (2001).

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High rate of local control & relatively high rate of toxicity → more favourable therapeutic ratio with lower radiation dose? Perez et al, IJROBP **89**, 127–136 (2014).

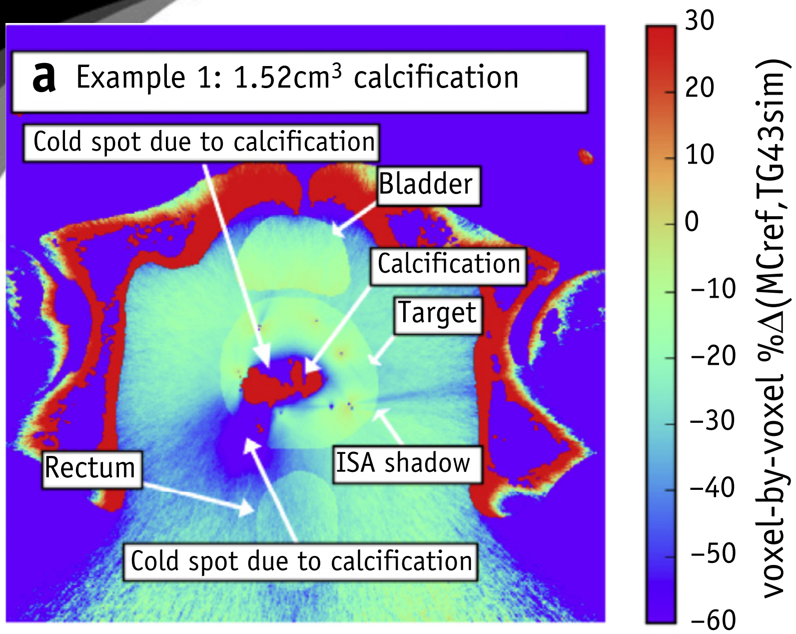
- All studies to date have employed TG43 (large dose errors; inconsistencies with different plaque models)
- Use MBDCA/MC to help understand treatment outcomes; improve plaque design.

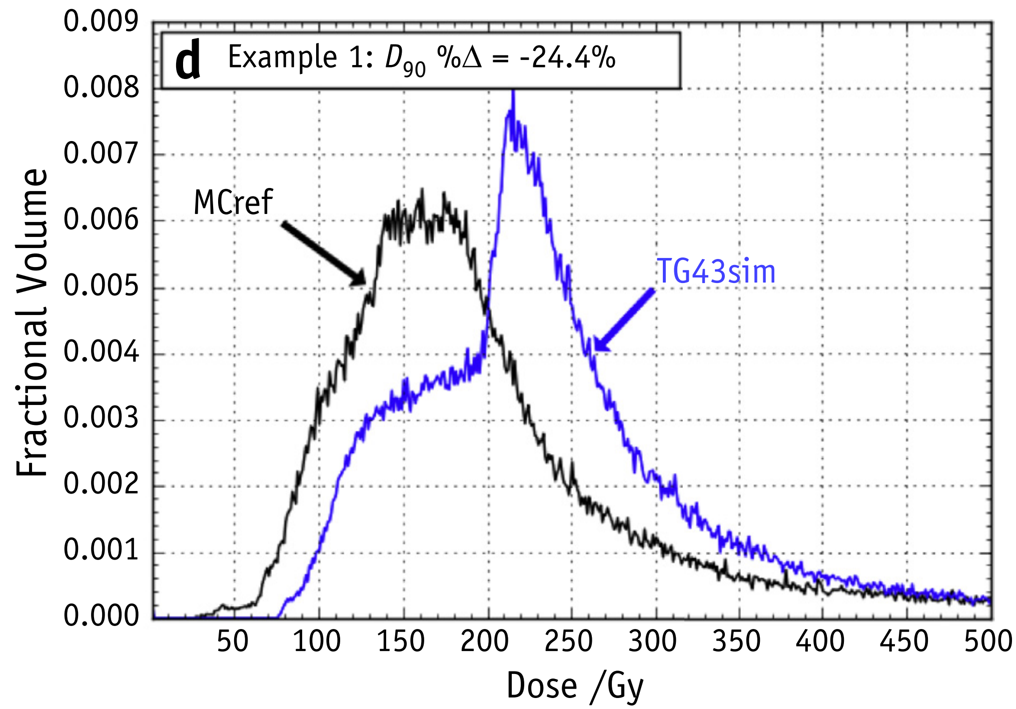
Prostate: ^{125}I brachytherapy

- Permanent implant prostate brachytherapy (^{125}I) commonly-used for low and intermediate risk prostate cancer

- Recent dosimetric and radiobiological analyses: Centre Hospitalier et Universitaire (CHU) de Quebec, 613 patients treated (2003 to 2012)
  Miksys et al, IJROBP 97 (2017); Miksys et al, Med. Phys. (under review).

Prostate: Patient with large calcification

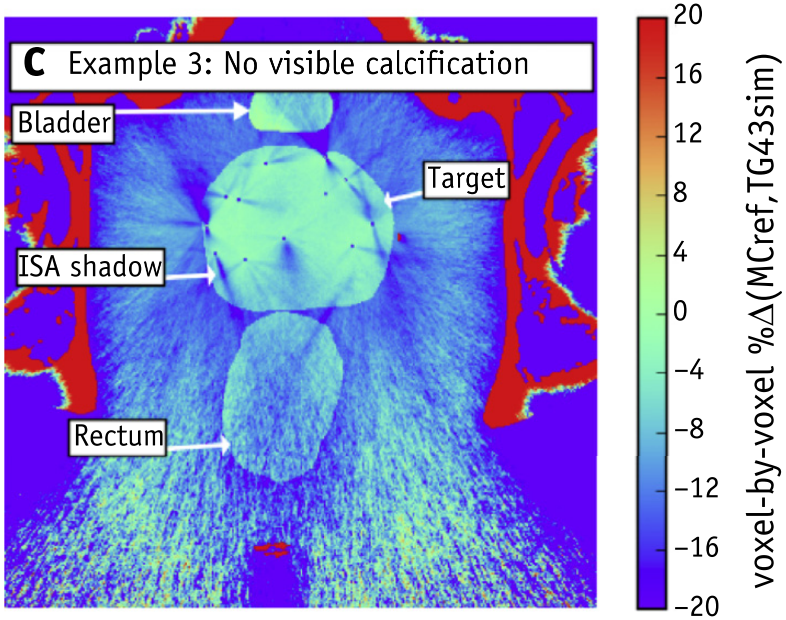


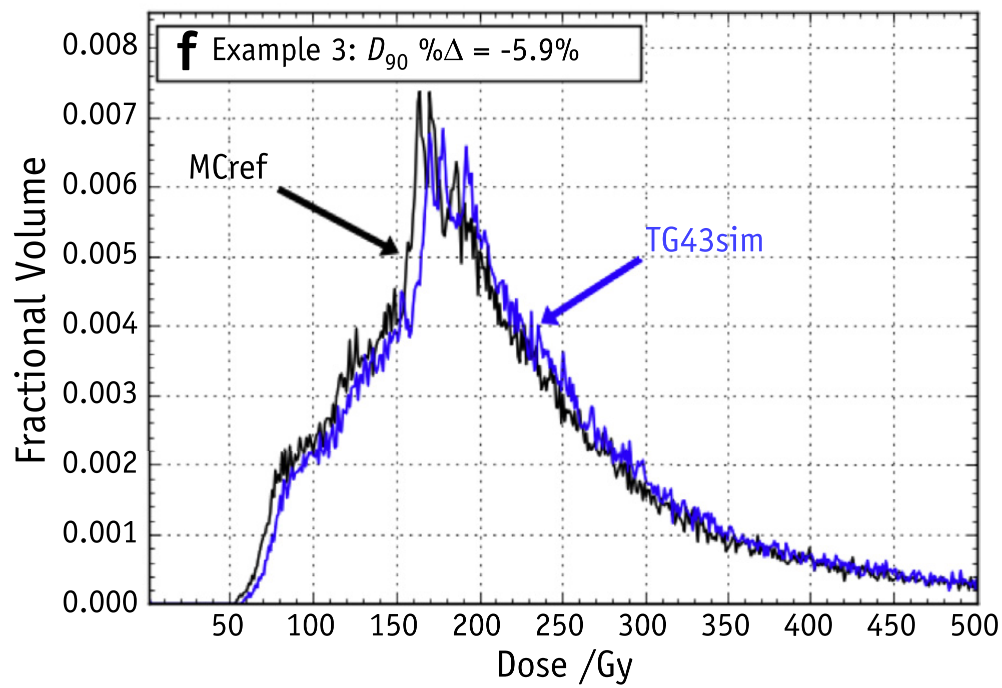


- **MC** yields relatively greater doses to calcifications and lower doses (possibly > 50%) to regions about calcifications.

→ Possibility of clinically underdosed volume

Prostate: ‘Average’ patient





- “Average” patient: D_{90} is 5.9% lower with **MC** than **TG43**

Prostate: cohort doses

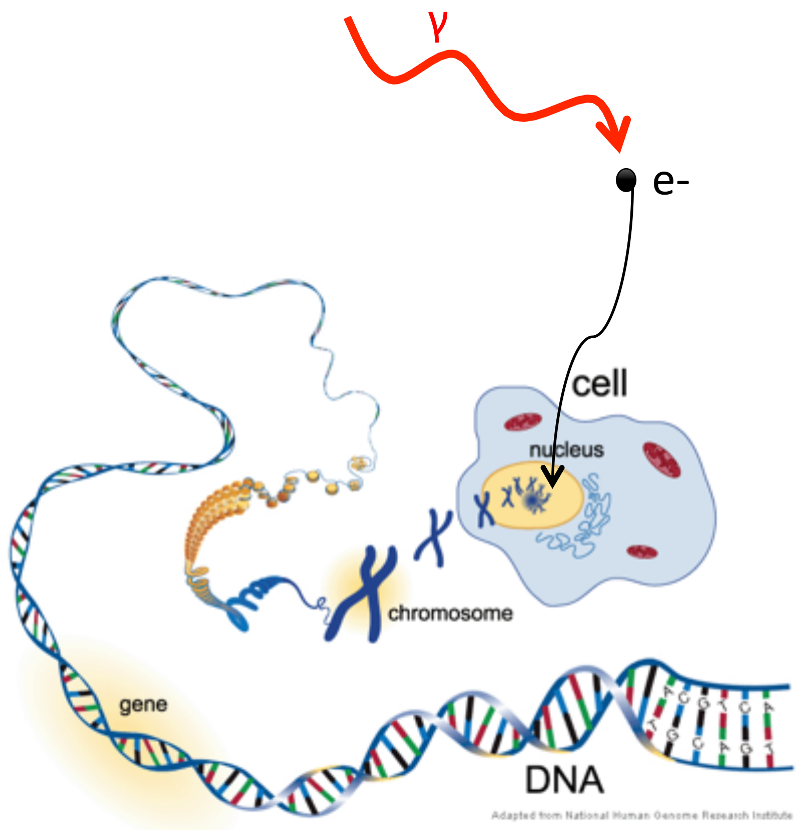
Table 2 Dose metrics evaluated with **MCref** and **TG43sim** for 613 patients and 3 example cases (Fig. 2)

	Target				Urethra			Rectum			Bladder		
	D_{90} (Gy)	D_{99} (Gy)	V_{100} (%)	V_{200} (%)	D_5 (Gy)	D_{30} (Gy)	V_{100} (%)	$D_{0.1cm3}$ (Gy)	D_{2cm3} (Gy)	D_{30} (Gy)	$D_{0.1cm3}$ (Gy)	D_5 (Gy)	D_{30} (Gy)
Overall results from 613 patients													
MCref	144.1	94.6	88.2	30.0	271.4	222.2	83.4	176.3	97.5	42.8	221.8	120.1	54.9
TG43sim	152.6	101.3	90.4	33.4	283.4	232.8	86.0	185.6	102.8	44.2	219.2	119.7	56.0
$\%\Delta_{av}$	−5.9	−7.2	−2.6	−11.5	−4.4	−4.7	−5.7	−5.2	−5.4	−3.2	1.3	0.4	−2.1
$\%\Delta_{std}$	1.6	2.5	1.7	3.2	1.8	1.9	6.5	1.8	1.7	5.3	1.8	1.5	2.0
IQR(**MCref**)	34.9	32.2	9.8	14.7	93.2	56.6	19.8	73.6	34.8	16.7	99.8	38.6	22.0
IQR(**TG43sim**)	36.6	33.8	9.2	16.9	97.5	58.6	17.7	76.0	36.8	18.4	98.9	38.5	22.1

- D_{90} is 5.9% lower with **MC** than **TG43**
- Considerable variation in D_{90} values over patient cohort:
  - 50% of patients have D_{90} between 127 and 162 Gy;
  - 95% of patients have D_{90} between 85 to 204 Gy.

Prostate: radiobiological models

- Goal of radiobiological modelling: provide insight by accounting for biological response to radiotherapy
- Previous work with TG43
- We investigated coupling of patient-specific MC dose calculations with biological dose and tumour control probability models



https://elcaminogmi.dnadirect.com/img/content/common/cellsToDNA.gif

N. Miksys, et al, Med Phys (under review)

What is biological dose?

Represents tissue-specific biological response to radiation damage over protracted radiotherapy treatments.

Quantified via "Biologically Effective Dose" (BED)*:

BED [Gy] = Dose [Gy] X Relative Effectiveness [dimensionless]

- Related to (the logarithm of the) surviving fraction of cells
- Predict/assess damage of a particular treatment
- Equivalent Uniform BED (EUBED) accounts for spatial dose variations in target

Tumour Control Probability (TCP) describes likelihood of a treatment to be curative

*Fowler, Br J Radiol **62** (1989)

Prostate: Radiobiological model parameters

Parameter	Reference Value
Single-hit radiosensitivity: α	0.15 Gy^{-1}
Double-hit radiosensitivity: β	0.05 Gy^{-2}
I-125 half life: $t_{1/2}$	59.4 days
I-125 decay constant: λ	0.01167 days^{-1}
Tumour potential doubling time: T_{pot}	42 days
Effective tumour repopulation rate: γ	0.0165 days^{-1}
Repair half-life: $T_{R1/2}$	0.01125 days
Sub lethal repair constant: μ	61.61 days^{-1}
Initial number of cancer cells: N_0	10^6

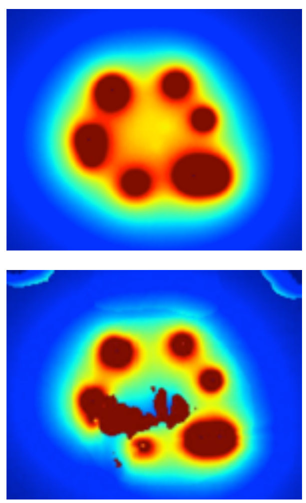
- Considerable uncertainty in parameters within population, unknown for particular patient
- Nath et al, AAPM Report TG-137 (2009)

Prostate - radiobiology: What did we do?

- Compare biological doses and TCPs calculated from full MC and TG-43 dose calculations
- Identify limitations and suggest (3) extensions to improve standard radiobiological models based on new considerations related to full tissue MC dose calculations

613 Patients:

TG43



MC

Biological dose
→ 11 models

Tumour control probability
→ 2 models

Prostate: Low doses within target

- Calculations of EUBED are highly sensitive to low doses in treatment volume – can yield TCP near zero (not consistent with clinical outcomes)
- To circumvent this, previous studies using TG-43 doses removed/omitted low doses in target (<D99*; < 110 Gy **)!

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Prostate: Low doses within target

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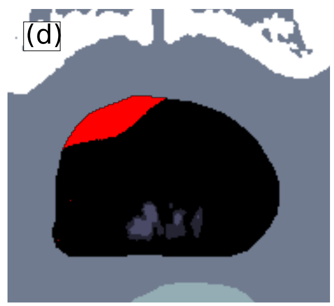
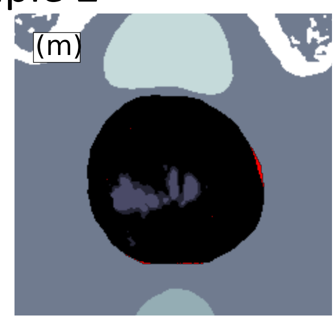
Doses<110 Gy

Example 1



TG43

Example 2



TG43

- Rationale: low doses typically exist near the periphery of treatment volume and subjective contouring should not significantly affect the EUBED/TCP calculations.

*Ling *et al*, IJROBP **28** (1994); **King et al, IJROBP **46** (2000).

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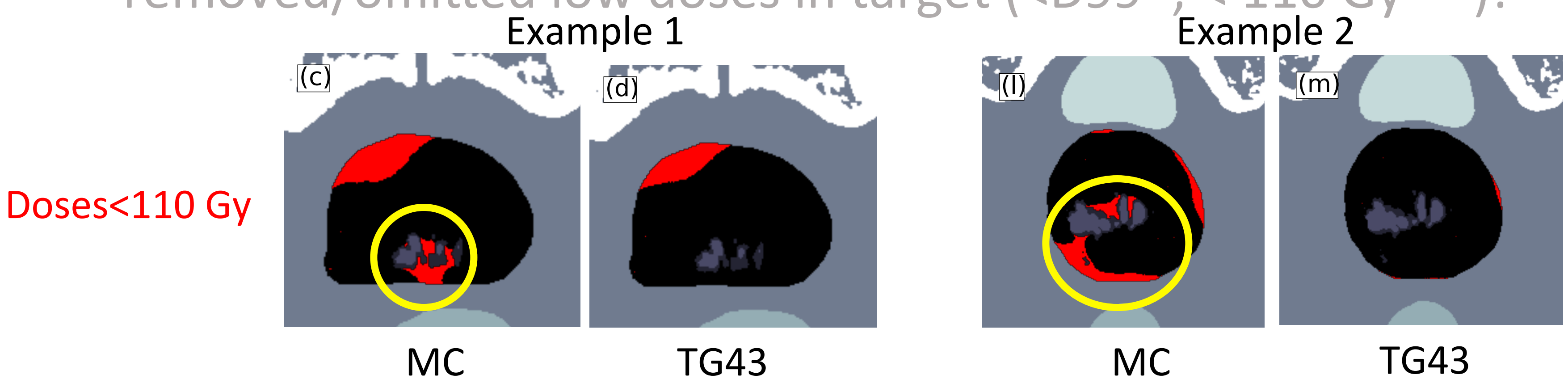

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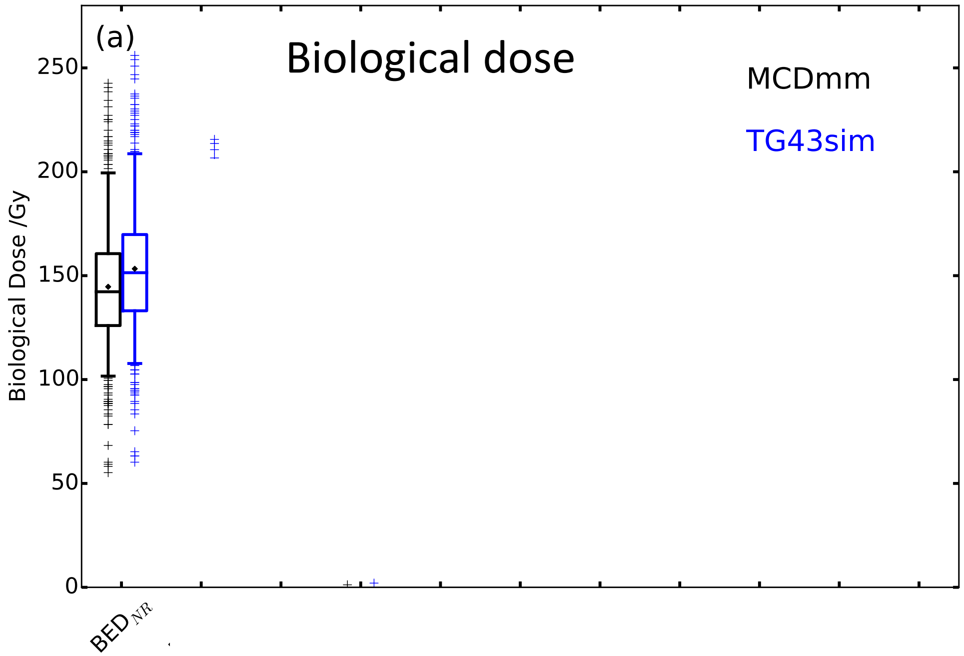
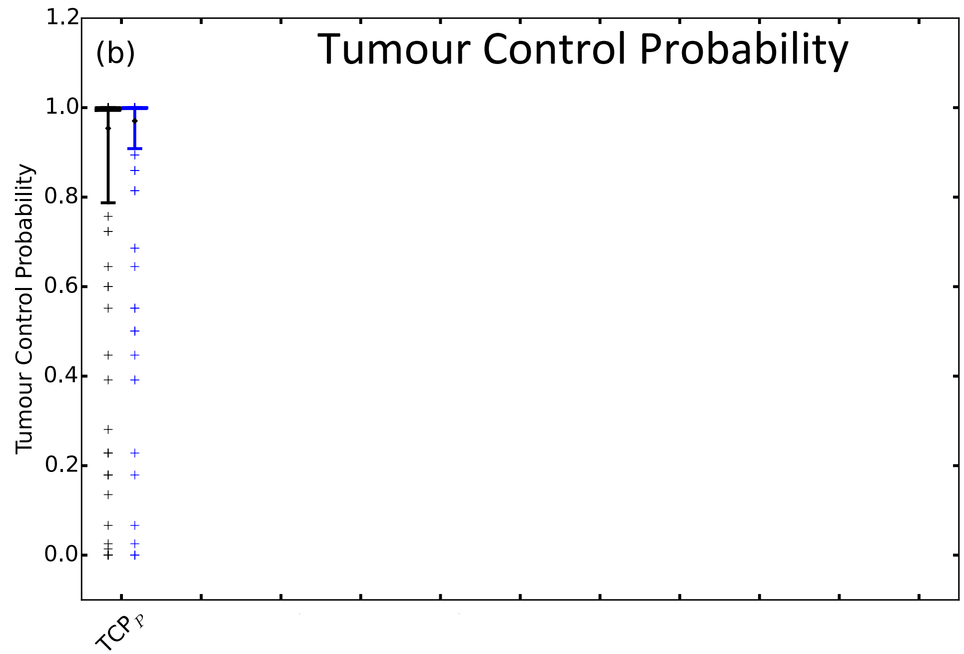
NOT TRUE with MC!

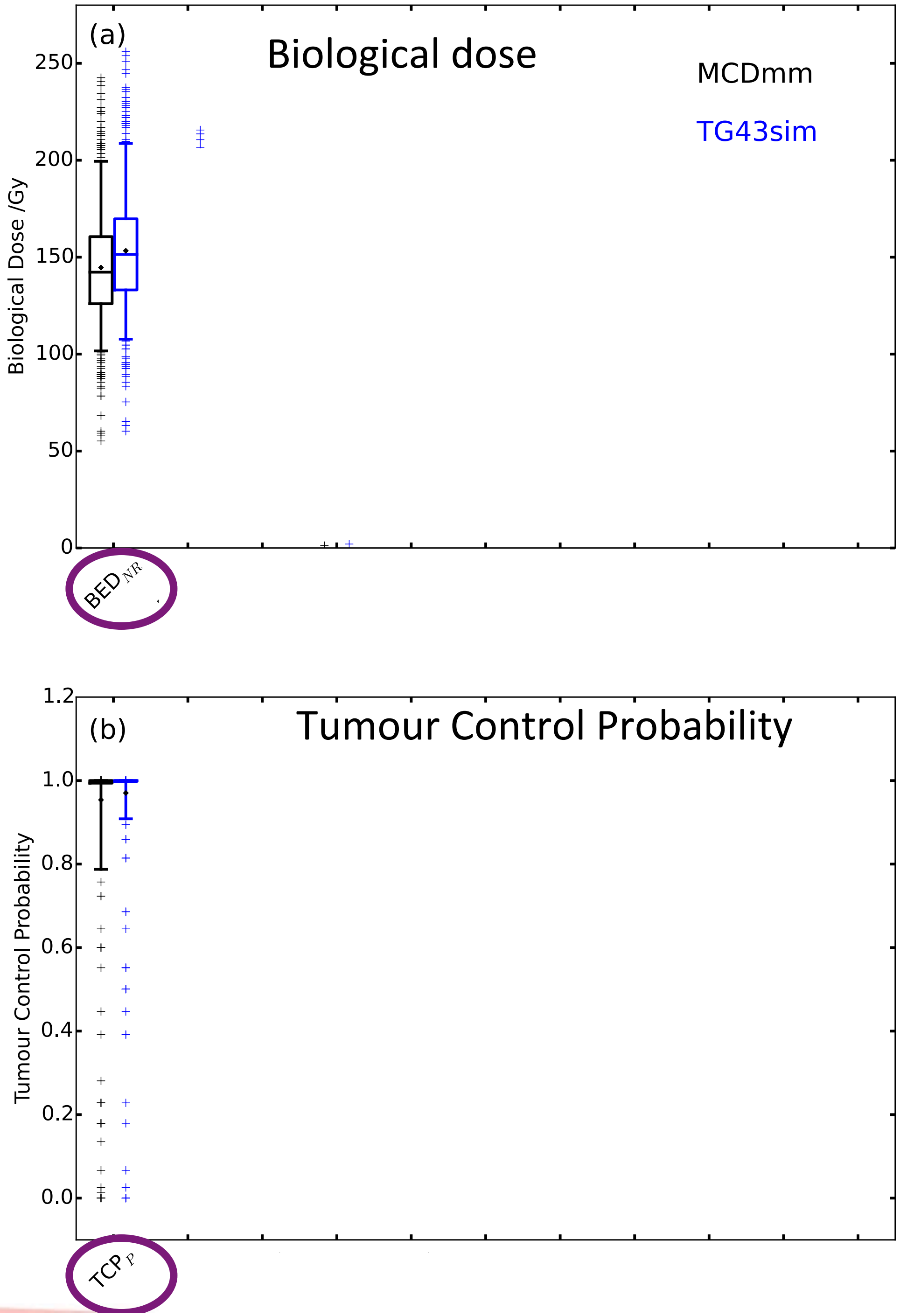
Some results



Box and whiskers plots:
-box plots represent median and 50th percentile range
-whiskers extend to 95th percentile
-crosses are outliers
-dots are mean



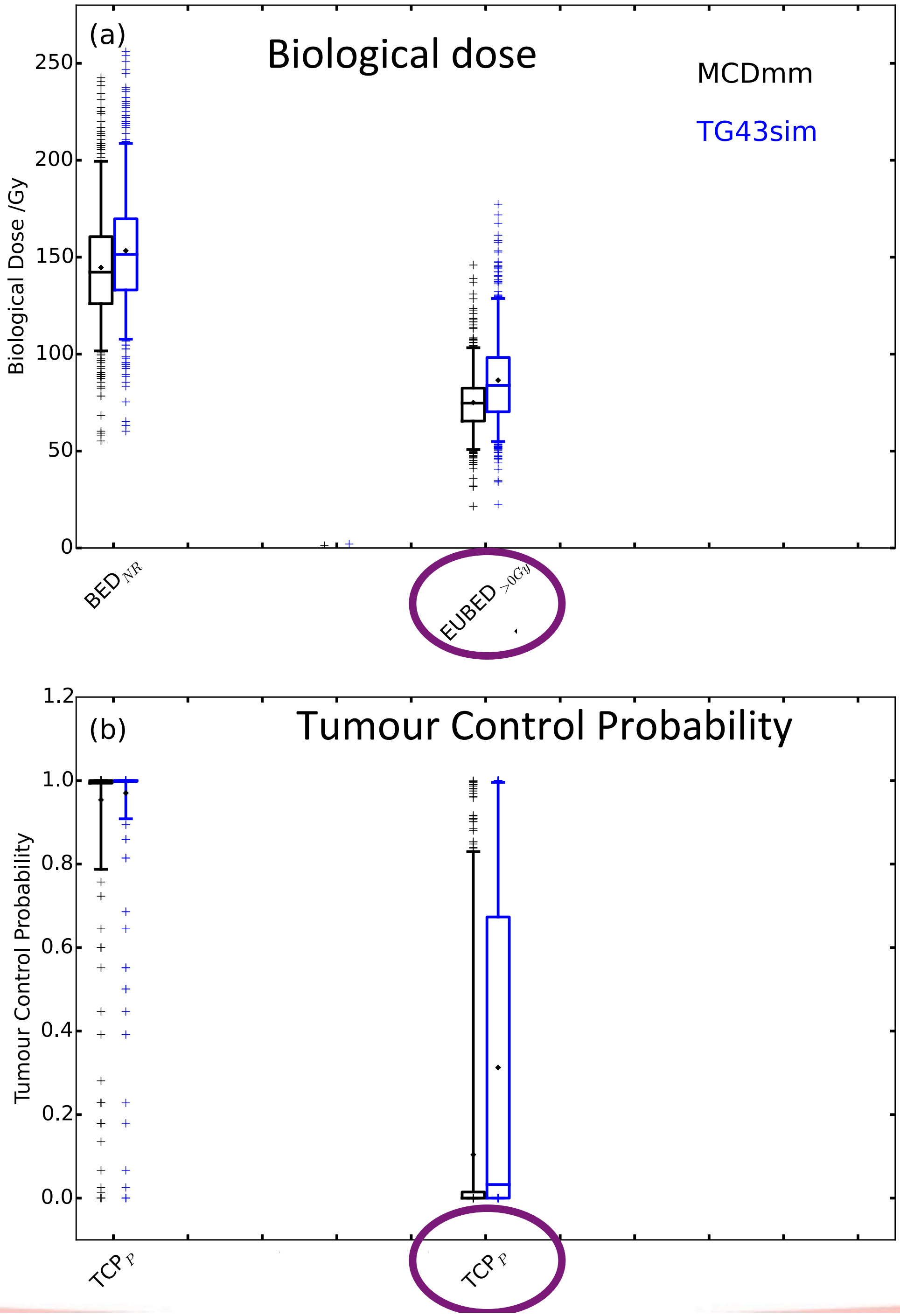
Lower plot gives TCP corresponding to Biological dose in upper plot



Some results

BED_{NR} – Simplest:

- uniform D_{90} dose, no repopulation
- BED_{NR} estimates for MC and TG43 differ by about the same amount as physical dose (~6%)
- Corresponding TCP population mean/median near 1.

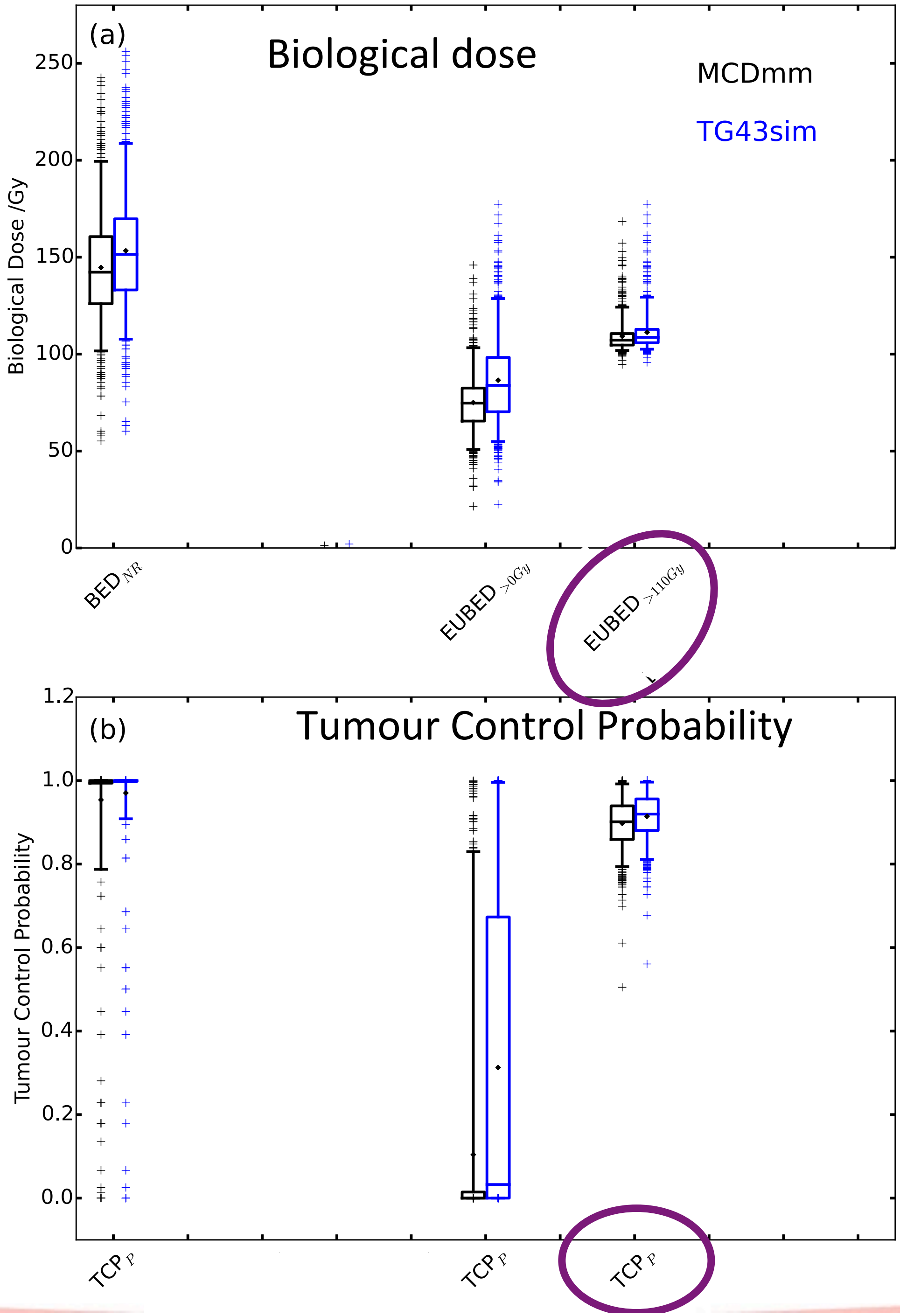


Some results

EUBED$_{>0Gy}$: non-uniform dose over target, no low dose rejection

- Corresponding TCP estimates are low.

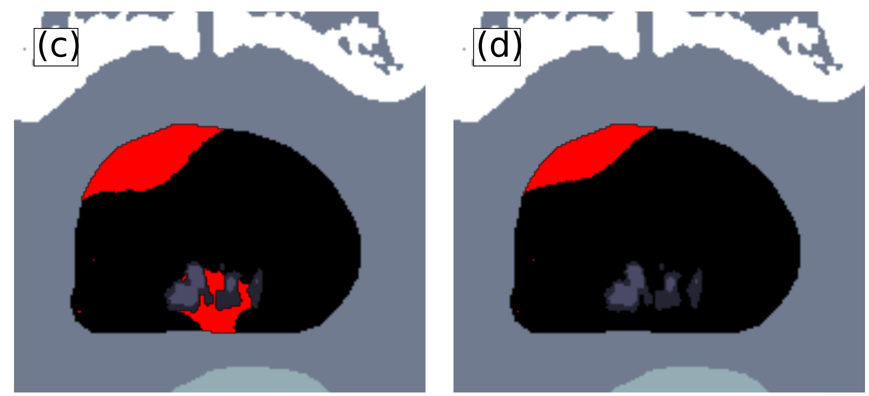
Some results



EUBED$_{>110Gy}$: non-uniform dose over target, retain doses >110 Gy

- Many doses omitted/ rejected
- TCP estimates increase relative to EUBED$_{>0Gy}$

MC TG43

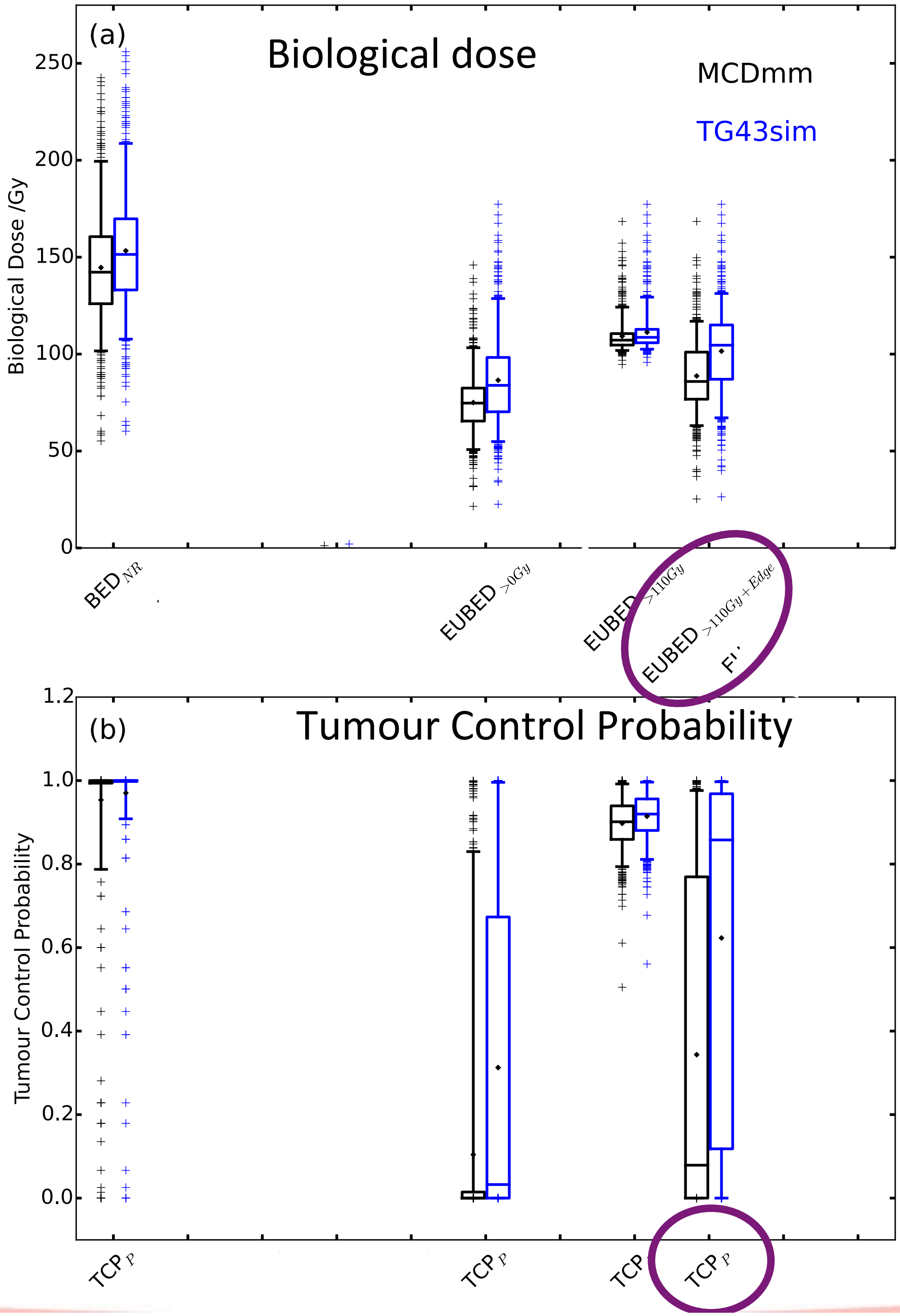


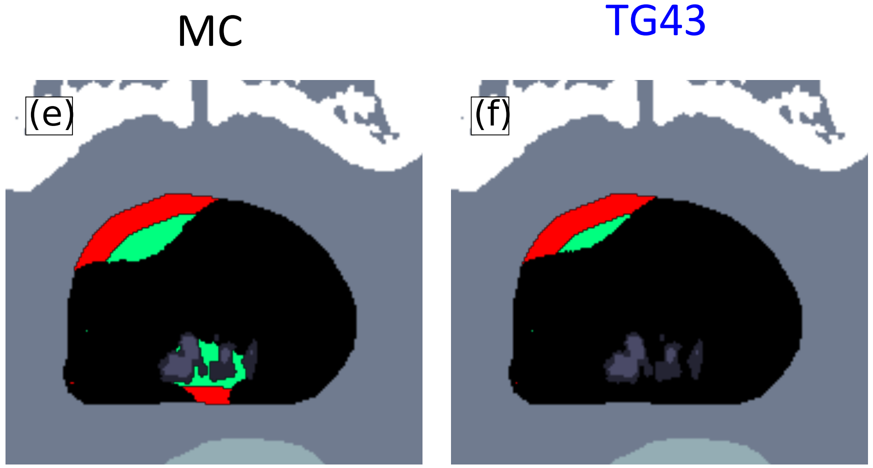
Doses<110 Gy

Some results

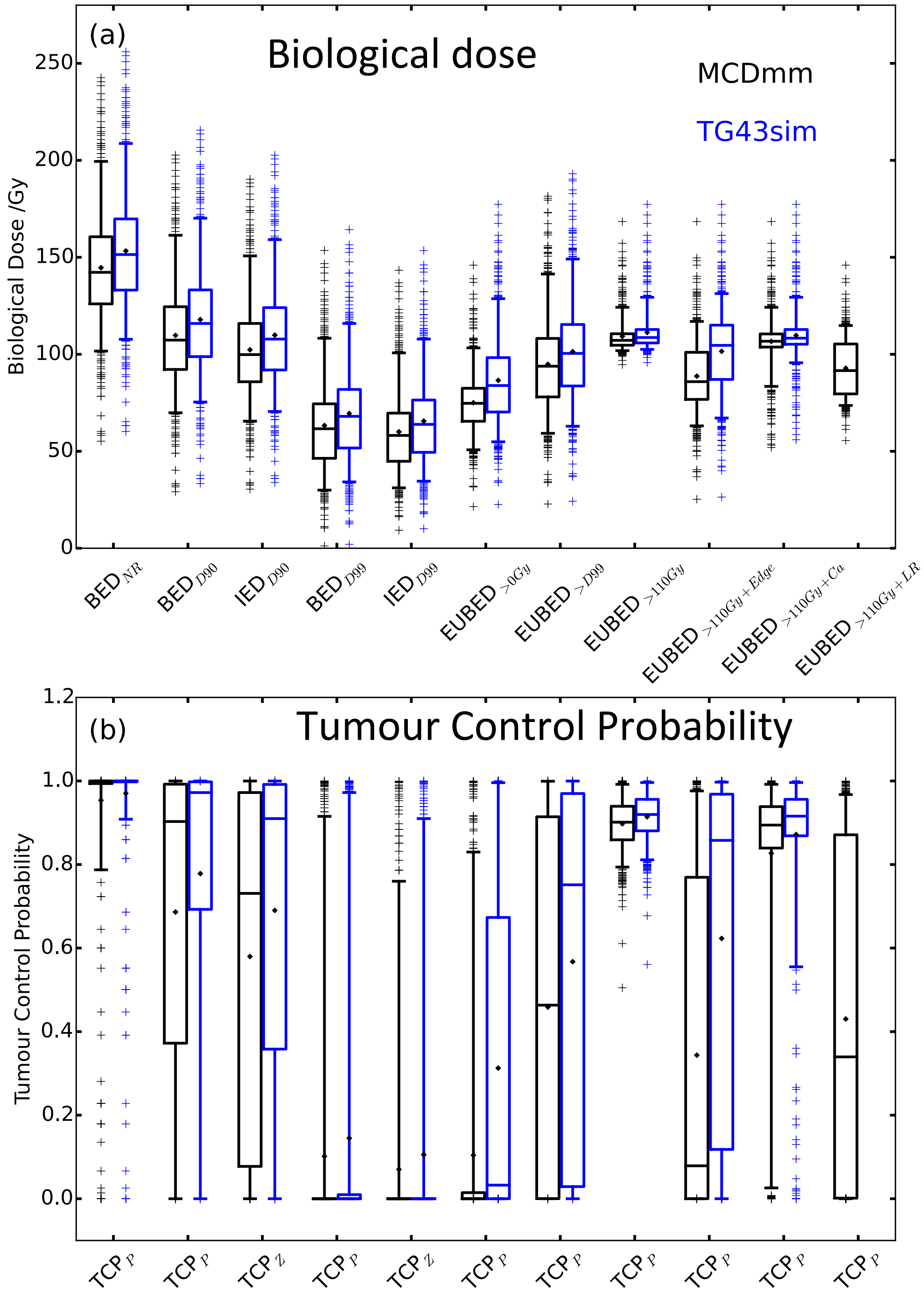
EUBED$_{>110Gy+Edge}$: reject doses < 110 Gy only if near target edge

- retain doses in the ‘interior’ of target
- reduces EUBED, TCP





Doses<110 Gy; Doses retained now but rejected with EUBED$_{>110Gy}$



Prostate: Summary of results

11 biological doses models (varying complexity) and corresponding TCP estimates

Prostate: TCP

- TCPs calculated with either MC or TG43 (ranging from 0 and 100%) do NOT accurately reflect patient outcomes.

- Outcomes:
  - 5 to 10 year biochemical failure free survival rates are 85% to 90% Martin et al, IJROBP **67**, 334-341 (2007); Zebentout et al, Cancer radiotherapie **14**, 183-188 (2010); Hinnen et al, IJROBP **76** (2010); Merrick et al, IJROBP **65** (2006).
  - Analysis started for this patient cohort.

→ Need to re-asses radiobiological model parameter values (e.g. α, β) to obtain results consistent with clinical observation

Prostate: Outcomes analysis

- Treatment failures:
  - Insights into treatment failures from more accurate (MC) dose distributions? (cold spots?)
  - Biopsy data from different parts of the prostate → spatial tumour cell density in relation to dose distribution
- Can we correlate doses with clinical endpoints? Local control; normal tissue damage
- Limited sample sizes → pool data from multiple institutions? Institutional differences, e.g., mean D_{90}:

  TOHCC: 138.3 Gy [TG43]; 134.2 Gy [MC]

  CHUQ: 152.6 Gy [TG43]; 144.1 Gy [MC]

TOHCC = The Ottawa Hospital Cancer Centre - Haidari (CU-MSc), Miksys, Cygler et al, in preparation

Summary

"the majority of our radiotherapy strategies were derived by empirical optimization of clinical experience performed with inferior technologies." Chapman & Nahum, 2015

- Today, focused on "new" technology of advanced model-based (MC) dose calculations for brachytherapy
- Applications in breast, ocular, prostate cancers

Summary

"the majority of our radiotherapy strategies were derived by empirical optimization of clinical experience performed with inferior technologies." Chapman & Nahum, 2015

- Today, focused on "new" technology of advanced model-based (MC) dose calculations for brachytherapy
- Applications in breast, ocular, prostate cancers
- Demonstrated differences between traditional, TG-43 approach and full-tissue MC of a few percent to 90%
- Possibility of clinically-underdosed volumes within target that would be missed with TG-43
- Opportunities for collaboration in many areas: from implementation of MBDC to outcomes modelling/analyses

Challenges, ongoing/future research

- Implementation of MBDCA/MC: accuracy of patient model, tissue elemental compositions
- Outcomes modelling:
  - Shortcomings in (analytic) radiobiological models, uncertainty in parameters (ex: prostate)
  - Other approaches – data-driven (phenomenological, statistical)
- Treatment evaluation:
  - Patient numbers
  - Institutional differences (ex: eye plaque design, prostate implant technique, patient selection)
- New treatment approaches (ex: nanodevices)

→ Potential for impact on patient well-being, costs

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