Uncertainties and Limitations in Adaptive Radiotherapy

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Adaptive radiotherapy (ART) – what is it ?

- Adapt plan to patient-specific changes that are unaccounted for in initial plan

- “ART” techniques range in sophistication

Overview

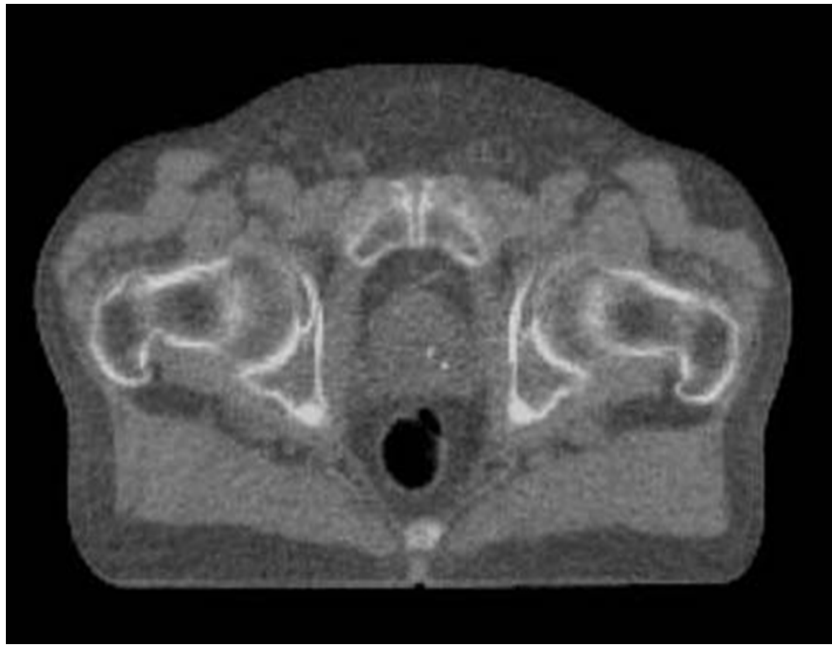
- Survey of adaptive radiotherapy techniques
  - ART to address random changes (on-line ART)
  - ART to address progressive changes (off-line ART)

- Limits and Accuracy of Adaptive Radiotherapy
  - depend on specifics of implementation
  - depend on specific tools that are used

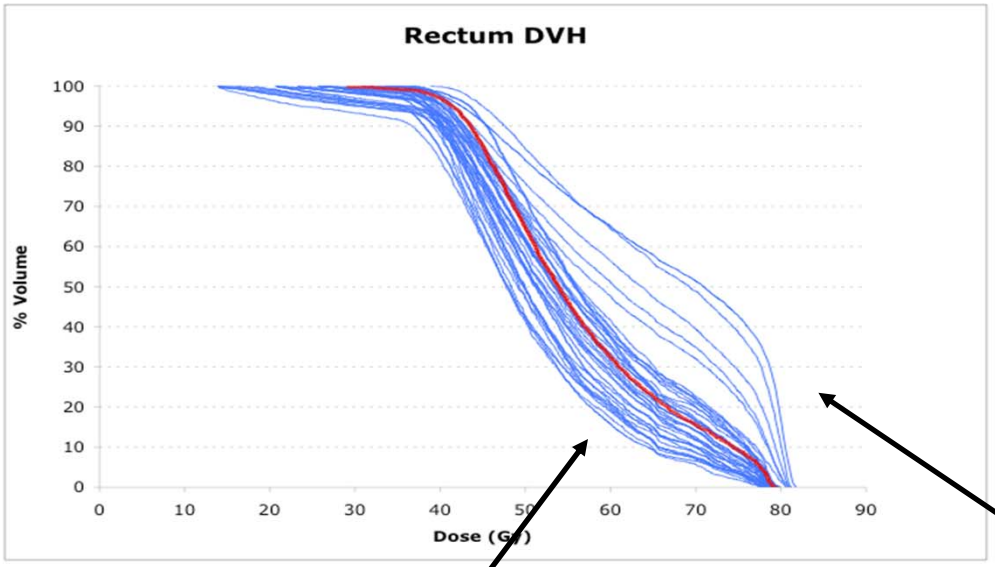
Survey of Adaptive Radiotherapy (ART) techniques

Random changes

- Example: Day-to-day prostate motion

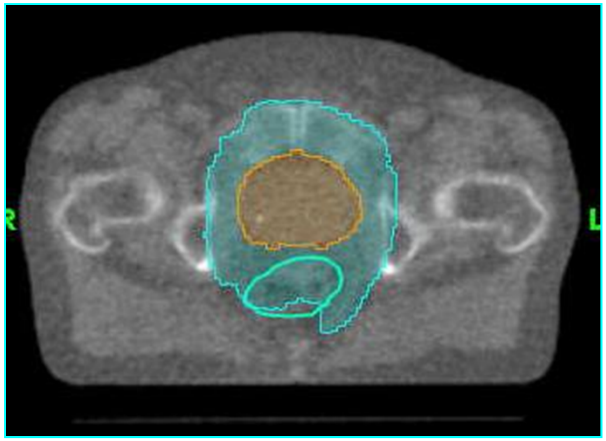


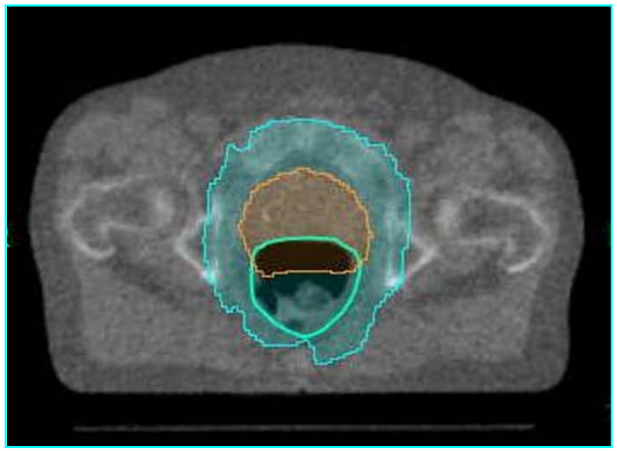
Dosimetric consequence of random changes



Plan DVH

39 “true” DVHs





ART techniques for random changes

- Patient specific margins
- Plan libraries
- Daily plan adjustments

ART techniques that address random changes

- Patient-specific margins:

  CTV-to-PTV margins are typically based on population averages

  Adapt margins to patient-specific observations measured during initial treatments (Yan et al.)

Yan et al. PMB,42,123 (1997) and IJROBP, 48, 289 (2000)

ART techniques that address random changes

- Use of plan libraries:
  - if target changes shape IGRT may no be sufficient
  - generate set of plans that anticipate shape changes
  - each day select best plan

Xia et al., MP 37, 5006 (2010); Foroudi et al., IJROBP (2010), in Press

ART techniques that address random changes

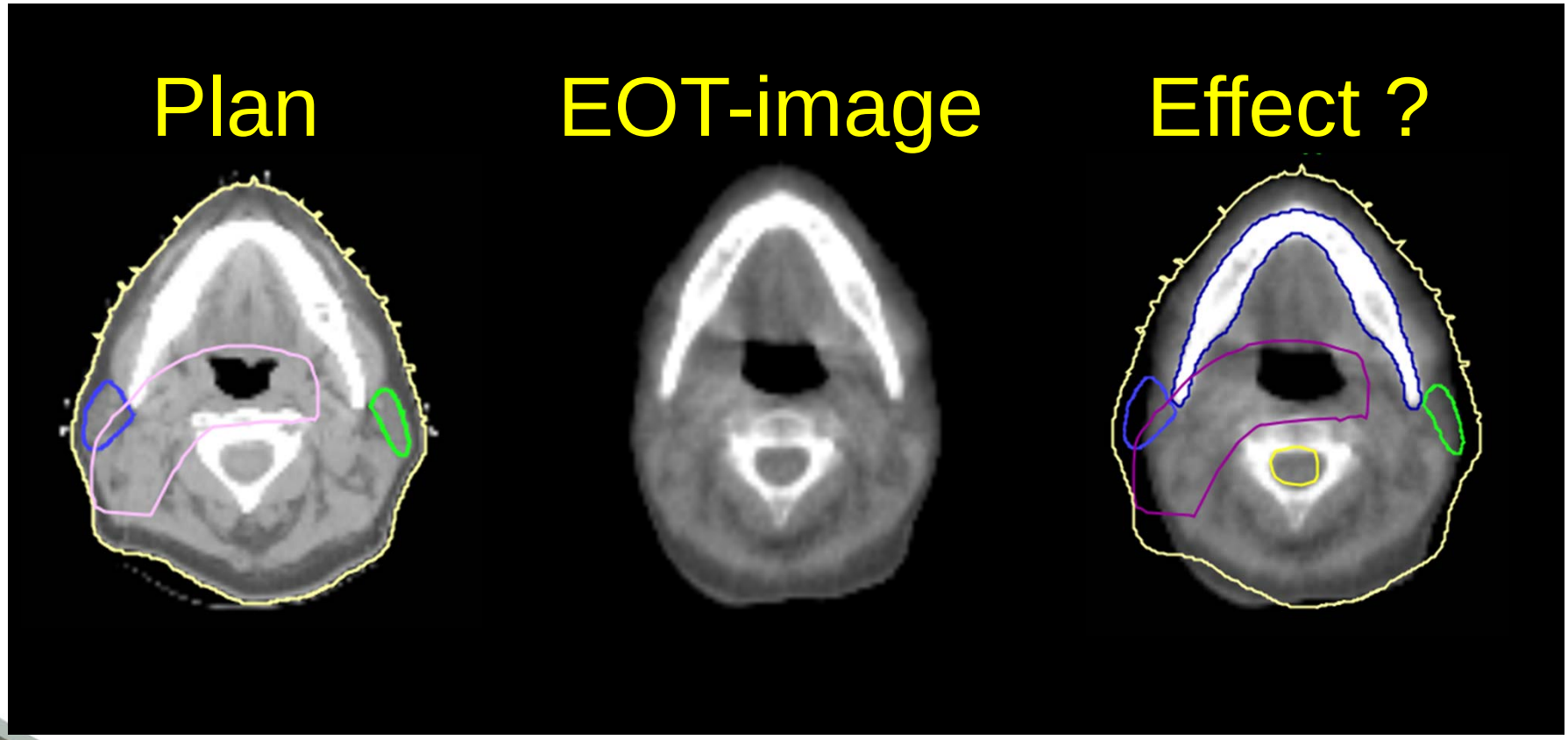
- Daily plan adjustments

  Daily MLC shape adjustments (Ludlum et al.)
  Deformable intensity maps (Mohan et al.)
  On-line reoptimization (Wu et al.)
  Segment aperture morphing followed by segment weight optimization (Ahunbay et al.)

Ludlum, MP, 34, 4750 (2010); Mohan, IJROBP, 61, 1258 (2005); Wu, PMB, 53, 673 (2008);Ahunbay, IJROBP, 77, 1561 (2010)

Progressive changes – Off-line ART

- Example: Head and Neck



Progressive changes – Off-line ART

- 2 step process

  Change in patient triggers replan

  Replan

What observation triggers an adaptive re-plan ?

- Clinical observations of weight loss or tumor shrinkage/growth
- Observations of volumetric or dosimetric changes made based on repeat imaging
- Observations of dosimetric changes, cumulative or daily, that are facilitated by deformable image registration (DIR)

ART techniques that address progressive changes

- Trigger - Clinical observations:
  - New CT is acquired, recalc old plan in new CT to quantify dosimetric effect
  - Reduced CTV coverage and increase in normal tissue doses
- Clinical observations of weight loss/tumor shrinkage are accompanied by degradation of dosimetric endpoints

Hansen, IJROBP, 64, 355, 2006; Zhao, Radiother Oncol, 98, 23 (2011)

ART techniques that address progressive changes

- Trigger- Observations of volumetric or dosimetric changes based on repeat imaging
  - Reimage at fraction number 25: in 50% of cases a normal tissue constraint was violated
  - Scheduled repeat CT scans: 65% of patients benefited from replanning

Wang, IJROBP, 77, 617 (2010); Ahn, IJROBP, 80, 677 (2011)

ART techniques that address progressive changes

- Trigger- Observations from repeat imaging and deformable registration analysis

  - Patients with scheduled weekly and daily CT
  - Deformable image registration is used transfer contours
  - Deformable image registration is used to accumulate dose

Lee, IJROBP, 70, 1563, 2008. Wu, IJROBP, 75, 924, 2009

What to do at time of adaptive re-planning ?

- Re-establish initial plan in new anatomy
- Correct dosimetric variations at time of re-planning

Limits and Accuracy of ART

Limits and Accuracy of Adaptive Radiotherapy

- ART mitigates delivery uncertainties
- Uncertainties inherent to the ART process should be evaluated and compared with treatment uncertainties
- Little information is available in literature about uncertainties of ART

- On-line ART techniques: Limitations and uncertainty

Limits and Accuracy – Patient specific margins

- Prostate: 3-4 mm setup and 3-4 mm organ motion uncertainty

- No technical barrier to implementation
- Initial observations made with any IGRT technology that is available in clinic
- Workload: initial observations, re-plan at time of implementation

Yan et al. PMB,42,123 (1997)

Limits and Accuracy – Patient specific margins

- Accuracy depends on number of initial observations
- Yan et al. : accuracy requirement:
  - Max 2% dose reduction in CTV for at least 80% of patients
  - Max 4.5% dose reduction in CTV for at least 95% of patient
- Required number of observations
  - One week for 4-field box
  - Two weeks for IMRT
- Reduced margin from 10 mm, on average

Yan et al. PMB,42,123 (1997)

Limits and Accuracy – Plan libraries

- Generate multiple plans- uncertainty no different than for regular plan
- Multiply planning effort
- Who decides what plan to use ? Staff training ?

- Limitation: finite amount of plans

Limits and Accuracy – Plan libraries

- Limitation: finite amount of plans
  - Xia et al., 5 plans for prostate plus nodal volume
  - 35% of fractions used standard plan as plan of choice
  - 65% of treatments achieved prescription goal

Xia et al., MP, 37, 5006 (2010)

Use of library plans for bladder cancer

CLINICAL INVESTIGATION

ONLINE ADAPTIVE RADIOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER: RESULTS OF A PILOT STUDY

Farshad Foroudi, M.B., B.S., M.P.A., F.R.A.N.Z.C.R.,* Jacky Wong, M.Sc., R.T.T.,† Tomas Kron, Ph.D.,‡ Aldo Rolfo, B.Sc., M.B.A., R.T.T.,† Annette Haworth, B.Sc., M.Sc., Ph.D.,‡ Paul Roxby, M.A., M.Sc.,‡ Jessica Thomas, M.Sc.,* A. Herschtal, B.Sc.,* Daniel Pham, R.T.T.,† Scott Williams, M.D., B.Sc., F.R.A.N.Z.C.R.,* Keen Hun Tai, M.B.B.S., F.R.A.N.Z.C.R.,* and Gillian Duchesne, M.D., F.R.C.R., F.R.A.N.Z.C.R.*

*Division of Radiation Oncology, †Radiation Therapy Services, and ‡Physical Sciences, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

Foroudi et al., IJROBP (2010), in Press

Bladder Cancer

Pos (2003): weekly CT, 15-20 mm GTV-PTV margin

42 % of scans: GTV was outside PTV
65 % of patients: GTV was outside PTV at least once
2/17 pat. GTV was outside PTV in each scan

Suggested margins:

Muren (2003)	Forkal (2004)
20/10 mm Sup./Inf.	35/5 mm Sup./Inf.
11/8 mm Left/Right	13/13 mm lateral
20/14 mm Ant./Post.	14/11 mm Ant./Post.

Muren *et al*., Radiother Oncol , 69, 291 (2003);
Forkal *et al*. IJROBP, 59, 436 (2004); Pos *et al*. IJROBP, 55, 835 (2003)

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Large margins are required

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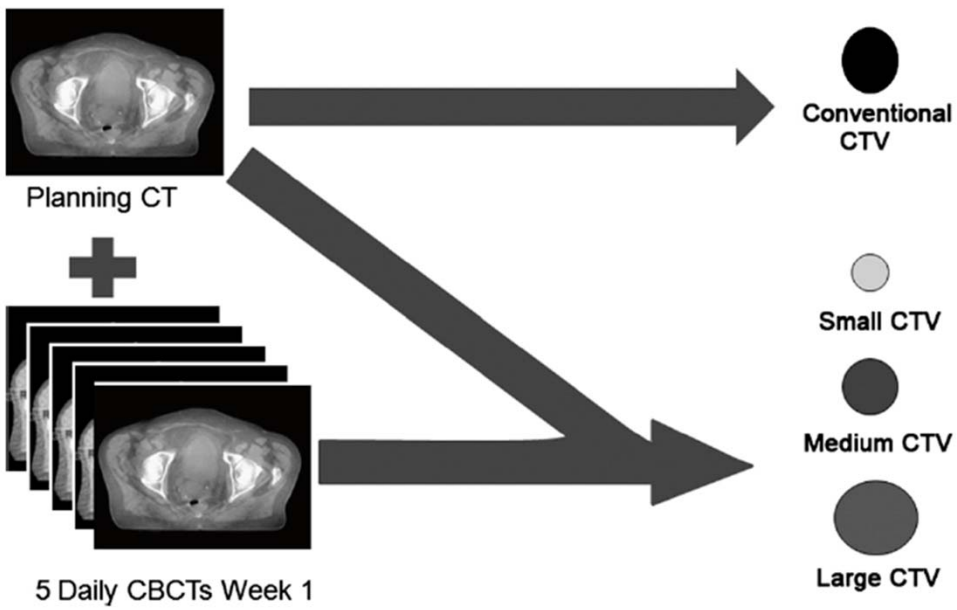
Foroudi Study-library plan for bladder cancer

- Prospective study, 27 patients
- Conventional plan 15 mm CTV-to-PTV margin
- After 5 fx:



+5 mm CTV-to-PTV margin

- Starting on fx 8: CBCT, then select best of four plans for each day

Foroudi et al., IJROBP (2010), in Press

Foroudi Study- Results

- Time: imaging and decision: about 11 minutes
- Plan usage: Small: 10 %, medium: 49%, large 40%
- CTV coverage was maintained with library plans
- Normal tissue > 45 Gy: 30% less with ART
- Substantial training effort

Foroudi et al., IJROBP (2010), in Press

Daily plan adjustment for prostate patients

- What dosimetric problem are we mitigating ?

Daily plan adjustment for prostate patients

- Deformation of prostate – dosimetric effect

Margin Posterior/Other (mm)	Dosimetric endpoint	Difference	Study
5/8	Volume receiving Rx dose	-2.80%	Mohan et al
1/3	D95% (rel. to plan)	1%	Ahunbay et al.
0/0	D95% (rel. to plan)	-6%	Ahunbay et al.
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Mohan, IJROBP, 61, 1258 (2005);
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- Little effect for prostate

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Daily plan adjustment for prostate patients

- Deformation of bladder – effect

Margin Posterior/Other (mm)	Dosimetric endpoint	Difference	Study
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Daily plan adjustment for prostate patients

- Deformation of rectum – effect

Margin Posterior/Other (mm)	Dosimetric endpoint	Difference	Study
5/8	% Vol > 92.5% of Rx	×4	Mohan et al
4/6	Volume at Rx dose	×2	Kupelian et al.

Mohan, IJROBP, 61, 1258 (2005); Kupelian, IJROBP, 66, 876 (2006)

Daily plan adjustment for prostate patients

- Deformation of rectum – effect

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- Rectal volume receiving prescription dose increases

Mohan, IJROBP, 61, 1258 (2005); Kupelian, IJROBP, 66, 876 (2006)

Daily plan adjustment for prostate patients

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Benefit of on-line ART for prostate

Mohan, IJROBP, 61, 1258 (2005); Kupelian, IJROBP, 66, 876 (2006)

Daily plan adjustment for prostate patients

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On-line ART for prostate may facilitate zero margin for target

Mohan, IJROBP, 61, 1258 (2005); Ahunbay, IJROBP, 77, 1561 (2010); Kupelian, IJROBP, 66, 876 (2006)

Implementation of on-line ART for prostate

- Requires in-house solutions
- Daily volumetric image (Quality ?)
- Fast contouring tools / deformable registration (Accuracy ?)
- Fast optimization / planning tools (Plan Quality ?)
  - Some information in literature

Plan Quality ?

- Segment aperture morphing/weight optimization (SAM/SWO) (Ahunbay et al.)
  - no significant difference in relevant dosimetric endpoints
  - 3 of 10 patients: re-optimized plan had better rectal sparing

- Deformed intensity maps (Mohan et al.)
  - Matched target dosimetry
  - High dose sparing of rectum and bladder was inferior to reoptimized plans

Mohan, IJROBP, 61, 1258 (2005);Ahunbay, IJROBP, 77, 1561 (2010)

Plan Quality – Does it matter ?

- Goal is to improve rectal dosimetry:
  - Deformed intensity map technique appears suboptimal
  - SAM/SWO can improve rectal dosimetry

- Goal is to reduce target margins
  - Both techniques achieve this goal

Mohan, IJROBP, 61, 1258 (2005);Ahunbay, IJROBP, 77, 1561 (2010)

- Off-line ART techniques: Limitations and uncertainty

Limits and Accuracy- ART for Progressive changes

What triggers a re-plan ?

Clinical Observation … cumulative dose ?

Limits and Accuracy- ART for Progressive changes

What triggers a re-plan ?

Clinical Observation … cumulative dose ?

Details of re-planning step ?

Simple re-plan…….address over/under dose ?

Dosimetric effect of progressive changes in head and neck patients

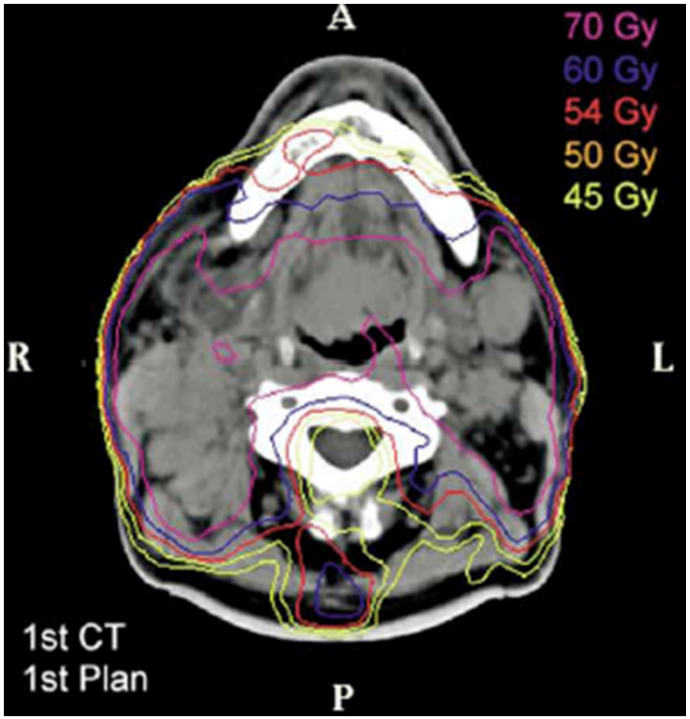
- What dosimetric problems are we mitigating ?

Dosimetric effect of progressive changes in head and neck patients

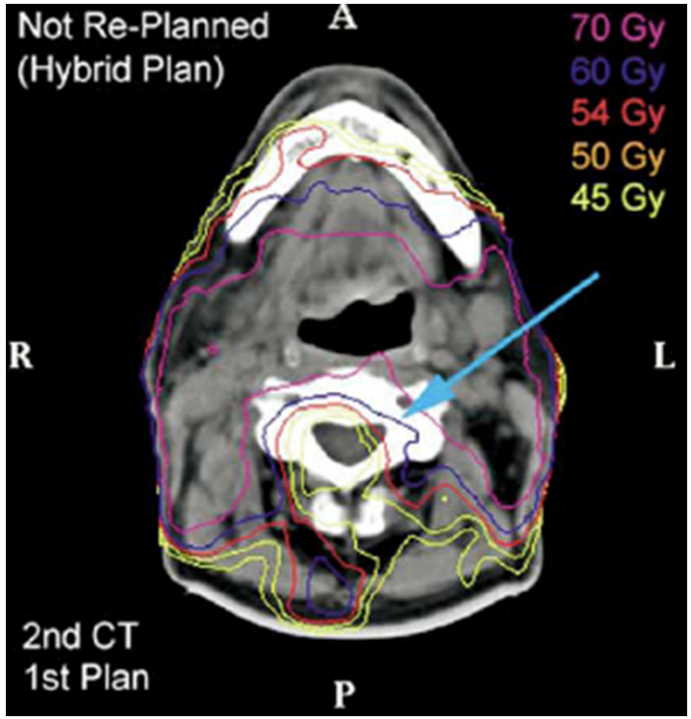
- In patients with observed weight loss, tumor shrinkage
  - CTV: $D_{95\%}$ -15%
  - Cord: D_{max} + 15%, D_{1cc} +2%
  - Brain Stem: D_{max} + 17%, D_{1cc} +3%
  - Parotid: D_{mean} +8-30%

Hansen, IJROBP, 64, 355, 2006; Zhao, Radiother. Oncol., 98, 23 (2011)

Dosimetric effect of progressive changes in head and neck patients



Plan



CT after 22 fx,
12 % weight loss

Hansen, IJROBP, 64, 355, 2006

Dosimetric effect of progressive changes in head and neck patients

- In patients with scheduled repeat CT imaging (week 2)
  - PTV: D_{min} -3-8%; $D_{95\%}$ -11-4%
  - Cord: D_{1cc} +7%
  - Parotid: D_{mean} +7-10%

Bhide, IJROBP, 76, 1360 (2010); Ahn, IJROBP, 80, 677 (2011)

Dosimetric effect of progressive changes in head and neck patients

- Observations from repeat imaging and deformable registration analysis

- Patients with scheduled weekly and daily CT
- Cumulative target, cord, brain stem: No significant change
- Cumulative parotid: D_{mean} +10-15%

Lee, IJROBP, 70, 1563 (2008); Wu, IJROBP, 75, 924 (2009)

Dosimetric effect of progressive changes in head and neck patients

- Target, cord, BS results vary
- Parotid mean dose increase is a consistent observations: 10-15%

Dosimetric effect of progressive changes in head and neck patients

- Target, cord, BS results vary
- Parotid mean dose increase is a consistent observations: 10-15%

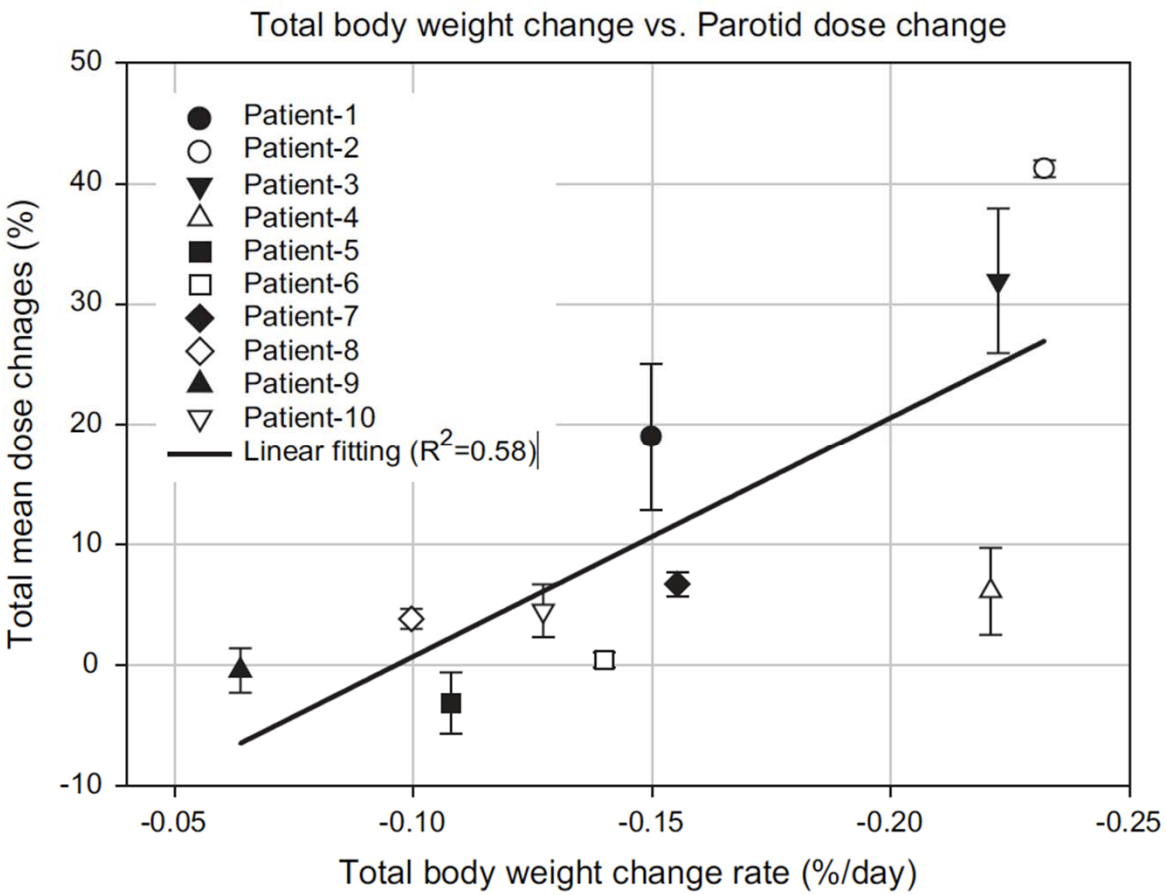
Benefit of off-line ART for Head and Neck

How good are the different triggers ?

- Clinical observations of weight loss
  - Correlations between weight loss and parotid mean dose: $r=0.35$ (Ahn), $r^2=0.58$ (Lee)

Ahn, IJROBP, 80, 677 (2011); Lee, IJROBP, 70, 1563, 2008

How good are the different triggers ?



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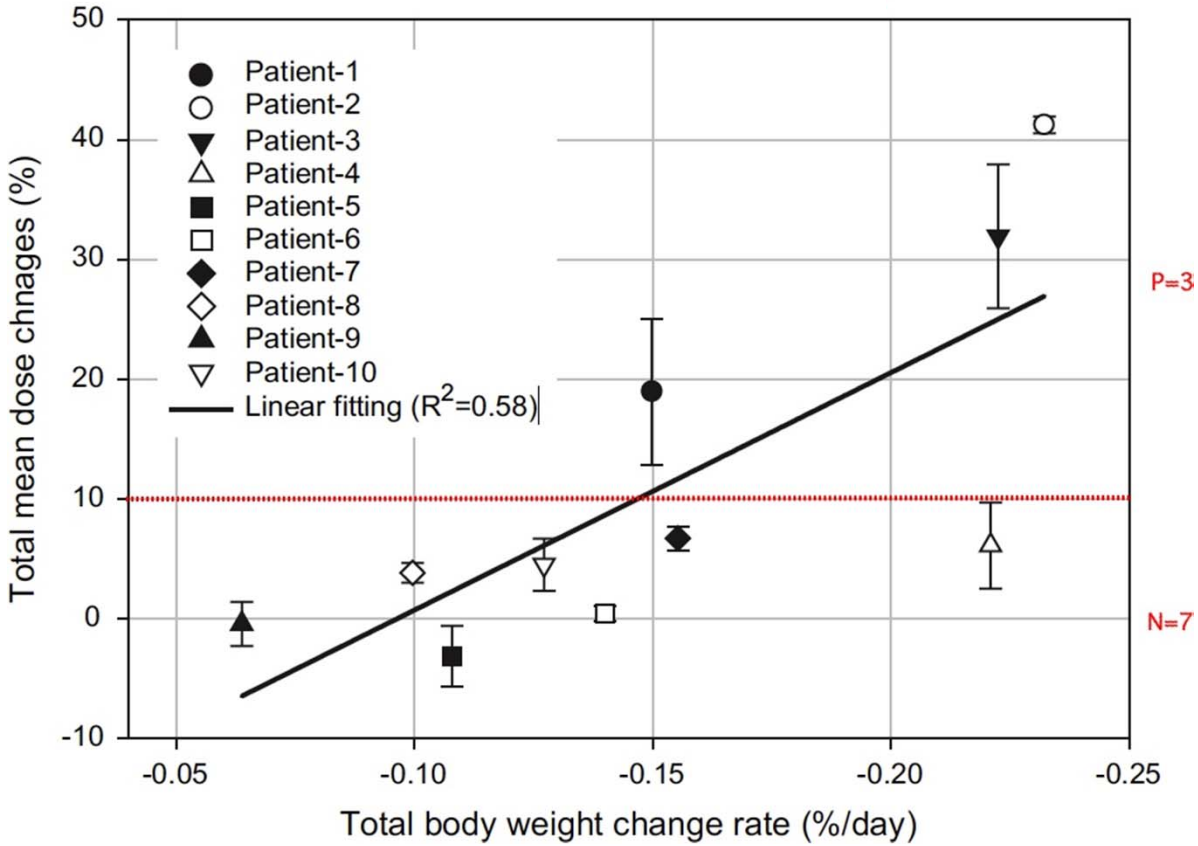

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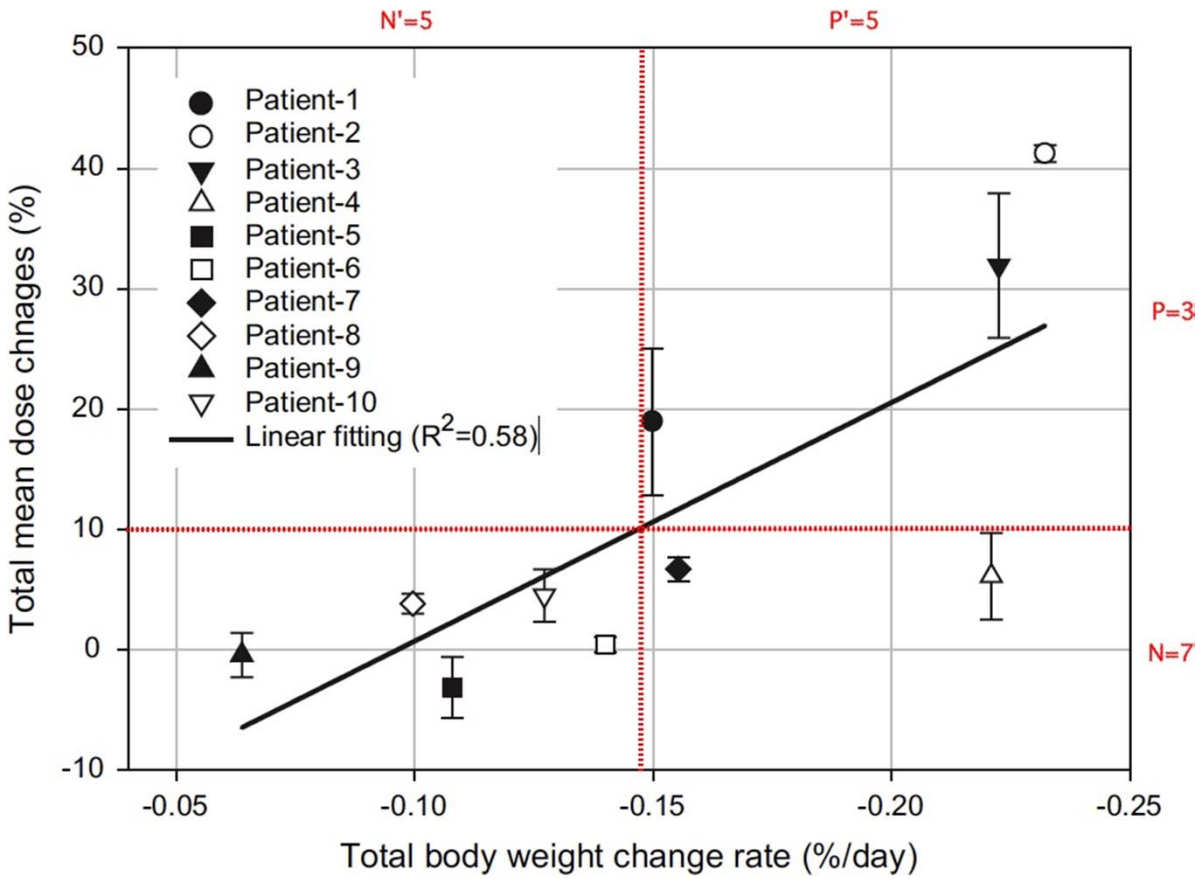

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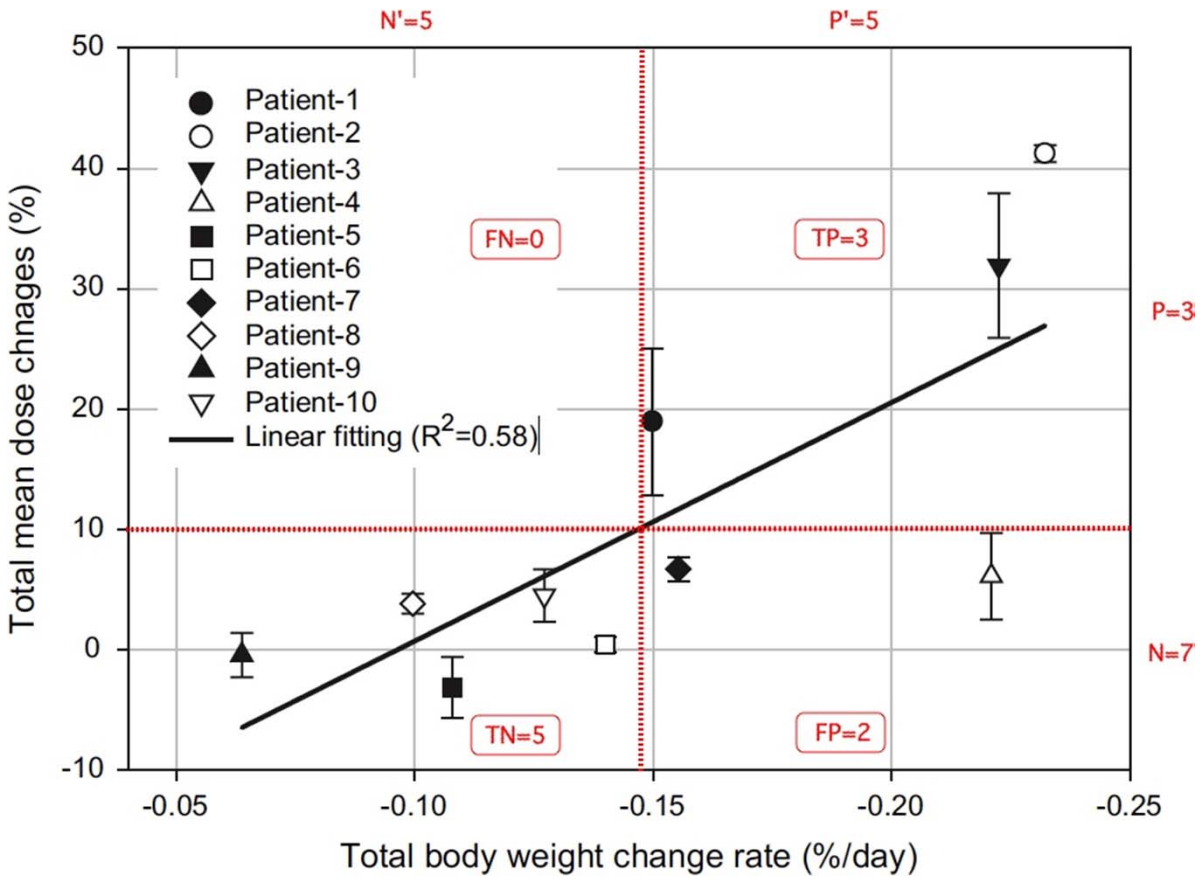

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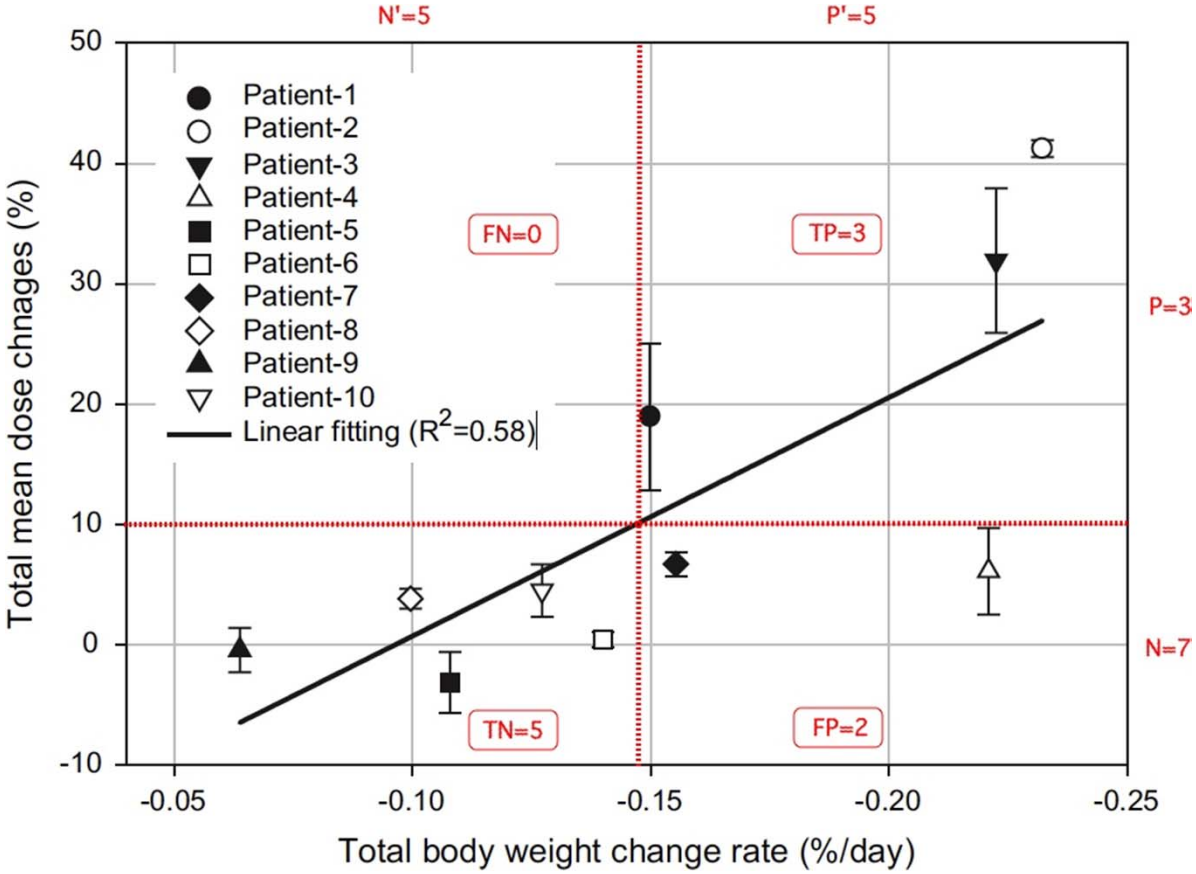

True positive rate (TP/P): 3/3

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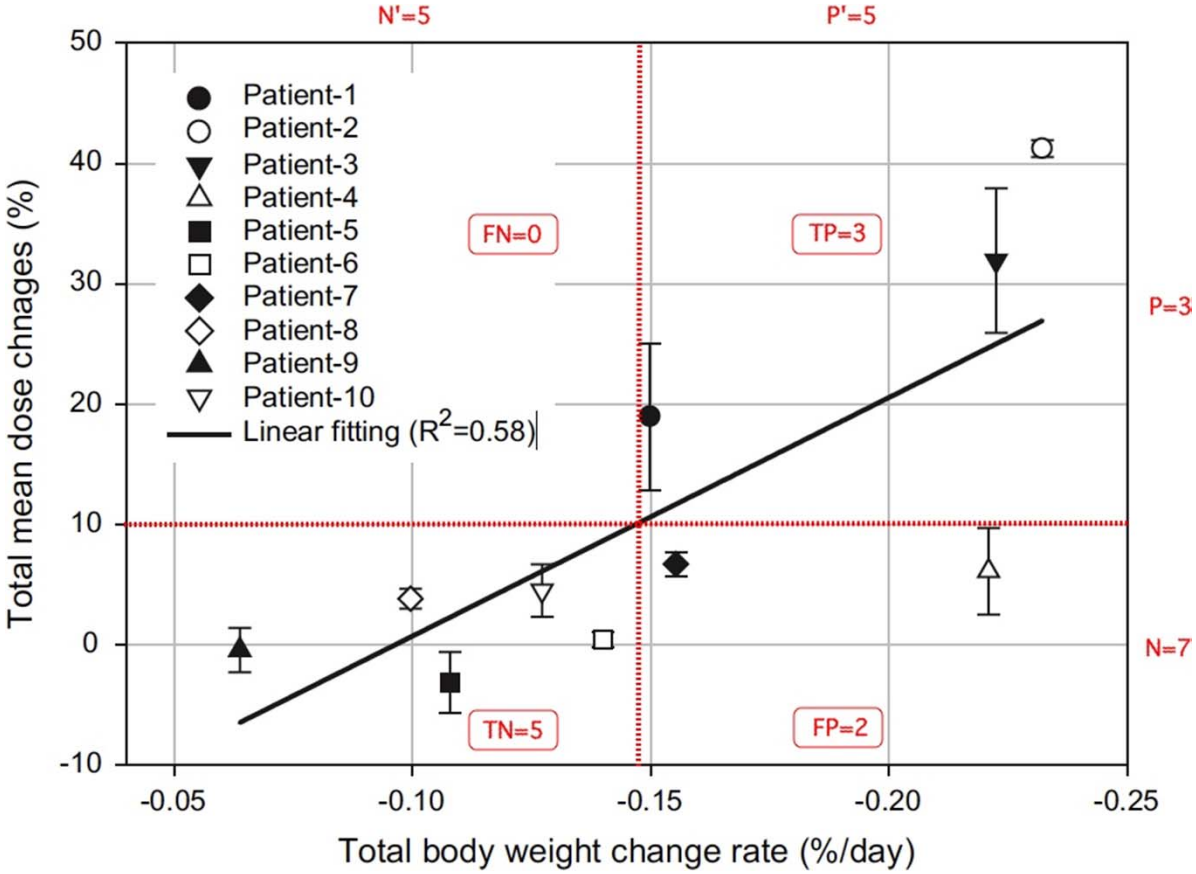
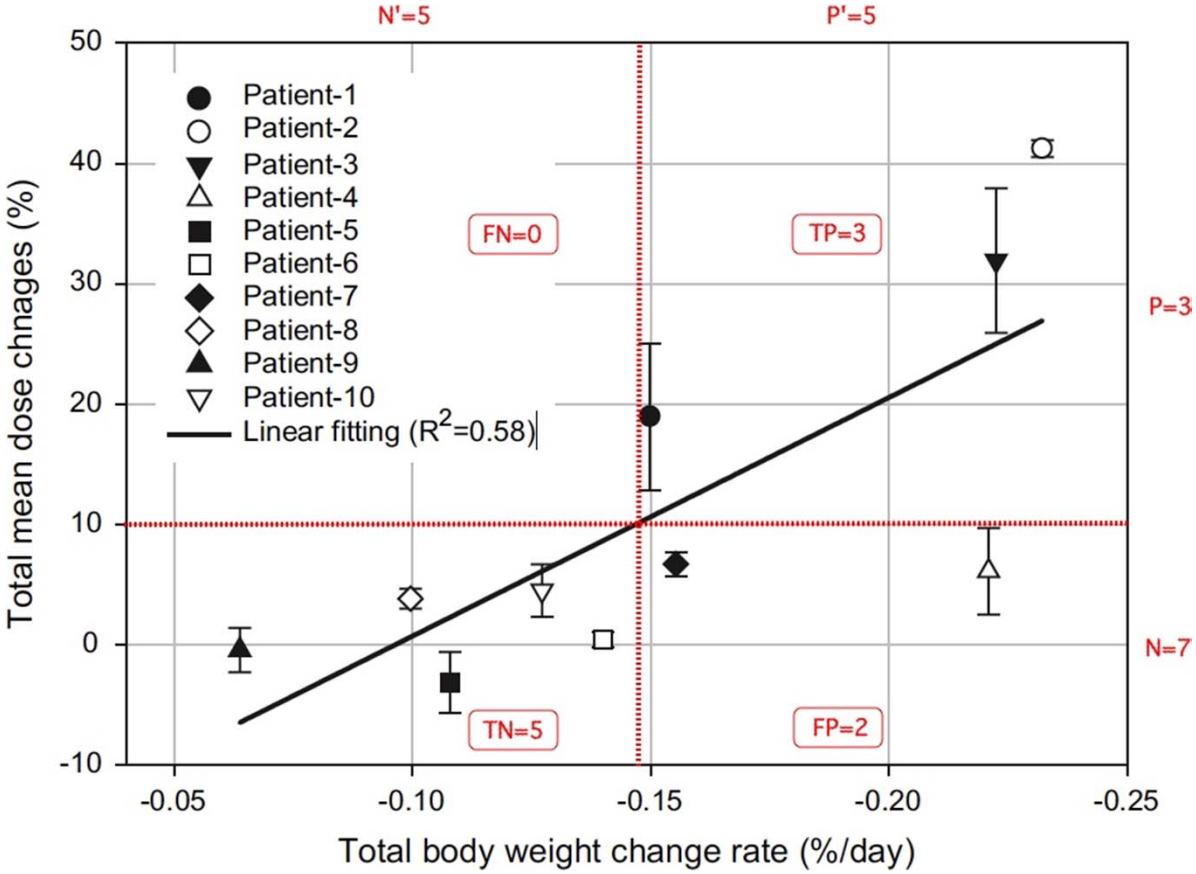


True negative rate (TN/N): 5/7

How good are the different triggers ?



Accuracy rate: 8/10

How good are the different triggers ?

- Anatomical changes on repeat CT

Correlation study by Ahn et al.

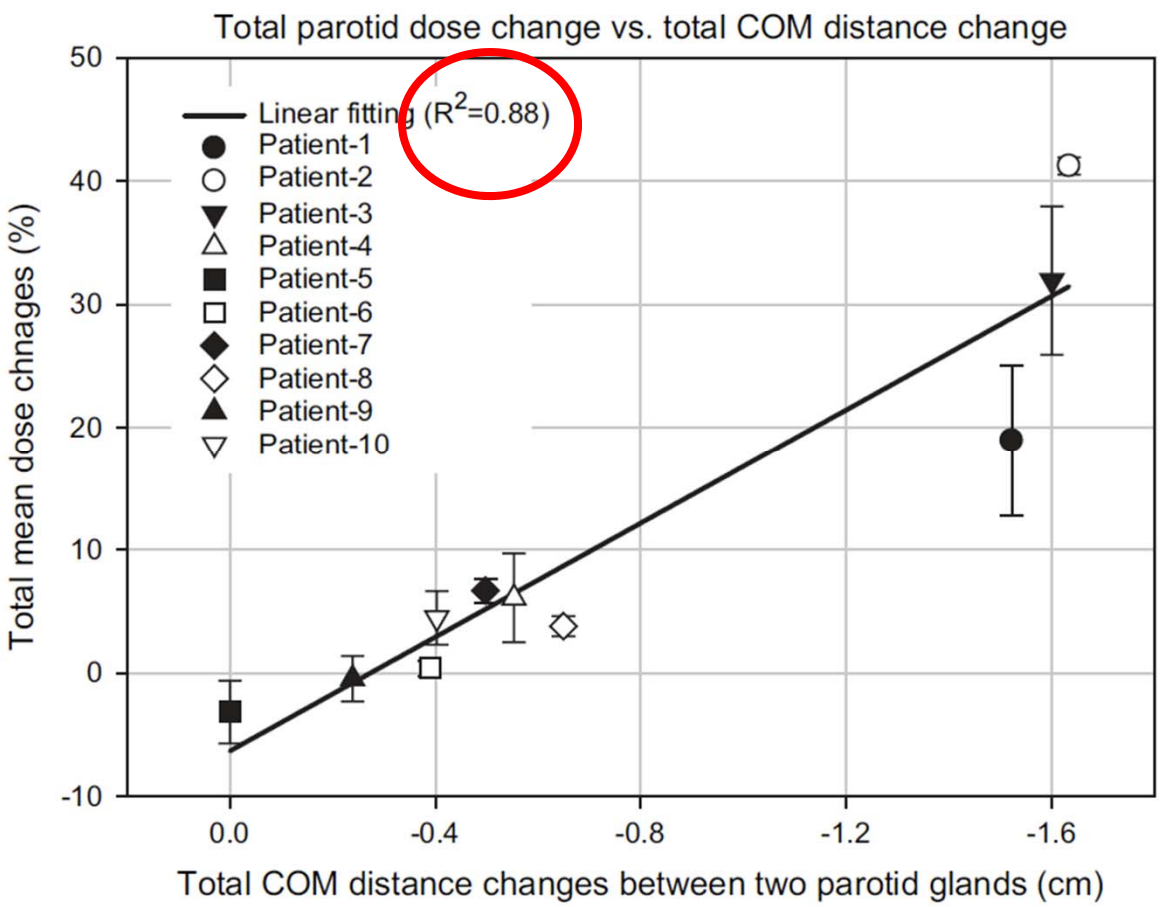
Tested correlation between weight loss, skin separation and target coverage and mean parotid dose

Conclusion: “No single positional or anatomical variable predicted the need for a re-plan”

Ahn, IJROBP, 80, 677 (2011)

How good are the different triggers ?

- Anatomical changes on repeat CT



Lee, IJROBP, 70, 1563, 2008

How good are the different triggers ?

- Dosimetric changes on repeat-imaging
  - What is uncertainty in results ?
  - Are we triggering on noise ?

How good are the different triggers ?

- Dosimetric changes on repeat-imaging
  - CT images can be used for dose calculation
  - If image is a MVCT, CBCT, MV-CBCT need to test dose calculation accuracy

Use of CBCT for dose calculation

- Yoo et al. and Yang et al: uncertainties of 1-3%
- Guan and Dong: 5% for 7-field IMRT plan, improved to 1.5% with different calibration phantom

Yoo et al., IJROBP, 66,1553 (2006); Yang et al., PMB, 52, 685 (2007); Guan and Dong, PMB, 54, 6239 (2009)

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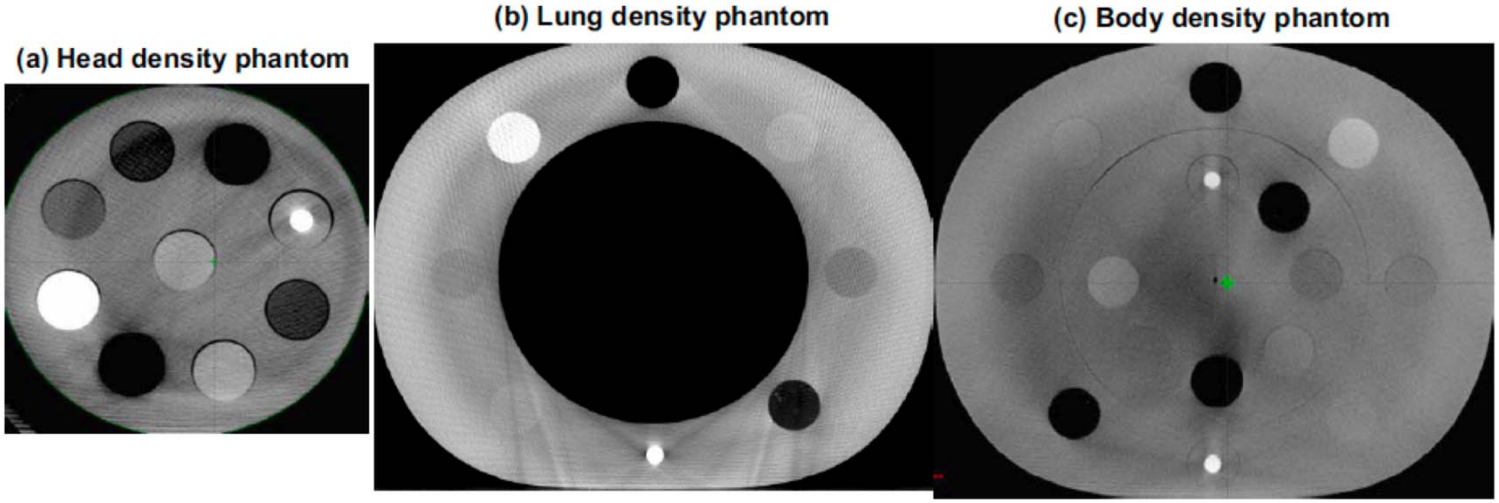
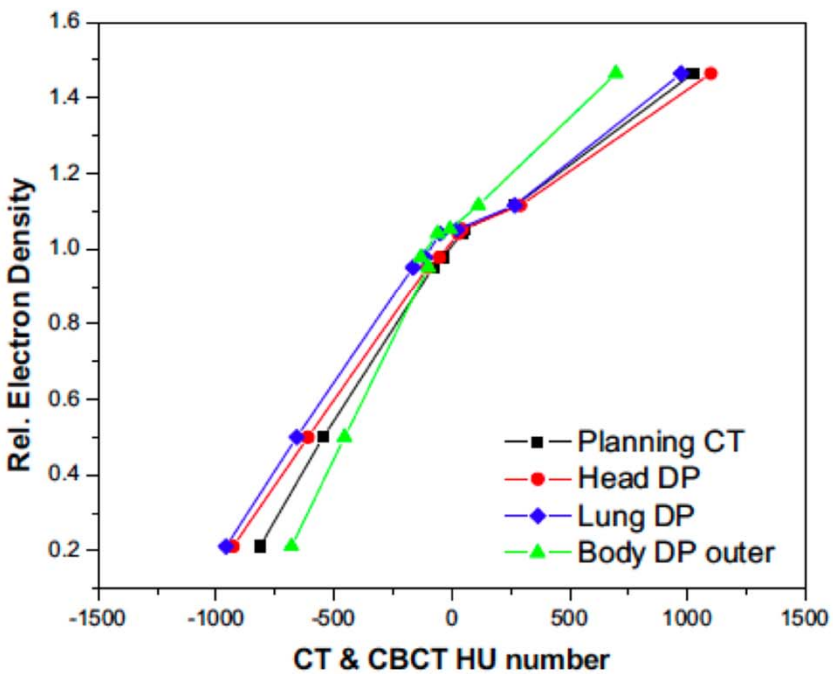
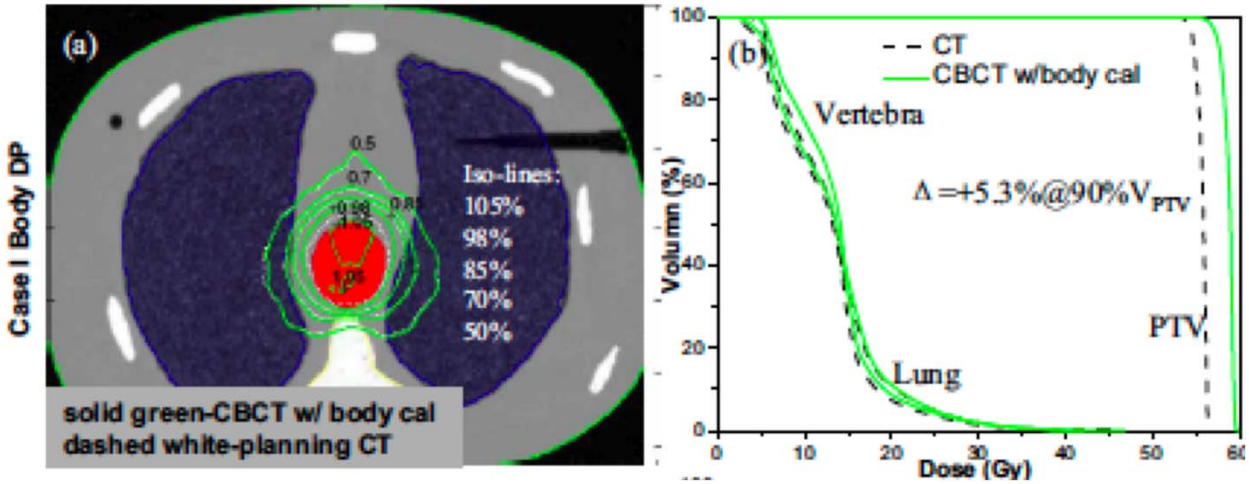


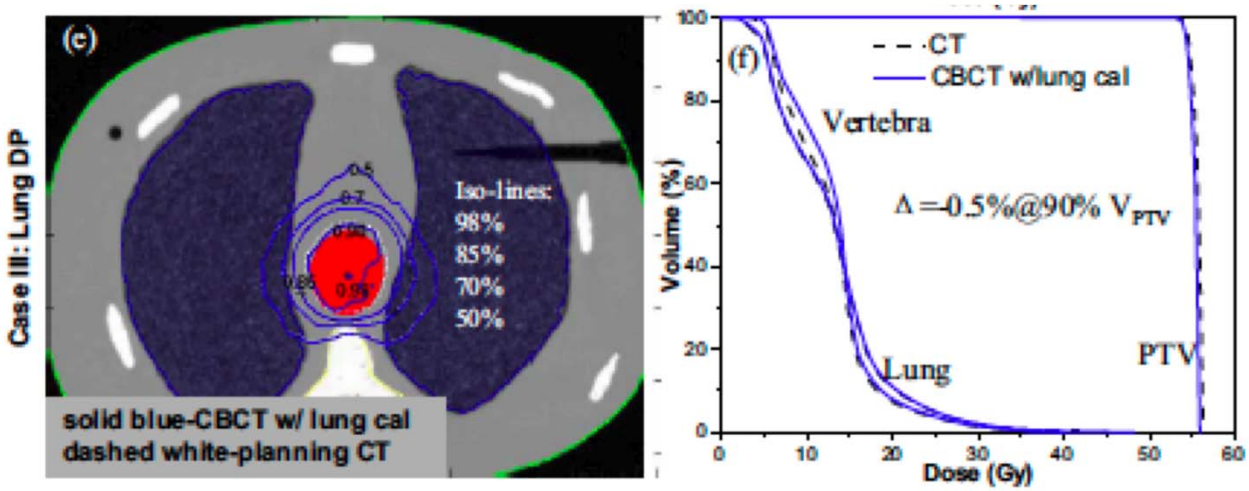


Rong et al, Med Dosim, 35, 195 (2010)

Use of CBCT for dose calculation



Lung scan,
Body HU cal.
5.3 % @V90%



Lung scan,
Lung HU cal.
0.5 % @V90%

Rong et al, Med Dosim, 35, 195 (2010)

Use of MV-images for dose calculation

- MV-CBCT: uncertainty of about 3% (Morin et al.)
- MVCT: uncertainty of about 3% (Langen et al.)

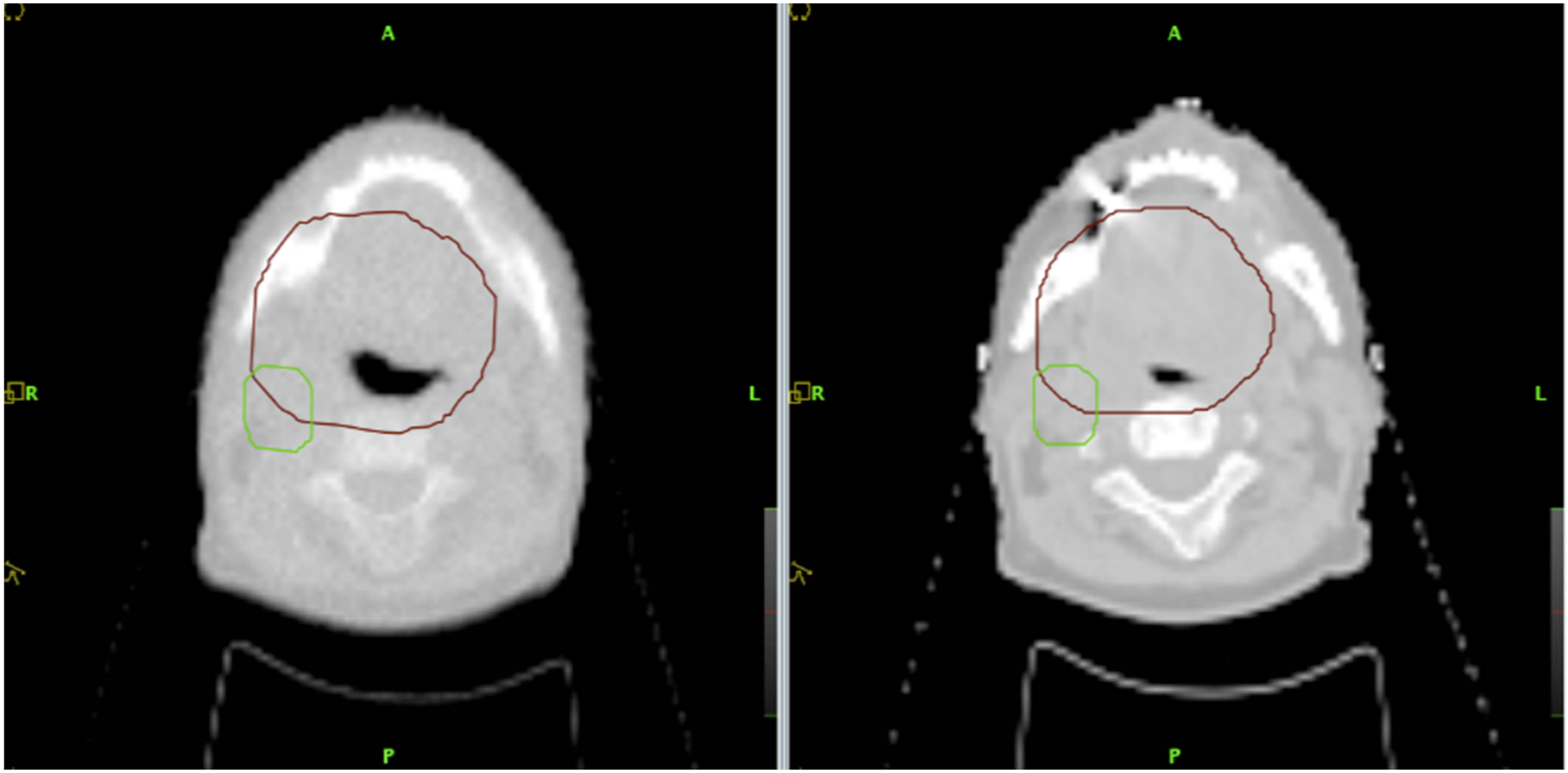
Morin et al., IJROBP, 67, 1201 (2007); Langen et al., PMB, 50, 4259 (2005)

Delineation of structures on repeat images

- Contouring uncertainty translate into dose volume histogram (DVH) uncertainties

- In cases of volumes that are surrounded by conformal dose gradient, small contour uncertainties will have large DVH uncertainties.

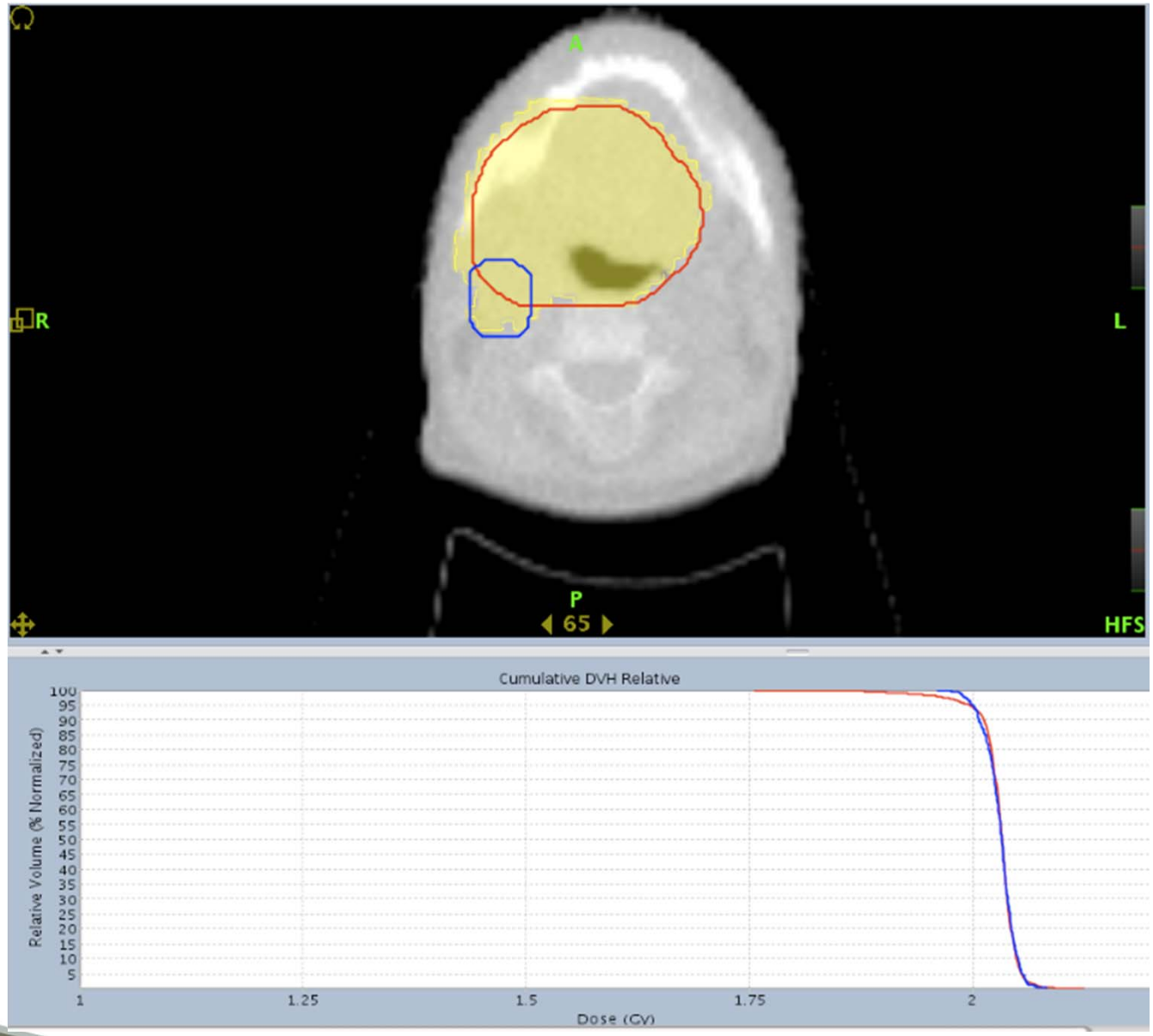
DVH variations with contour changes



Daily MVCT
Re-contoured structures

Original kVCT
Original structures

DVH variations with contour changes



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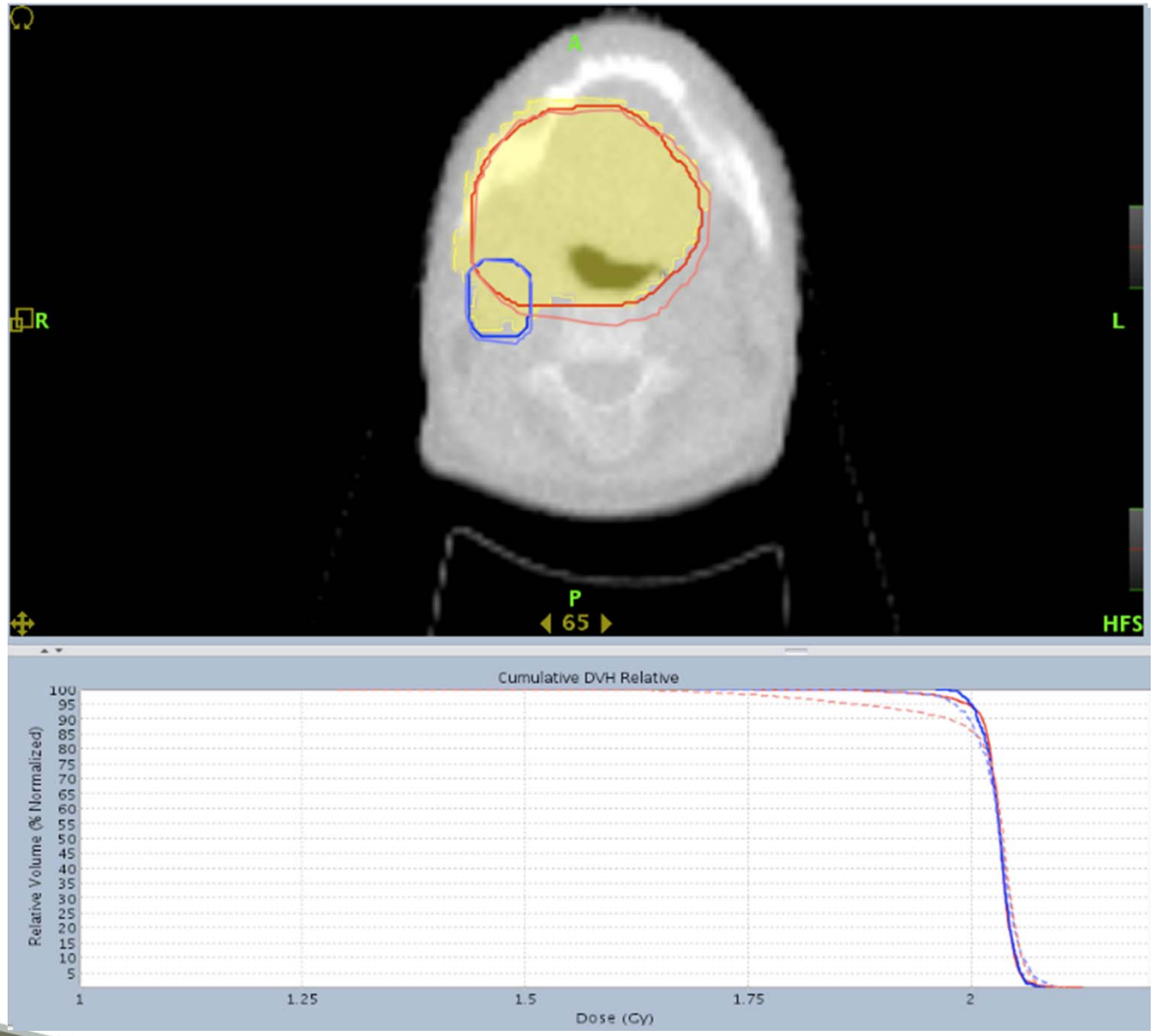
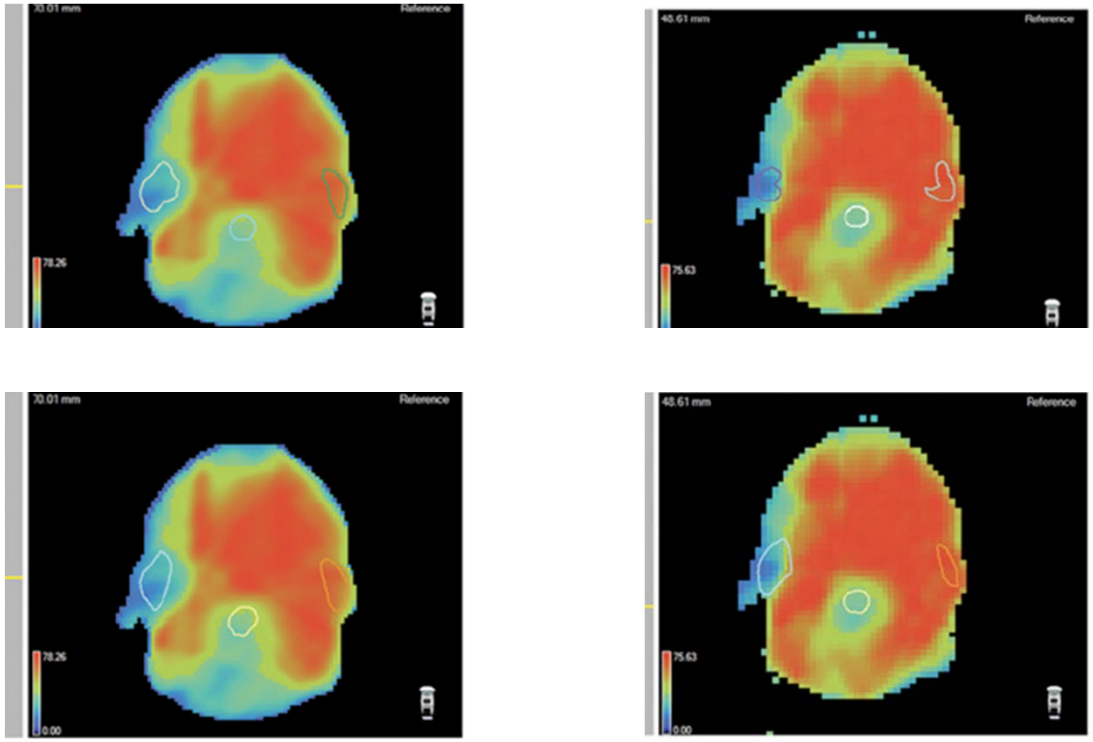


DVH variations with contour changes

- For targets: D_{min}, $D_{95\%}$ are very sensitive to contouring uncertainties
- Different DVH parameters will have different sensitivities to contouring uncertainties

DVH variations with contour changes



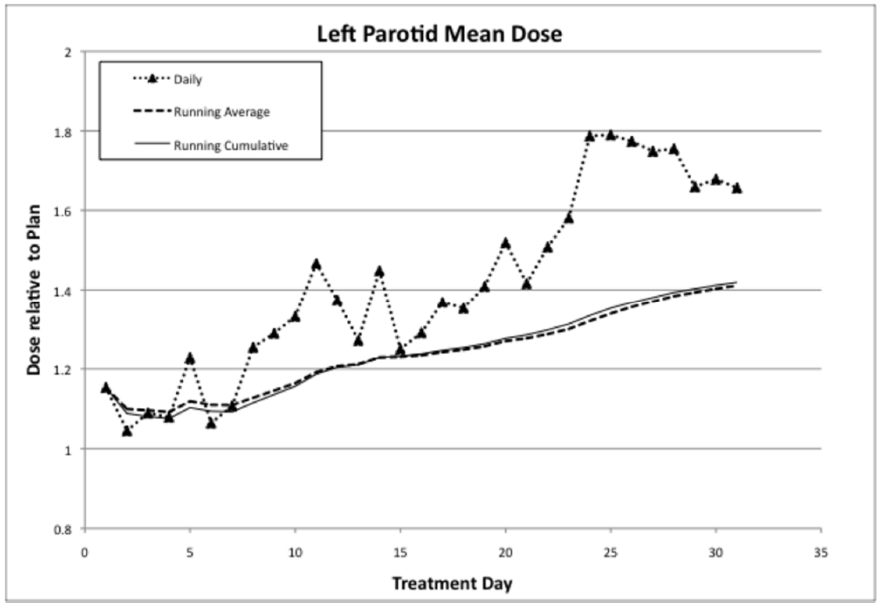
n=32
Right Parotid
D_{mean}=-6% to 45%

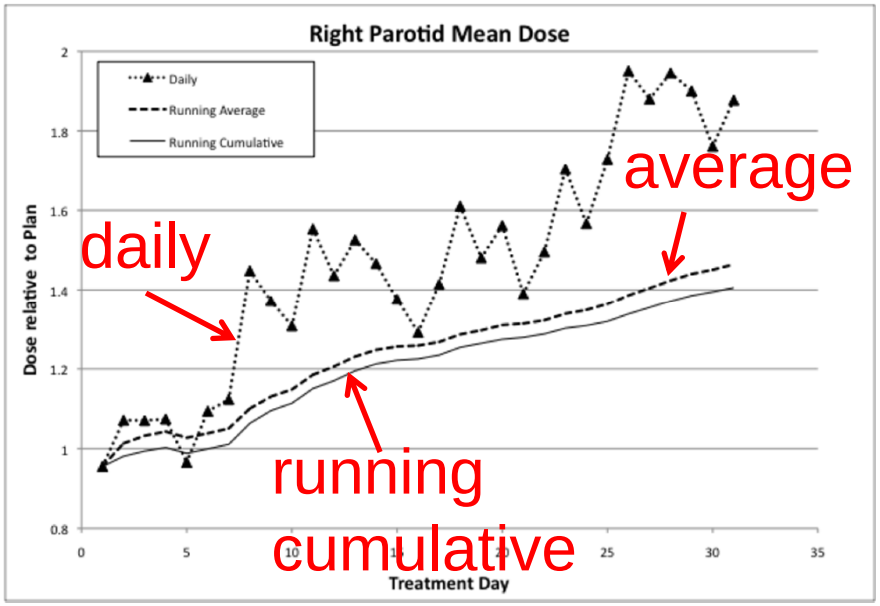
Nelms et al, IJROBP, in Press (2011)

Inability to calculate cumulative dose

- Assume correct dose calculation
- Assume correct delineation
- Without DIR, dose distributions cannot be summed
- Only have daily doses
- Accuracy of average dosimetric endpoints?

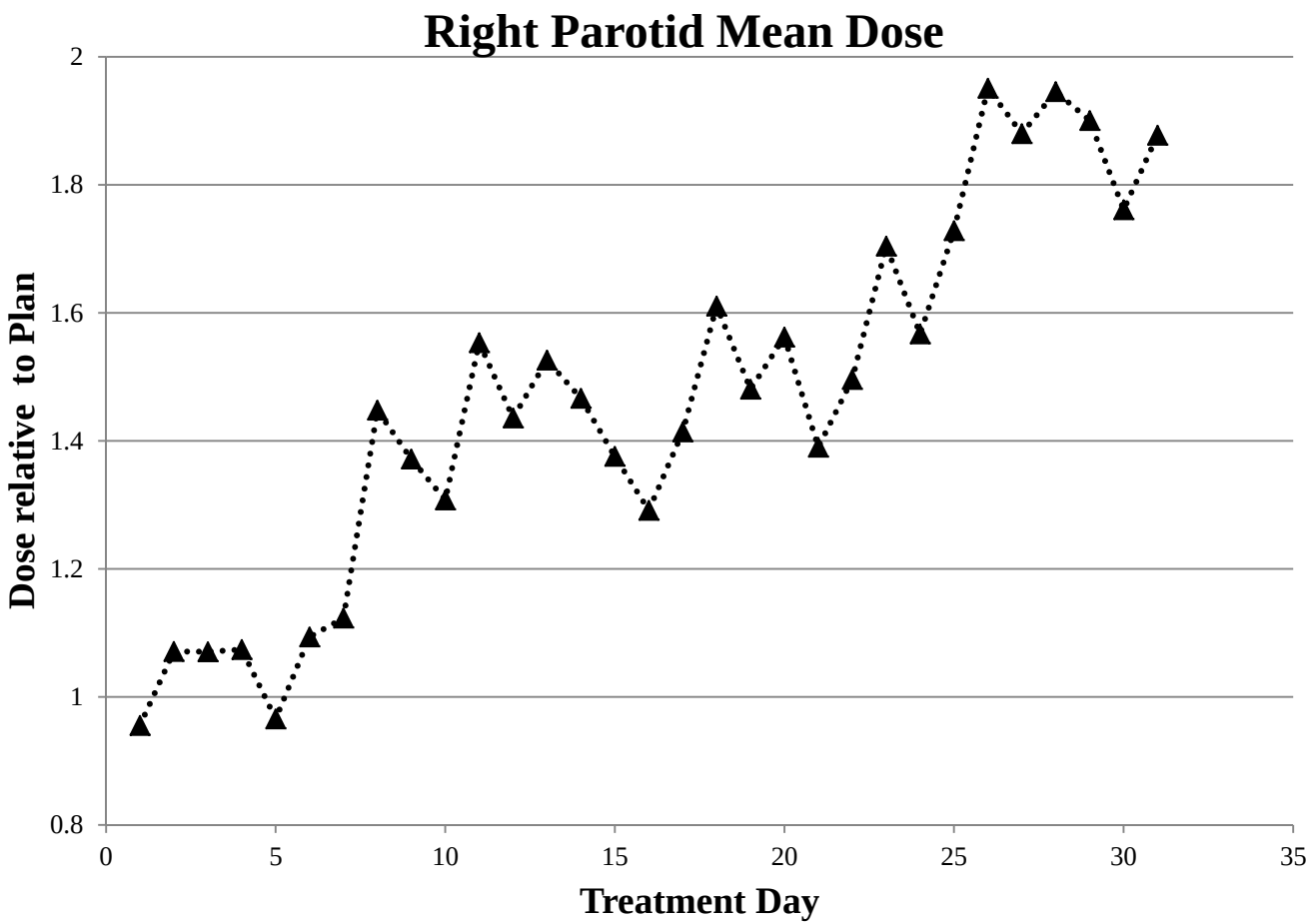
Inability to calculate cumulative dose





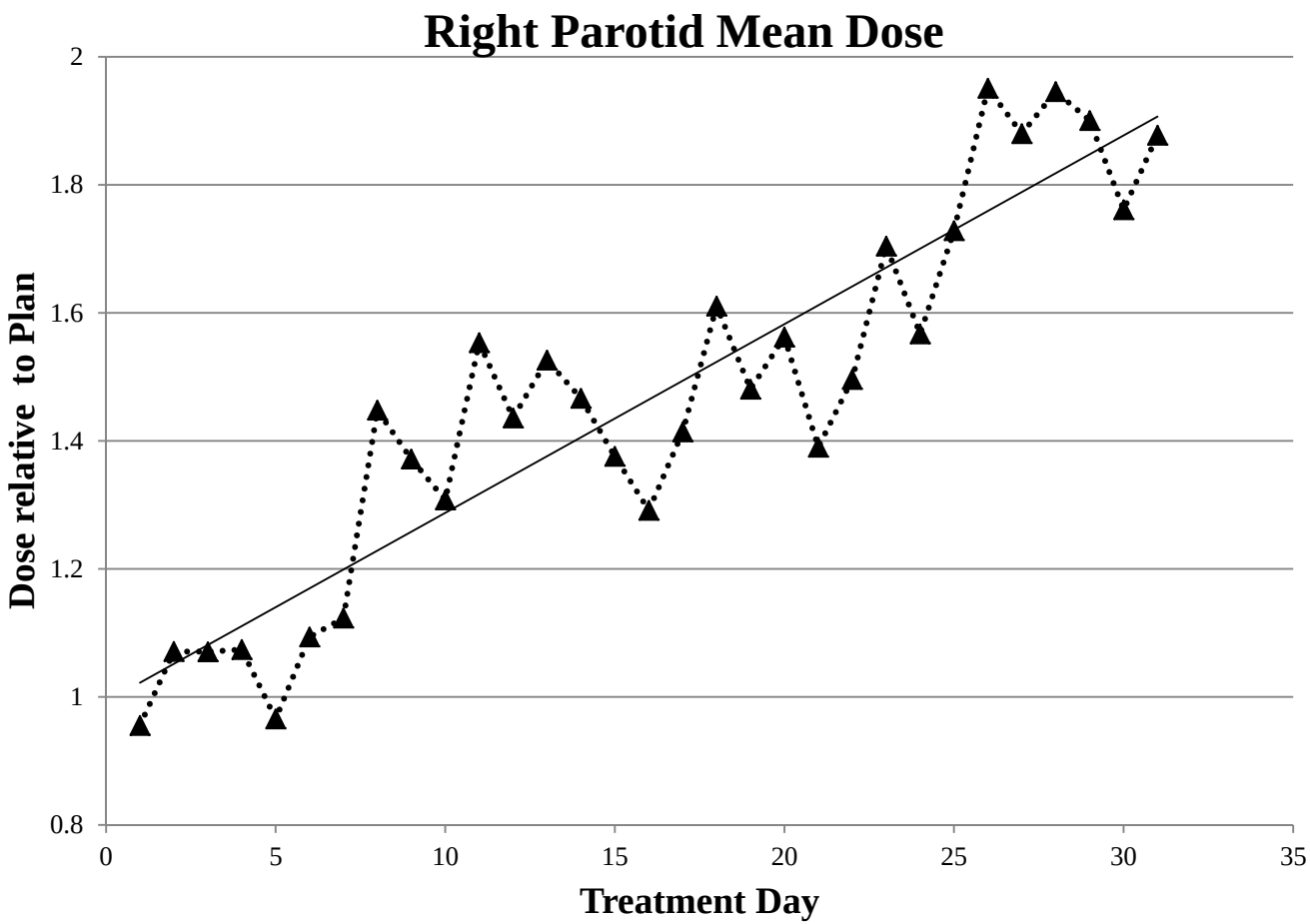
Difference between average and cumulative: right parotid= 4%

Noise in daily data



Assume linear growth of mean parotid dose

Noise in daily data



Standard deviation of daily vs. linear fit is about 7%

Limits and uncertainty of DIR analysis of repeat imaging

- Facilitates generation of daily contours
- Allows accumulation of dose
- Should be less subjective than clinical observations of changes in patient anatomy

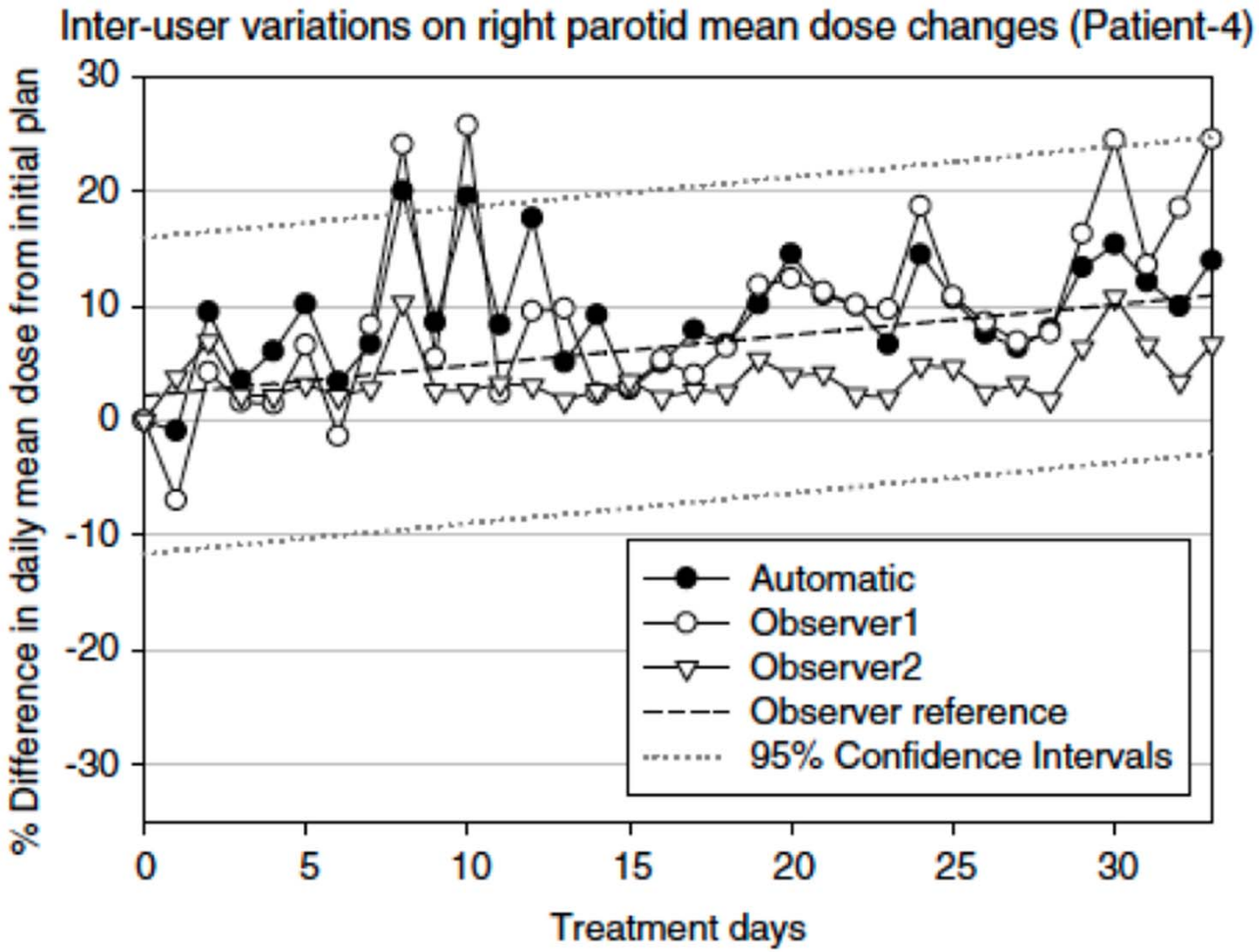
- DIR have their own inaccuracies
- Typically DIR uncertainties are reported in geometric terms
- Need to translate this to dosimetric uncertainties

  to help decide if observed dosimetric change is “real”

How to assess DIR accuracy

- Visual inspection:
  - Sanity test
  - Ok for daily DVH, not sufficient for dose accumulation
  - Mapped location of each voxel matters
- Challenge: True deformation is typically unknown
  - Active field of research

Manual vs. DIR parotid contours

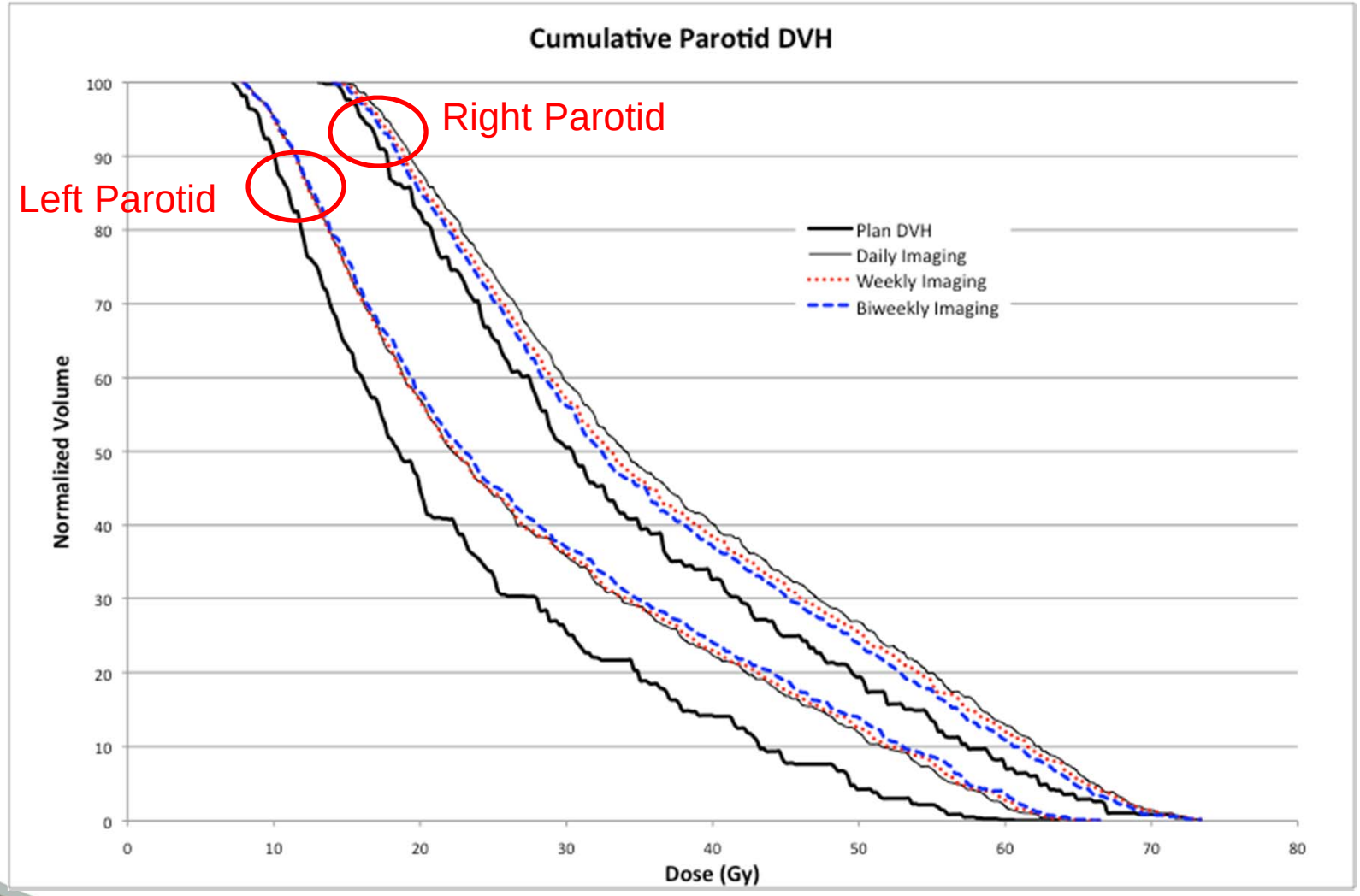


Confidence interval derived from difference between two manual contours

Lee et al., Radiother Oncol, 89, 81 (2008)

Imaging frequency

- Is daily imaging needed for progressive deformation ?



Uncertainty and Limits of re-planning

- Conventional replan: no more uncertain than initial plan
  - Additional uncertainties may be present if tools are used in replanning process
- Correct dosimetric variations at time of re-planning
  - Any uncertainties in determining cumulative dose translate into uncertainties in delivery !!!

Tsuji study: DIR for contours transfer for replanning

- 16 patients with clinical observations of anatomical changes
- 2nd CT was manually contoured, plan was generated
- Retrospectively, use commercial DIR to morph planning structures to 2nd CT set, “auto-plan” was generated
- Scored dose difference to manual structures between the two plans

Tsuji et al., IJROBP, 77, 707 (2010)

Tsuji study: DIR for contours transfer for re-planning

- Manual GTV and CTV were under-dosed in “Auto-Plan” ($D_{95\%}$: -7%, $V_{95\%}$: -9%)

  Reason: in manual structure set a deliberate effort was made to maintain target volumes. DIR target volumes were smaller

- Normal structure dosimetry for spinal cord, brain stem, parotids, mandible: no significant difference

  But.. in one patient spinal cord was not correct, manual spinal cord dose of 57 Gy with “Auto-plan”

Tsuji et al., IJROBP, 77, 707 (2010)

Tsuji study: DIR for contours transfer for re-planning

- Conclusions

  DIR is useful but manual review of contours is required

Tsuji et al., IJROBP, 77, 707 (2010)

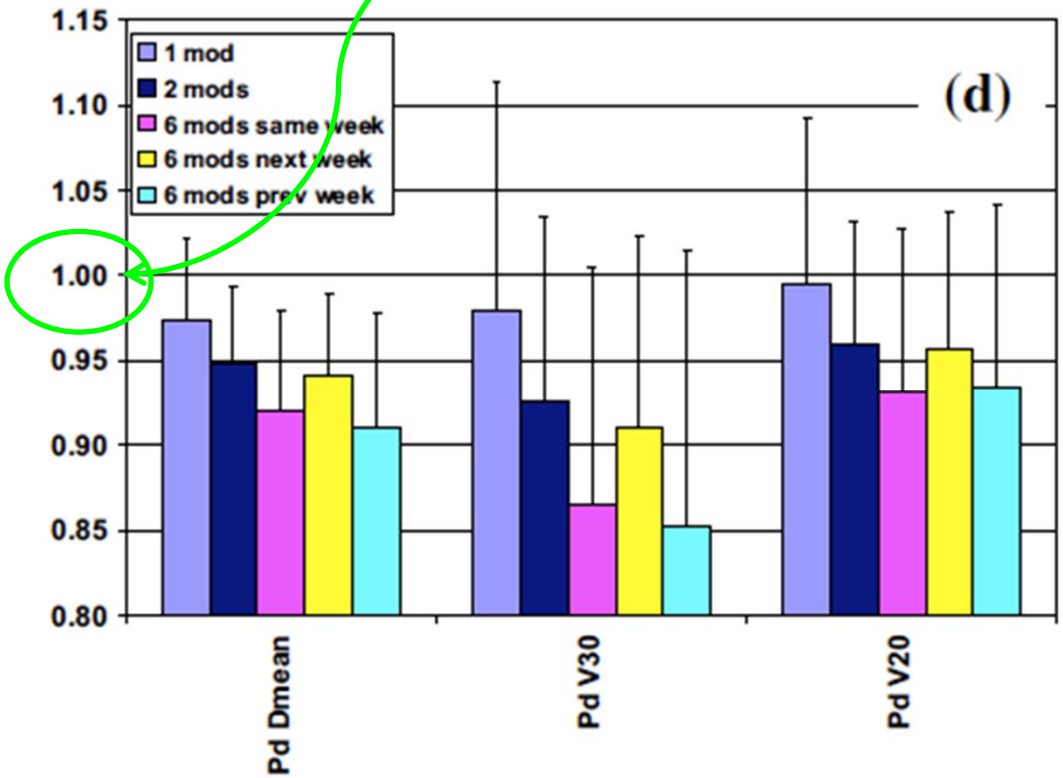
When and how often to re-plan ?

- Wu et al. study
- 11 Head and Neck patients
- One re-plan at mid-course, biweekly, and weekly plans
- Weekly plan implementation was varied in time

Wu *et al*. , IJROBP, 75 (3), 924-932, 2009

Results

1=no replan (+10%)

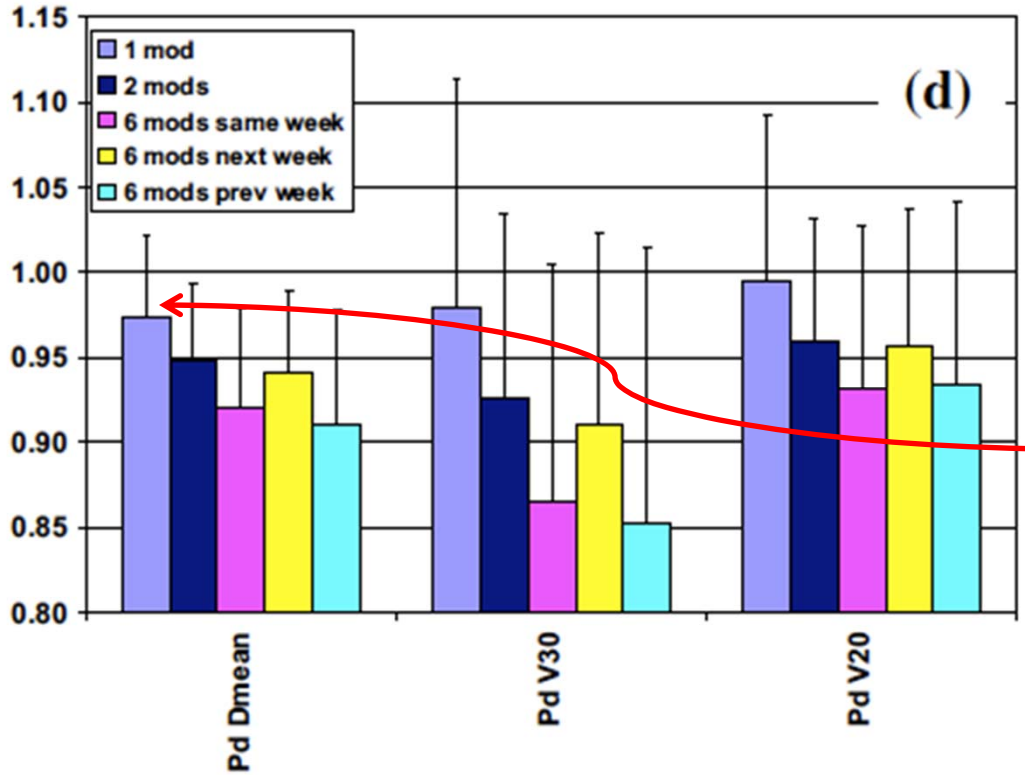


Quick impl. of replan

Delay in impl. of replan

Wu *et al*. , IJROBP, 75 (3), 924-932, 2009

Results



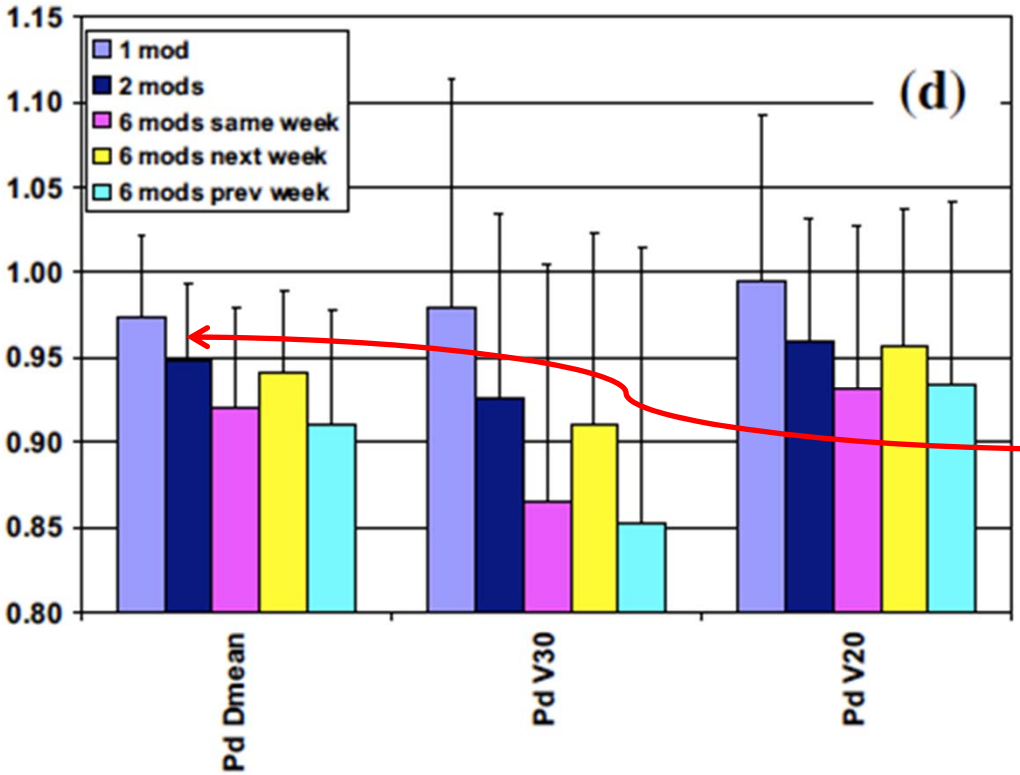
Quick impl. of replan

Delay in impl. of replan

Mean parotid dose: -3%

Wu *et al*. , IJROBP, 75 (3), 924-932, 2009

Results



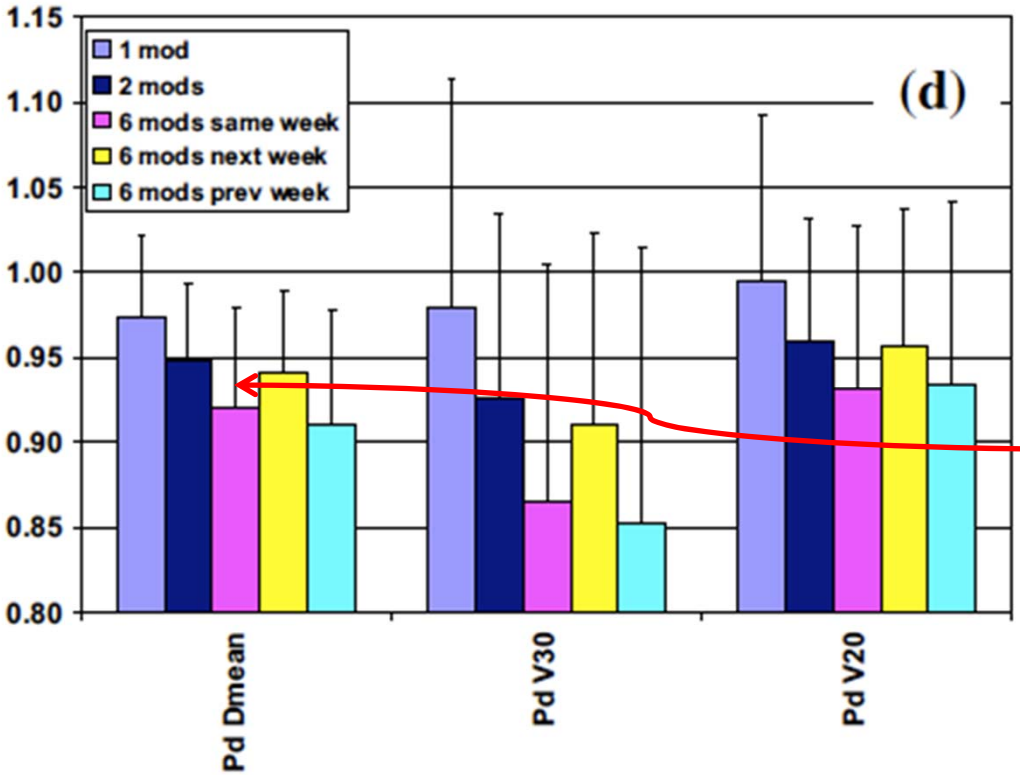
Quick impl. of replan

Delay in impl. of replan

Mean parotid dose: -5%

Wu *et al*. , IJROBP, 75 (3), 924-932, 2009

Results



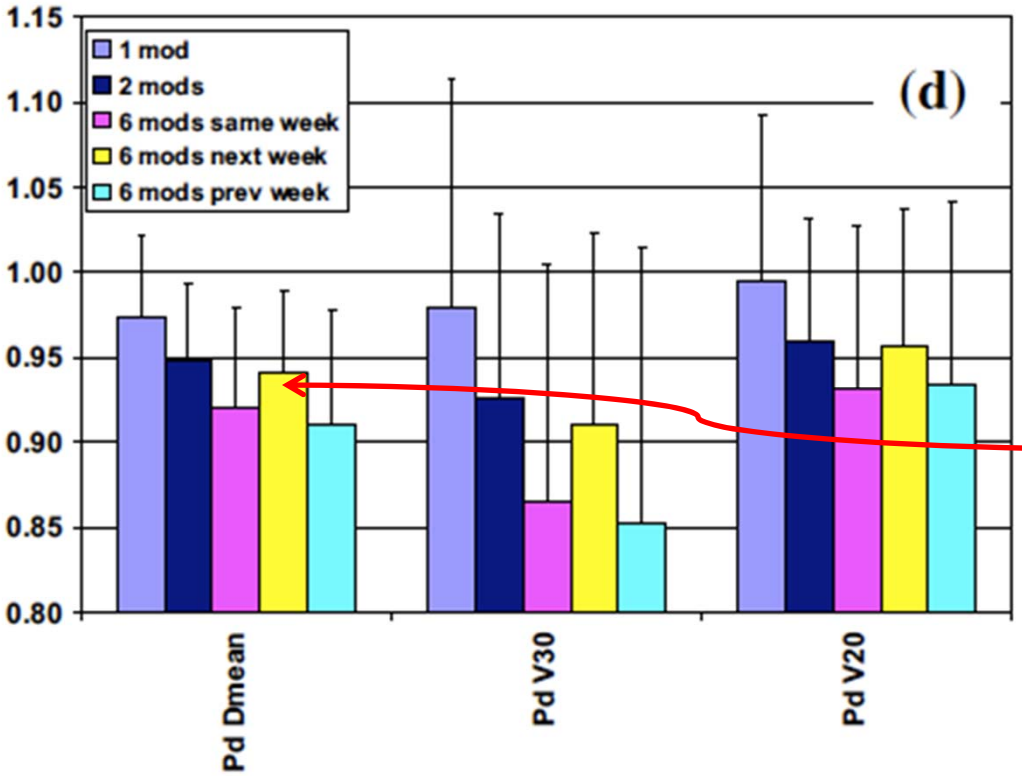
Quick impl. of replan

Delay in impl. of replan

Mean parotid dose: -8%

Wu *et al*. , IJROBP, 75 (3), 924-932, 2009

Results



Quick impl. of replan

Delay in impl. of replan

Mean parotid dose: -6%

Wu *et al*. , IJROBP, 75 (3), 924-932, 2009

Conclusions

- Limits and Accuracy of ART depend on particular implementation

- Uncertainties are present
  - Maybe acceptable if data is used for triggering replan (trigger on noise)
  - Maybe unacceptable is data is used in re-planning process

Uncertainties of ART are, in general, not well researched

Conclusions

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Much work left to do