Uncertainties and Limitations in Adaptive Radiotherapy

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MD Anderson Cancer Center Orlando
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.)

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 to 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
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:

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Bladder Cancer

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Suggested margins:

Muren (2003)  
20/10 mm Sup./Inf. 
11/8 mm Left/Right 
20/14 mm Ant./Post.  

Forkal (2004)  
35/5 mm Sup./Inf. 
13/13 mm lateral 
14/11 mm Ant./Post.

Large margins are required

Foroudi Study-library plan for bladder cancer

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

  • 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

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- Deformation of bladder – effect

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Benefit of on-line ART for prostate

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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: $D_{\text{max}} + 15\%, D_{1cc} + 2\%$
- Brain Stem: $D_{\text{max}} + 17\%, D_{1cc} + 3\%$
- Parotid: $D_{\text{mean}} +8-30\%$

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: $D_{\text{min}}$ -3-8%; $D_{95\%}$ -11-4%
  - Cord: $D_{1\text{cc}}$ +7%
  - Parotid: $D_{\text{mean}}$ +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: $D_{\text{mean}} +10-15\%$

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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True positive rate (TP/P): 3/3
How good are the different triggers?

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)
Use of CBCT for dose calculation

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.)
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
DVH variations with contour changes
DVH variations with contour changes

- For targets: $D_{\text{min}}$, $D_{95\%}$ 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
$D_{\text{mean}} = -6\%$ 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

Inter-user variations on right parotid mean dose changes (Patient-4)

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
- 2\textsuperscript{nd} CT was manually contoured, plan was generated
- Retrospectively, use commercial DIR to morph planning structures to 2\textsuperscript{nd} 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
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

Mean parotid dose: -3%

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: -5%

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

Mean parotid dose: -8%

Quick impl. of replan
Delay in impl. of replan

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

Mean parotid dose: -6%

Quick impl. of replan
Delay in impl. of replan

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