List-mode proton imaging, adaptive proton therapy, and early cancer detection

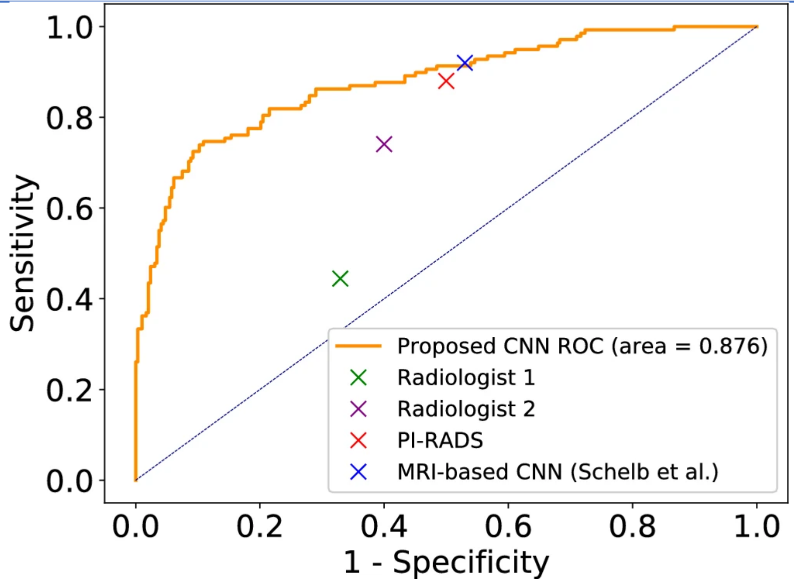
- What is the opportunity with widespread cancer screening?
- What is the technical roadmap?
- Are there new horizons in research for proton imaging?

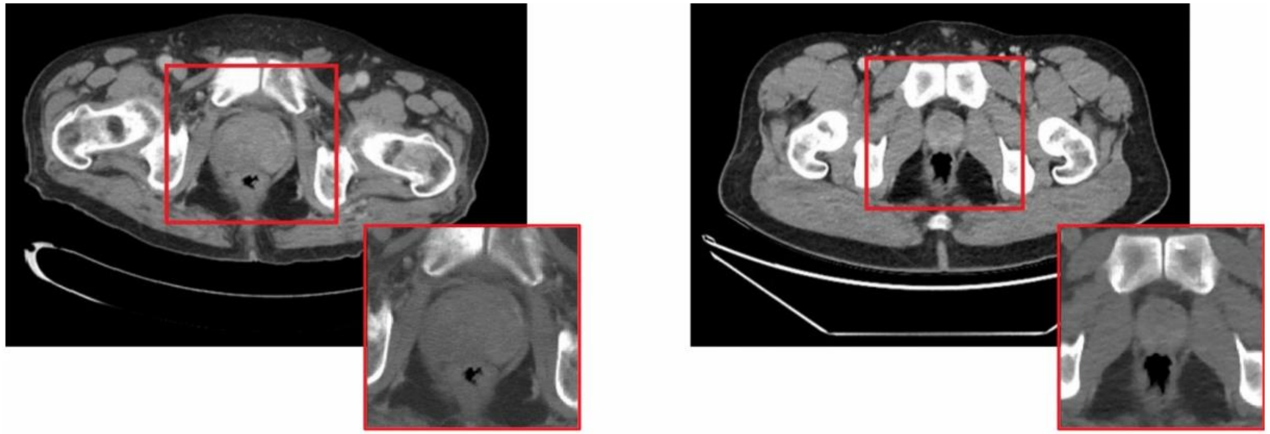
- Fritz DeJongh, CEO
- fritz.dejongh@protonvda.com
- +1 630 631 8188
- protonvda.com

Ethan DeJongh
Victor Rykalin
Reng Ashokan

Studies of incidental detection from single CT: x-ray CT + AI look promising

Korevaar, S., Tennakoon, R., Page, M. *et al.*
Incidental detection of prostate cancer with computed tomography scans. *Sci Rep* **11**, 7956 (2021).

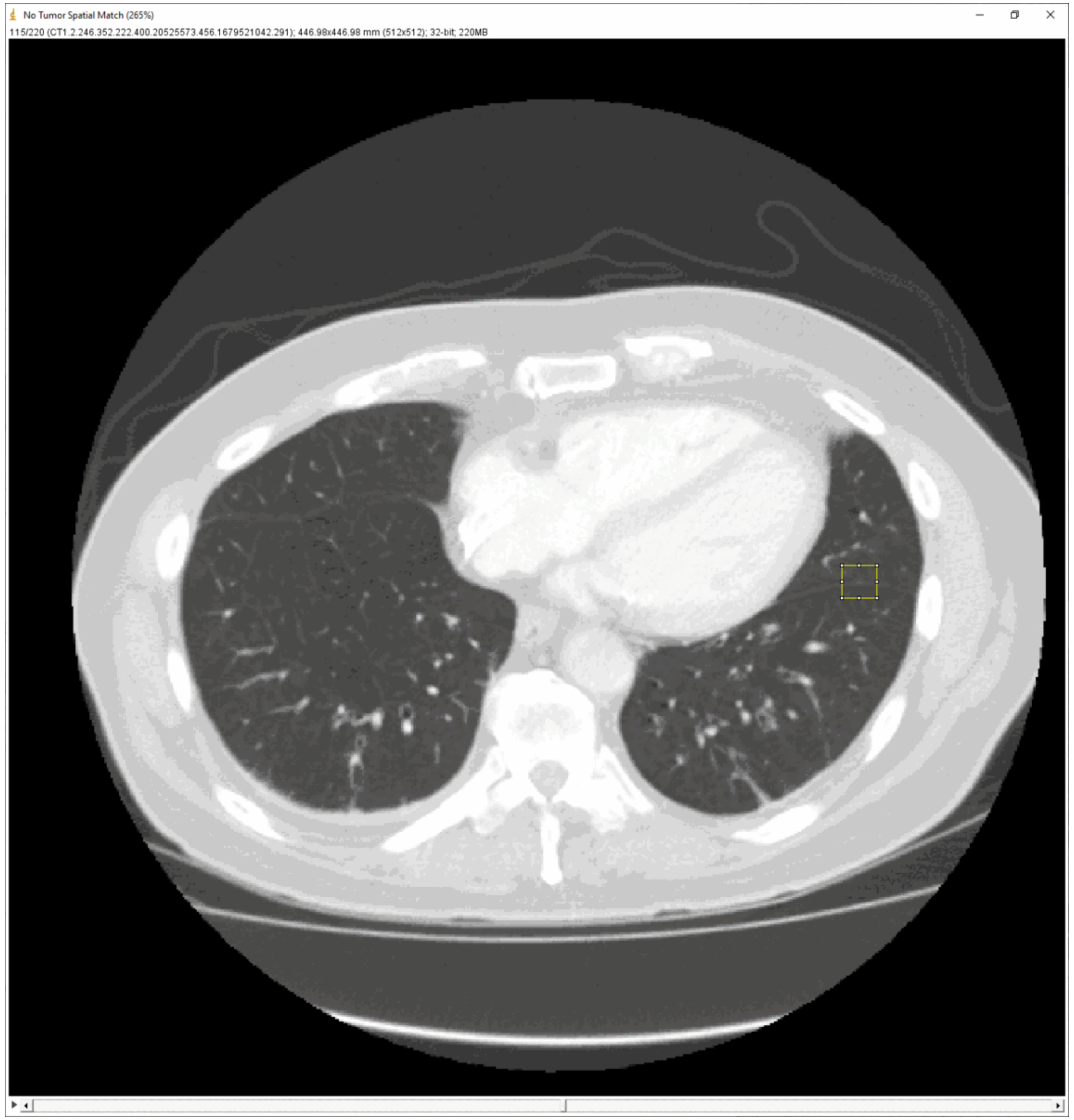


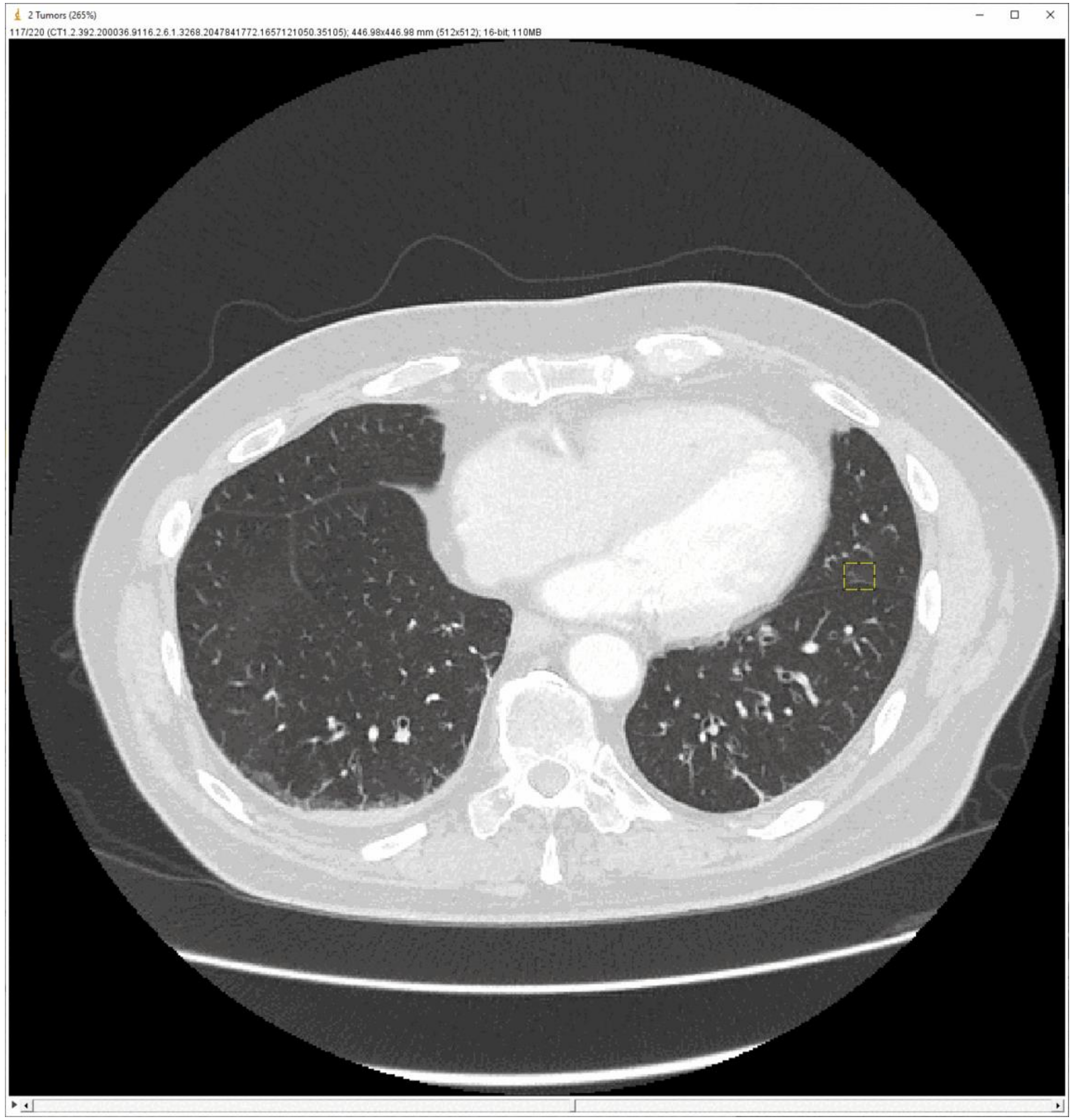


Two CT scan slices from the dataset: (**a**) from a confirmed csPCa patient, and (**b**) from a patient with no known prostate cancer (control).

Sui He, Ma Ruhang, *et al.*
Detection of Incidental Esophageal Cancers on Chest CT by Deep Learning *Frontiers in Oncology* **11** (2021)
Results: The sensitivity and specificity of the esophageal cancer detection model were 88.8% and 90.9%, respectively, for the validation dataset set.

Northwestern cancer patient being monitored for lung metastases:
Two CT-scan fly-throughs one year apart



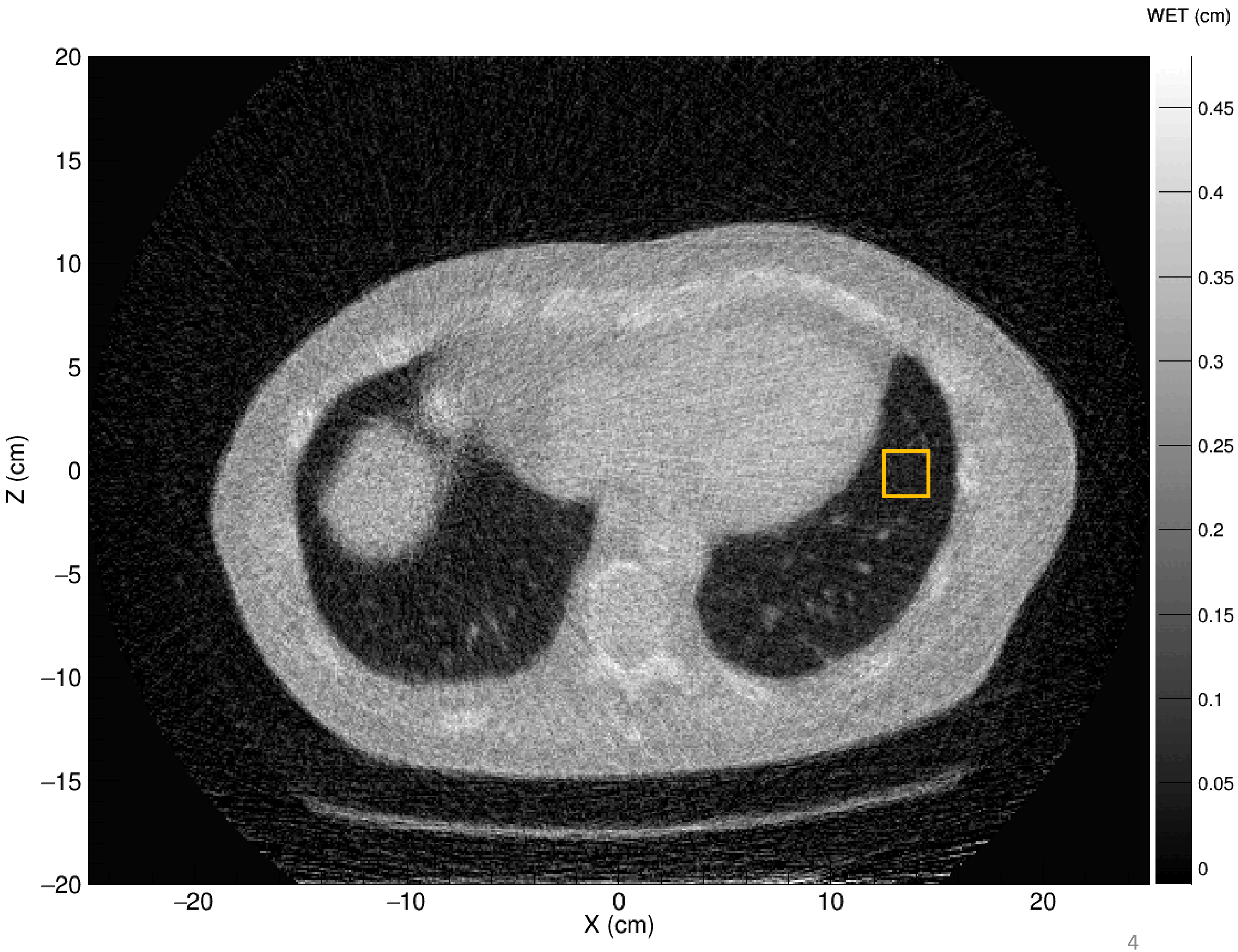


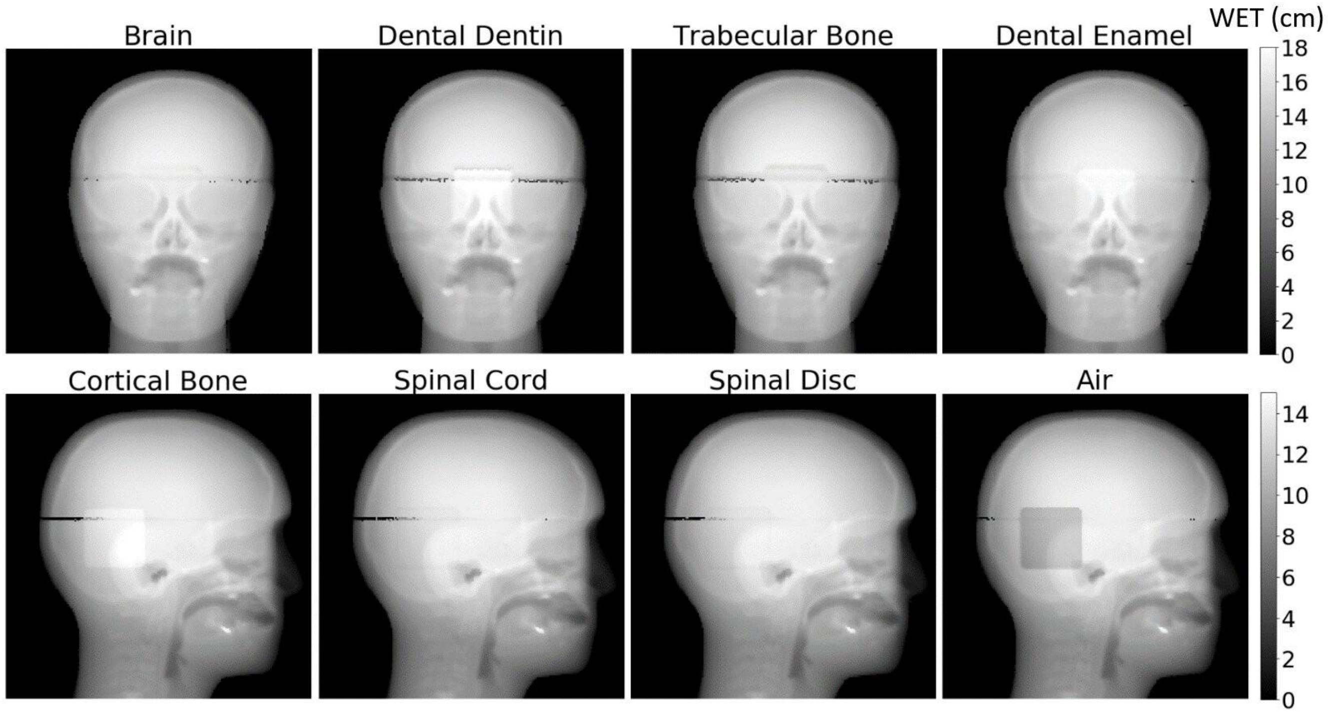
Simulated Proton CT
based on real X-Ray CT.

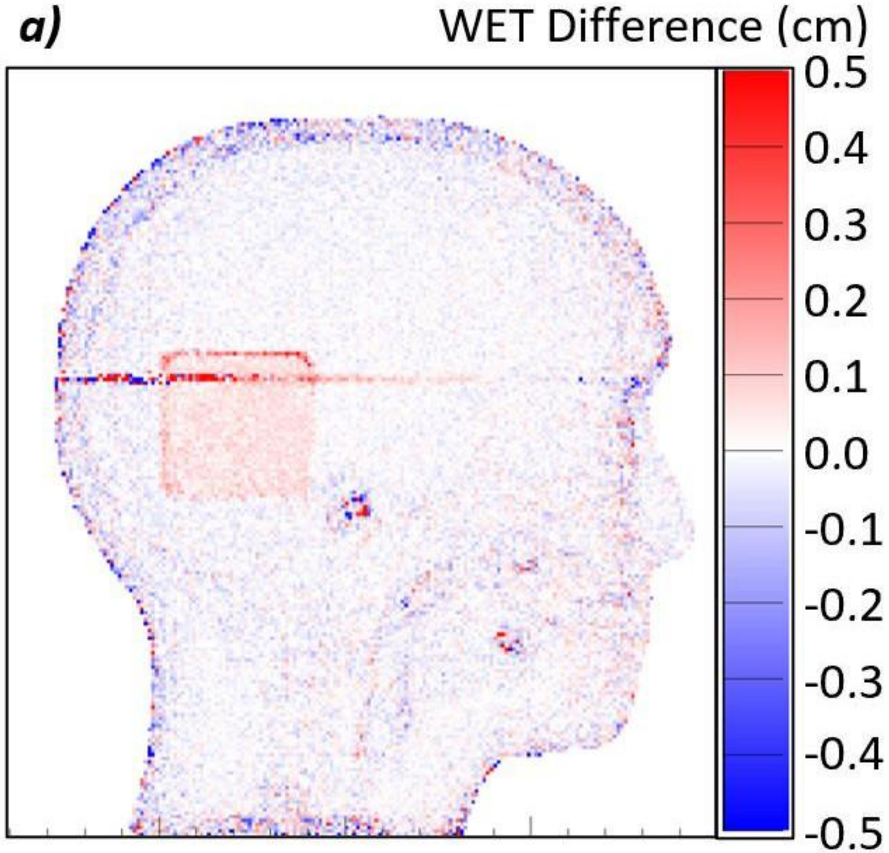
Animation shows steps
through patient volume.

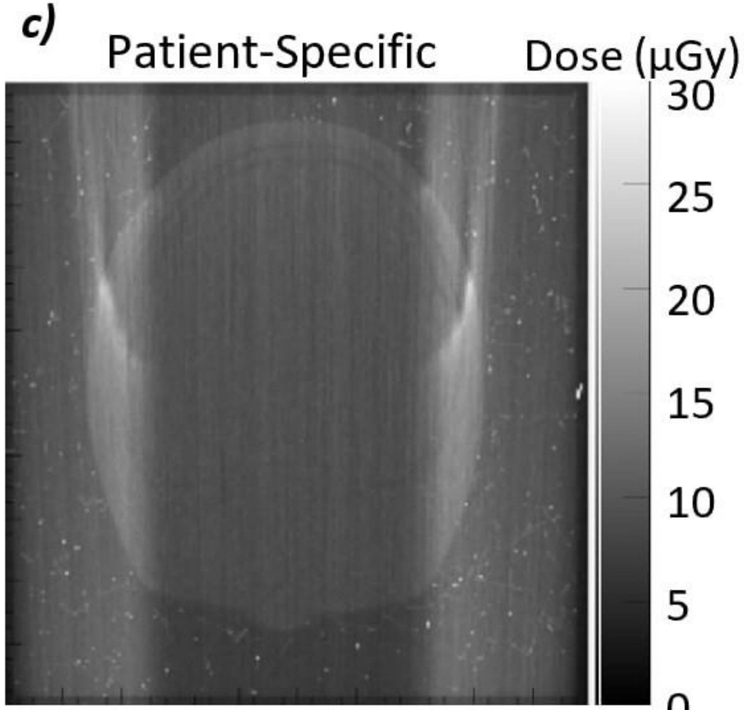
Lung tumor clearly seen.

Simulation used 50 µGy
<1% of X-Ray
CT radiation dose.





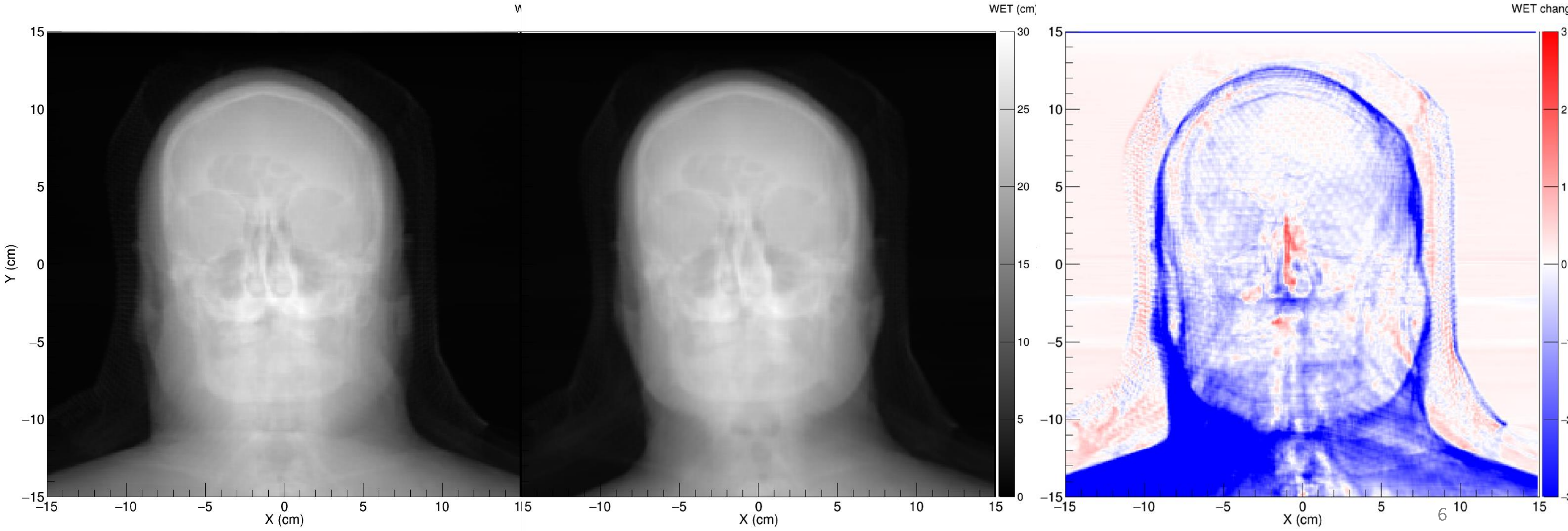




Proton imaging potential:

- High sensitivity to changes
- Low dose
- Low artifacts
  - Even with metallic implants

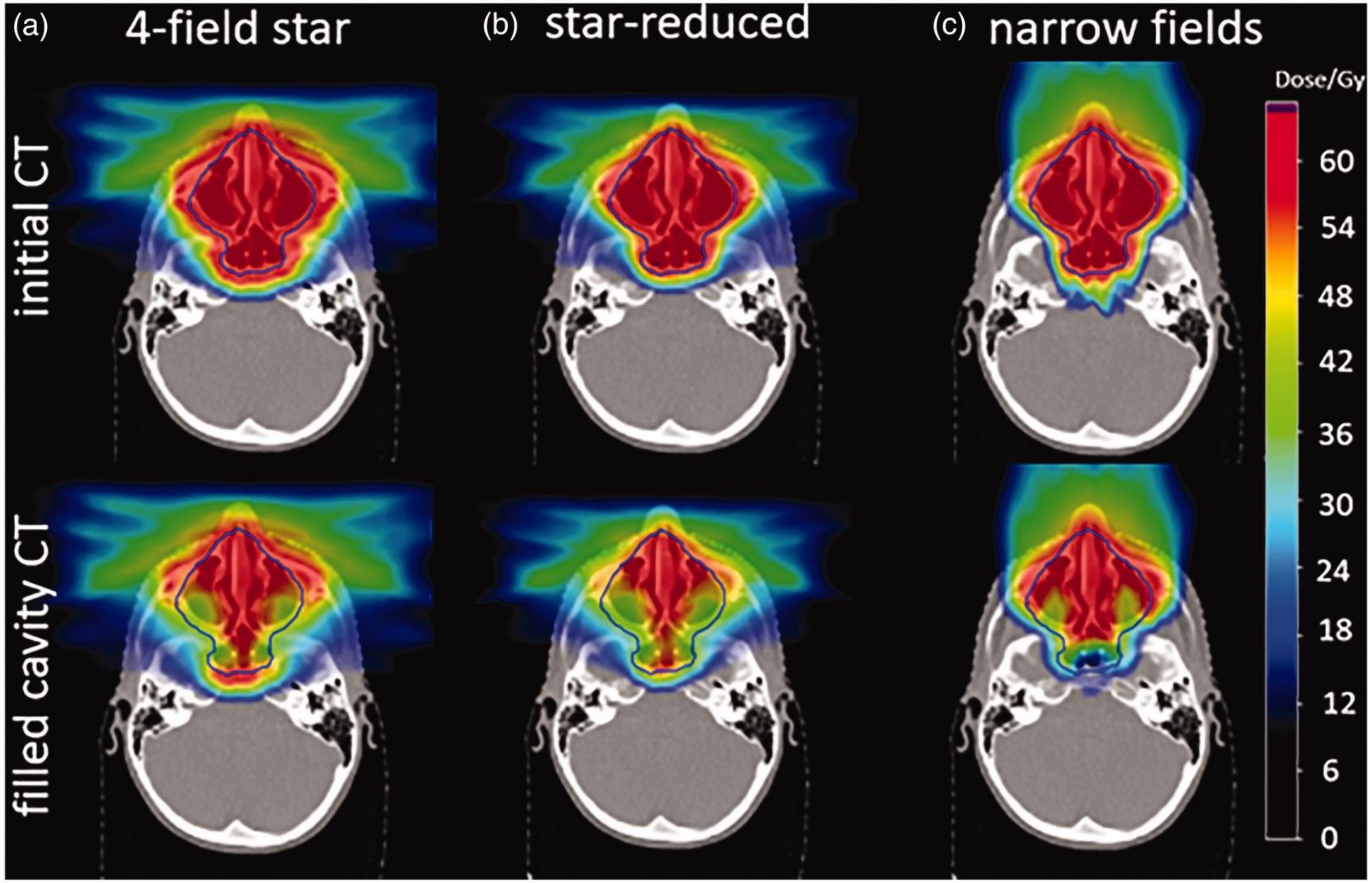
Example: Northwestern Nasopharynx case.
Patient lost weight and sinus filled between two CT scans
Two simulated pRADs and difference
Based on 1st CT scan, and a 2nd scan later in the treatment



Example of clinical benefit

From: ***Daily adaptive proton therapy – the key to innovative planning approaches for paranasal cancer treatments***

Nenoff, Matter, Lindmar, Weber, Lomax & Albertini

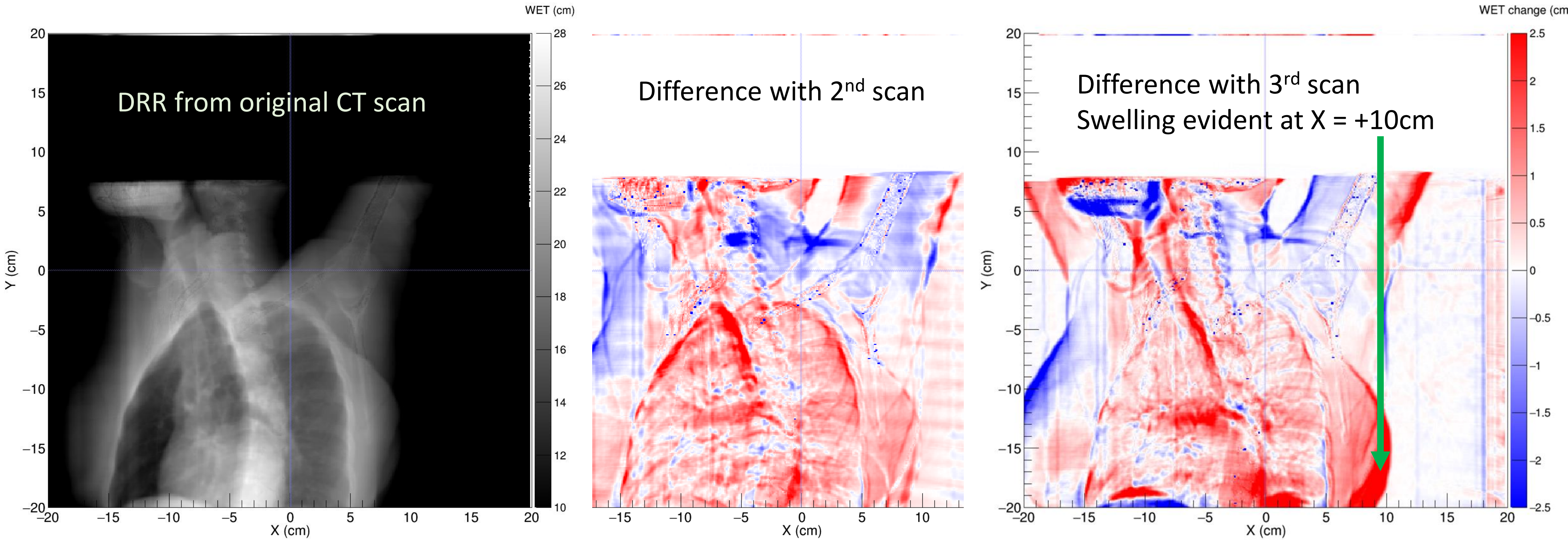


Adaptation can:

- Increase plan robustness to anatomical and positional uncertainties.
- Open use of improved and more conformal field arrangements.

Example: Northwestern breast cancer patient.

- Adaptive planning: Can we update the RSP map with the patient in treatment position?
  - Will need a good DIR
- Cancer screening: Can we distinguish changes due to tumor growth from changes such as those due to posture, or weight gain/loss?

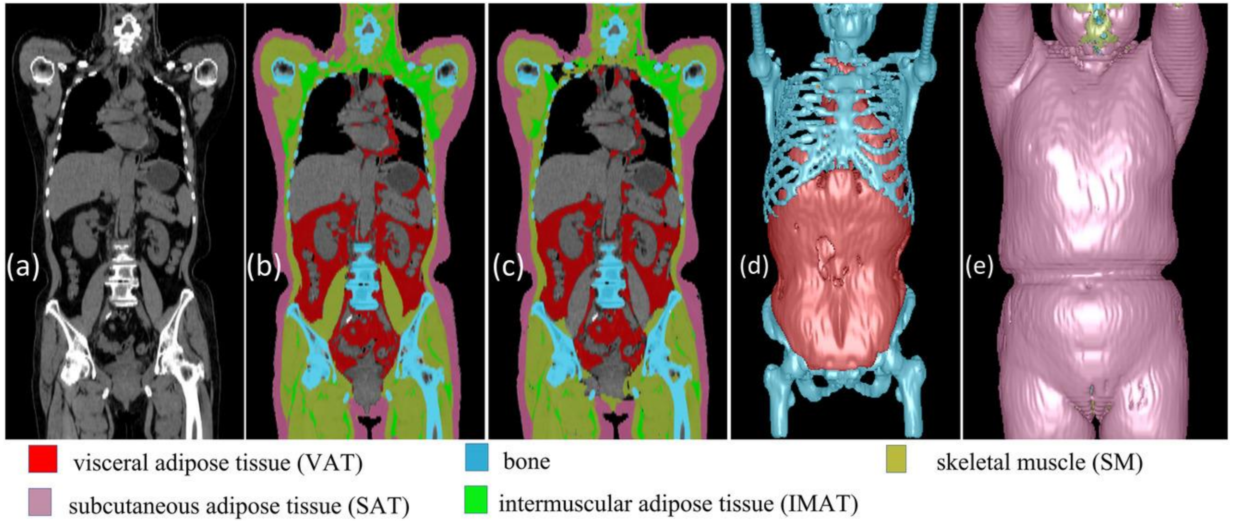


Segmentation techniques: Possible input for improving DIR?

Estimating 3-D whole-body composition from a chest CT scan

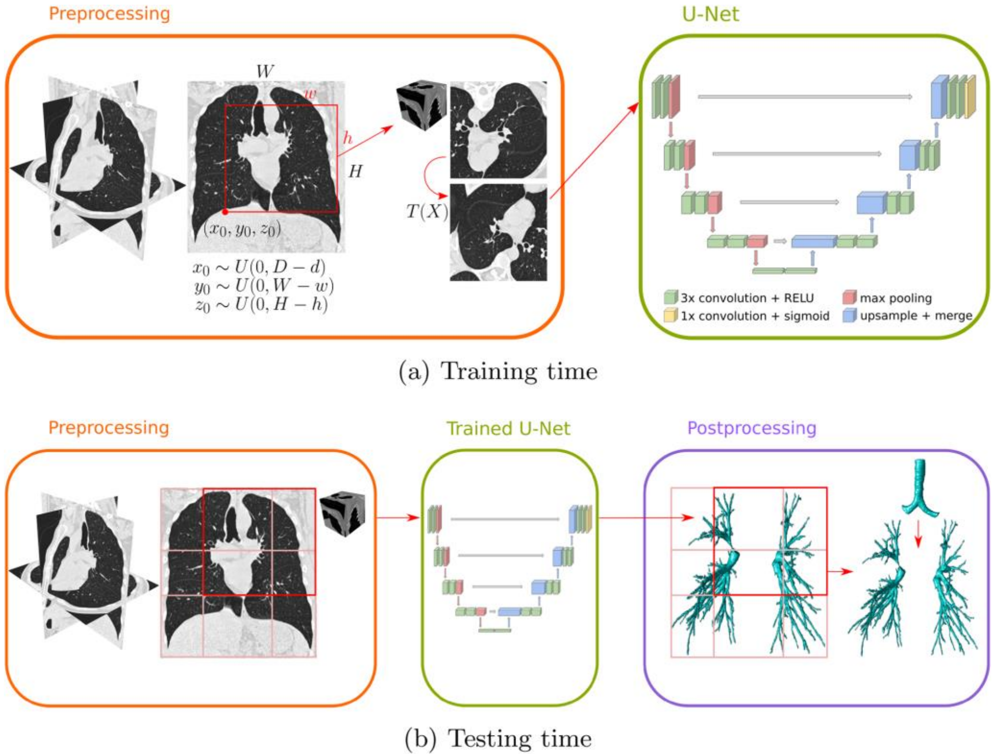
Lucy Pu, Syed F. Ashraf, Naciye S. Gezer, Iclal Ocak, Daniel E. Dresser, Joseph K. Leader, Rajeev Dhupar

First published: 23 June 2022 | https://doi.org/10.1002/mp.15821 | Citations: 4



Automatic airway segmentation from computed tomography using robust and efficient 3-D convolutional neural networks

Antonio Garcia-Uceda[1,2], Raghavendra Selvan[3,4], Zaigham Saghir[5], Harm A. W. M. Tiddens[1,2] & Marleen de Bruijne[1,3]



Proton Imaging for adaptive planning

Lots of other instrumentation and analysis can be brought to bear

- CT or DECT or CBCT
  - Available upright
- Surface Guidance (cameras)
  - Very helpful input to DIR
- Prompt gamma (and also prompt PET)
  - Verify delivered dose distribution.
  - Perhaps provide O_2 data.
- Dosimetry to enable FLASH treatments of deep tumors.
  - Conformal FLASH with proton cyclotrons.
- Segmentation
- AI may play role
  - Incorporate knowledge into DIR and RSP maps
  - Remove artifacts

What can list-mode proton imaging add?

- pRAD: Image and treat with same pencil beam scanning system
  - Alignment check
  - Range check
- pCT: Very helpful in many cases. Want it in the tool kit
  - Create new RSP map for treatment planning.
  - Not enough proton energy in many cases.
- Adaptive planning: An essential role
  - Aim to provide very high doses with very tight tolerances.
  - **What does it take to have confidence in treatment plan?**
- Proton imaging provides direct measurements of proton stopping power with patient in treatment position.
  - Data can be from a partial set of angles and positions.
  - Final update of DIR
  - Final update of RSP map (whether RSP came from DECT or pCT).
  - Check treatment plan. Ultimately, update treatment plan.
- **The essential role for proton imaging:**
  - Treatment plan may have come from many sources.
  - **Use proton imaging for the final update with direct measurements.**

Proton Imaging for Early Cancer Detection

- MCED: Multi-Cancer Early Detection
  - Single test for multiple cancers rather than one test per cancer type
- Cancer survival rates improve dramatically with early detection
  - Example: Lung cancer
    - Five-year survival rate of only 10–20% in most countries.
    - International Early Lung Cancer Action Program findings (2022):
      - 1285 patients diagnosed with early-stage lung cancer.
      - 20-year survival rate was 80%.
- Proton imaging:
  - Can we exploit the ability to detect changes from repeated low-dose scans to detect tumors in the whole body?
  - Can this ability also be used for monitoring: Distinguish slow-growing tumors from aggressive cancer?

Eight goals of the National Cancer Plan

1. **Prevent Cancer**
   All people and society adopt proven strategies that reduce the risk of cancer.

2. **Detect Cancers Early**
   Cancers are detected and treated at early stages, enabling more effective treatment and reducing morbidity and mortality.

3. **Develop Effective Treatments**
   Effective treatment, with minimal side effects, is accessible to all people with all cancers, including those with rare cancers, metastatic cancers, and treatment-resistant disease.

4. **Eliminate Inequities**
   Disparities in cancer risk factors, incidence, treatment side effects, and mortality eliminated through equitable access to prevention, screening, treatment, and survivorship care.

National Cancer Plan

National Cancer Institute
April 3, 2023

5. **Deliver Optimal Care**
   The health care system delivers to all people evidence-based, patient-centered care that prioritizes prevention, reduces cancer morbidity and mortality, and improves the lives of cancer survivors, including people living with cancer.

6. **Engage Every Person**
   Every person with cancer or at risk for cancer has an opportunity to participate in research or otherwise contribute to the collective knowledge base, and barriers to their participation are eliminated.

7. **Maximize Data Utility**
   Secure sharing of privacy-protected health data is standard practice throughout research, and researchers share and use available data to achieve rapid progress against cancer.

8. **Optimize the Workforce**
   The cancer care and research workforce is diverse, reflects the communities served, and meets the needs of all people with cancer and those at risk for cancer, ensuring they live longer and healthier lives.

- Launches Cancer Moonshot:
  - Reduce cancer mortality by 50% over the next 25 years

DETECT CANCERS EARLY

Cancers are detected and treated at early stages, enabling more effective treatment, and reducing morbidity and mortality.

Strategies

- Develop new methods to detect cancers, particularly for those cancers where no effective screening tests currently exist
- Develop novel imaging technologies for early cancer detection for use alone or in combination with other tests
- Develop methods to identify precancerous cells and eliminate them while minimizing side effects
- Conduct rigorous clinical trials to capture evidence about the benefits and harms of novel cancer detection tests
- Develop research partnerships that include primary care providers, researchers, and communities at increased risk for cancer to improve the testing and adoption of effective cancer screening
- Conduct research to identify and overcome barriers to the treatment of early-stage cancers in communities with disparities, including financial toxicity and policies that limit effective system-level and community-sourced patient navigation services

Previous MCED initiatives: Blood assays

- Principle: Identify DNA shed by tumors into bloodstream
- Have received billions of dollars of investment
- 14 companies engaged with an NCI request for information.
- Example: DETECT-A test from Exact Sciences:
  - 26 cases first found with DETECT-A
  - 24 cases first found with Standard of Care image-based screening

There is currently no imaging method for MCED

- Blood assays do not detect all early tumors:
  - Need imaging as well as assays for best MCED.
- Standard of Care x-ray imaging exists only for single cancers:
  - Mammograms for breast cancer.
  - Low-dose CT for patients at high-risk for lung cancer.
- Whole-body CT scans: Radiation dose is too high for screening.
- MRI: Does not have the combination of cost, resolution, and speed needed for large-scale screening.

Imaging may also help to manage detections

- A cancer screening program needs more than MCED:
  - Improve cancer sensitivity while also reducing harms.
- Each screen is a potential source of harm to the patient
  - False positives, un-needed biopsies, overtreatment.
    - Often, this leads to recommendations to screen less.
- Mehra Golshan, clinical director (breast program) at Yale.
  - “The goal should not be to find less cancer but to be more thoughtful about what to do with the cancer we find.” (NYTimes, May 16, 2023)
  - When to treat aggressively?
  - When to monitor slow-growing detections that may never harm the patient?

Could Proton Imaging be the ideal imaging modality for MCED?

- Much less radiation dose than x-ray imaging.
- Minimal artifacts even with metallic implants.
- Very sensitive to changes in patients.

Dedicated imaging facilities

- Build on existing proton therapy technology.
- High-throughput, fast and convenient for the patient.
- Enable frequent, low-dose, widespread screening.

Challenge: Distinguish changes from tumor growth from everyday changes such as weight change or even just different posture.

Proton imaging as the best general purpose imaging modality.

- Any specific use has a specialized best imaging technology
  - How do we know when a specialized imaging type is needed?
- Proton imaging fills a gap to trigger the use of specialized imaging at an earlier stage.

Frequent, fast, convenient, low dose proton imaging for

- Cancer detection
- Primary care more generally:
  - Major expansion of imaging infrastructure
  - Provide 3D maps of patients over time

Costs

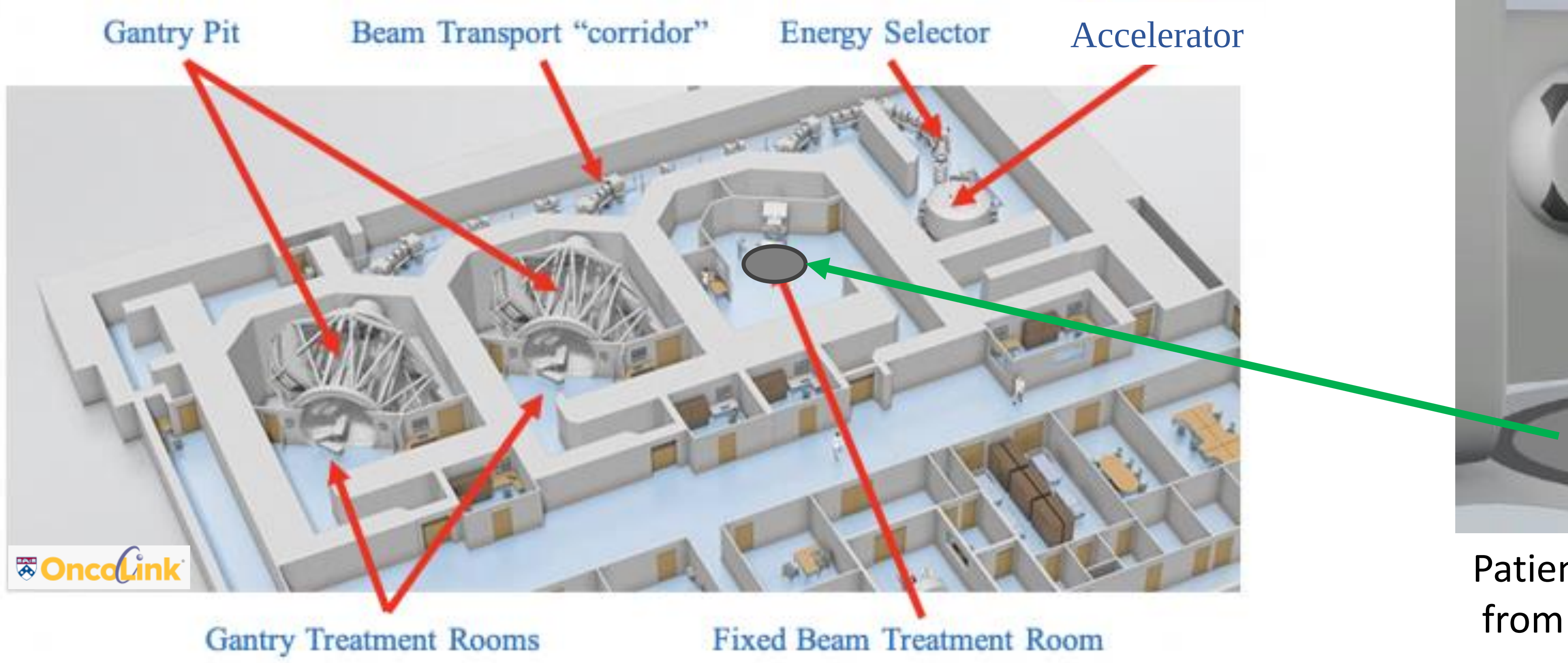
- Blood assays
  - Galleri test, made by GRAIL:
    - List price is $949 for a single yearly test
- Proton therapy
  - Estimates are around $1100 per treatment session
- Proton image for MCED
  - Cost will be much lower than for a treatment session
  - Our estimates:
    - Could provide 6 scans per patient per year for $1000 per year.
    - Or, 1 scan per patient per year for $300 per year.

Current treatment facilities:

- One accelerator (proton source)
- 1 to 5 large treatment rooms
- Huge patient gantry volume
- High intensity proton beams
    - Massive radiation shielding

Future dedicated imaging facility for MCED:

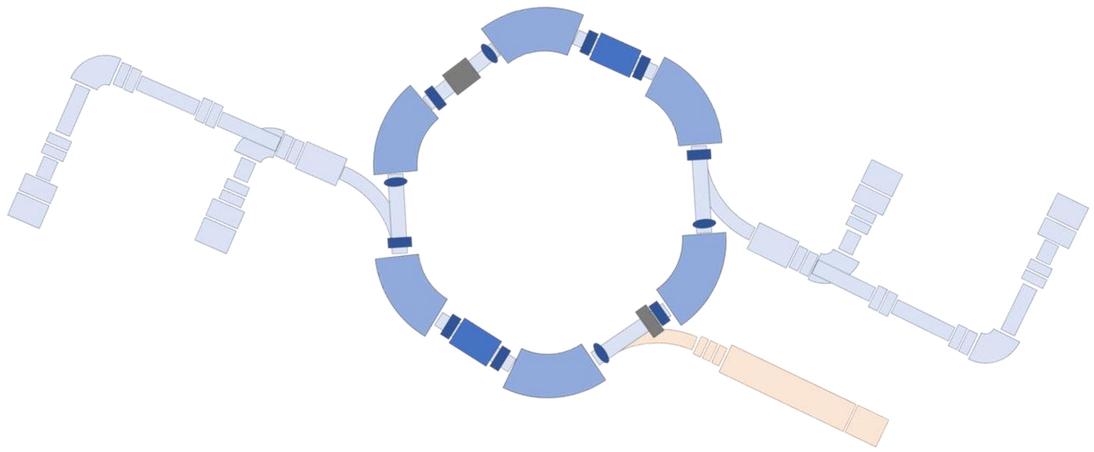
- One accelerator (proton source)
- 10 to 30 small imaging rooms
- Compact rotating patient chairs
- Ultra-low intensity proton beams
    - Minimal radiation shielding (other than near accelerator)



Patient positioning chair from Leo Cancer Care

Synchrotron options (energy up to 330 MeV)

- Patient specific scan patterns
  - Multiple energies per patient tailored to patient size.
  - Multiple angles per patient. Possibly, a full set of angles for pCT.
  - May want to gate on heartbeat cycle, breathing cycle, or both.
  - Possible scenario:
    - Patient is in chair for ~5 minutes.
    - Beam is on for a total of ~ a few seconds.
- Synchrotron operation
  - Each fill: Cycle through a set of energies from high to low.
  - Each imaging room sends signal for ready / not ready.
    - Energies wanted
    - Scan patterns ready for each energy
  - Beam extraction to rooms that are ready
    - Multiple extraction lines possible
    - Multiple imaging rooms per extraction line
    - Simultaneous extraction to multiple rooms may be possible.

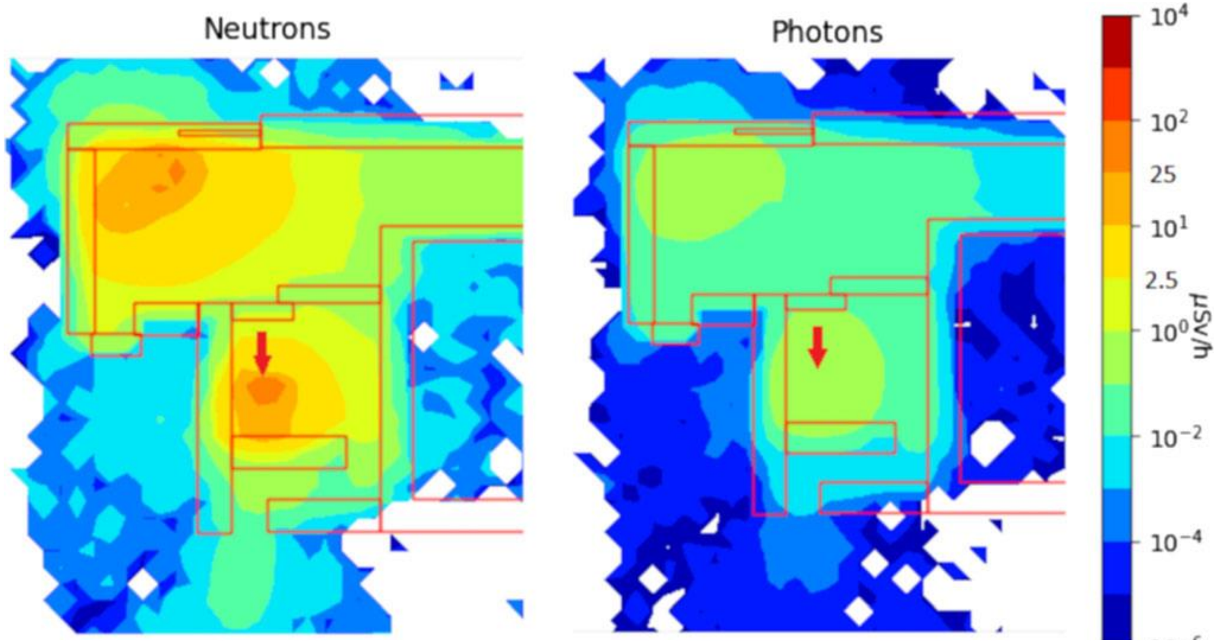


Concept from Alexander Pryanichnikov

Shielding Assessment, 330 MeV synchrotron

Scott Penfold, DOI: 10.1002/mp.15727 (Published in Medical Physics 2022)

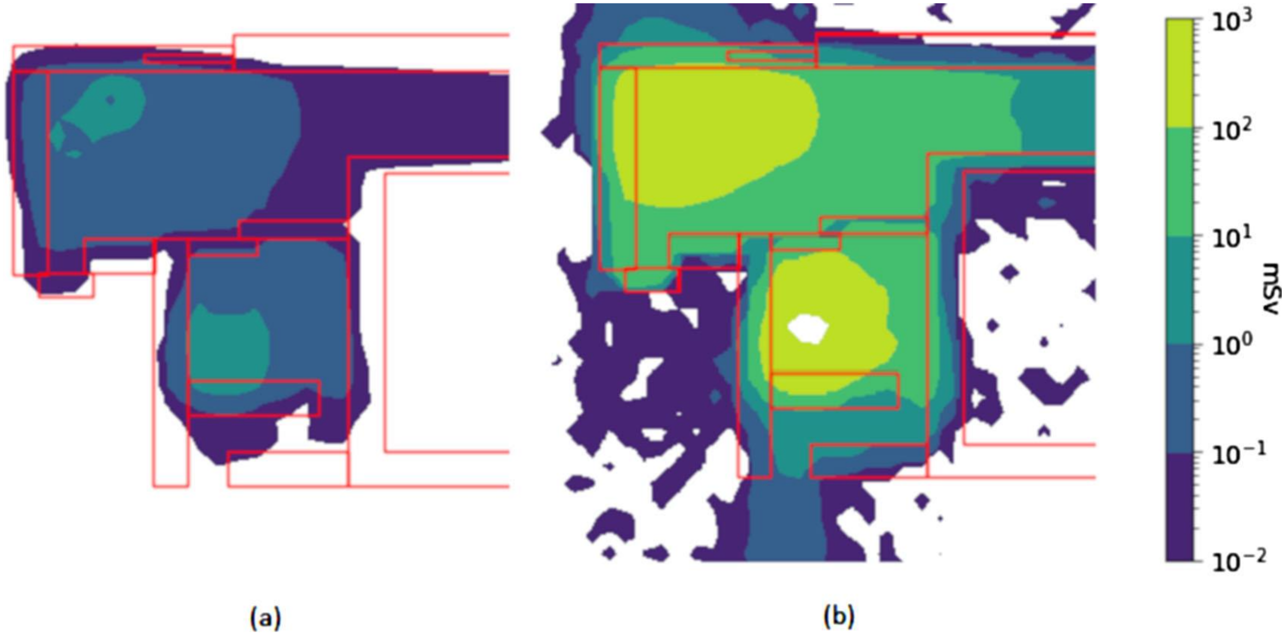
Instantaneous dose, 330 MeV protons



Annual effective dose estimate

Imaging only

Imaging + therapy



Main concern for imaging center: Minimize long-term neutron dose for staff

Many feasible algorithms have already been published for DIR / RSP update (Typically, DIR first, then update RSP).

Papers on combining proton and x-ray data

Hansen DC, Petersen JBB, Bassler N, Sørensen TS. **Improved proton computed tomography by dual modality image reconstruction**. *Med Phys*. 2014;41(3):031904.

Collins-Fekete CA, Brousmiche S, Hansen DC, Beaulieu L, Seco J. **Pre-treatment patient-specific stopping power by combining list-mode proton radiography and x-ray CT**. *Phys Med Biol*. 2017;62(17):6836-6852.

Krah N, Patera V, Rit S, Schiavi A, Rinaldi I. **Regularised patient specific stopping power calibration for proton therapy planning based on proton radiographic images**. *Phys Med Biol*. 2019;64(6):065008.

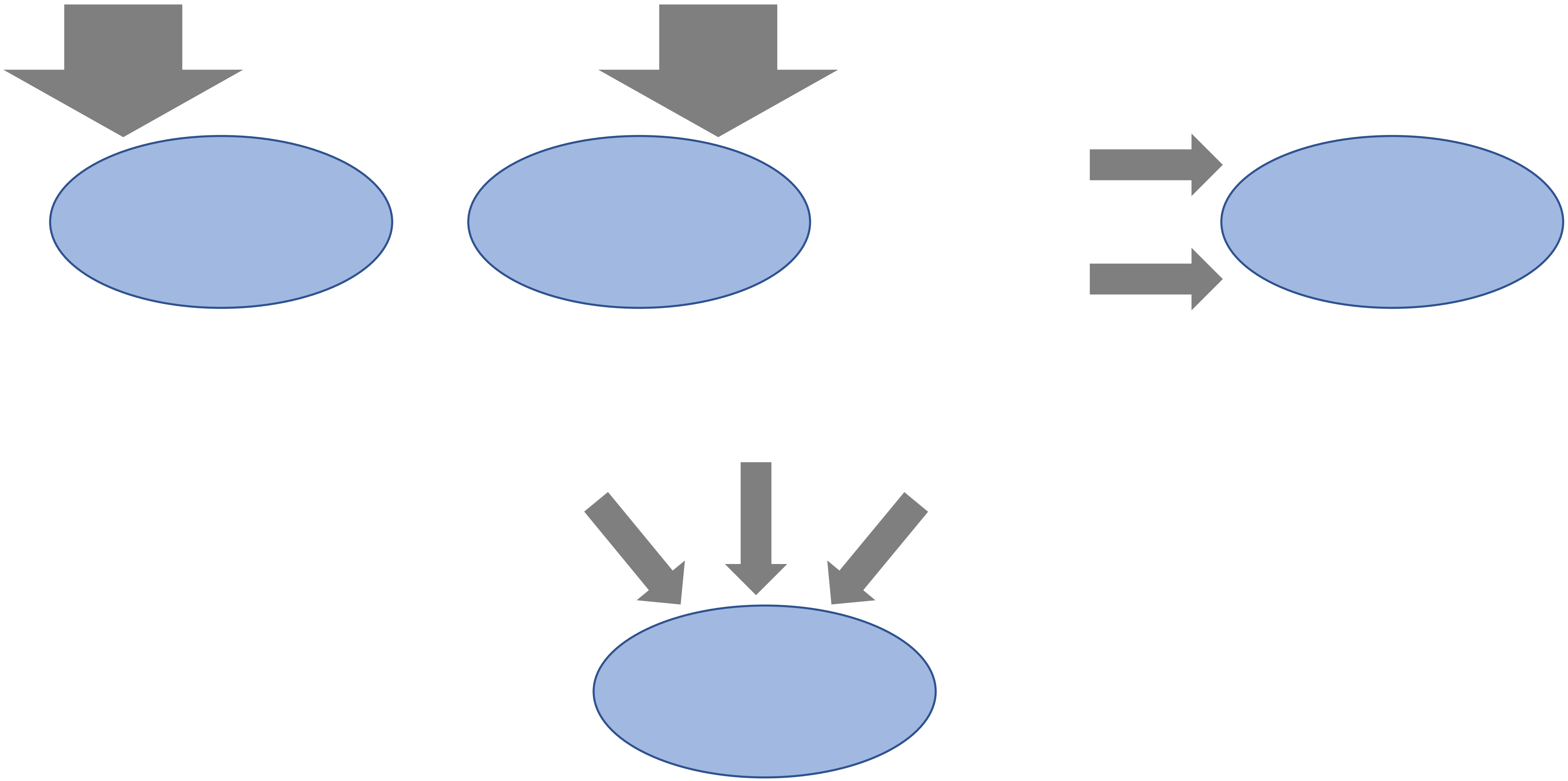
Gianoli C, Göppel M, Meyer S, et al. **Patient-specific CT calibration based on ion radiography for different detector configurations in 1H, 4He and 12C ion pencil beam scanning**. *Phys Med Biol*. 2020;65(24):245014.

Papers on deformable registration

Deformable image registration of the treatment planning CT with proton radiographies in perspective of adaptive proton therapy
Prasannakumar Palaniappan, Sebastian Meyer, Florian Kamp, Claus Belka, Marco Riboldi, Katia Parodi and Chiara Gianoli
2020 *Phys. Med. Biol.*
https://doi.org/10.1088/1361-6560/ab8fc3

X-ray CT adaptation based on a 2D-3D deformable image registration framework using simulated in-room proton radiographies
Prasannakumar Palaniappan, Sebastian Meyer, Martin Rädler, Florian Kamp, Claus Belka, Marco Riboldi, Katia Parodi and Chiara Gianoli
2022 *Phys. Med. Biol.*
https://doi.org/10.1088/1361-6560/ac4ed9

Proton data may be acquired with a complex set of positions and angles



New algorithm for updating RSP map

(Extension of our least-squares algorithm)

- Uses proton “list-mode” information so can use any proton data set from all spots and angles that might be helpful.
    - Not restricted to, eg, one or more reconstructed pRADs
    - Need a good starting 3D map, but then may be able to update with much less data than needed for a full pCT.
- Can incorporate knowledge of which tissues have potentially larger RSP uncertainties.
    - Assign different uncertainties for different segments in initial RSP map.
    - Can correlate RSP adjustments of voxels within segments.
- DIR also uses protons list-mode information.
    - Optimizes use of statistical power of the data.
    - More flexibility in choosing spots and angles.

Simple first try:

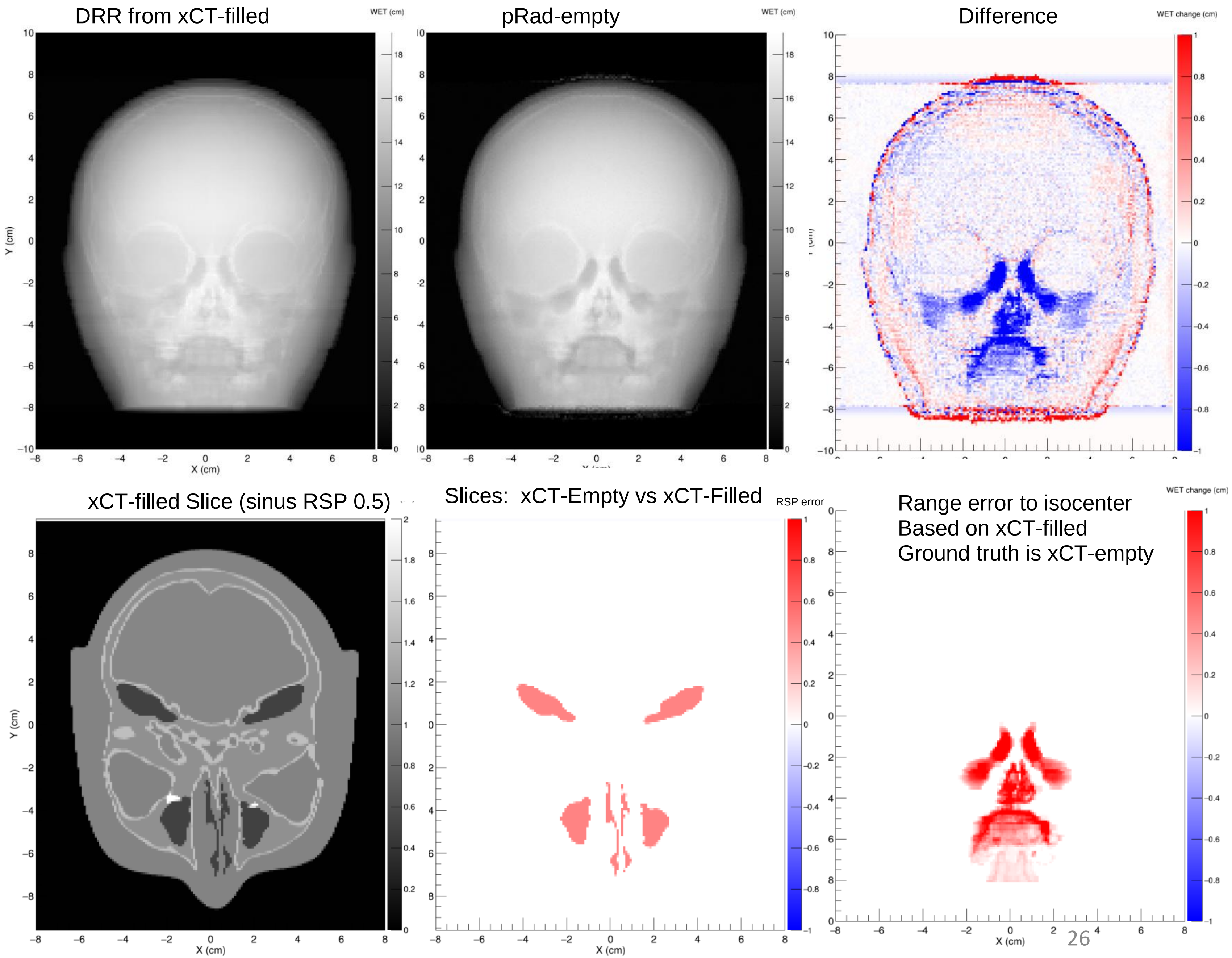
Pediatric head phantom.
Simulations with
1. sinus filled
2. sinus empty

Scenario:

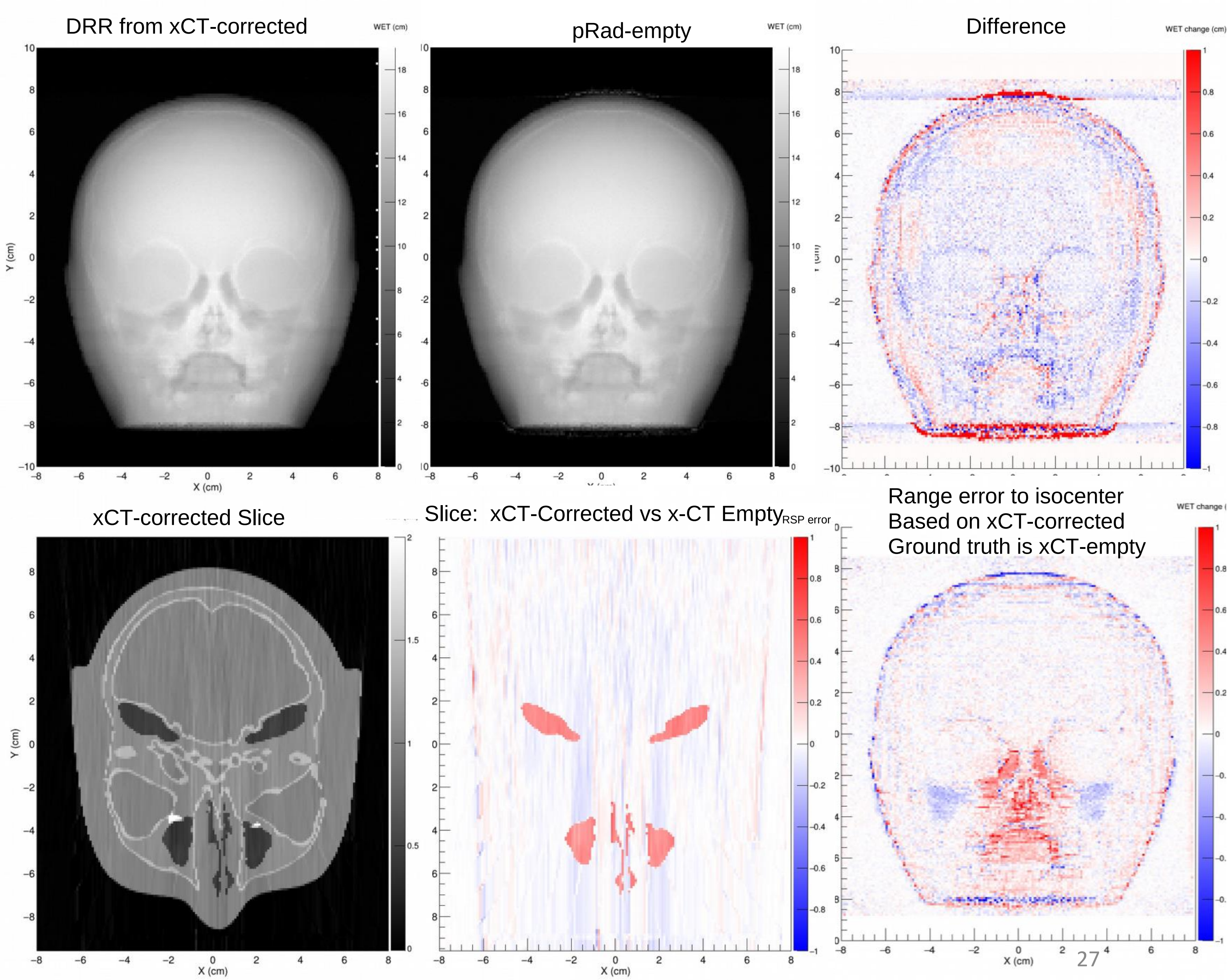
- xCT with sinus filled.
- pRad with sinus empty.

- Combine xCT-filled and pRad-empty to create:
    - xCT-corrected

Compare xCT-corrected
- with -
xCT-empty made for comparison
- Ideally, they would be identical

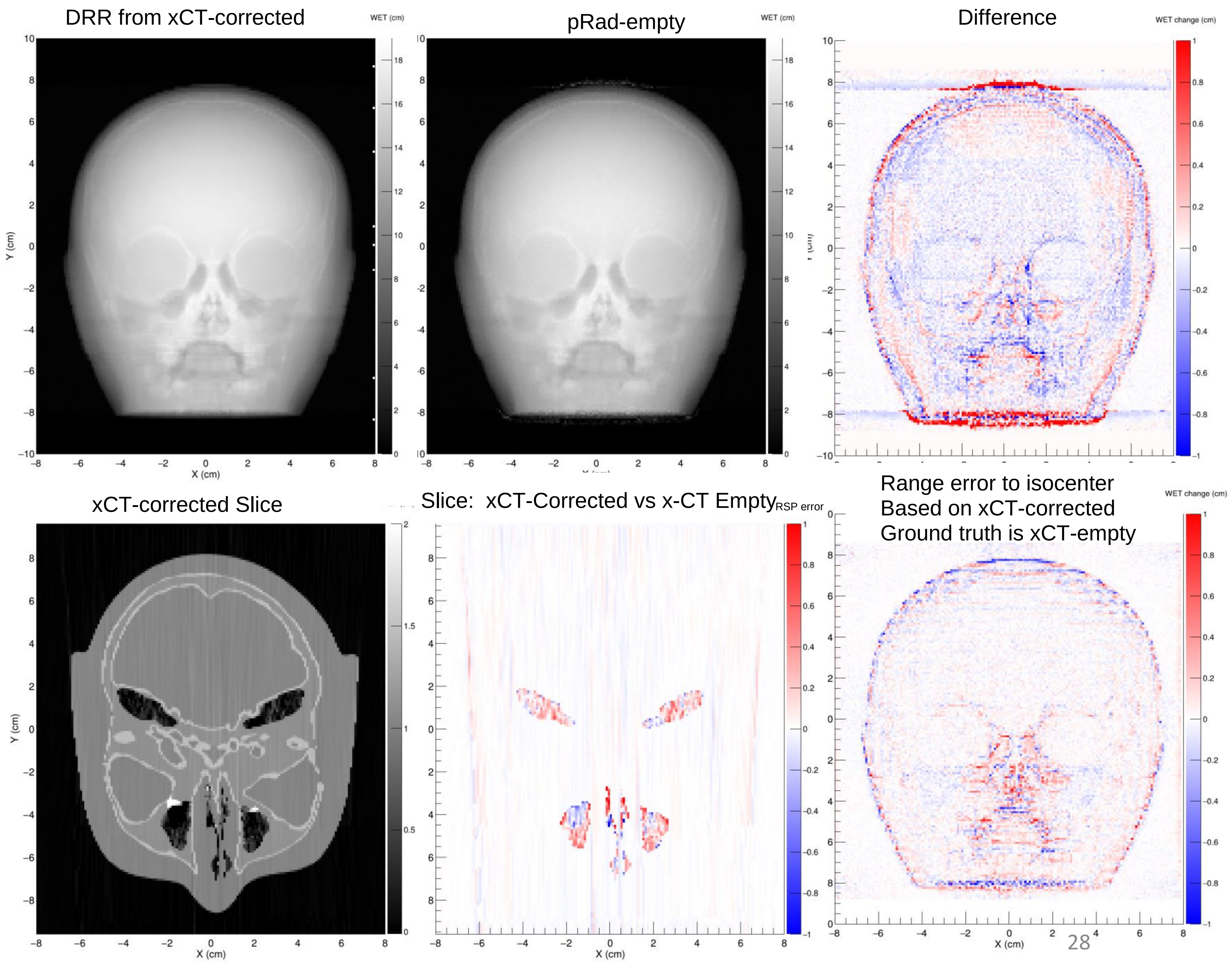


Combine :
xCT-filled with pRad-empty –



Combine :
xCT-filled with pRad-empty –

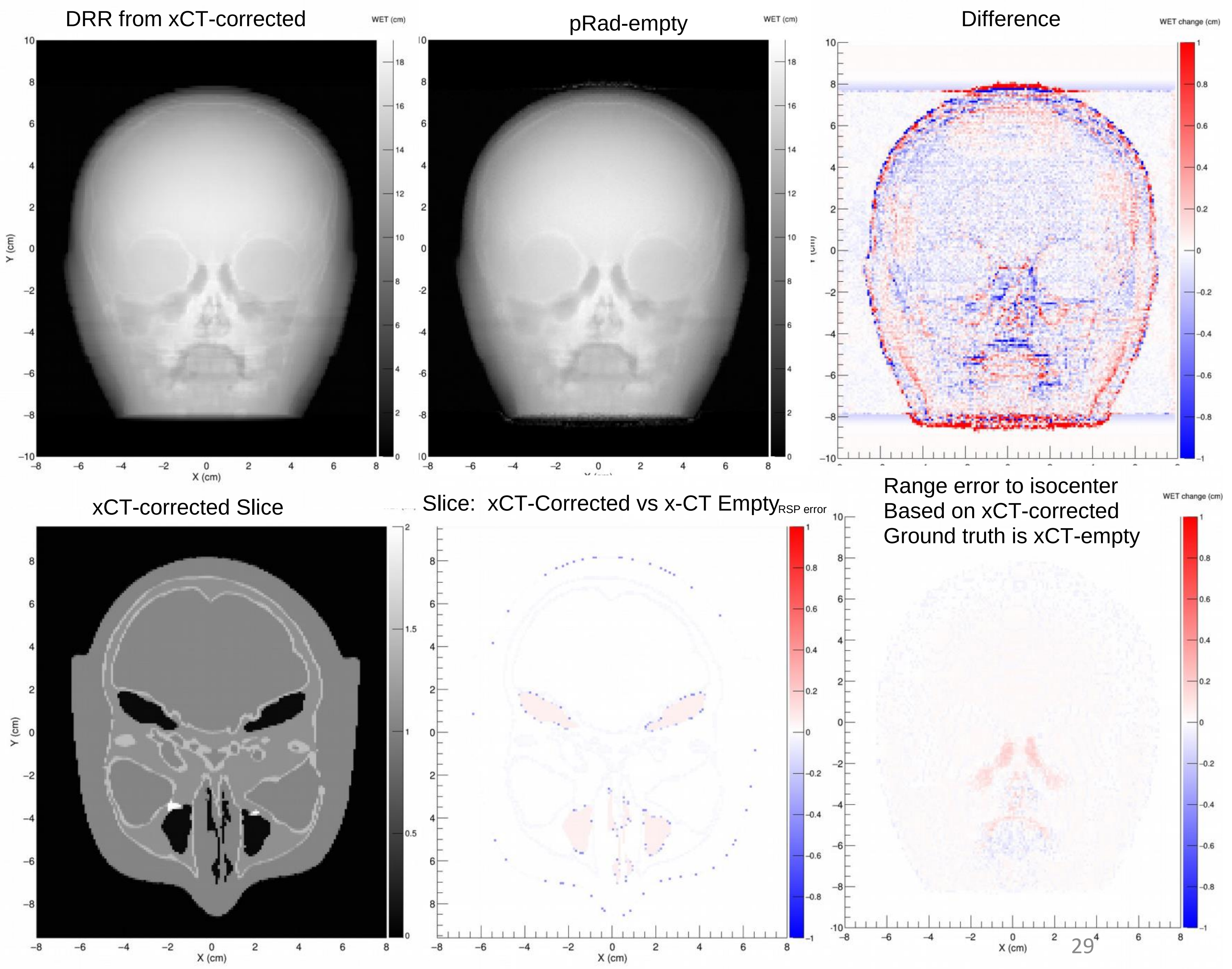
Assign large uncertainty to sinus cavity segments



Combine :
xCT-filled with pRad-empty –

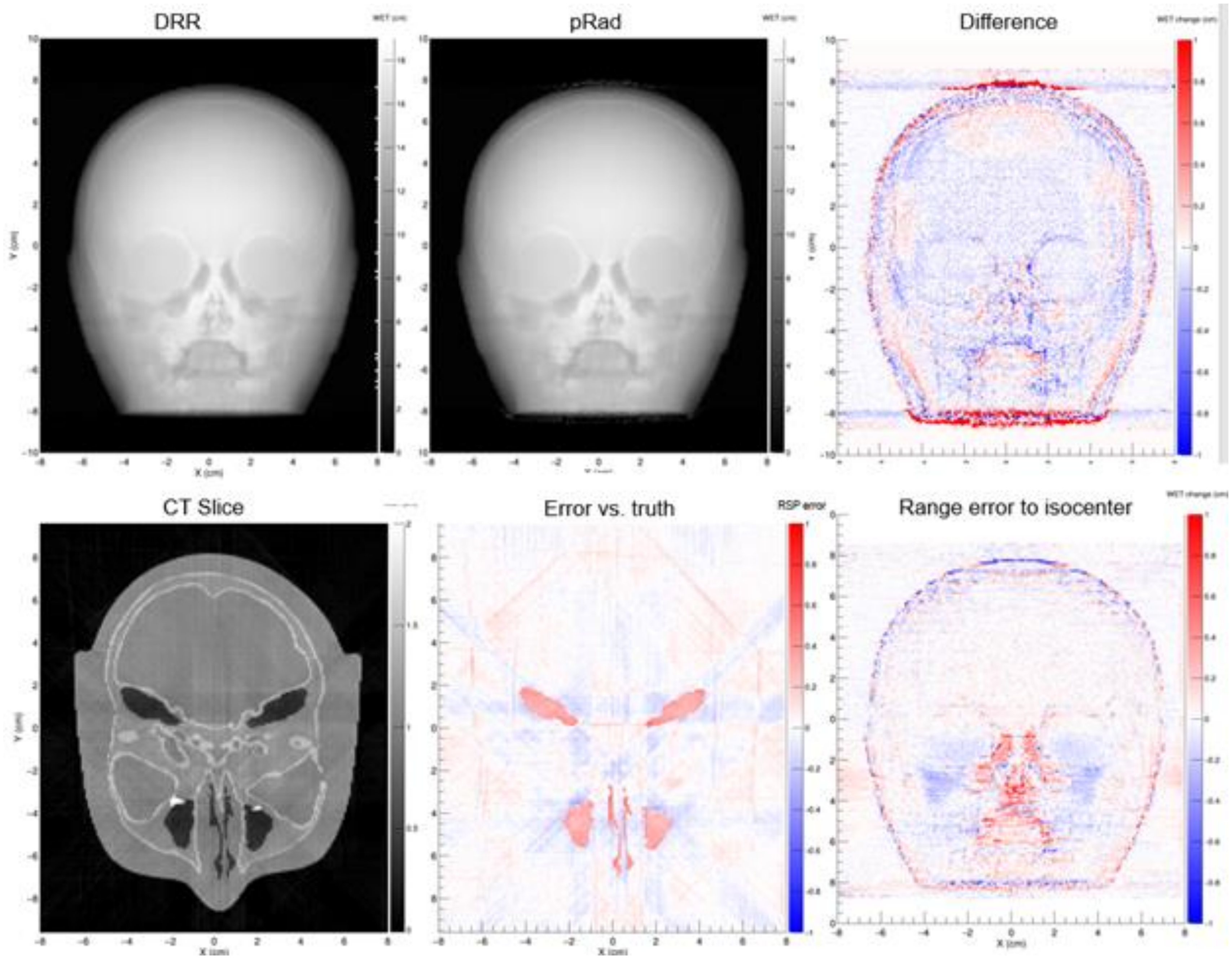
Assign large uncertainty to sinus cavity segments

Add correlations between voxels within segments



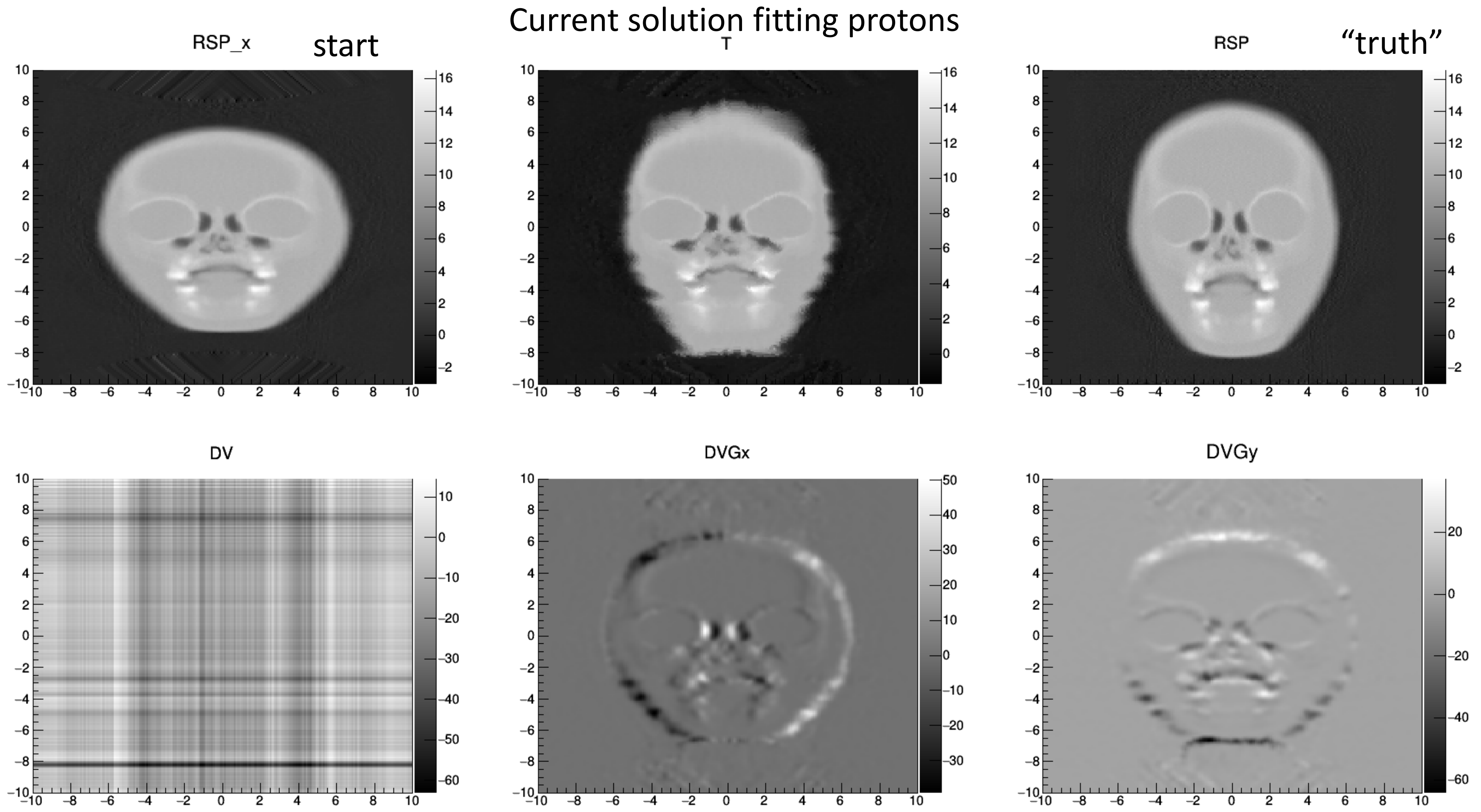
Combine :
xCT-filled with pRad-empty –

Use two beam directions



First try at DIR with list-mode protons

Using two beam directions



Iterates on a convolution of Dv and image gradients.

Dv is the average deviation

(predicted – measured, or Ax-b),

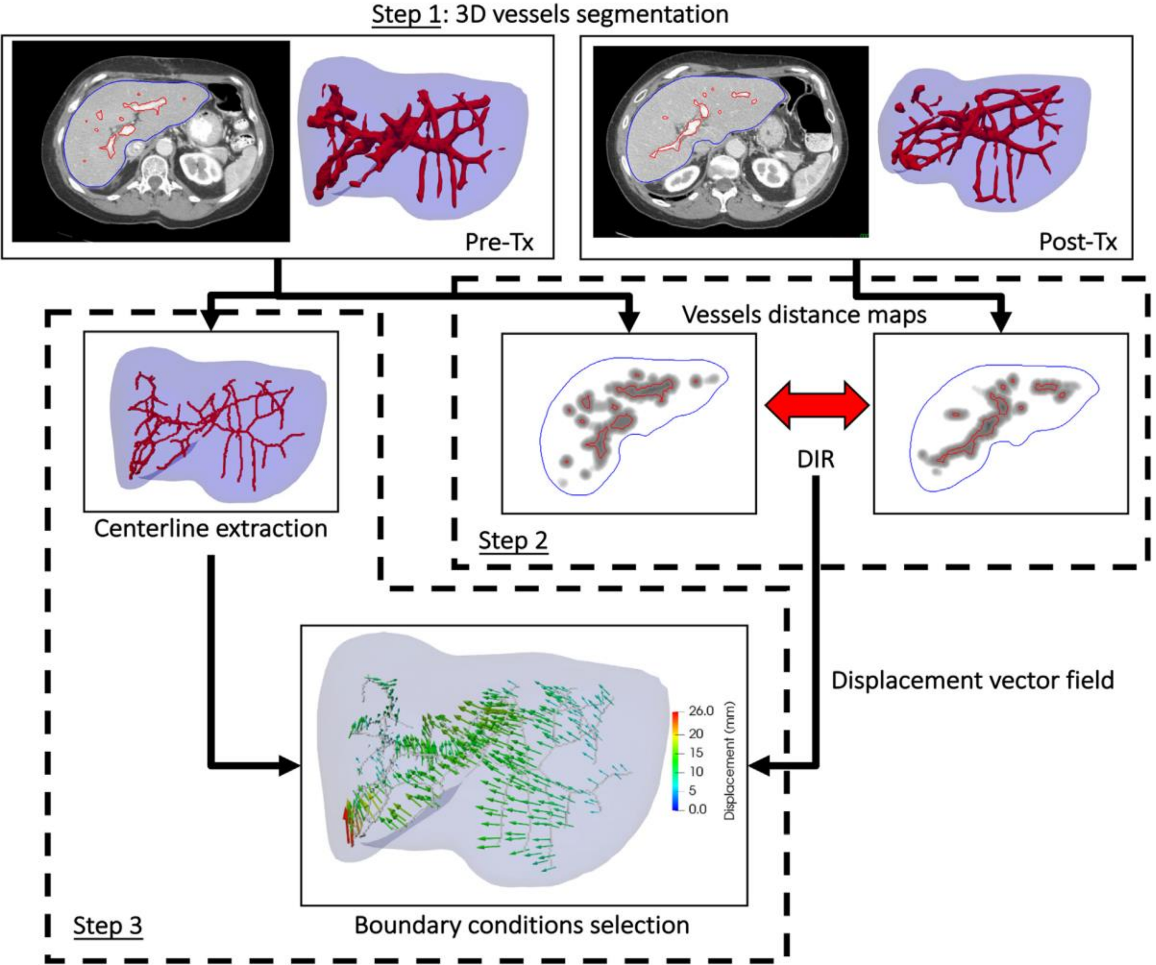
of protons through each voxel

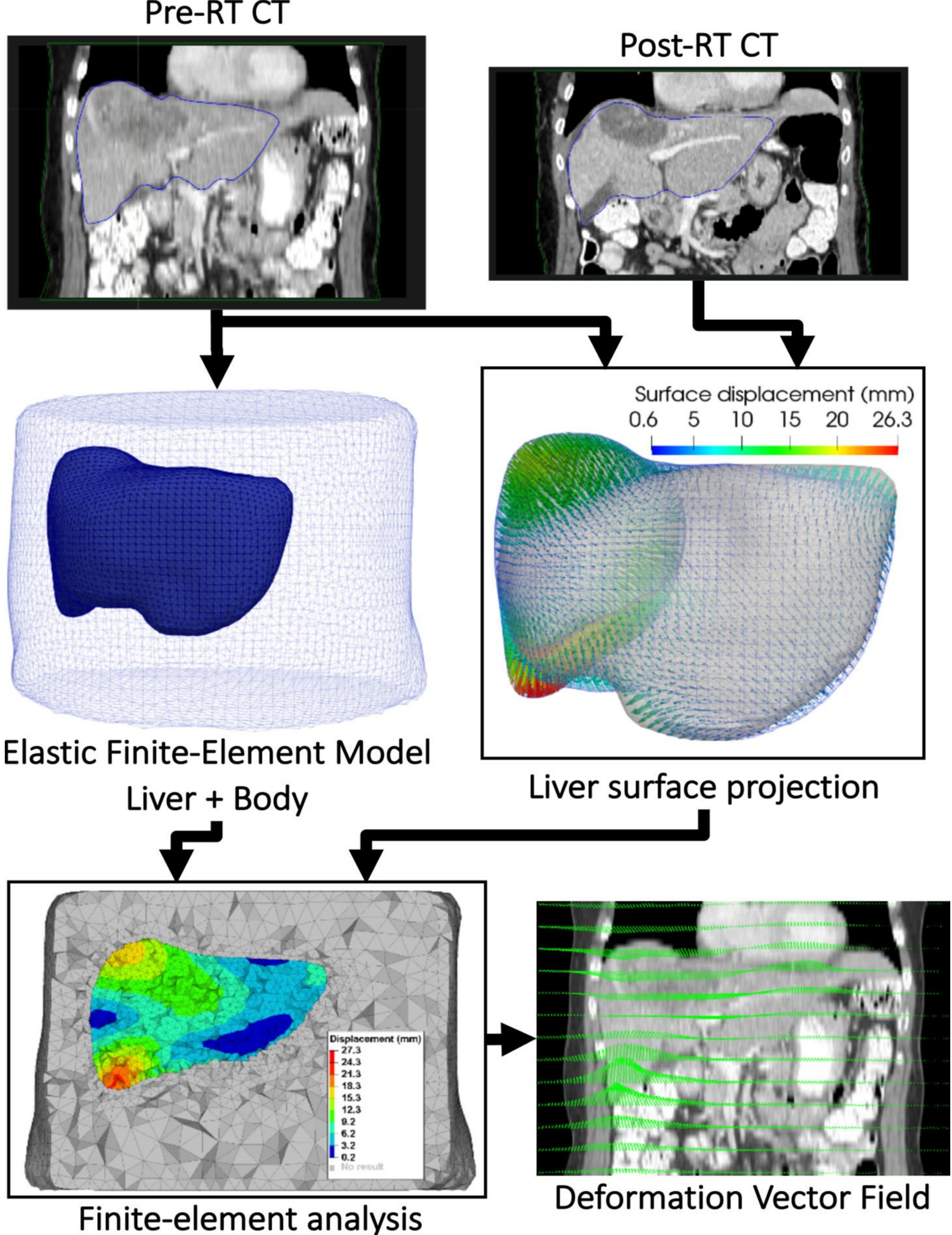
DIR will probably benefit from using knowledge of segmentation

Vasculature-Driven Biomechanical Deformable Image Registration of Longitudinal Liver Cholangiocarcinoma Computed Tomographic Scans

Guillaume Cazoulat, PhD,[a,*] Dalia Elganainy, MD,[b] Brian M. Anderson, MS,[a] Mohamed Zaid, MD,[b] Peter C. Park, PhD,[c] Eugene J. Koay, MD, PhD,[b] and Kristy K. Brock, PhD[a,c]

https://doi.org/10.1016/j.adro.2019.10.002





Application of AI: At many levels

1. Use knowledge of segments to optimize DIR
2. Analyze images for suspicious detections
3. Analyze sequences of images to monitor potential detections.
4. Ultimately: A powerful data set enabling extraordinary applications
    1. 3D maps of large numbers of patients over time combined with clinical outcomes
    2. Patient data should be available to the patient and physicians but kept private.
5. Implement regulation starting at conceptual stage.
    1. Also, at stages of design, improvement, and dissemination.
    2. “Data is our new natural resource.” Orly Lobel, *The Equality Machine.*
        1. Anonymized data on a population level should be available for evidence-based research as a public good and not be siloed for use by corporations.
    3. Policies should make data sets easy to access for research.
    4. Governments should fund creation of fuller data sets and research for purposes such as monitoring and promoting equity.

Conclusion:
Potential to transform health care system

- Can this work? Why not?
- How well can we do today?
  - We could probably find large tumors, perhaps ~2 cm.
  - Improved algorithms could improve this over time down to the mm level.
  - Look for available imaging data sets for simulated screening trials.
- Many opportunities for interdisciplinary research in proton imaging.
  - If it works, it will make a big impact.