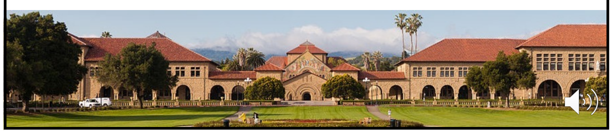
Department of Radiation Oncology
School of Medicine
Stanford University

Initial Experience On a Real-Time Biologically-Guided Radiotherapy System

Bin Han, Ph.D.



1

Outline

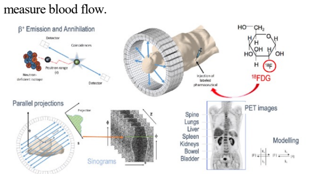
- PET imaging
- PET based BGRT
- Stanford IDE study
- RefleXion system overview
- RefleXion X1 commissioning and QA

Stanford University 2

2

Positron emission tomography (PET)

- PET is a functional imaging technique that uses radiotracers to visualize changes in metabolic processes, and activities including blood flow, regional chemical composition, and absorption.
- A radiotracer is injected into the body as a tracer. The e-p annihilation process emitted gamma rays and the signals are detected by detector arrays to form a 3D PET image.
- Tracer: 18F-FDG → cancer and GTV delineation, NaF-F18 → bone formation, oxygen-15 → measure blood flow.



Beyer et al, 2020 Cancer imaging

Stanford University

3

Biological Imaging in Radiation Therapy

- CT and MRI improved structure visualization with enhanced sptial resolution.
- PET imaging visualize biological and molecular level in tumor
- Wide spectrum of positron-emitting tracer to cover more disease sites with high sensitivity

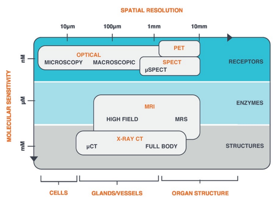


Figure adapted from Ticher, K., et al. Phys. Med. Biol. 60 (2015) R239-R269

Stanford University

4

Why PET-based BGRT?

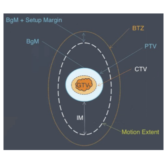
- Oligometastatic disease -- 3 to 5 or fewer metastases
- Clinical trial of 3 sited and 5 sited NSCLC shows the improved overall survival (6~24 months). (Gomez 2019 JCO, Iyengar JAMA 2018)
- Biologically tracking the oligometastases: Redefining the role for radiotherapy in metastatic cancer.
- PET imaging reveals tumor characteristics of tumors and biological response to treatment: perfect tools BGRT

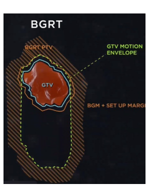
Stanford University

5

PET-based BGRT

- Biology tracking zone (BTZ):
  - Encompass ITV + Setup Margin
- Biological Margin (BgM):
  - Tracking margin ~5mm (PET latency ~400ms)
  - PET to planning CT alignment margin





RefleXion

Stanford University

6

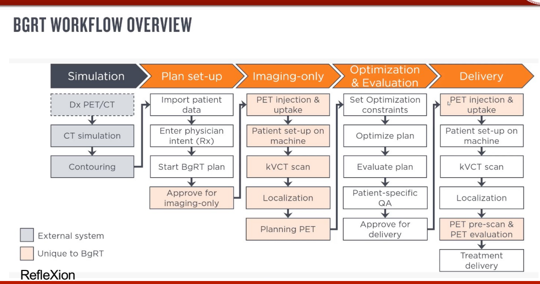
BGRT Planning Studies

- Lung BGRT studies by City of Hope: (Liang et al, ASTRO 2019)
  - 6 lung SBRT patients.
  - BGRT vs ITV-based SBRT, PTV volume reduced 21.5% in average.
  - OAR sparing is better for the lungs, spinal cord, esophagus, and heart
- Emory's study to investiage stability of FDG F18 as a "fiducial" for SBRT (Tian et al, ASTRO 2019)
  - 14 lung SBRT patients, 10Gy x 5fx
  - 3 PET/CTs acquired before the 1, 2, and 5th fx.
  - mean SUVmax change from PET1-2 = -8.2%, from PET1-3 = -7.0%.
  - [SUVmax/liver SUVmean] was stable over time; PET1-2= -0.3%, PET1-3 = +1.8%.
- Reflexion set SUVmax/SUVmean in BTZ threshold is 2.7 for simulation, 2.0 for treatment tracking.

Stanford University

7

BGRT Worlkflow

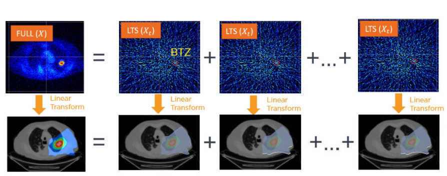


Stanford University

8

PET-based BGRT

- Full time PET ~ 500ms (half rotation) in 60 RPM
- Limited-time-sample (LTS) PET image to track tumor: 100ms per image.
- Phantom measurement validation performed

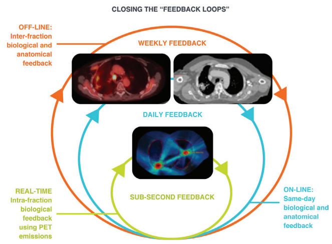


SHIRVANI et al, 2021. BJR.

Stanford University

9

PET-based BGRT



SHIRVANI et al, 2021. BJR.

Stanford University

10

Stanford IDE Study

- Primary Objectives:
  - To identify the Recommended RefleXion FDG Dose (RRFD) that enables the use of biology-guided radiotherapy (BgRT) on the RefleXion system. (Cohort I: RRFD)
  - To determine whether BgRT dose distributions generated from Limited Time Sample (LTS) Positron Emission Tomography (PET) images obtained at the time of treatment delivery are consistent with the approved BgRT plan. (Cohort II: Emulated Delivery)
- Design
  - Cohort I - RRFD: 6 to 12 subjects (3 to 6 bone tumors, 3 to 6 lung tumors)
  - Cohort II - Emulated Delivery: 8 to 12 subjects (4 or more bone tumors, 4 or more lung tumors)
- Primary End Point:
  - Cohort I: Recommended RefleXion FDG Dose (RRFD): The FDG dose that results in Activity Concentration necessary for BgRT functioning: 5 kBq/ml or higher.
  - Cohort II: The percent of radiotherapy fractions where the emulated BgRT dose distribution in silico is shown to be consistent with the approved BgRT treatment plan

Stanford University

11

RefleXion project timeline

- RefleXion X1 FDA clearance for IGRT- Mar 2020.
- Construction start – May 2020
- Physics Training – July 2020
- Machine delivery – Aug 3, 2020
- Installation – Aug, 2020
- Acceptance testing – Sep 2020
- Commissioning Start – Oct 2020
- Software upgrades – Dec 2020, Feb 2021, Apr 2021
- First patient imaged using RefleXion PET on the IDE study – Apr 2, 2021
- First patient treated using RefleXion – IMRT – May 17, 2021

Stanford University School of Medicine

Stanford University

12

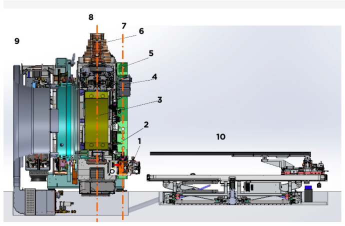
RefleXion BGRT X1 system overview

Stanford University School of Medicine

Stanford University

13

X1 Cross-section



Item	Description
1	kVCT X-ray Tube
2	EPID
3	PET Detectors
4	kVCY Detector
5	Collimation
6	6 MV Linac
7	kVCT Plane
8	Therapy Plane (Linac and PET)
9	Cooling System
10	Couch

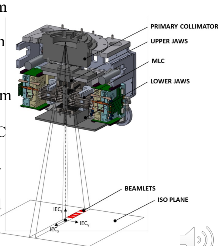
Stanford University School of Medicine

Stanford University

14

RefleXion X1 system overview

- RefleXion X1 is a 6MV-FFF linac mounted on the 85cm O-ring gantry rotating at 60 rpm
- Axial step and shoot delivery: couch advances in 2.1mm increments
- The modulation is achieved via 50 firing positions with 64 binary MLCs (6.25mm at 85cm SAD) with either 1cm or 2cm jaws
- Maximum field sizes: 1X40cm; 2x40cm; Maximum IEC Y target size = 50cm
- 3 delivery modes: IMRT (1 pass SUP to INF), SBRT (4 passes), BgRT (4 passes)
- Dose calculation: Collapsed Cone Convolution reported to tissue with a dose calculation grid: 2.1mm



Stanford University School of Medicine

Stanford University

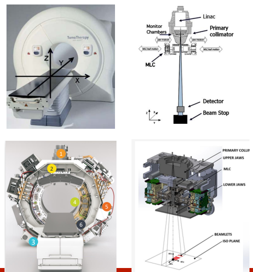
15

Reference: AAPM TG-148

QA for helical tomotherapy: Report of the AAPM Task Group 148[a)]

Katja M. Langen[b)]
Department of Radiation Oncology, M. D. Anderson Cancer Center Orlando, Orlando, Florida 32806

Helical tomotherapy is a relatively new modality with integrated treatment planning and delivery hardware for radiation therapy treatments. In view of the uniqueness of the hardware design of the helical tomotherapy unit and its implications in routine quality assurance, the Therapy Physics Committee of the American Association of Physicists in Medicine commissioned Task Group 148 to review this modality and make recommendations for quality assurance related methodologies. The specific objectives of this Task Group are: (a) To discuss quality assurance techniques, frequencies, and tolerances and (b) discuss dosimetric verification techniques applicable to this unit. This report summarizes the findings of the Task Group and aims to provide the practicing clinical medical physicist with the insight into the technology that is necessary to establish an independent and comprehensive quality assurance program for a helical tomotherapy unit. The emphasis of the report is to describe the rationale for the proposed QA program and to provide example tests that can be performed, drawing from the collective experience of the task group members and the published literature. It is expected that as technology continues to evolve, so will the test procedures that may be used in the future to perform comprehensive quality assurance for helical tomotherapy units. © *2010 American Association of Physicists in Medicine*. [DOI: 10.1118/1.3462971]



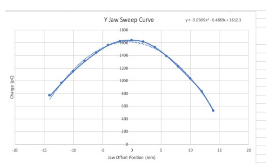
Stanford University

16

Source to Y-Jaw Alignment (V.B.1.a)

- Check that the source is centered in the collimated field by the y-jaws **< 0.3mm**
- Setup A17 ion chamber to the beam center to measure a narrow-slit beam (1 mm y-jaw opening) that is moved in 15 steps along the y-direction (14mm to +14mm)
- Plot the Output-Y jaw sweep curve: The peak offset is -0.64mm at the iso. Project back to the source location, the actual source misalignment is **0.049mm**

Exradin A17 (8cm)



Stanford University

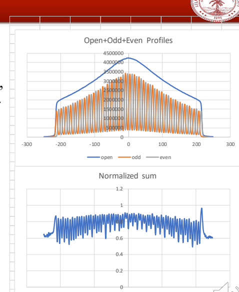
17

Source to X-alignment (V.B.1.b)

- Use the MLC tongue and groove (T&G) effect to check x-centering of the source. Out of focus < **2%**.
- Crossline water tank beam scan of fields: 40x2 open, all even-numbered MLC leaves opened, and all odd-numbered MLC leaves opened.
- Add odd and even profile -> T&G profile.

$$\% \text{ out-of-focus} = 100\% \times (1 - (a+b)/2).$$

- Out of focus = **0.66%**

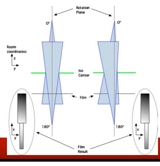


Stanford University

18

Y- jaw divergence and twist (V.B.1.c, V.B.1.d)

- To assure that the central transverse axis of the treatment beam intersects the rotational axis perpendicularly: Divergence at the iso < **0.5mm**
- To assure that the y-jaw be parallel to the plane of rotation: The jaw twist <**0.5°** .
- Position a film 21cm below the isocenter (Z=-21). Open right half of MLC leaves. Deliver the beam @ gantry 0 deg and 180 deg. Analyzed the film using RIT.
- The jaw divergence is **0.36mm <0.5mm**. The jaw twist is **0.03°** <**0.5°** .



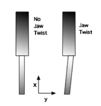
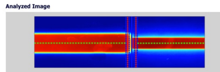


FIG. 12. Illustrations of jaw twist film results.

Analyzed Image



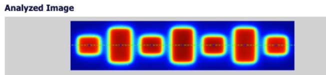
Stanford University

19

Treatment Field Centering (V.B.1.e)

- To check if all clinical treatment fields share a common center: agree within **0.5mm**
- Setup a film perpendicularly to the beam axis at an 85 cm source-to-film distance
- Gantry 0deg, Deliver different rectangular fields to the film and check the center variations = **0.03mm**

Analyzed Image



Analysis Results

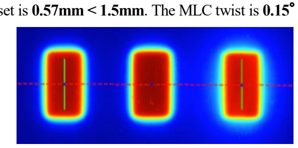
Measurement	Value
Max difference between centers of any two exposures (IEC Y)	0.03 mm
Field 1 center - average (IEC Y)(Object on the Left)	-0.01 mm
Field 2 center - average (IEC Y)	0.00 mm
Field 3 center - average (IEC Y)	-0.02 mm
Field 4 center - average (IEC Y)	0.01 mm
Field 5 center - average (IEC Y)	0.00 mm
Field 6 center - average (IEC Y)	0.02 mm
Field 7 center - average (IEC Y) (Object on the Right)	0.01 mm

Stanford University

20

MLC Alignment Test (V.B.1.f)

- To test: the lateral alignment of the MLC relative to the center of rotation < **1.5 mm**; and the MLC aligned parallel to the rotational plane < **0.5°** .
- A film is positioned at isocenter and two central MLC leaves (31 and 32) are opened in addition to two off-center leaves (26 and 27). The film is exposed with the gantry at 0° . The gantry is moved to 180° and only the two off-center leaves (26 and 27) are opened.
- The MLC offset is **0.57mm < 1.5mm**. The MLC twist is **0.15°** <**0.5°** .

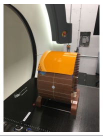


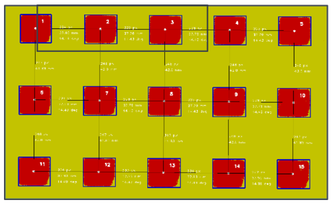
Stanford University

21

Synchronicity Test (V.B.1)

- Designed to test the accurate transmission of beam through the MLC to the isocenter within tolerance of angular deviation and offset (0.5 mm, 0.5 degrees at isocenter)

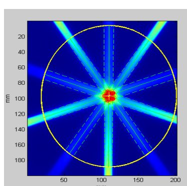


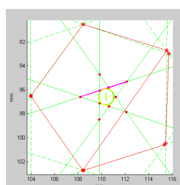


22

Starshot with gantry rotation

- Sandwich a film in between two 30x30x5cm^3 solid water blocks, deliver 1.25x2cm beam at the following angles: 0, 72, 144, 216, 288 degrees.
- The minimum tangent circle radius is **0.67mm < 1mm**.

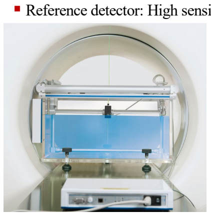




23

Equipment

- IBA Blue Phantom Helix 3D Water Scanning System
- Field detector: Edge Diode detector, Exradin A14 ion chamber, W2 1x1 scintillator.
- Reference detector: High sensitivity reference diode and Exradin A17 ion chamber

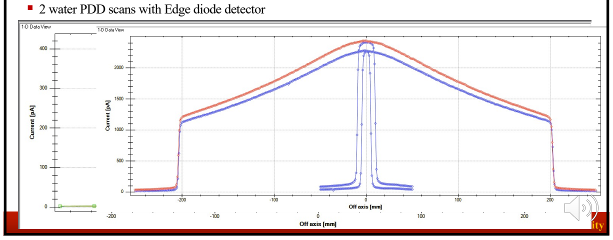


Beam parameters	
Beam quality (each slice width)	1% PDD_{10} or TMR^{20}_{10}
Transverse profile (each slice width)	1% average difference in field core
Longitudinal profiles (each slice width)	1% of slice width at FWHM
TG-51 calibration	1%

24

TPS Beam Input Measurements

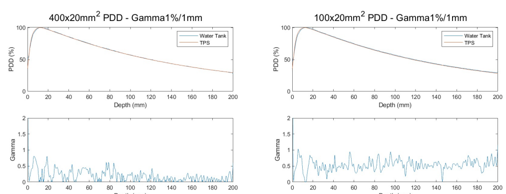
- 16 Air scans with Edge diode detector
- Tongue and groove leaf crossline X-profile scans: 8 single leaf scans/8 double leaf
- Open field profile X & Y scans: : 40x2 and 40x1cm open fields
- 2 water PDD scans with Edge diode detector



25

TPS Beam Input Measurements

- 2 water PDD scans with Edge diode detector
  - 40x2 and 10x2cm open fields

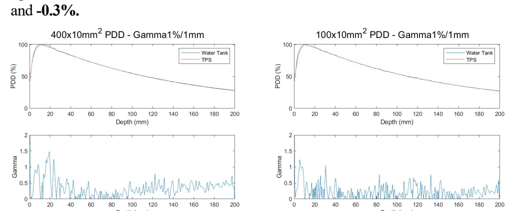


Stanford University

26

Measurement Vs. TPS: PDD

- PDD: TG-148 suggested the measured and TPS modeled PDD_{10} for each jaw width agrees **within 1%**. For the 40x2cm^2 field and 40x1cm^2 field, the differences are **0.2%** and **-0.3%.**



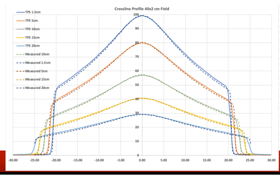
Stanford University

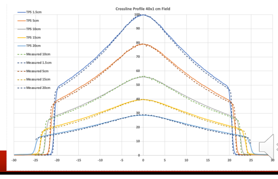
27

Measurement Vs. TPS: Transverse Profile

- TG-148 suggested transverse (crossline) profile difference in the field core (80% of the nominal field) is **within 1%** for each jaw width **.**

	Mean profile difference (%) in the field core				
Depth (cm)	1.5	5	10	15	20
40x2cm^2	0.75	0.67	0.47	0.47	0.37
40x1cm^2	0.93	0.96	0.72	0.66	0.38





28

Measurement Vs. TPS: Longitudinal Profile

- RefleXion suggested slice width (FWHM) between the measure and TPS modeled longitudinal profiles for each jaw width **<0.5mm**.

Y-jaw (mm)	Field size X (mm)	Depth (mm)	TPS FWHM (mm)	Measured FWHM (mm)
20mm	400.0	15.0	20.0	20.0
		50.0	21.1	20.9
		100.0	22.7	22.0
		150.0	23.8	23.4
		200.0	25.0	24.6
10mm	400.0	15.0	10.0	9.9
		50.0	10.5	10.4
		100.0	11.1	11.0
		150.0	11.9	11.7
		200.0	12.5	12.3

Stanford University

29

TPS Commissioning: dosimetric tests

Commissioning Plan

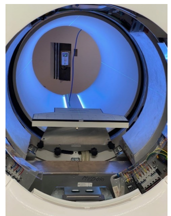
Dosimetric Tests	(Jaw x MLC)	Depth	SSD	Completed
Dose Profiles/PDDs in Water Phantom				
7.1 PDDs	(1 x 0.625, 1.25, 2.5, 5, 10, 20, 40); (2 x 0.625, 1.25, 2.5, 5, 10, 20, 40)		85	☑ Pass
7.2 Profiles	(1 x 0.625, 1.25, 2.5, 5, 10, 20, 40); (2 x 0.625, 1.25, 2.5, 5, 10, 20, 40)	1.5, 5, 10, 15, 20	85	☑ Pass
7.3 PDDs	(1 x 5, 10, 20, 40); (2 x 5, 10, 20, 40)		70	☑ Pass
7.4 Profiles	(1 x 5, 10, 20, 40); (2 x 5, 10, 20, 40)	1.5	70	☑ Pass
Point Doses in Water Phantom				
8.1 Output factors	(1 x 0.625, 1.25, 2.5, 3.75, 5, 7.5, 10, 15, 20, 30, 40); (2 x 0.625, 1.25, 2.5, 3.75, 5, 7.5, 10, 15, 20, 30, 40)	10	85	☑ Pass
8.2 Reference calibration condition check	(2, 10); 85 SSD	1.5	85	☑ Pass
8.3 70 cm SSD	(2, 10); 70 SSD	1.5	70	☑ Pass
ArcCheck				
9.1 Gantry 0, various field sizes	(1 x 1.25, 2.5, 5, 10, 20, 40); (2 x 1.25, 2.5, 5, 10, 20, 40)		85cm SAD	☑ Pass
9.2 TG-244 plans (Abdomen, Thorax, Lung, HN, Prostate, Anal)				☑ Pass
9.3 TG-119 Prostate, HN, Cshape, Brain met 1.5, 2 and 3cm				☑ Pass
9.4 3 HN plans				☑ Pass
9.5 3 prostate plans				☑ Pass
9.6 3 lung plans				☑ Pass
9.7 3 SBRT lung				☑ Pass
Solid water phantom	IC and film			
10.1 TG119 IMRT Prostate				☑ Pass
10.2 TG119 IMRT HN				☑ Pass
10.3 TG119 C shape easy and hard				☑ Pass
10.4 Brain met 1.5cm				☑ Pass
10.5 Brain met 2cm				☑ Pass
10.6 Brain met 3cm				☑ Pass
Solid water phantom with heterogeneous slabs	IC and film			
11.1 Lung and bone				☑ Pass
Motion management/heterogeneity - Lung Phantom				
12.1 Single target lung ITV-based plan - static				☑ Pass
12.2 Single target lung ITV-based plan - with motion				☑ Pass
Off-Axis Targets				
13.1 Brain E2E in CK Head phantom				☑ Pass
13.2 SBRT Mets in solid water phantom				☑ Pass
Beam interruption (E-2-E)				
14.1 Plan interrupted				☑ Pass
Couch transmission				
15.1 Couch transmission				☑ Pass

30

Reproducibility of dose output and symmetry with gantry angle

- Tomodose diode array was mounted to the gantry head perpendicular to the beam axis. Set field size to 40cm x 2cm and take measurement at the gantry positions of 0˚, 90˚, 180˚ and 270˚. The dose and symmetry vs. gantry angle variation **<2%**.

Deviation to average	Dose %	Symmetry X %	Symmetry Y %
Gantry 0	0.113	0.2	0.44
Gantry 90	0.213	0.13	0.27
Gantry 180	0.054	0.07	0.09
Gantry 270	0.154	0.00	0.08
Max Percent Error:	0.213	0.2	0.44

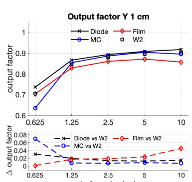


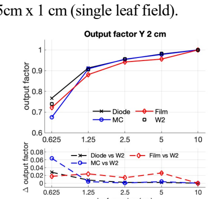
Stanford University

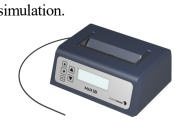
31

Relative Output Factor Measurement

- Detectors: Edge Diode, Exradin W2 1x1 scintillator, Film, MC simulation.
- Smallest field measured 0.625cm x 1 cm (single leaf field).







Stanford University

32

Absolute Beam Calibration

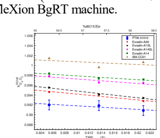
- AAPM TG-51 / IAEA TRS398. MV Beam calibration. (PDD10/TPR20,10)

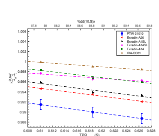
$$D_{w,Q_{ref}}^{f_{ref}} = M_{Q_{ref}}^{f_{ref}} \cdot N_{D,w,Q_0} \cdot k_{Q,Q_0}$$

- IAEA TRS483: small machine-specific reference (MSR) field calibration

$$D_{w,Q_{msr}}^{f_{msr}} = M_{Q_{msr}}^{f_{msr}} \cdot N_{D,w,Q_0} \cdot k_{Q_{msr},Q_0}^{f_{msr},f_{ref}}$$

  - *Introduced* the quality factor to correct for the differences between the conventional reference field fref of quality Q0 (Co-60) and the MSR field fmsr of quality Q(msr). **>4cm**.
- MC simulation: (Mirzakhanian et al 2020) IAEA-AAPM TRS-483-based reference dosimetry of the new RefleXion BgRT machine.
-



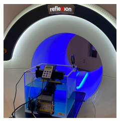


Stanford University

33

Absolute Beam Calibration

- Exradin A14 ion chamber:
  - **Collecting Volume** 0.015 cm3
  - **Collector Diameter** 0.3 mm
  - **Collector Diameter** 0.3 mm



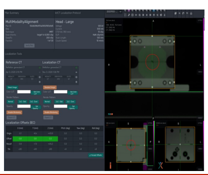
- MSR field: 10x 3cm^2:
- Reference Clinical Field A: 10 x 2cm^2.
- Calibrate machine output to **1cGy/MU** for Clinical Field at Nominal dmax = 1.5cm.
- Considering PDD=0.575, and OF= 0.952
- Dcal @ At 10cm Depth of MSR field expected value **0.6044cGy/MU**.

Stanford University

34

Laser Vs. kVCT Vs. Radiation Center

- Setup UMA phantom to laser. Perform kVCT scan and 3D-3D match. The offset laser to kVCT is: X = 0.8mm, Y = 0.8mm Z = -0.3mm.
- Re-Setup UMA phantom to laser. Move the couch sup 1m. Take 0 and 90 deg MV image pair. The offset laser to radiation center is: X = 0.8mm, Y = -0.2mm Z = -0.2mm.



MV image at Gantry 0 degree.

MV image at Gantry 90 degree.

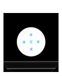
Stanford University

35

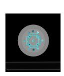
kVCT Commissioning

- kVCT scans of Catphan504 in different dose and couch speed: Comparable to simulation CT.

ROI	CT# Uniformity	Image Noise
1	14.52	9.83
2	14.74	6.16
3	15.56	7.05
4	15.15	6.69
5	14.95	6.61



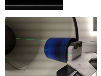
Material	Measured HU
Air	-960
PMP	-172
LDPE	-86
Polystyrene	-30
Acrylic	127
Delrin	343
Teflon	923



F50 (lp/mm)	F40 (lp/mm)	F30 (lp/mm)
0.480	0.595	0.691

Contrast level	Lowest detected (mm)	Percent detected (%)
0.5	5.0	66.7
1.0	6.0	55.6

Geometric Distortion =0.12mm.
Slice thickness =1.38 (vendor's tolerance: 1.25mm ± 0.5mm)
Low contrast visibility: 0.734.



Stanford University

36

kVCT Tube Votage, Current and Imaging Dose

- RTI MAS-2 and Piranha are used to verify the mA and voltage
- The CTDI phantom was set up with a Standard Imaging A101 pencil chamber with a protocol of 120kVp, 150mAs and 1.25mm slice thickness.

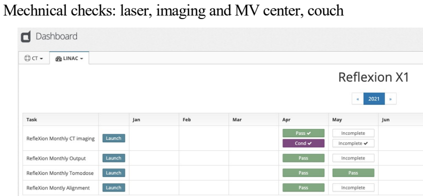
- The voltage and current are **within 5%** of the setting of 120 kV and 150 mA.
- CTDI100(center) = 3cGy.
- CTDI periphery =3.6cGy.
- The CTDIw = **1.4cGy** (body) and **3cGy** (head)

Stanford University

37

Monthly QA

- kVCT using normal and fast couch speed – Catphan504
- Output calibration / Beam Quality: TG51 in solid water or 1D water tank
- Tomodose measurement for profile constancy checks
- Mechnical checks: laser, imaging and MV center, couch

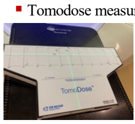


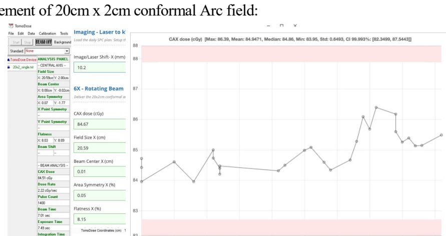
Stanford University

38

Daily QA

- Tomodose measurement of 20cm x 2cm conformal Arc field:



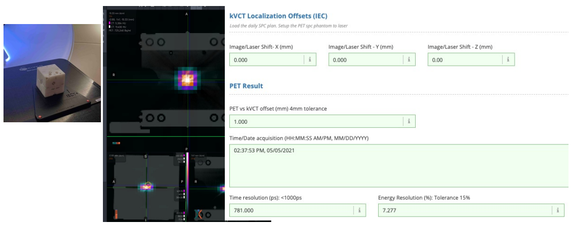


Stanford University

39

Daily PET QA

- UMA phantom with reference source inserted



Stanford University

40

Summary

- Reviewed PET imaging and PET based BGRT
- Introduced Stanford IDE study
- Overviewed RefleXion X1 system
- Presented reults of RefleXion X1's commissioning and QA

41

Stanford University

41

Acknowledge

- Stanford Team
  - Murat Surucu
  - Nataliya Kovalchuk
  - Cynthia F. Chuang
  - Karl Bush
  - Residents and etc
- RefleXion Team
  - Daniel Zaks
  - John White
  - And etc

Stanford University

42