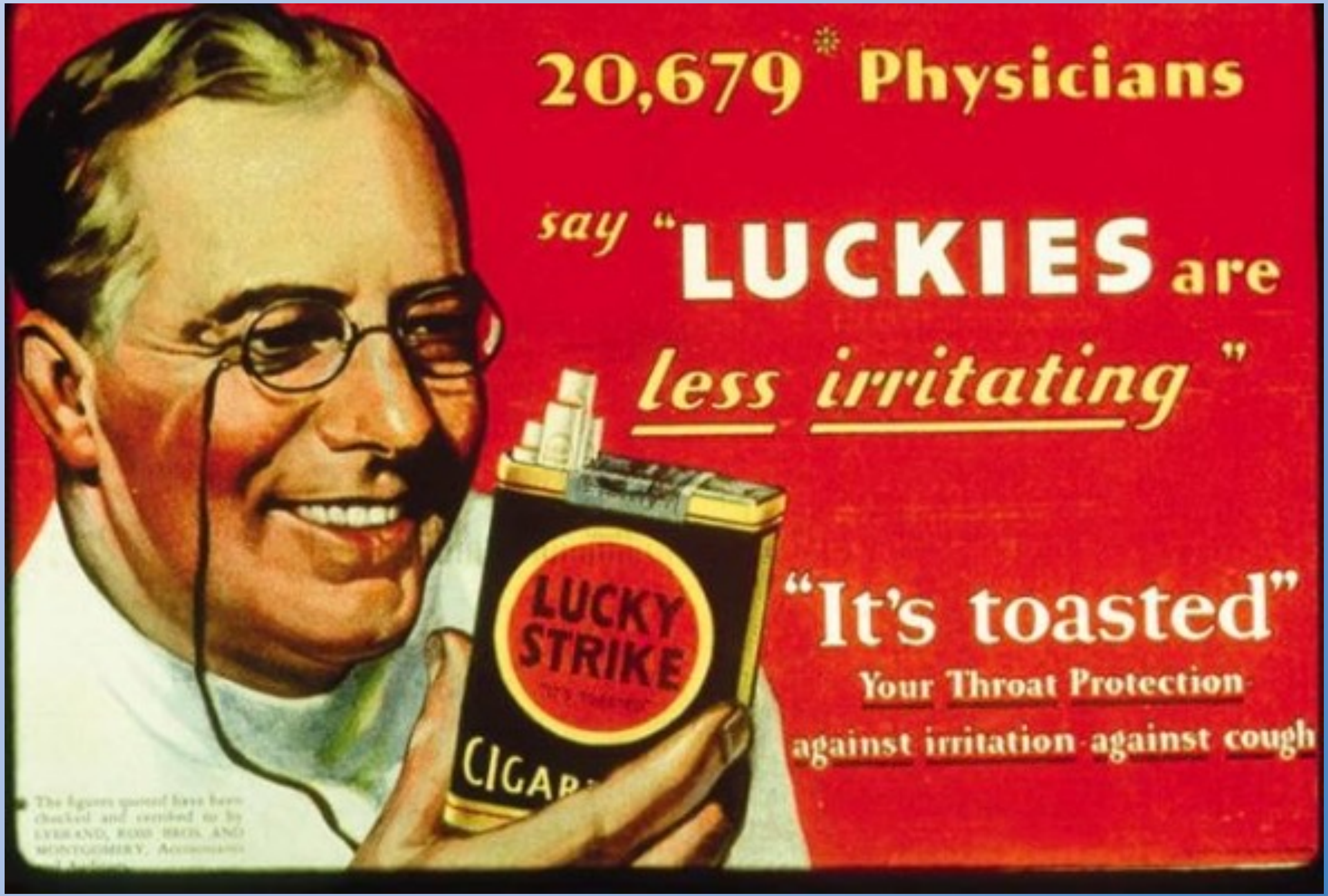
Novel Innovations in Proton Therapy

Tim R. Williams, MD FACR FASTRO

Medical Director

South Florida Proton Therapy Institute



Conflicts: None


The Economist
The state of the race
Afghanistan votes
Reinventing McDonald's
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Beating cancer
The new frontier of molecular medicine


TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.
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BusinessWeek
DRUGS GET SMART
How new medicines will more effectively target what ails you —and help prevent another Vioxx


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NEW DIGITAL TELEVISIONS
Forbes
She was 18 and dying of lung cancer. This pill saved her life—but failed to help almost everyone else. Should it be approved?
MIRACLE PILL
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COMPANIES THAT KNOW EVERYTHING ABOUT YOU
THE RICHEST PEOPLE IN CHINA
DIVIDEND HEIST: WHEN COMPANIES WANT THEM BACK


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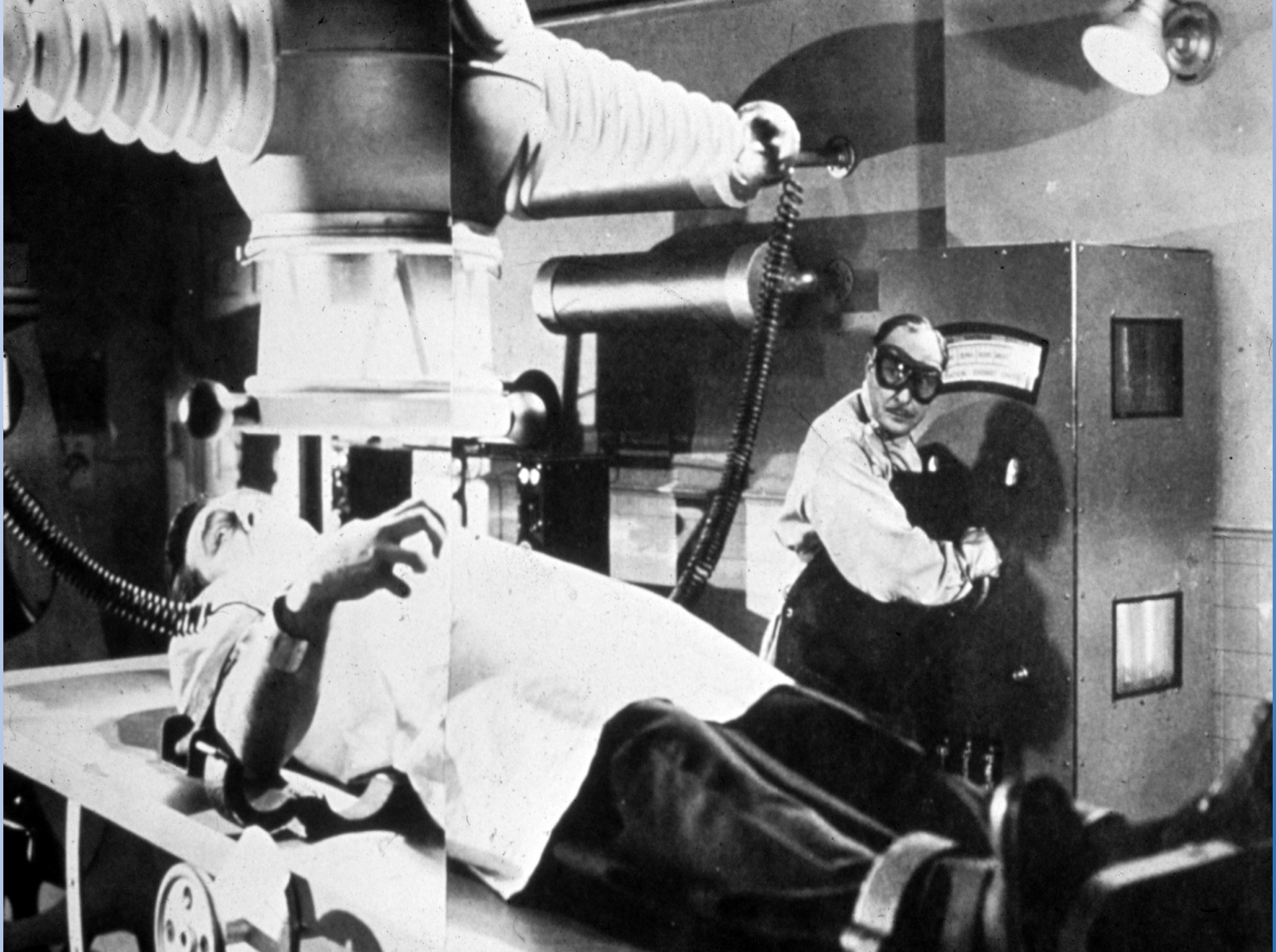
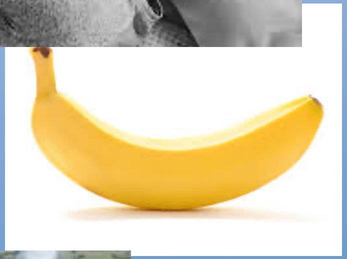
MUTUAL FUNDS FOR THE LONG HAUL
U.S.News & WORLD REPORT
THIS DRUG'S FOR YOU
NEW TARGETED MEDICINES PROMISE BREAKTHROUGH CURES



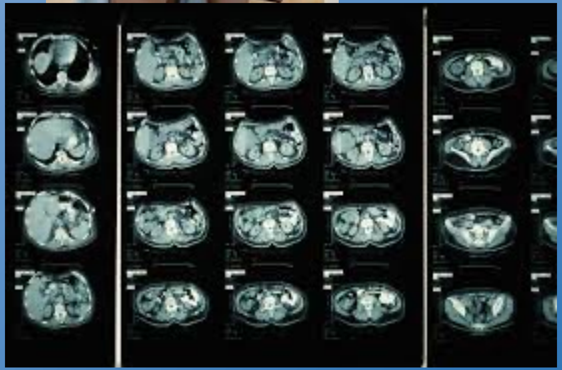

VARIAN

Activity	Dose (rads)
Average background radiation dose, typical day	**0.001**
Sleeping next to someone, 8 hours	0.000005
Eating one banana	0.00001
Living within 50 miles of a nuclear power plant for a year	0.00001
Living within 50 miles of a coal-fired power plant for a year	0.00003
Dental x-ray	0.0005
Airline flight from New York to Los Angeles	0.004

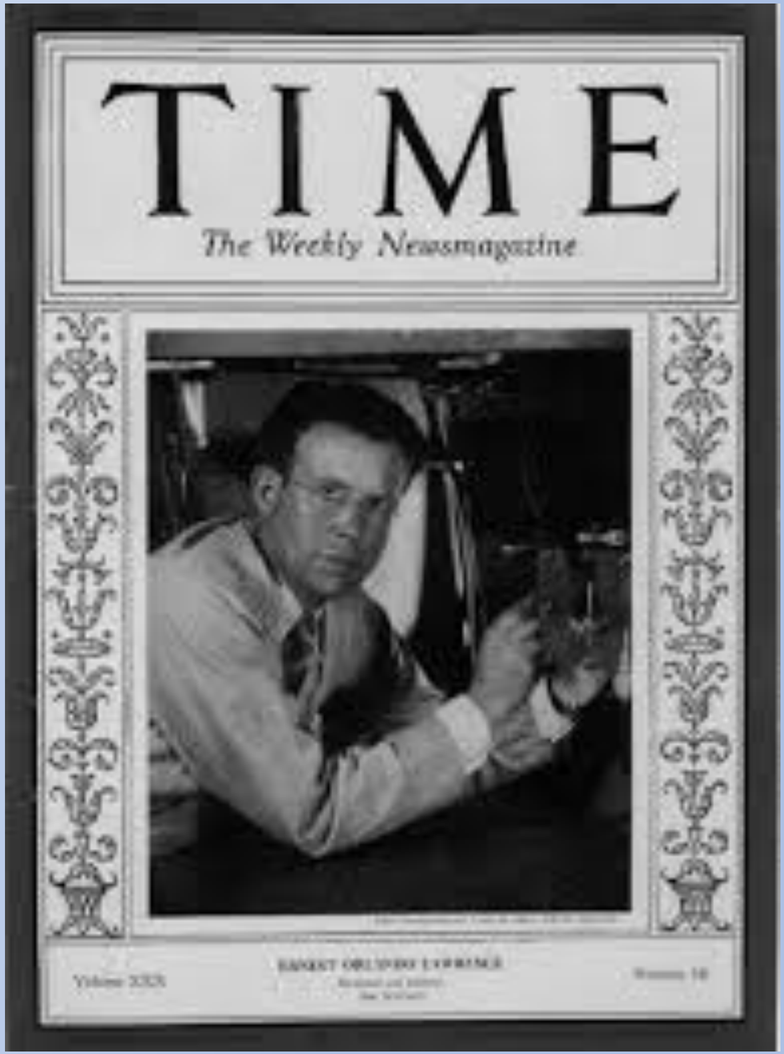



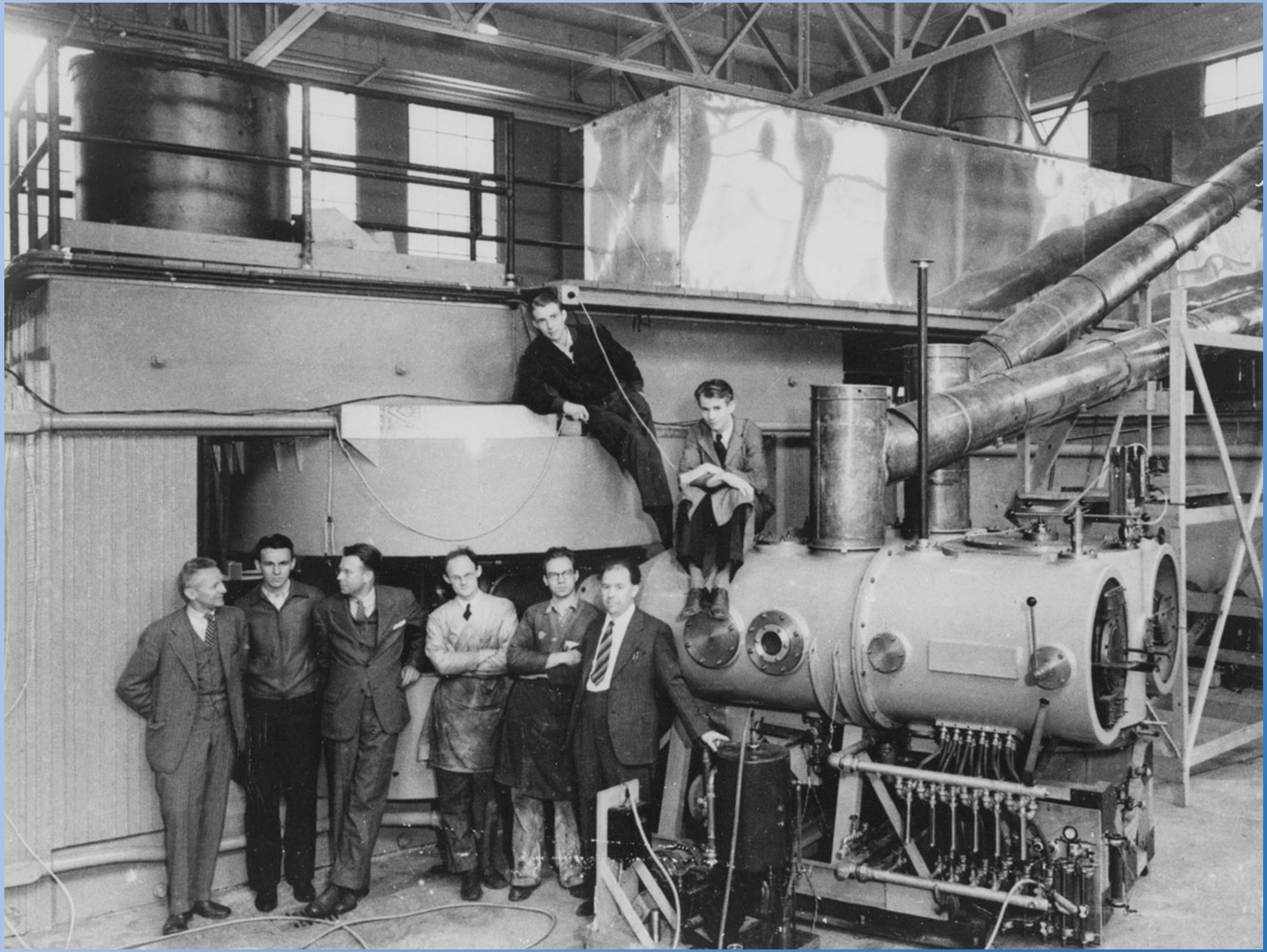

Activity	Dose (rads)
Average background radiation dose, typical day	**0.001**
Living in a concrete building for a year	0.007
Yearly dose from naturally occurring P-32 in your body	0.039
Screening mammogram	0.04
CT Brain	0.2
CT Chest	0.7
Dose from one hour exposure on the grounds at Chernobyl in 2010	0.6






Activity	Dose (rads)
Average background radiation dose, typical day	**0.001**
Maximum yearly dose allowed for US radiation workers	5.0
Lowest annual dose clearly related to increased cancer risk	100
Typical localized daily dose in radiation oncology	200
Whole-body dose causing non-fatal radiation poisoning	200
Whole body single fraction fatal dose	400
Ten minutes next to reactor core, Chernobyl after explosion and meltdown	5000


TIME
The Weekly Newsmagazine

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varian R.F.Deinstall./Pack.
AP: 1.075
C16
Project: 2059
Delray, Florida
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SPECIALIZED
INC.
Heavy & Specialized Transportation
169
OVERSIZE LOAD


BEYEL


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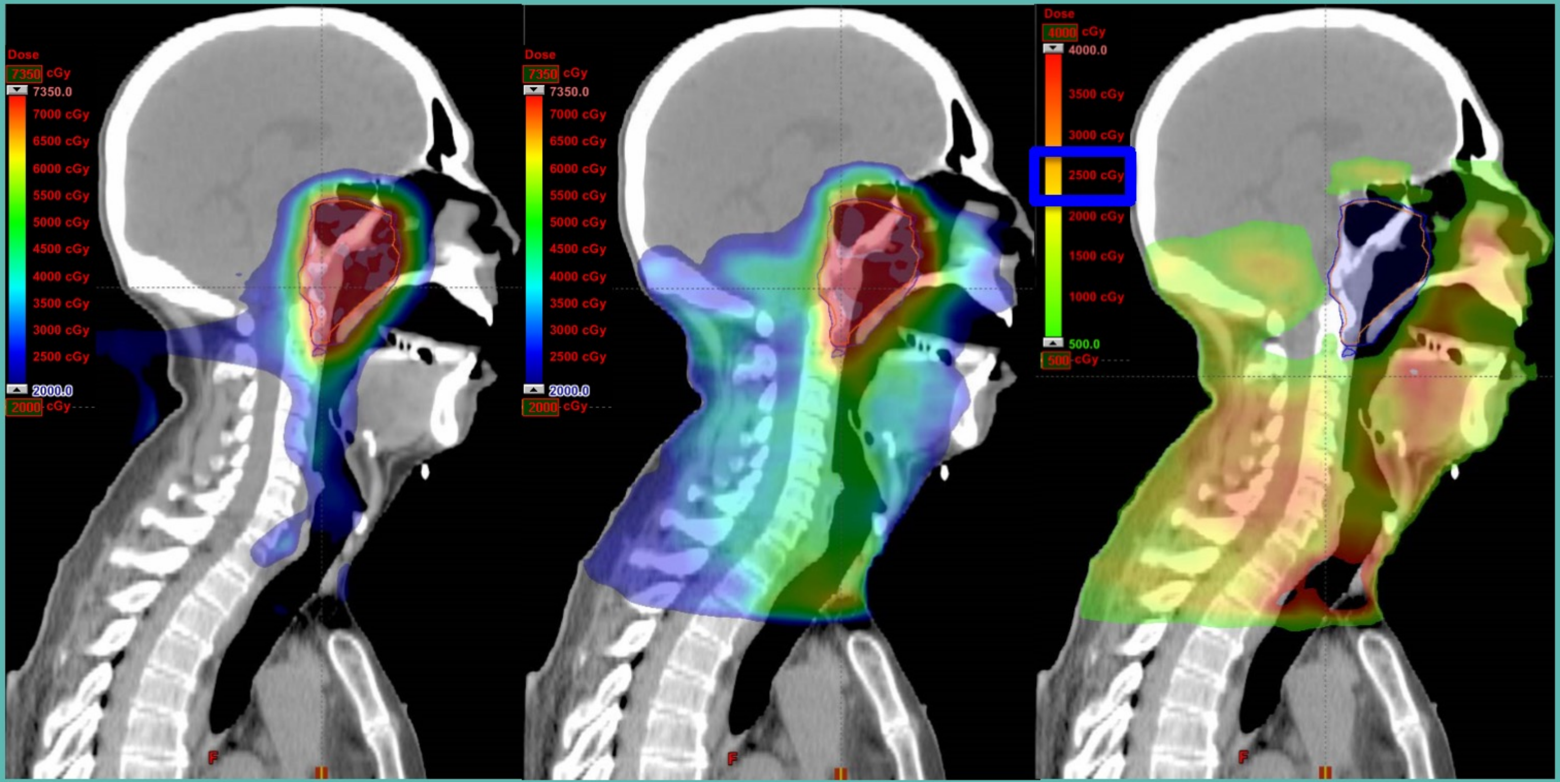
ELIMINATION OF UNNECESSARY RADIATION

Proton Therapy (IMPT) | **X-Ray** Therapy (IMRT) | Added Radiation w/ IMRT (X-Rays)

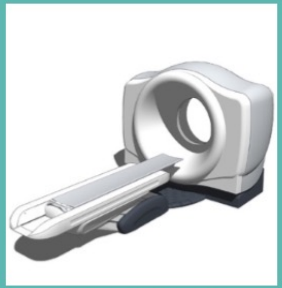


*25 Gy (25 Sv) of Unnecessary Radiation

Goughenour 2017

ELIMINATION OF UNNECESSARY RADIATION

*25 Gy (25 Sv) of Unnecessary Radiation =

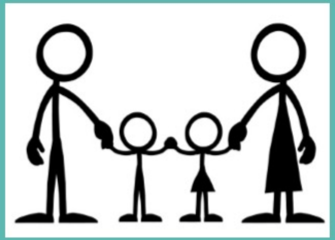


12,500

H&N CTs
(2 mSv)

5,000,000

Intraoral X-Rays
(0.002 mSv)

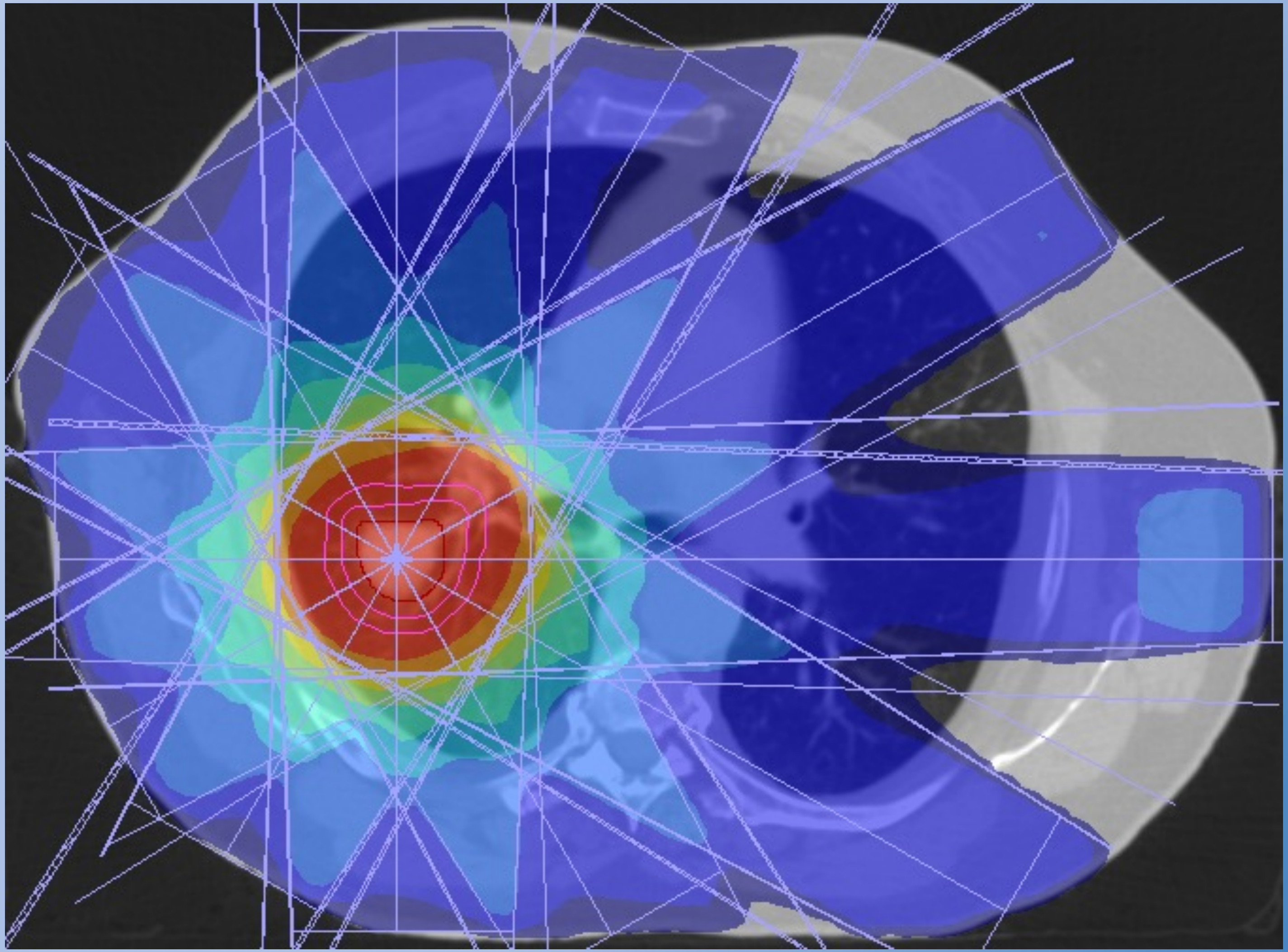


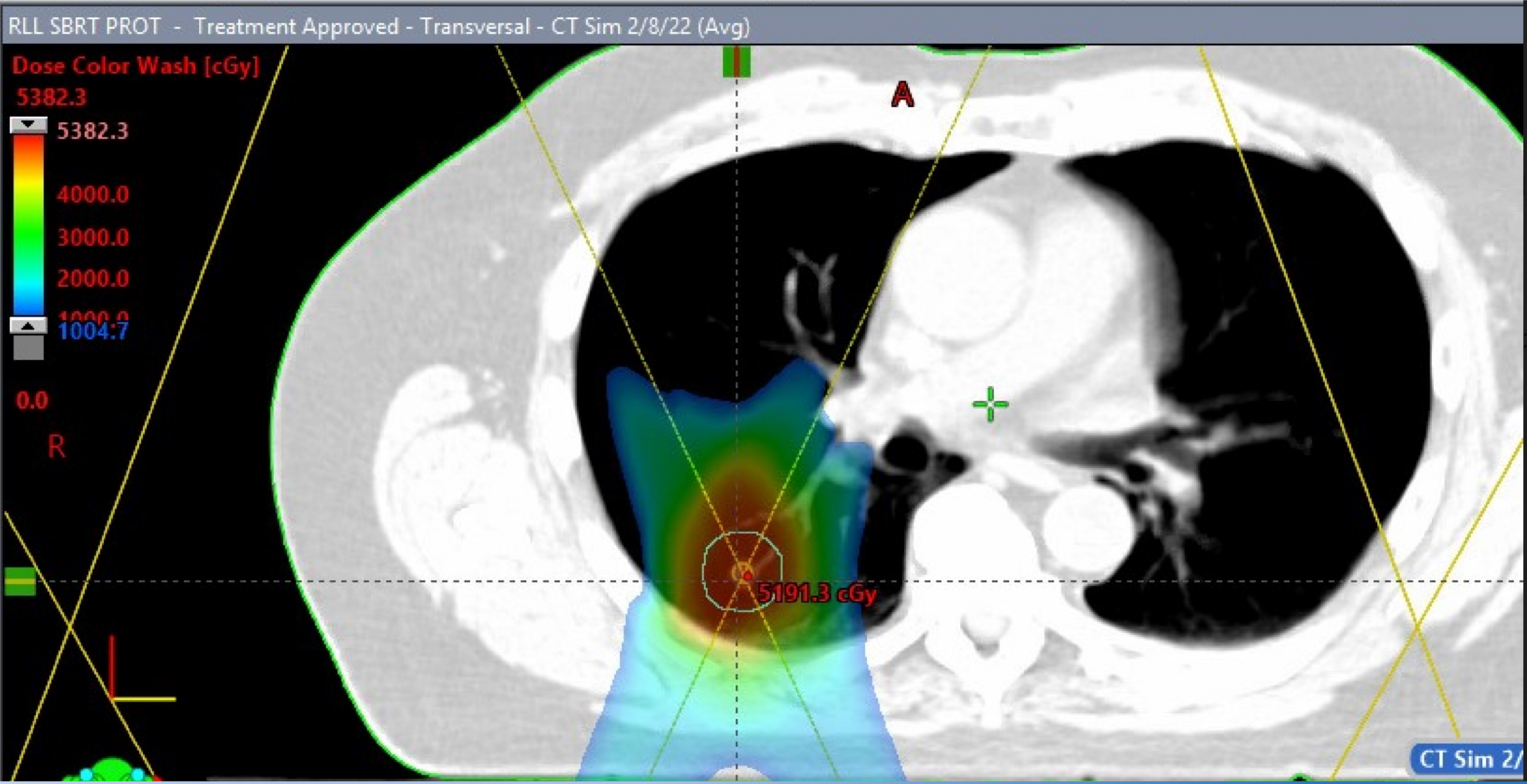
25,000x

General Public
Annual Limit (1.0 mSv)

Added Radiation w/
IMRT (X-Rays)

Solitary Lung Nodule: Linac Based SBRT





RLL SBRT PROT - Treatment Approved - Transversal - CT Sim 2/8/22 (Avg)
Dose Color Wash [cGy]
5382.3
5382.3
4000.0
3000.0
2000.0
1004.7
0.0
R
A
5191.3 cGy
CT Sim 2/

Early Findings on Toxicity of Proton Beam Therapy With Concurrent Chemotherapy for Nonsmall Cell Lung Cancer

Samir Sejpal, MD[1]; Ritsuko Komaki, MD[1]; Anne Tsao, MD[2]; Joe Y. Chang, MD, PhD[1]; Zhongxing Liao, MD[1]; Xiong Wei, MD[1]; Pamela K. Allen, PhD[1]; Charles Lu, MD[2]; Michael Gillin, PhD[3]; and James D Cox, MD[1]

Table 2. Acute Nonhematologic Toxicity After Photon Versus Proton Therapy for Nonsmall Cell Lung Cancer

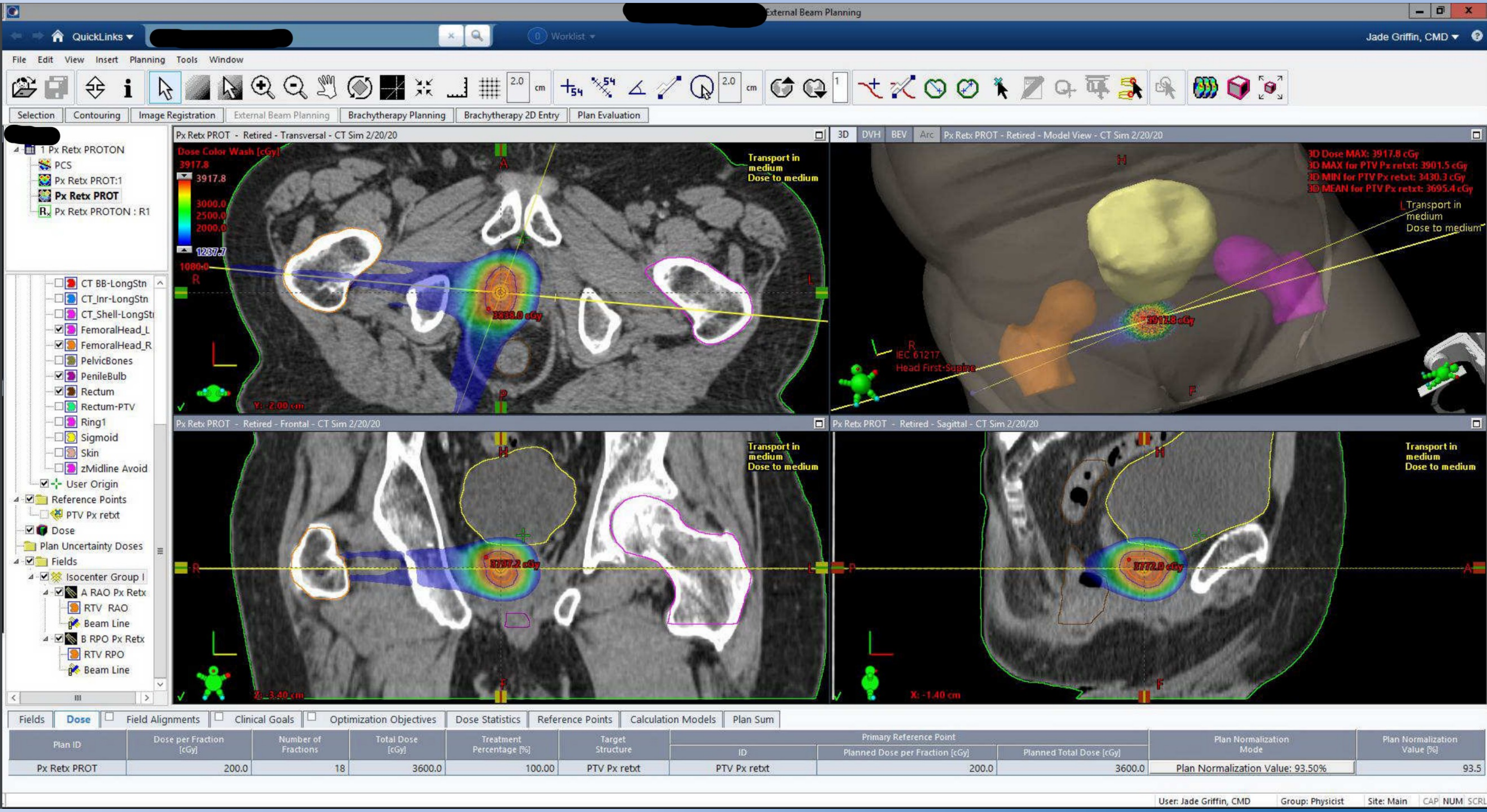
Toxicity and Treatment	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Unknown	*P*
Esophagitis								<.001
Chemotherapy+3D-CRT	3 (4)	25 (34)	33 (45)	13 (18)	0	0	0	
Chemotherapy+IMRT	4 (6)	9 (14)	24 (36)	26 (39)	3 (4.5)	0	0	
Chemotherapy+PBT	13 (21)	22 (35.5)	24 (39)	3 (5)	0	0	0	
Pneumonitis								<.001
Chemotherapy+3D-CRT	23 (31)	9 (12)	20 (27)	22 (30)	0	0	0	
Chemotherapy+IMRT	19 (29)	24 (36)	17 (26)	4 (6)	0	2 (3)	0	
Chemotherapy+PBT	13 (21)	30 (48)	18 (29)	1 (2)	0	0	0	
Dermatitis								<.001
Chemotherapy+3D-CRT	6 (8)	54 (73)	9 (12)	5 (7)	0	0	0	
Chemotherapy+IMRT	5 (8)	33 (50)	17 (26)	11 (17)	0	0	0	
Chemotherapy+PBT	2 (3)	22 (35.5)	23 (37)	15 (24)	0	0	0	
Fatigue								.002
Chemotherapy+3D-CRT	0	20 (24)	28 (34)	24 (29)	2 (2)	0	0	
Chemotherapy+IMRT	12 (18)	16 (24)	27 (41)	10 (15)	1 (1.5)	0	0	
Chemotherapy+PBT	3 (5)	12 (19)	32 (52)	12 (19)	3 (5)	0	0	

All data are expressed as No. of patients (%).
3D-CRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy.

Retreatment of Locally Relapsed Prostate Cancer (Early Analysis)

- 35 Patients
- Previous full dose radiation
- Treated between 11/2019 and 4/2022
- Prior RT between 2002 and 2020
- Median follow-up 9 months (range 2-27 months)

- Minimal acute toxicity
- Too soon for late toxicity
- 11/34 PSA <1.0
- 15/35 PSA <2.0
- 9/35 PSA increase
- 3/35 Patients died, all of co-morbidities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QuickLinks
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Image Registration
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Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
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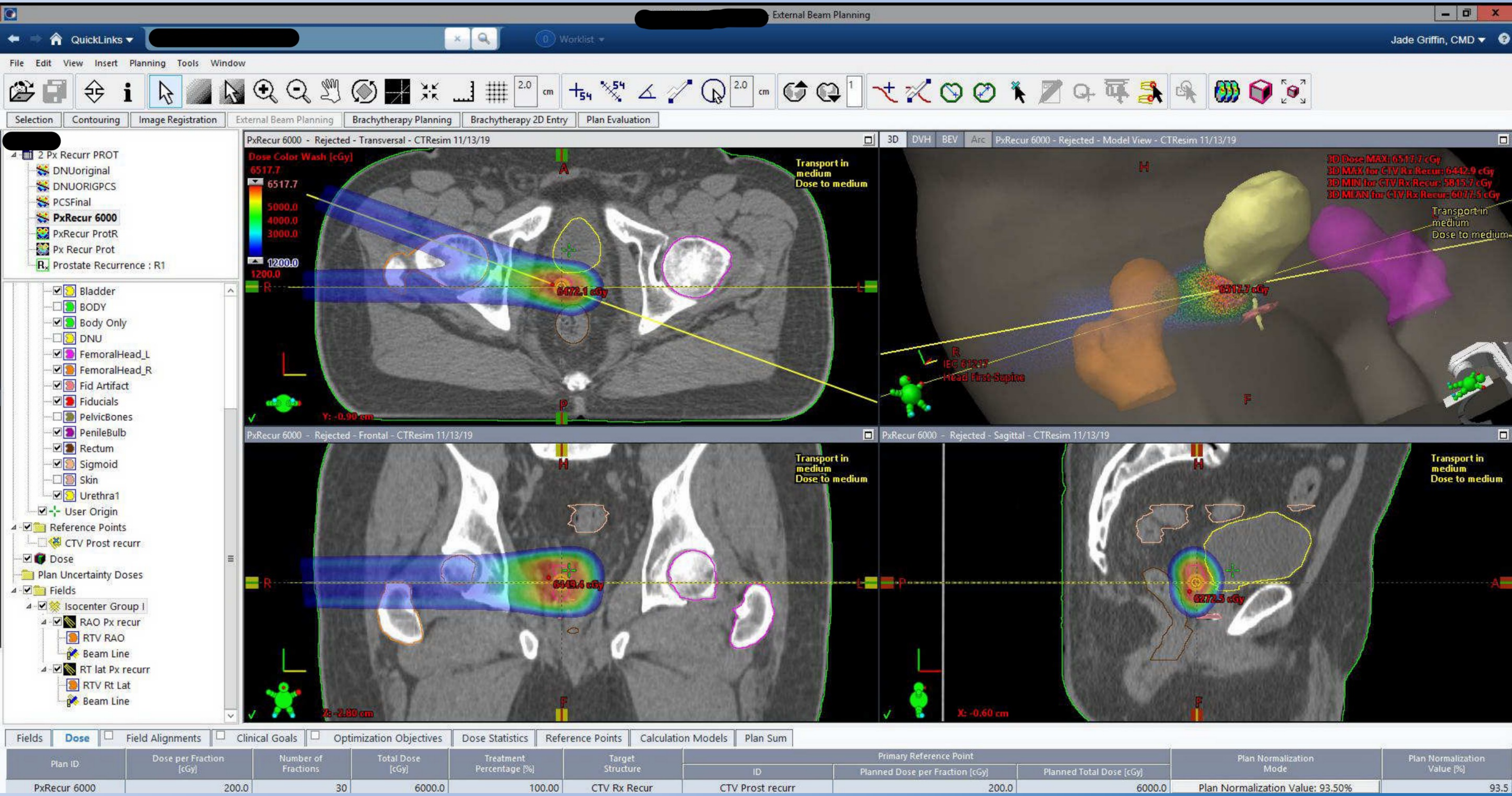
1 Px Retx PROTON
PCS
Px Retx PROT:1
Px Retx PROT
Px Retx PROTON : R1
CT BB-LongStn
CT_Inr-LongStn
CT_Shell-LongSt
FemoralHead_L
FemoralHead_R
PelvicBones
PenileBulb
Rectum
Rectum-PTV
Ring1
Sigmoid
Skin
zMidline Avoid
User Origin
Reference Points
PTV Px retxt
Dose
Plan Uncertainty Doses
Fields
Isocenter Group I
A RAO Px Retx
RTV RAO
Beam Line
B RPO Px Retx
RTV RPO
Beam Line
Px Retx PROT - Retired - Transversal - CT Sim 2/20/20
Dose Color Wash [cGy]
3917.8
3917.8
3000.0
2500.0
2000.0
1237.7
1080.0
3838.0 cGy
Transport in medium
Dose to medium
Y: -2.00 cm
3D
DVH
BEV
Arc
Px Retx PROT - Retired - Model View - CT Sim 2/20/20
3D Dose MAX: 3917.8 cGy
3D MAX for PTV Px retxt: 3901.5 cGy
3D MIN for PTV Px retxt: 3430.3 cGy
3D MEAN for PTV Px retxt: 3695.4 cGy
Transport in medium
Dose to medium
3917.8 cGy
IEC 61217
Head First-Supine
Px Retx PROT - Retired - Frontal - CT Sim 2/20/20
Transport in medium
Dose to medium
3797.2 cGy
Z: -3.40 cm
Px Retx PROT - Retired - Sagittal - CT Sim 2/20/20
Transport in medium
Dose to medium
3772.0 cGy
X: -1.40 cm
Fields
Dose
Field Alignments
Clinical Goals
Optimization Objectives
Dose Statistics
Reference Points
Calculation Models
Plan Sum
Plan ID | Dose per Fraction [cGy] | Number of Fractions | Total Dose [cGy] | Treatment Percentage [%] | Target Structure | Primary Reference Point ID | Planned Dose per Fraction [cGy] | Planned Total Dose [cGy] | Plan Normalization Mode | Plan Normalization Value [%]
Px Retx PROT | 200.0 | 18 | 3600.0 | 100.00 | PTV Px retxt | PTV Px retxt | 200.0 | 3600.0 | Plan Normalization Value: 93.50% | 93.5
User: Jade Griffin, CMD
Group: Physicist
Site: Main
CAP NUM SCRL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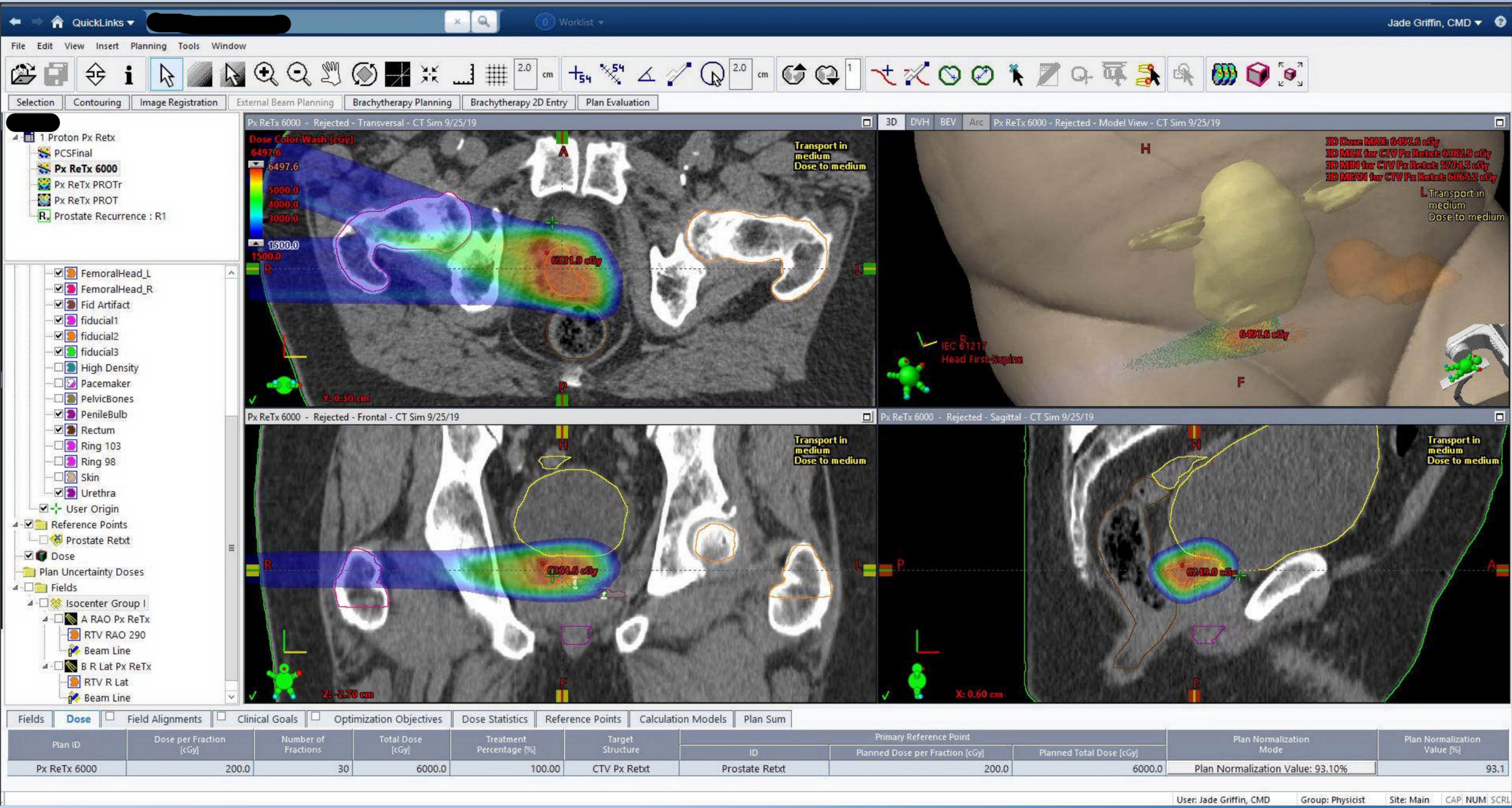
2 Px Recurr PROT
DNUoriginal
DNUORIGPCS
PCSFinal
PxRecur 6000
PxRecur ProtR
Px Recur Prot
Prostate Recurrence : R1
Bladder
BODY
Body Only
DNU
FemoralHead_L
FemoralHead_R
Fid Artifact
Fiducials
PelvicBones
PenileBulb
Rectum
Sigmoid
Skin
Urethra1
User Origin
Reference Points
CTV Prost recurr
Dose
Plan Uncertainty Doses
Fields
Isocenter Group I
RAO Px recur
RTV RAO
Beam Line
RT lat Px recurr
RTV Rt Lat
Beam Line
PxRecur 6000 - Rejected - Transversal - CTResim 11/13/19
Dose Color Wash [cGy]
6517.7
5000.0
4000.0
3000.0
1200.0
Transport in medium Dose to medium
6472.1 cGy
3D DVH BEV Arc PxRecur 6000 - Rejected - Model View - CTResim 11/13/19
3D Dose MAX: 6517.7 cGy
3D MAX for CTV Rx Recur: 6442.9 cGy
3D MIN for CTV Rx Recur: 5815.7 cGy
3D MEAN for CTV Rx Recur: 6077.5 cGy
IEC 61217
Head First-Supine
PxRecur 6000 - Rejected - Frontal - CTResim 11/13/19
6449.4 cGy
PxRecur 6000 - Rejected - Sagittal - CTResim 11/13/19
6272.5 cGy
X: -0.60 cm
Fields Dose Field Alignments Clinical Goals Optimization Objectives Dose Statistics Reference Points Calculation Models Plan Sum
Plan ID | Dose per Fraction [cGy] | Number of Fractions | Total Dose [cGy] | Treatment Percentage [%] | Target Structure | Primary Reference Point ID | Planned Dose per Fraction [cGy] | Planned Total Dose [cGy] | Plan Normalization Mode | Plan Normalization Value [%]
PxRecur 6000 | 200.0 | 30 | 6000.0 | 100.00 | CTV Rx Recur | CTV Prost recurr | 200.0 | 6000.0 | Plan Normalization Value: 93.50% | 93.5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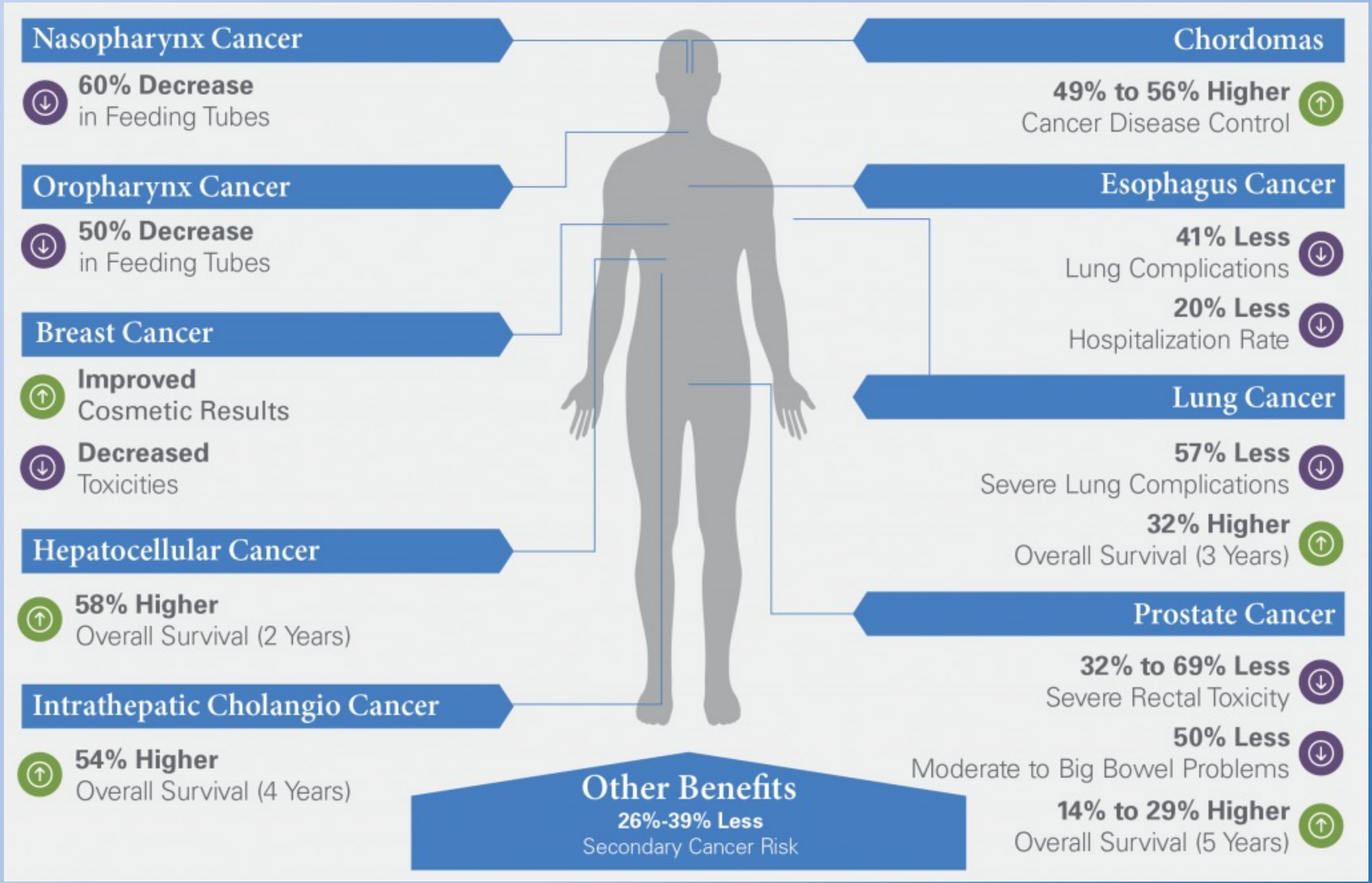
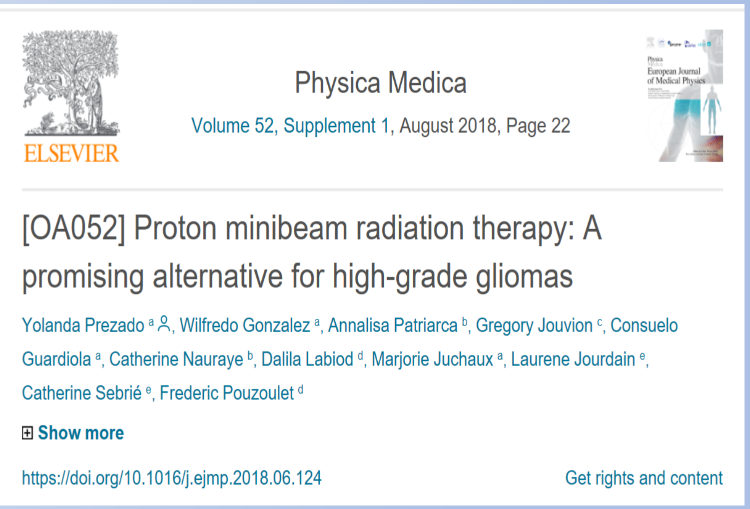
Contouring
Image Registration
External Beam Planning
Brachytherapy Planning
Brachytherapy 2D Entry
Plan Evaluation
[redacted]
1 Proton Px Retx
PCSFinal
Px ReTx 6000
Px ReTx PROTr
Px ReTx PROT
Prostate Recurrence : R1
FemoralHead_L
FemoralHead_R
Fid Artifact
fiducial1
fiducial2
fiducial3
High Density
Pacemaker
PelvicBones
PenileBulb
Rectum
Ring 103
Ring 98
Skin
Urethra
User Origin
Reference Points
Prostate Retxt
Dose
Plan Uncertainty Doses
Fields
Isocenter Group I
A RAO Px ReTx
RTV RAO 290
Beam Line
B R Lat Px ReTx
RTV R Lat
Beam Line
Px ReTx 6000 - Rejected - Transversal - CT Sim 9/25/19
Dose Color Wash [cGy]
6497.6
5000.0
4000.0
3000.0
1500.0
Transport in medium
Dose to medium
Y: 0.30 cm
3D DVH BEV Arc
Px ReTx 6000 - Rejected - Model View - CT Sim 9/25/19
3D Dose MAX: 6497.6 cGy
3D MAX for CTV Px Retxt: 6382.9 cGy
3D MIN for CTV Px Retxt: 5274.5 cGy
3D MEAN for CTV Px Retxt: 6063.2 cGy
Transport in medium
Dose to medium
IEC 61217
Head First-Supine
Px ReTx 6000 - Rejected - Frontal - CT Sim 9/25/19
Transport in medium
Dose to medium
Z: -2.70 cm
Px ReTx 6000 - Rejected - Sagittal - CT Sim 9/25/19
Transport in medium
Dose to medium
X: 0.60 cm
Fields
Dose
Field Alignments
Clinical Goals
Optimization Objectives
Dose Statistics
Reference Points
Calculation Models
Plan Sum
Plan ID | Dose per Fraction [cGy] | Number of Fractions | Total Dose [cGy] | Treatment Percentage [%] | Target Structure | Primary Reference Point: ID | Planned Dose per Fraction [cGy] | Planned Total Dose [cGy] | Plan Normalization Mode | Plan Normalization Value [%]
Px ReTx 6000 | 200.0 | 30 | 6000.0 | 100.00 | CTV Px Retxt | Prostate Retxt | 200.0 | 6000.0 | Plan Normalization Value: 93.10% | 93.1
User: Jade Griffin, CMD
Group: Physicist
Site: Main
CAP NUM SCRL



Nasopharynx Cancer
60% Decrease
in Feeding Tubes
Oropharynx Cancer
50% Decrease
in Feeding Tubes
Breast Cancer
Improved
Cosmetic Results
Decreased
Toxicities
Hepatocellular Cancer
58% Higher
Overall Survival (2 Years)
Intrathepatic Cholangio Cancer
54% Higher
Overall Survival (4 Years)
Chordomas
49% to 56% Higher
Cancer Disease Control
Esophagus Cancer
41% Less
Lung Complications
20% Less
Hospitalization Rate
Lung Cancer
57% Less
Severe Lung Complications
32% Higher
Overall Survival (3 Years)
Prostate Cancer
32% to 69% Less
Severe Rectal Toxicity
50% Less
Moderate to Big Bowel Problems
14% to 29% Higher
Overall Survival (5 Years)
Other Benefits
26%-39% Less
Secondary Cancer Risk



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Physica Medica

Volume 52, Supplement 1, August 2018, Page 22

[OA052] Proton minibeam radiation therapy: A promising alternative for high-grade gliomas

Yolanda Prezado [a], Wilfredo Gonzalez [a], Annalisa Patriarca [b], Gregory Jouvion [c], Consuelo Guardiola [a], Catherine Nauraye [b], Dalila Labiod [d], Marjorie Juchaux [a], Laurene Jourdain [e], Catherine Sebrié [e], Frederic Pouzoulet [d]

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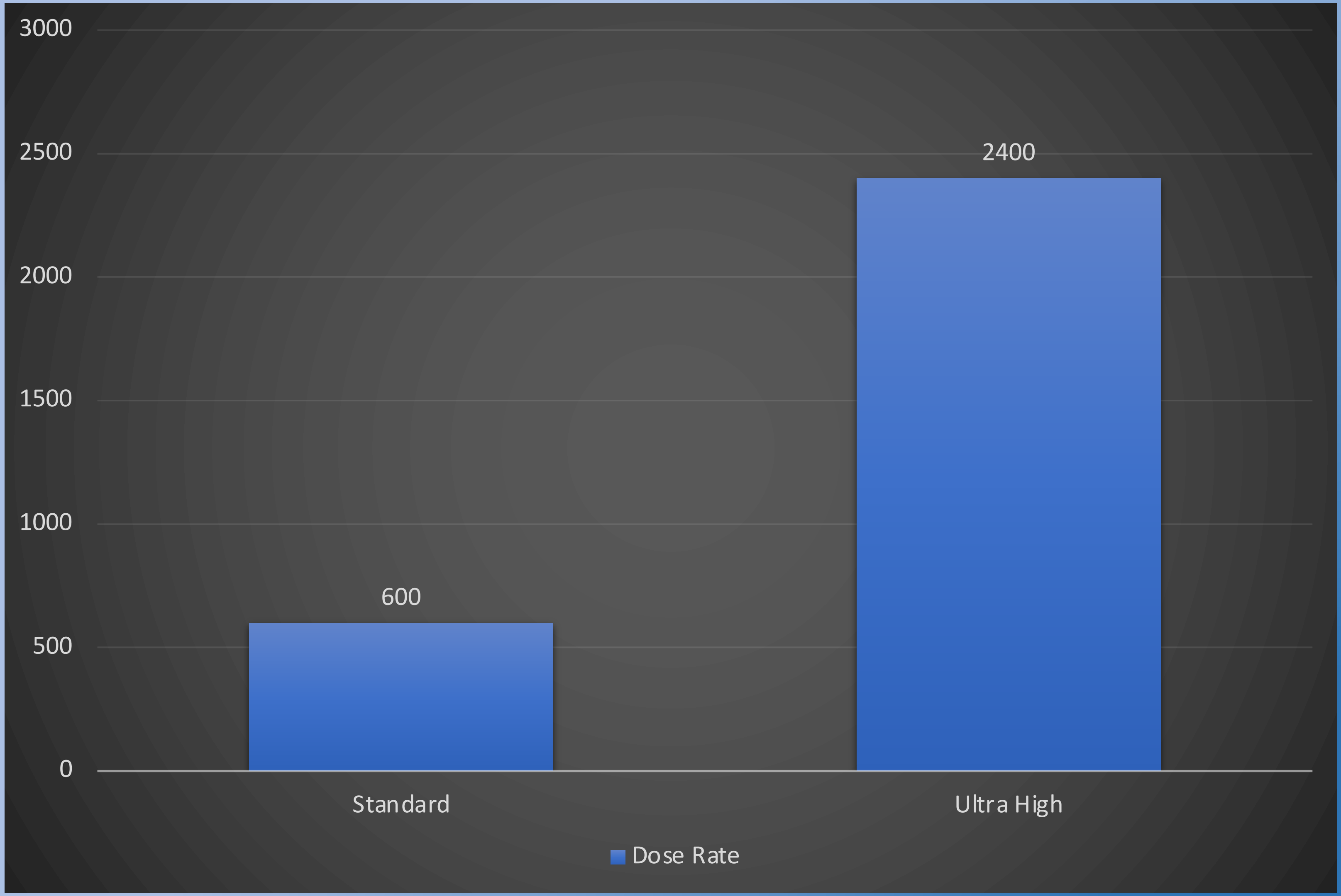
https://doi.org/10.1016/j.ejmp.2018.06.124

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Physica Medica
Volume 52, Supplement 1, August 2018, Page 22

[OA052] Proton minibeam radiation therapy: A promising alternative for high-grade gliomas

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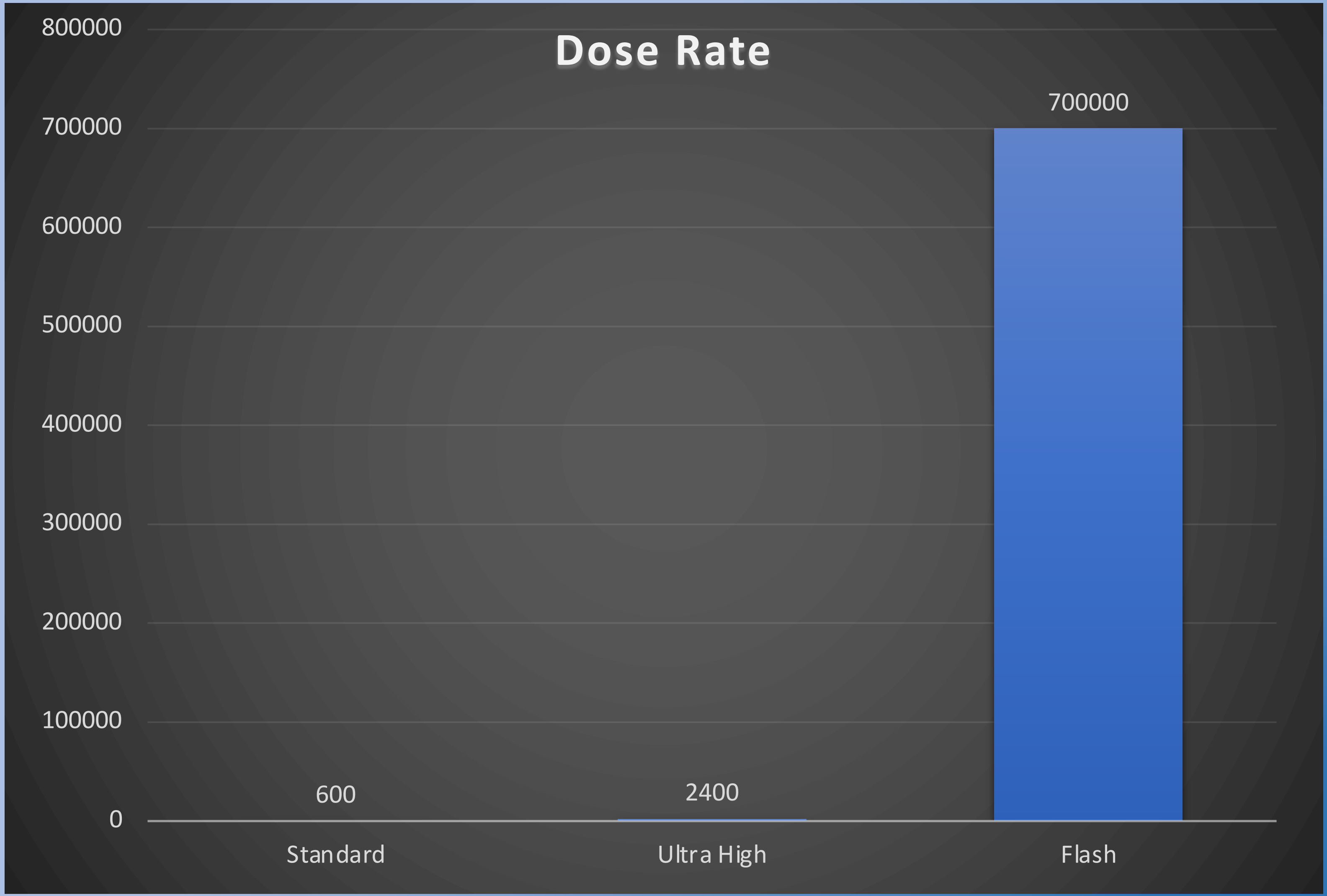


Proton minibeam radiation therapy spares normal rat brain: Long-Term Clinical, Radiological and Histopathological Analysis

Yolanda Prezado[1], Gregory Jouvion[2], David Hardy[2], Annalisa Patriarca[3], Catherine Nauraye[3], Judith Bergs[1], Wilfredo González[1], Consuelo Guardiola[1], Marjorie Juchaux[1], Dalila Labiod[4,5], Remi Dendale[3], Laurène Jourdain[6], Catherine Sebrie[6] & Frederic Pouzoulet[4,5]

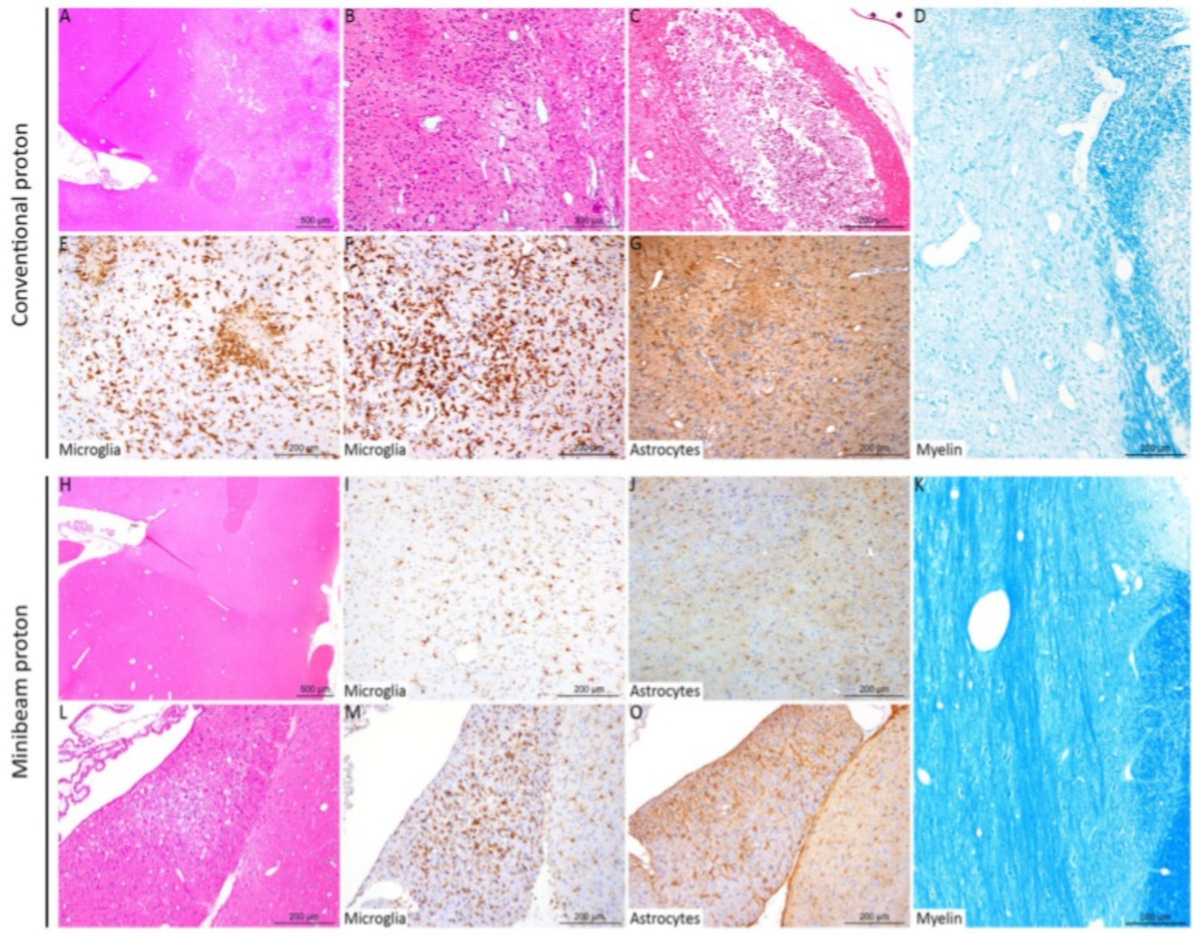


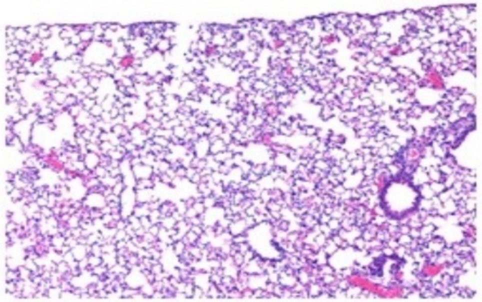
Figure 3. Histopathological and immunohistochemical analyses revealed different lesion profiles between the conventional (A–F) and minibeam (G–L) irradiation groups. A, B, C, H and L: HE staining. D and K: Luxol Fast Blue staining. E, F, I and M: anti-Iba-1 immunohistochemistry (microglia). G, J and O: anti-GFAP immunohistochemistry (astrocytes). The rats were 32 weeks old when sacrificed. Conventional irradiation: (A) Multifocal to coalescing lesion characterized by (B) oedema, necrosis and gliosis. (C) More severe lesion with cavitation and mineralisation. (D) Destruction of the myelin was also observed. (E,F) Microglial activation and microglial nodules (microgliosis). (G) Astrocyte activation with a marked increase in the GFAP immunolabeling (astrogliosis). Minibeam irradiation: (H) At low magnification, no lesion was observed in most rats, with (I,J) normal microglial and astrocytic networks, and (K) normal myelin organization. For just one rat: (L) One inflammatory infiltrate and mild neuropil destruction was observed, associated with focal (M) microgliosis and (O) astrogliosis.

Flash resulted in a reduction in radiation induced dermatitis and fibrosis

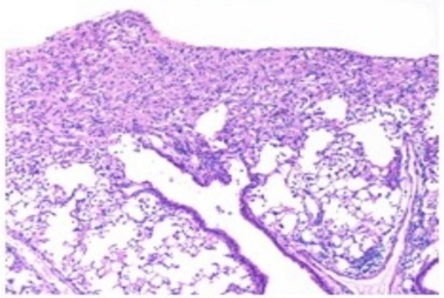
Normal tissue toxicity studies

25% reduction in fibrosis* with FLASH vs. Conventional (17.5 Gy)

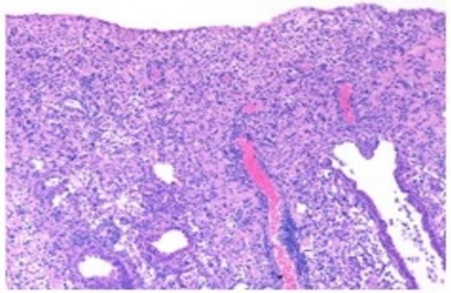
Control



Flash Protons



Conventional Protons



LUNG FIBROSIS

(Graded by independent pathologist, blinded on treatment groups)

35%

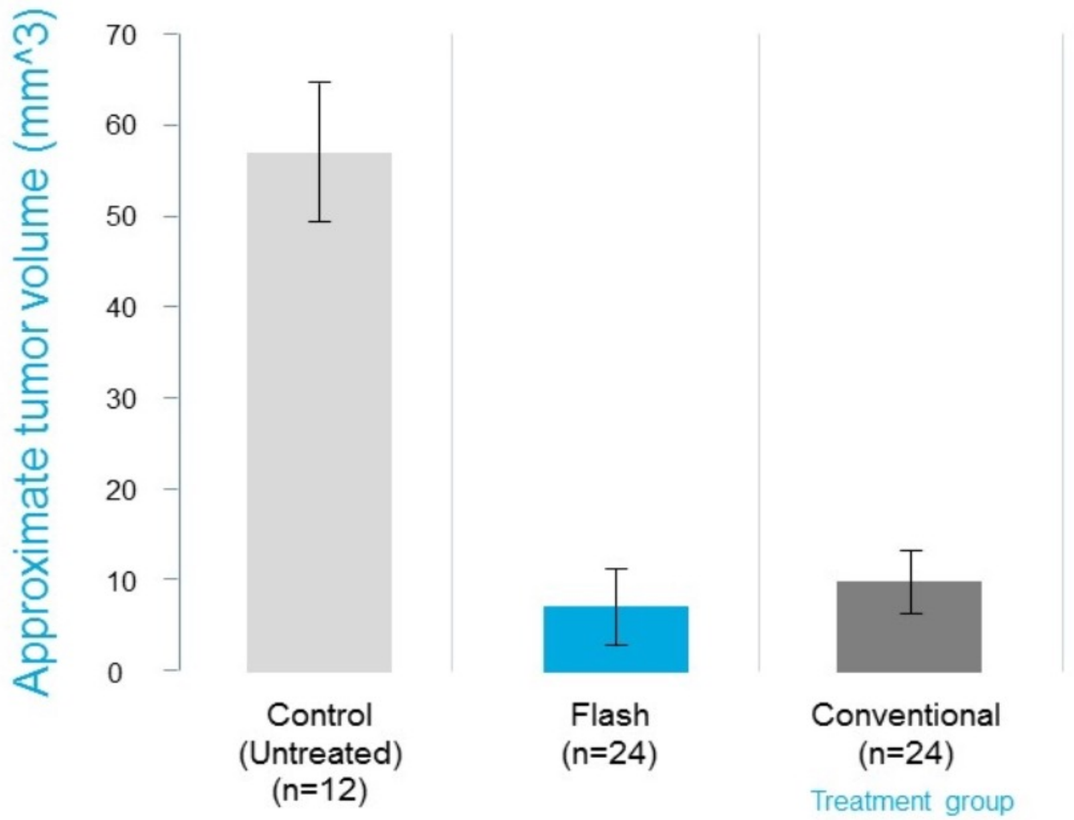
reduction in dermatitis* with FLASH vs. Conventional (17.5 Gy)

*Average dermatitis scores

DERMATITIS

Tumor control preliminary results:

Proton FLASH vs Proton Conventional vs No RT



 [redacted]

Cincinnati
Proton Therapy Center

Tumor control was the same or better with Flash compared to conventional dose rate

Lung Ca

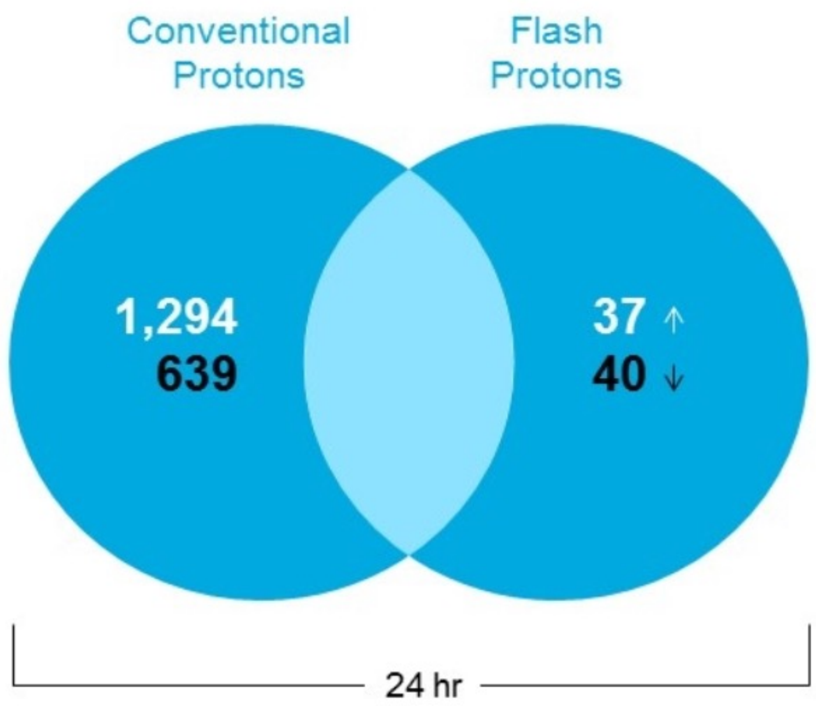
[redacted]

Flash reduces differential gene expression normally observed with radiation therapy

Different genes are up or down regulated when comparing treatment groups versus the (untreated) control group.

FLASH Protons have a gene expression profile closer to the (untreated) control group.

Normal Lung Tissue



Up-regulated genes
Down-regulated genes

Source: Varian proprietary data

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Thank You!!