PARTICULAR NEEDS FOR PEDIATRIC RADIOTHERAPY

John A. Kalapurakal MD, FACR, FASTRO
Northwestern University, Chicago, IL
Chair, Radiation Oncology, Children's Oncology Group

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

DISCLOSURES

NONE

CHILDREN'S ONCOLOGY GROUP The world's childhood cancer experts

INTRODUCTION

- Special thanks to Dr. Bruce Thomadsen and the AAPM
- AAPM 2018 - *"BEYOND THE FUTURE"*
- *COG AND AAPM - "BEYOND THE FUTURE IN PEDIATRIC RADIATION THERAPY"*

CHILDREN'S ONCOLOGY GROUP The world's childhood cancer experts

LEARNING OBJECTIVES

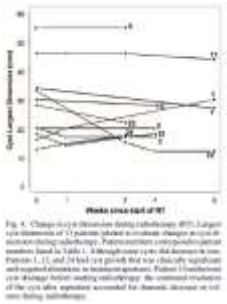
a) To describe the particular needs for pediatric radiotherapy planning, delivery and quality assurance and the important role for radiation physicists in this context.
b) To highlight the opportunities for radiation physicists to conduct clinical and basic research in pediatric radiation oncology in the Children's Oncology Group.
c) To describe the advantages of becoming a member of the Children's Oncology Group
d) To promote a long-term collaboration between the COG and AAPM to improve the quality of pediatric radiation therapy and the clinical outcomes of children stricken with cancer.

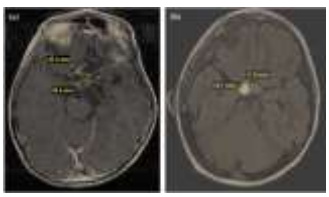
CHILDREN'S ONCOLOGY GROUP The world's childhood cancer experts

PARTICULAR NEEDS FOR RT IN CHILDREN

- Both tumor and normal tissues are growing
- Normal tissues vulnerable to lifelong RT injury
- IGRT – *Imaging* modalities add to risk of late effects
- Proton therapy – Pros and Cons
- Anesthesia - Immobilization
- Organ motion
- Tissue density changes (craniopharyngioma, sinuses, Lungs especially for protons)
- Patient anatomy (bladder, rectum, GI – adaptive RT)
- Organ maturity and target volumes (bone, brain)

CHILDREN'S ONCOLOGY GROUP The world's childhood cancer experts

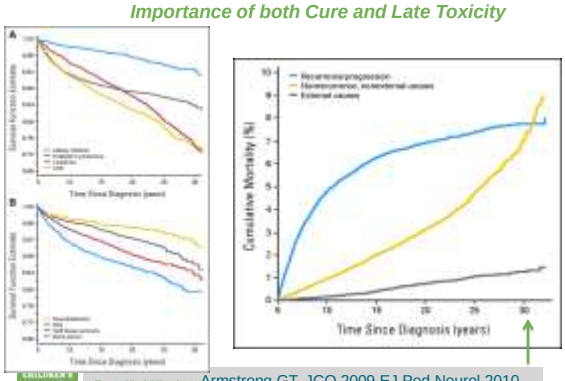




IJROBP 2009, Winkfield KM

CHILDREN'S ONCOLOGY GROUP The world's childhood cancer experts

Importance of both Cure and Late Toxicity

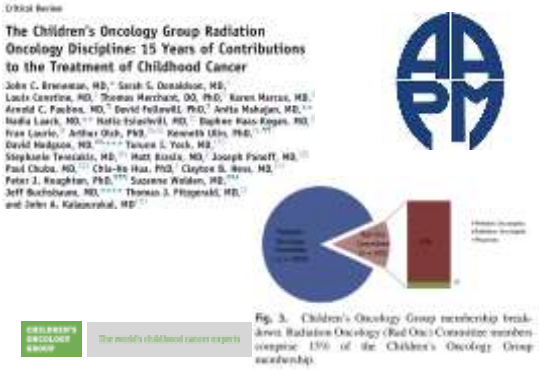


Armstrong GT, JCO 2009 EJ Ped Neurol 2010

COG

- The world's largest organization devoted exclusively to childhood and adolescent cancer research
- > 10,000 experts in childhood cancer > 200 leading hospitals across North America, Australia, New Zealand, and Europe
- 220 sites and about 250 RT facilities accrue patients
- 249 sites have IMRT credentialing
- 21 proton centers, 10-15 new proton centers are expected to open in the next few years

Challenges and Opportunities



The Children's Oncology Group Radiation Oncology Discipline: 15 Years of Contributions to the Treatment of Childhood Cancer

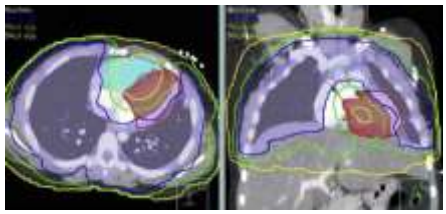
Fig. 3. Children's Oncology Group membership breakdown. Radiation Oncology (Rad Onc) Committee members comprise 13% of the Children's Oncology Group membership.

Research Opportunities: RT Physics

- Develop novel RT techniques in pediatric cancer
- Improve current strategies for normal tissue and target definition
- Provide consensus recommendations for proton therapy planning and delivery
- Explore strategies to limit RT exposure during IGRT
- Improve techniques currently used for TBI
- Application for novel physics research techniques - deep machine learning, phantom dosimetry, QA, RT Compliance **(COG database, IROC archive, COG Research Platform, NIH Grants)**

Cardiac-Sparing Whole Lung IMRT in Children With Lung Metastasis

John A. Kalapurakal, MD,* Yunkai Zhang, PhD,* Alan Kapka, PhD,*
Brian Zawislak, BS,* Vythialingam Sathiaseelan, PhD,* Cynthia Rigsby, MD,†
and Mahesh Gopalakrishnan, MS*



CARDIAC-SPARING WHOLE LUNG IMRT IN CHILDREN AND YOUNG ADULTS WITH LUNG METASTASES: A FEASIBILITY STUDY

R21CA159547 Kalapurakal (Completed). (06/01/11 - 05/31/14)

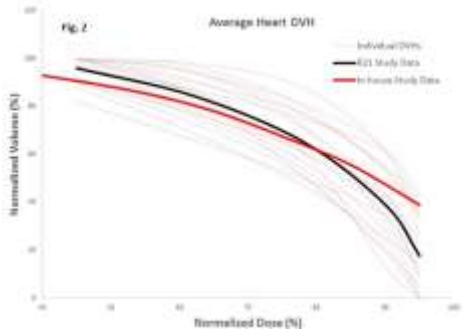
- John A. Kalapurakal MD Radiation Oncology; David Walterhouse MD Pediatric Oncology; Cynthia Rigsby MD, Diagnostic Radiology; TJ Fitzgerald MD, QARC; Mahesh Gopalakrishnan MS, Radiation Physics (Northwestern University); David Followill Ph.D Radiology Physics Center, Houston TX; Fred Rademaker PhD (Statistics, Northwestern)

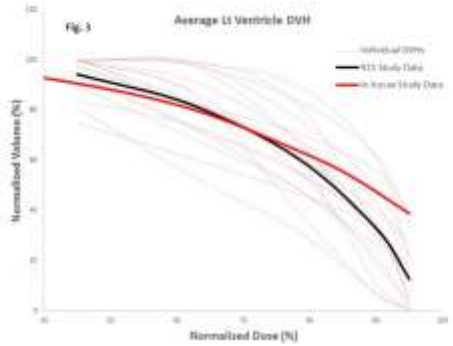
- *Northwestern University; Boston Children's hospital; Emory University; Memorial Sloan Kettering Cancer Center; MD Anderson Cancer Center*

- The target 20 patients (1-25yrs, 11males) were accrued from 5 centers in 2 years
- Pediatric sarcomas (14), Wilms tumor (5), hepatoblastoma (1)
- CS-IMRT WLI technique was feasible in all 20 patients
- Median RT dose was 15Gy using a mean of 9 fields
- Pre-treatment central review resulted in target contour changes in 7, re-planning in 3 and minor deviations in 2 patients. There were no major deviations
- Mean whole heart and cardiac volume doses V_{95}, V_{83} , V_{67} and V_{50} for AP-WLI was 96-100%
- Mean Whole Heart 39%(<0.0001), 65% (<0.0001), 85% (<0.0001) and 96% (0.0083);
- Mean Left Ventricle 33% (<0.0001), 61% (<0.0001), 82% (<0.0001) and 95% (0.006); (similar data myocardium, atria, coronaries)
- 4D lung volumes were significantly larger than 3D volumes (<0.0001)
- AP-WLI technique significantly under dosed 4D lung volumes (0.008)
- CS-IMRT was well tolerated with no AE, CT changes consolidation or fibrosis (minimum 2 yr. FU for all patients)
- 18 were in CR and 2 had progressive disease in lungs before IMRT
- 2 &3 year OS 90%; 90% lung metastasis PFS 65%; 52%

Conclusions

- This trial has demonstrated the feasibility of CS-IMRT
- Confirmed the reported advantages of CS-IMRT including: superior cardiac protection and superior dose coverage of 4D lung volumes
- CS-IMRT was well tolerated. One patient had reduced LVEF at 5 years
- CS-IMRT resulted in good survival outcomes
- CS-IMRT targeting 4D lung volumes with IROC QA pre-review will be used in the next generation of COG renal tumor protocols





Title: CARDIAC SPARING WHOLE LUNG IMRT IN CHILDREN WITH WILMS TUMOR: FINAL REPORT ON TECHNIQUE AND ABDOMINAL FIELD MATCHING TO MAXIMIZE NORMAL TISSUE PROTECTION

Accuracy of A Computational Human Phantom Model for Retrospective Target-Organ Dosimetry of Patients treated with Radiation Therapy on National Wilms Tumor Study Protocols

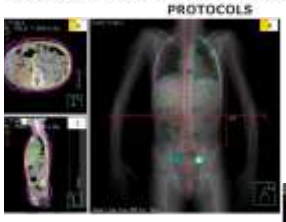
- *J. A. Kalapurakal[1], M. Gopalakrishnan[2], M. Mille[8] , J. W. Jung[3], S. Peterson[4], W. Leisenring[4], F. Laurie[5], C. Rigsby[6], T. Fitzgerald[7], and C. Lee[8]*

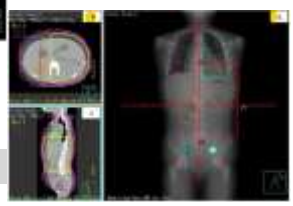
- *[1]Department of Radiation Oncology, Northwestern University, Chicago, IL, [2]Northwestern Memorial Hospital, Chicago, IL, [3]East Carolina University, Greenville, NC, [4]Fred Hutchison Cancer Center, Seattle, WA, [5]Quality Assurance Review Center, Lincoln, RI, [6]Lurie Childrens Hospital, Chicago, IL, [7]University of Massachusetts Medical Center, Worcester, MA, [8]National Cancer Institute, National Institutes of Health, Rockville, MD*

Introduction

- NWTS late effect study: correlation with late effects was analyzed by Prescribed RT fields/doses and not target organ dosimetry.
- Childhood Cancer Survivor Study (CCSS): used a mathematical phantom model and point doses to ascertain organ dosimetry *(this model lacked both CT accuracy and 3D organ anatomy data and thus led to the* inability to accurately co-relate RT-late effects to 3D organ dosimetry).
- UF/NCI Computational Human Phantoms (CHP's) model: patient dependent phantoms that preserve the anatomic position of organs and they are scaled based on Age, Sex, Height and Weight.

FEASIBILITY AND ACCURACY OF THE UF/NCI PHANTOMS AND MONTE CARLO RETROSPECTIVE DOSIMETRTY IN CHILDREN TREATED ON NATIONAL WILMS TUMOR STUDY PROTOCOLS

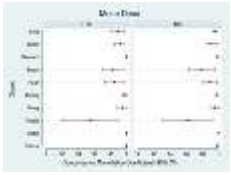


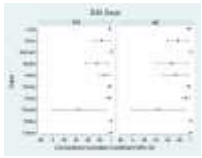


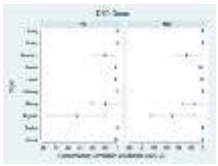
Pediatric Blood Cancer 2018

R01CA159547 (Kalapurakal) RETROSPECTIVE NCI PHANTOM-MONTE CARLO DOSIMETRY FOR LATE EFFECTS IN WILMS TUMOR 08/01/17 - 07/31/22

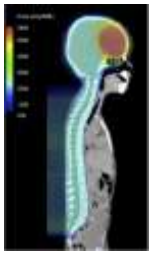
- AIM 1 - Estimate RT doses (mean dose, D30, D70) to specific organs of 5000 irradiated NWTS Subjects using the 3D NCI Phantom and TPS- MC dosimetry model
- AIM 2 - Study the association between RT dose (mean dose, D30 and D70) estimated using the 3D NCI Phantom and TPS-MC dosimetry model and NWTS late effects.
- We will study the five 5 targeted late effects: CHF (Total heart, ventricles, myocardium); ESRD (Solitary or partial kidneys); Restrictive Pulmonary Disease (Lungs and chest wall); Adverse Pregnancy Outcomes (Ovaries, uterus and pelvis); Second Malignant Neoplasms (breast, thyroid, stomach, colon, liver, kidney) and reproductive impairment in males (testes) and females (ovaries, uterus, pelvis)

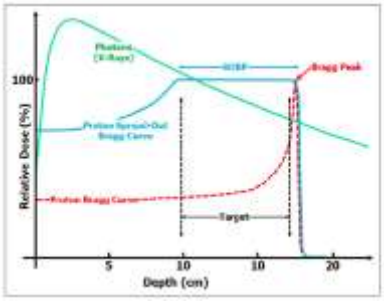






PROTON THERAPY – OPPORTUNITY AND CHALLENGES





Caution – clinical application of protons

- More sensitive to organ motion, set up errors that can lead to anatomic changes in tumor or tissue density in the path of the beam
- Re-simulation and re-planning: Normal tissue (NT) density change (sinuses, anatomic cavities), edema, hydrocephalus, Wt loss; Tr. Size - Under/over ranging can affect tumor/NT dose
- RBE protons 1.1(10% less dose for isoeffect) meta-analysis of photon/proton in-vivo-vitro data
- Entrance to mid SOBP DNA damage response similar low LET x-rays (1.1-1.15), distal end → complex DNA damage, slow repair kinetics (↑LET) and higher RBE(~1.35 distal edge, ~1.7 distal fall-off at 2Gy/fr
- Thus dose extends 1-2mm beyond distal fall-off in NT (not estimated TPS) "biologic range extension"
- RBE- physical (dose/fr, LET) biologic factors (tissue type, cell cycle, end point, oxygenation, sensitizers)

Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy

DANIEL J. INDELICATO[1], STELLA FLAMPOURI[1], BONNY L. BOTOMDO[1], JULIE A. BRADLEY[1], CHRISTOPHER G. MORRIS[1], PHILIPP R. ALDANA[2], ERIC SANDLER[3] & NANCY P. MENDENHALL[1]

[1]Department of Radiation Oncology, University of Florida, Jacksonville, Florida, USA, [2]Department of Neurosurgery, University of Florida, Jacksonville, Florida, USA and [3]Department of Pediatrics, University of Florida, Jacksonville, Florida, USA

ABSTRACT

Background. Proton therapy offers superior low and intermediate radiation dose distribution compared with photon-based radiation for brain and skull base tumors; yet tissue within and adjacent to the target volume may receive a comparable radiation dose. We investigated the tolerance of the pediatric brainstem to proton therapy and identified prognostic variables.

Material and methods. All patients < 18 years old with tumors of the brain or skull base treated from 2007 to 2013 were reviewed; 313 who received > 50.4 CGE to the brainstem were included in this study. Brainstem toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events v4.0.

Results. The three most common histologies were ependymoma, craniopharyngioma, and low-grade glioma. Median patient age was 5.9 years (range 0.5–17.8 years) and median prescribed dose was 54 CGE (range 46.6–75.6 CGE). The two-year cumulative incidence of toxicity was 3.8% ± 1.1%. The two-year cumulative incidence of grade 3 + toxicity was 2.1% ± 0.9%. Univariate analysis identified age < 5 years, posterior fossa tumor location and specific dosimetric parameters as factors associated with an increased risk of toxicity.

Conclusions. Utilization of current national brainstem dose guidelines is associated with a low risk of brainstem toxicity in pediatric patients. For young patients with posterior fossa tumors, particularly those who undergo aggressive surgery, our data suggest more conservative dosimetric guidelines should be considered.

Table II. Clinical and dosimetric variables potentially associated with brainstem toxicity.

Variables	Factor	Percent toxicity rate: if factor was present	Percent toxicity rate: if factor was absent	p-Value
Clinical variables				
Focal vs. craniospinal (CSI) radiotherapy	CSI	2.6%	3.6%	>0.5
Radiotherapy modality	Mixed	5.2%	3.5%	>0.5
Sex	Male	2.4%	4.9%	>0.1
Race	Nonwhite	3.6%	4.0%	>0.1
Age	< 5 yrs	6.0%	1.1%	0.01
Ependymoma	Yes	5.7%	0.7%	>0.1
Hydrocephalus	Yes	3.6%	4.3%	>0.1
Tumor location	Posterior fossa	10.7%	0%	<<0.001
Number of operations	>1	4.9%	4.1%	>0.1
CSF shunt needed	Yes	1.6%	4.2%	>0.1
Degree of resection	GTR/NTR	7.3%	1.5%	>0.1
Chemotherapy	Any given	5%	2.9%	>0.1
Type of chemotherapy	IT or HD methotrexate-based	6.3%	3.0%	>0.1
Dosimetric variables				
Mean dose	< 44.2 Gy	0.0%	8.0%	0
D10%	< 55.6 Gy	0.0%	10.5%	0
D50%	< 52.6 Gy	0.0%	10.5%	0
V40 Gy	< 21.5%	0.5%	8.5%	0
V45 Gy	< 17.5%	0.6%	8.6%	0
V50 Gy	< 14.2%	0.8%	8.8%	0
V55 Gy	< 17.1%	1.3%	10.5%	< 0.01
V60 Gy	0	2.5%	14.8%	0.01
Max dose* to brainstem	< 56.0 Gy	1.0%	10.0%	< 0.01
Max dose* to brainstem surface	< 59.1 Gy	1.3%	11.2%	< 0.01
Max dose* to brainstem core	< 56.0 Gy	1.0%	11.1%	< 0.01

Critical Review

National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury

Daphne Haas-Kogan, MD,* Daniel Indelicato, MD,† Harald Paganetti, PhD,‡ Natia Esiashvili, MD,§ Anita Mahajan, MD,‖,¶ Torunn Yock, MD,† Stella Flampouri, PhD,† Shannon MacDonald, MD,† Maryam Fouladi, MD,# Kry Stephen, PhD,** John Kalapurakal, MD,†† Stephanie Terezakis, MD,‡‡ Hanne Kooy, PhD,‡ David Grosshans, MD, PhD,** Mike Makrigiorgos, PhD,§§ Kavita Mishra, MD, MPH,‖‖ Tina Young Poussaint, MD,¶¶ Kenneth Cohen, MD,## Thomas Fitzgerald, MD,*** Vinai Gondi, MD,††† Arthur Liu, MD, PhD,‡‡‡ Jeff Michalski, MD,§§§ Dragan Mirkovic, PhD,** Radhe Mohan, PhD,** Stephanie Perkins, MD,‖‖‖ Kenneth Wong, MD,¶¶¶ Bhadrasain Vikram, MD,#### Jeff Buchsbaum, MD,**** and Larry Kun, MD####

CHILDREN'S ONCOLOGY GROUP — The world's childhood cancer experts

CHILDREN'S ONCOLOGY GROUP

ACNS0831

Phase III Randomized Trial of Post Radiation Chemotherapy in Patients with Newly Diagnosed Ependymoma Ages 1 to 21 years

Brainstem – Proton Therapy

- D50% ≤ 5240CcGE and D0.1cc ≤ 5660CcGE – Goal
- D50% ≤ 5400CcGE and D0.1cc ≤ 5800CcGE – Maximum

Brainstem – Photon Therapy

- D50% ≤ 6100cGy and D10% ≤ 6300cGy - Goal
- D50% ≤ 6200cGy and D10% ≤ 6400cGy – Maximum

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

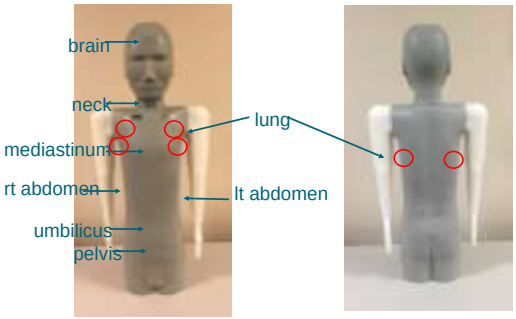
Imaging and Radiation Oncology Core
Houston QA Center Activities

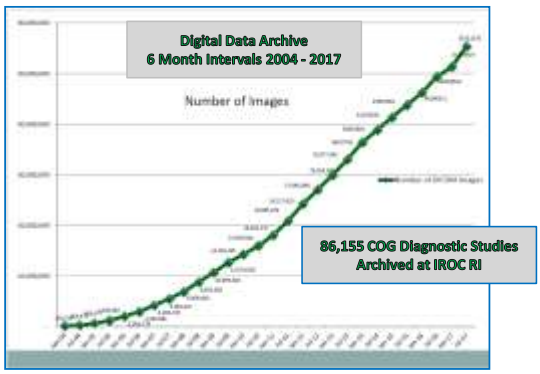
IROC
IMAGING AND RADIATION ONCOLOGY CORE

ACR

David Followill, Ph.D., and
Thomas J. Fitzgerald MD

Hansel and Gretel





Research Resource

Committee	#Protocols	#Patients	DICOM Diagnostic Studies	DICOM RT Treatment Plans
AALL	14	3,144	1,104	8
ACNS	22	3,149	16,983	1,589
AEWS	7	1,599	4,897	477
AHOD	10	2,892	30,558	638
ANBL	14	2,714	8,383	464
ARAR	3	420	2,320	77
AREN	5	7,432	11,340	896
ARST	11	2,148	6,381	983

1. Chair's Report. John Kalapurakal MD (5 min)

DISEASE COMMITTEE REPORTS

1. Rhabdomyosarcoma. Sarah Donaldson MD (10min)
2. NCI grants, Medulloblastoma. Jeff Buchsbaum MD (10min)
3. CNS Tumors. Daphne Haas Kogan MD (10 min)
4. Neuroblastoma. Daphne Haas Kogan (10 min)
5. Leukemia Natia Esiashvili MD (10min)
6. Renal Tumors. Arnold Paulino MD (10min)
7. Ewing Sarcoma. Nadia Laack, Ralph Vatner, Thomas Cash, Richard Gorlick (10min)
8. Hodgkin Lymphoma. David Hodgson MD (10min)
9. Rare Tumors. Matthew Krasin (5 min)

QA REPORTS

1. IROC Houston. David Followill PhD (10min)
2. IROC Rhode Island. TJ Fitzgerald MD/Fran Laurie (10min)

WORKING GROUP REPORTS

1. Proton Committee. Anita Mahajan/T Yock MD (10min)
2. Education Committee. John Breneman/Ken Roberts MD (10min)
3. Late Effects/Publications Committee. Louis Constine MD (10min)
4. Physics Committee. Chia-Ho PhD (10min)
5. PROS/SIOP update. Karen Marcus MD (5min)
6. International Outreach. Natia Esiashvili MD (5min)
7. Membership Committee. Paul Chuba MD (5min)
8. IPMC Report. Arthur Liu MD (5min)
9. Young Investigators. Erin Murphy MD (5min)
10. Cancer Control (CCL) Committee. Anita Mahajan (5min)

NIH Funding Opportunities for (Radiation) Scientists with a Focus on Pediatrics

Jeff Buchsbaum
Radiation Research Program
Division of Cancer Treatment & Diagnosis
National Cancer Institute, National Institutes of Health

NIH NATIONAL CANCER INSTITUTE

CONCLUSIONS: Physicists and YIs

- √ COG WELCOMES YOU TO JOIN OUR TEAM!
- √ Develop novel RT techniques in pediatric cancer
- √ Improve current strategies for normal tissue and target definition
- √ Provide consensus recommendations for proton therapy planning and delivery
- √ Explore strategies to limit RT exposure during IGRT
- √ Improve techniques currently used for TBI
- √ Application for novel physics research techniques - deep machine learning, phantom dosimetry, QA, RT Compliance, **(COG database, IROC archive, COG Research Platform, NIH Grants)**

THANK YOU

- j-kalapurakal@northwestern.edu