NRG Cancer Prevention and Control Meeting

Lisa Kachnic, MD, Cancer Control Chair
Warner Huh, MD, Prevention Chair
Debra Barton, PhD, Cancer Control Vice-Chair
Julie Bauman, MD, Prevention Vice-Chair

July 22, 2021

NRG Oncology NCORP Org Chart

NRG ONCOLOGY™

NRG NCORP Cancer Prevention and Control Priorities

- Improvement or delay in decline of neurocognitive function
- Reducing of gender-specific symptoms including lymphedema and sexual function
- Testing therapeutic delivery modifications to improve QoL and cost-effectiveness in localized cancers while maintaining efficacy
- Reducing cancer risk through optimal screening, biomarker evaluation and risk reduction strategies and
- Assessing behavioral interventions to decrease cancer risk and mitigate cancer treatment-related symptoms

Announcements

NCORP Spotlight

NRG will begin highlighting one NCORP site each month in the NRG newsletter. If you'd like your NCORP site to participate please contact Erica Field, fielde@nrgoncology.org

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Welcome Dr. Huh!

Warner Huh, MD, Chair of the Department of Obstetrics and Gynecology at the University of Alabama at Birmingham (UAB), appointed new chair of the NRG Oncology Cancer Prevention Committee efforts.

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CPC Trials

NRG ONCOLOGY™

Opened NRG CPC Trials

****accrual as of June 30, 2021**

Study No	Disease Site	Description	Date Activated	Target Accrual	Total Accrual	NCORP Accrual (%)	Expected Closure Date
GOG 0278	Cervix	Physical function/QoL before and after non-radical surgical therapy for stage IA1 (LVSI+) and IA2-IBI (=2CM) cervical cancer	10/1/12	220	217	<1%	December 2021
NRG CC003	Lung	Seamless phase II/III PCI vs. PCI with hippocampal sparing for cognitive fx preservation in small cell lung cancer	12/7/15	172 (II) 392 (III)	176 of 172 (II) 353 of 392 (III)	30%	February 2022

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Opened NRG CPC Trials

****accrual as of June 30, 2021**

Study No	Disease Site	Description	Date Activated	Target Accrual	Total Accrual	NCORP Accrual (%)	Expected Closure Date
NRG CC005	GI	FORTE/Five or Ten Year	Activating late July	9,500			
NRG CC008	Ovarian	Non-rand. prospective trial comparing non-inferiority of **S**alpingectomy to salpingo-**O**ophorectomy to **R**educe risk of **O**varian **C**a among *BRCA1* carriers (**SOROCk**)	6/23/2020	2262	50	13%	March 2031
NRG CC009	Lung	SRS vs. HA-WBRT for 10 or Fewer Brain Metastases from SCLC	2/24/2021	200	2	100%	August 2024

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GOG 0278
PI Covens

Women with IA1- IB1 (≤2cm) carcinoma of the cervix **who have been consented for surgery** will be approached for study participation. Pre-entry cone biopsy/LEEP (depth of invasion ≤ 10mm)

↓

Study Entry

↓

Pre-operative QOL Study Survey

↙ ↘

Fertility Preservation Group:
Conization with pelvic lymphadenectomy (If the lateral margins were positive on the first cone biopsy/LEEP, patients must have a second cone biopsy/LEEP at the time of the pelvic lymphadenectomy)

No Wish for Future Fertility Group: Simple hysterectomy with pelvic lymphadenectomy (If the lateral margins were positive on the first cone biopsy/LEEP, patients must have a second cone biopsy/LEEP prior to hysterectomy)

↙ ↘ ↙ ↘

If depth of invasion (sum of the pre and post entry biopsies) is ≤10 mm, only ECC is required.

If any of the following criteria are met, patient will be followed for survival only:

- Depth of invasion (sum of the pre and post entry biopsies) is >10 mm
- Positive pelvic lymph nodes on final pathology
- Adjuvant therapy required

If depth of invasion (sum of the pre and post entry biopsies) is ≤10 mm, proceed to hysterectomy.

↓

Post-Operative
Follow-up Visits 4-6 weeks Post-op and every 3 months (3, 6, 9, 12) for 1 year then every 6 months (18, 24, 30, 36) for 2 years \and QOL Study Surveys1 4-6 weeks Post-Op and every 6 months (6, 12, 18, 24) for two years

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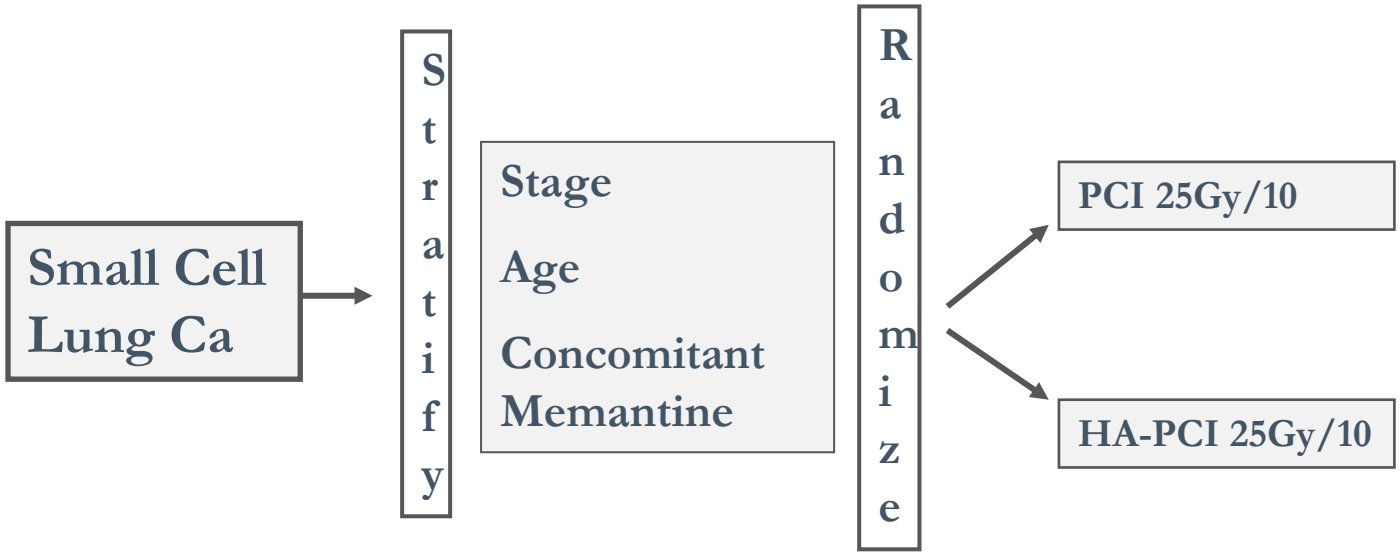
NRG CC003: Phase IIR/III Trial Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer

PIs: Minesh Mehta (Miami Cancer Institute) + Vinai Gondi (Northwestern)

Basic Eligibility: Small cell lung cancer; PR or CR to chemo; ECOG PS≤70; MRI scan



Sample Size: Phase IIR: 172 patients; Phase III:392 patients

Primary endpts: Phase IIR—Intracranial relapse rate at 12 months
Phase III—HVLT-R delayed recall deterioration at 6 months

Statistical Design: Phase IIR: Non-inferiority margin of >20% difference. 164 analyzable pts.
Phase III: 29% with PCI vs. 14.5% with HA-PCI. 196 analyzable pts

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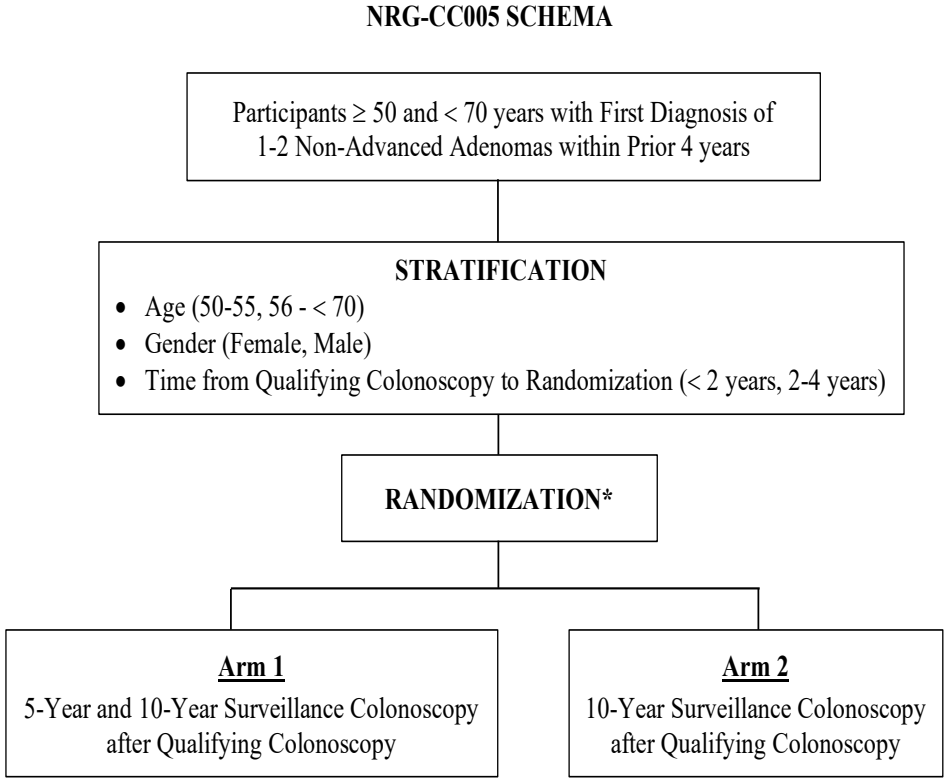
NRG-CC005/FORTE

PI: Robert Schoen, MD

Sample size = 9500

Biospecimen collection:

- Streck tube (1)
- Stool sample (3)
- FFPE tissue



* Randomization is 1:1.

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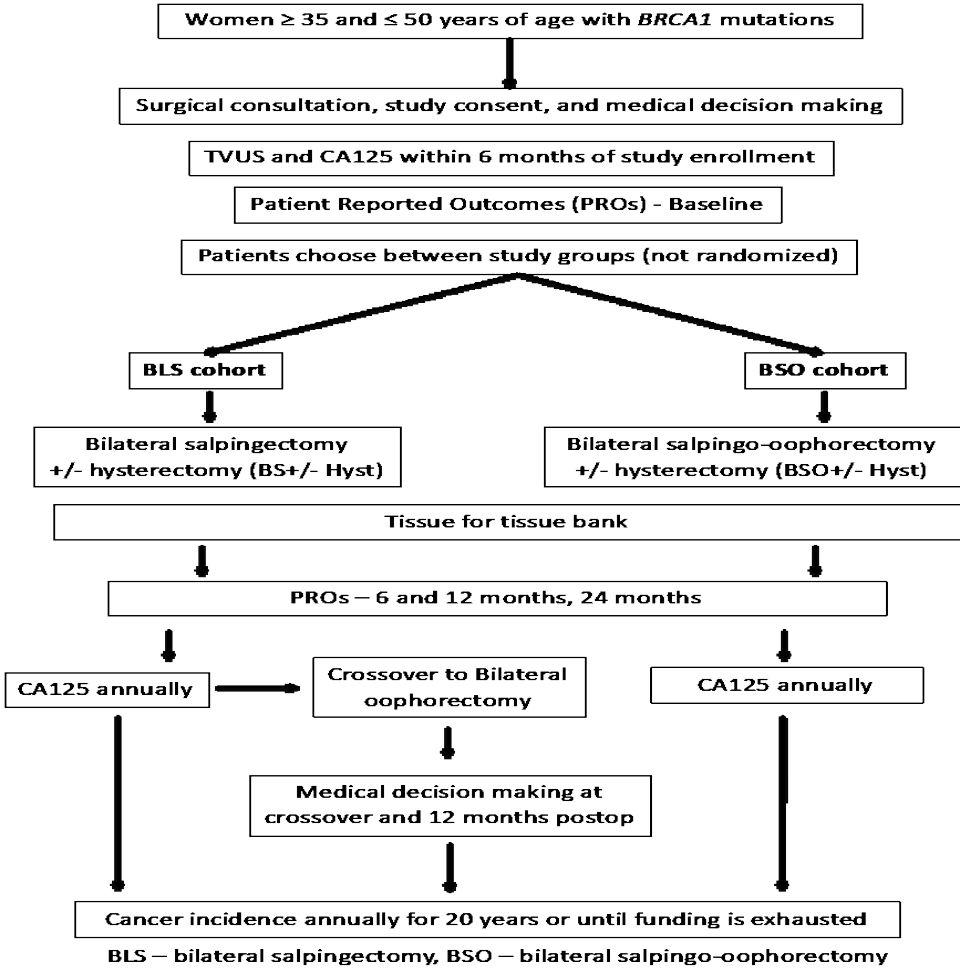
NRG-CC008

Co-PIs: Joan Walker, MD; Warner Huh, MD; Kathryn Pennington, MD

Sample size = 2262

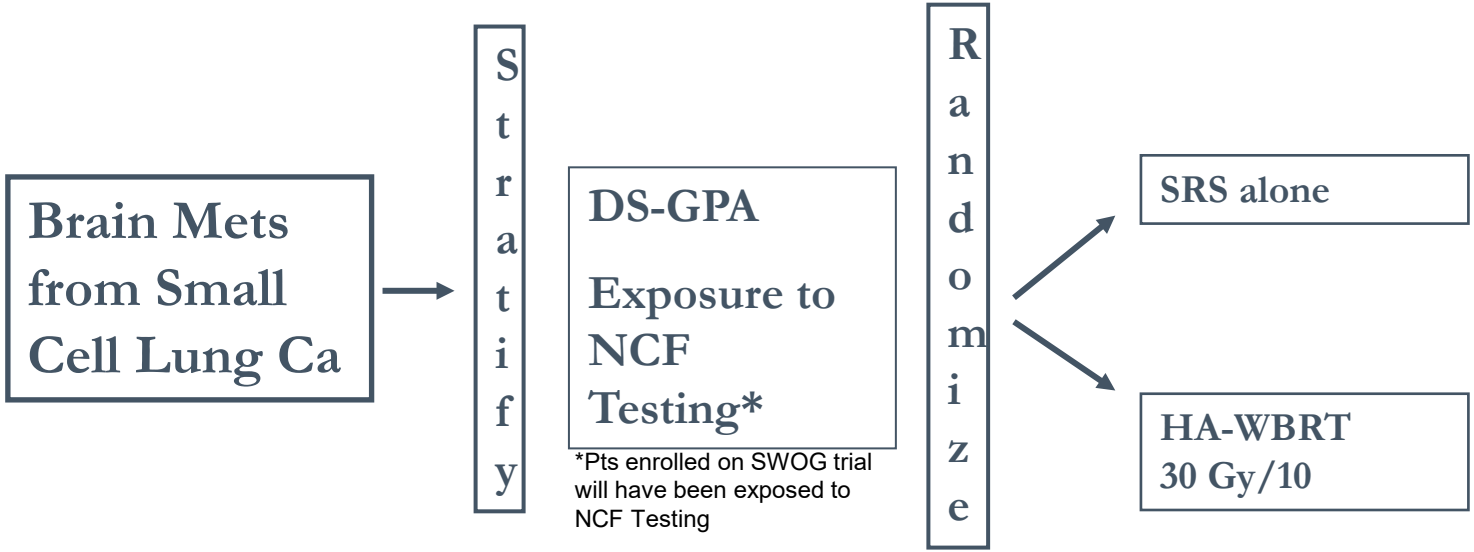
Primary objective: To compare the non-inferiority BLS with delayed oophorectomy to BSO to reduce the risk of ovarian cancer among women with deleterious *BRCA1* germline mutations



NRG CC009: Phase III Trial Stereotactic Radiosurgery versus Hippocampal-Avoidant Whole-Brain Radiotherapy for 10 or Fewer Brain Metastases from Small Cell Lung Cancer

PIs: Chad Rusthoven (Univ of Colorado) + Vinai Gondi (Northwestern)

Basic Eligibility: Small cell lung cancer; ≤10 brain mets≤3cm; total vol 30cc; KPS≥70



Sample Size: 200 patients

Primary endpt: Time to cognitive failure--HVLT-R, COWA, and TMT A and B

Basic Statistical Design:
Cognitive fxn failure 58.8% at 6 mos with HA-WBRT+mem vs. 41.8% at 6 mos with SRS.
150 analyzable pts

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Questions

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Study Champions

Study	Protocol Title	Accrual (6/30/121)	Comments
S1820	Testing Diet Intervention vs. Non-Diet Intervention for Management of Bowel Symptoms in Rectal Cancer Survivors (PI Sun)	63/126	Tracy Crane is the NRG Study Champion; NRG has enrolled 17 participants
S0820	Double Blind Placebo-Controlled Trial to Prevent Recurrence of High-Risk Adenomas and Second Primary Colorectal Cancers (PACES) (PI Zell)	316/491	Jenny Dorth is the NRG Study Champion; NRG has enrolled 35 participants
EA1151	Tomosynthesis Mammographic Imaging Screening Trial (TMIST) (PI Pisano)	49,860/ 164,946	NRG enrolled 3,363 participants
A221805	Duloxetine To Prevent Oxaliplatin-Induced CIPN: Rand. Double-Bind, Placebo-Controlled Phase II To Phase III Study (PI Smith)	59/327	Jordan Kharofa is the NRG Study Champion; NRG has enrolled 7 participants
EA2185	Comparing the Clinical Impact of Pancreatic Cyst Surveillance Programs	62/4606	Aasma Shaukat is the NRG Study Champion; NRG has enrolled 8 participants

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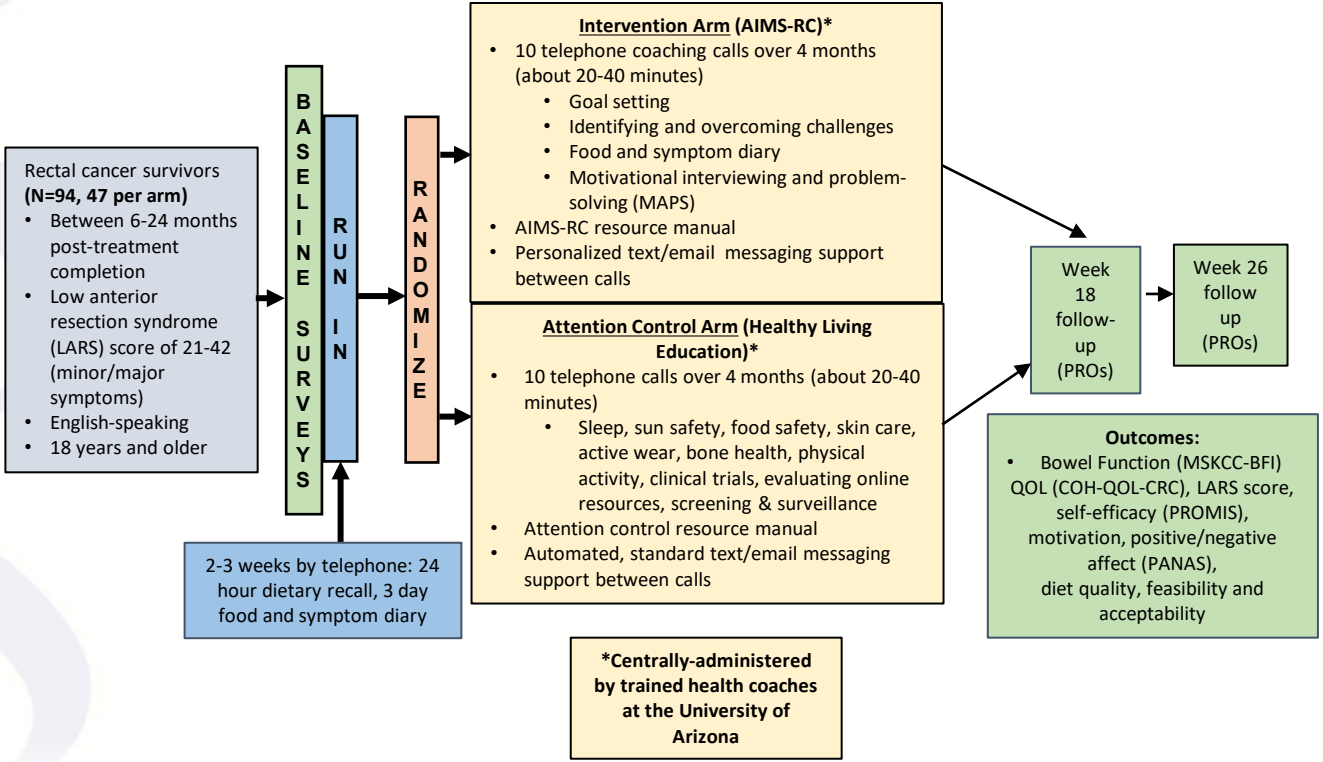
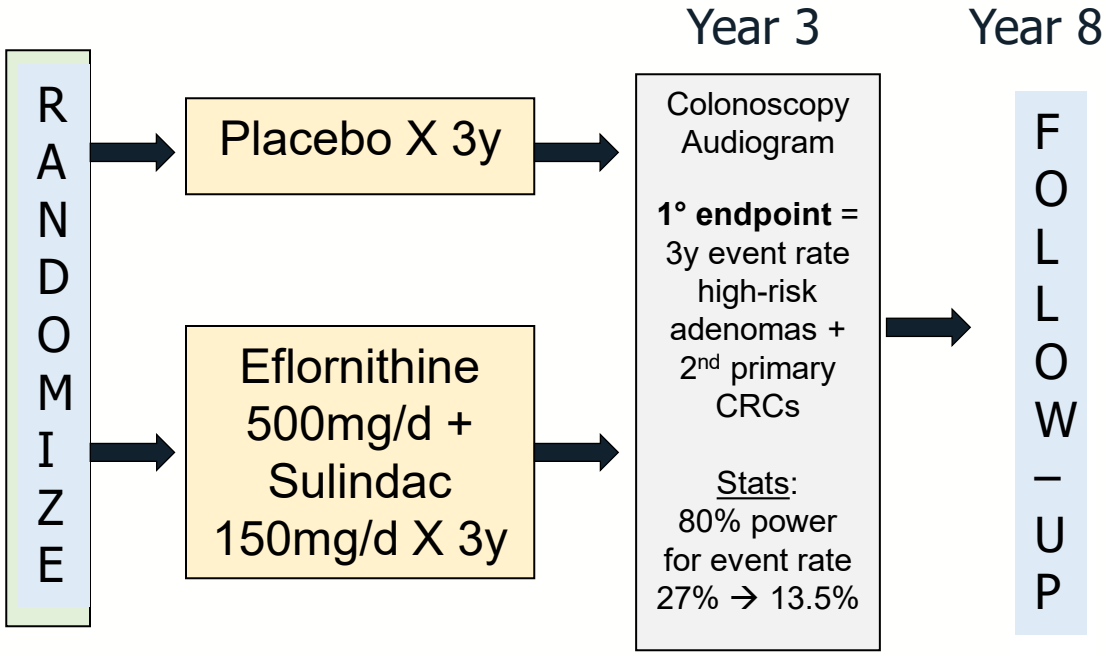
SWOG 1820: Testing Diet Intervention vs. Non-Diet Intervention for Management of Bowel Symptoms in Rectal Cancer Survivors



SWOG 0820: Double Blind Placebo-Controlled Trial to Prevent Recurrence of High Risk Adenomas and Second Primary Colorectal Cancers (PACES)

Inclusion:
- Stage 0-III colorectal adenoCa
- s/p partial colectomy, polypectomy, TAE +/- chemo(RT)
- Register 6 mo -15 mo postop, ≥30 d post chemo(RT)
- NED at colonoscopy +/- CT scan ≥ 6 mo postop

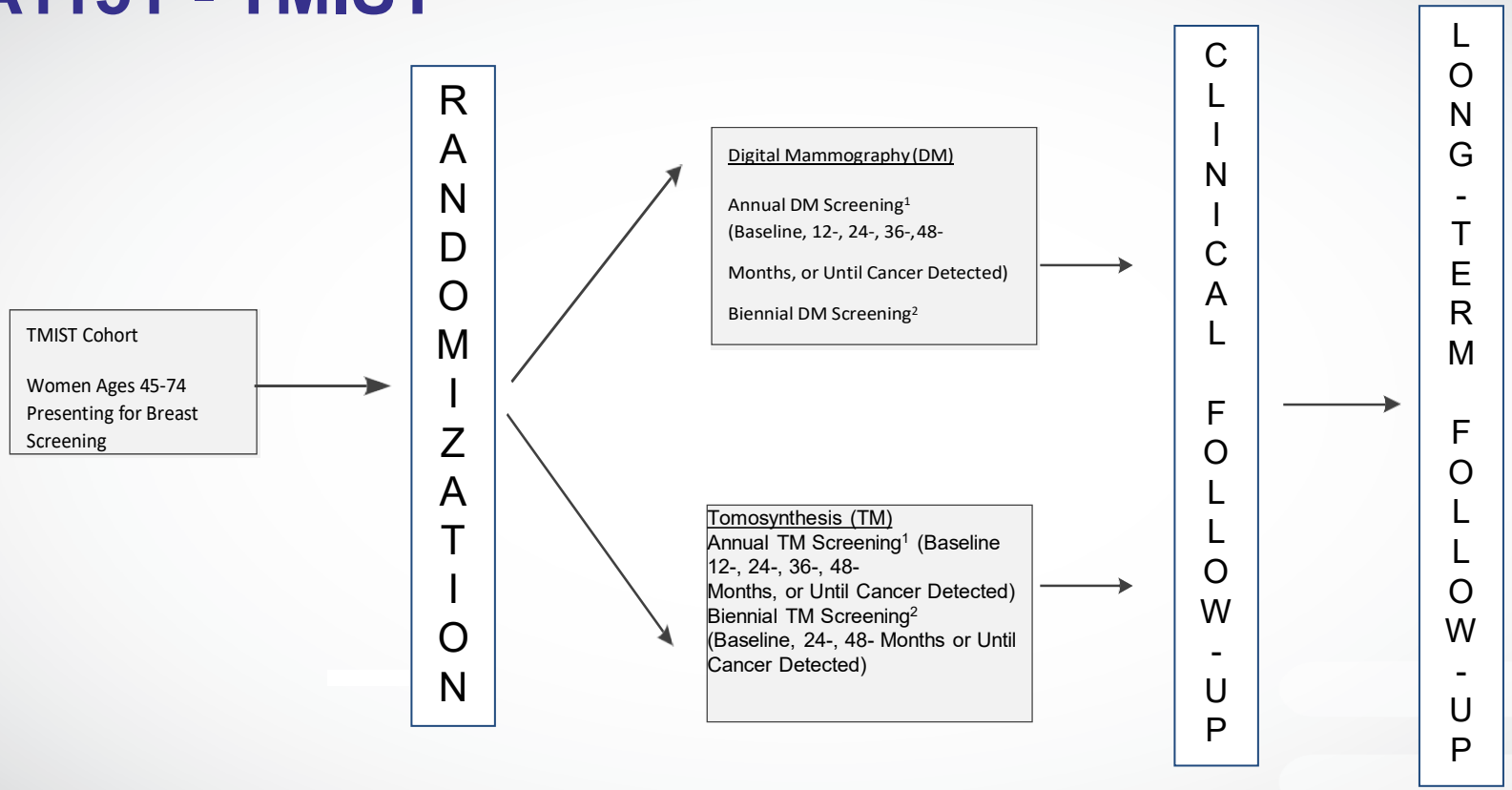
Exclusion:
- No high CV risk
- No hearing loss
- No high-dose NSAID
- No GI ulcer
- No family hx FAP, HNPCC, IBD



*Stratify by stage/adjuvant tx

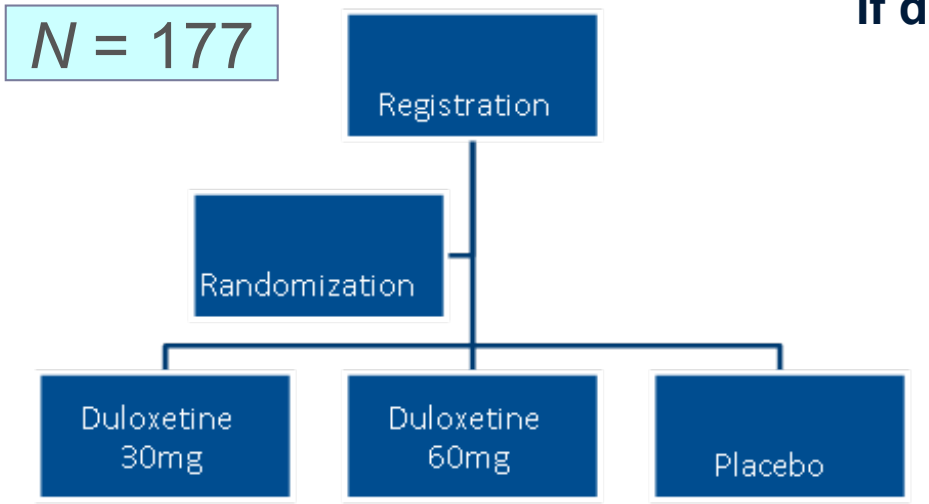
F/U schedule:
q3mo X 1y → q6mo X 2y → q1y X 5y
Colonoscopy at years 3 and 8

EA1151 - TMIST



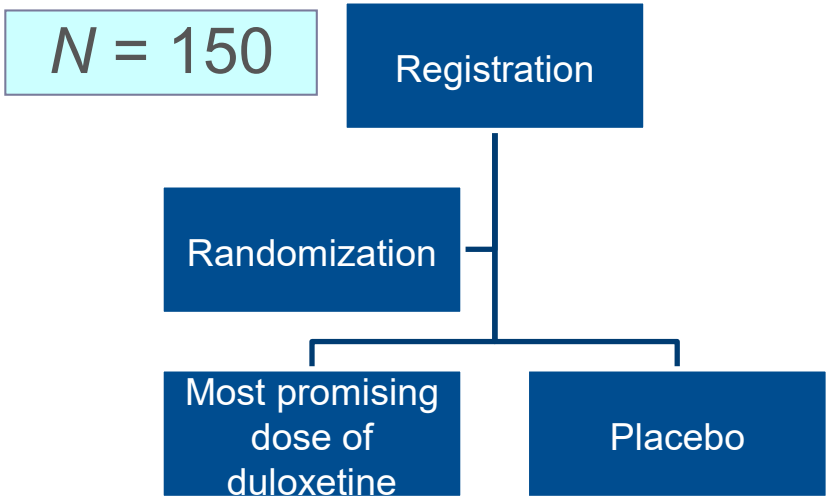
A221805

Schema Phase II



- 3-arm
- Double-blind
- Placebo-controlled
- Stratification
  - Male / Female
  - CAPOX / FOLFOX

Schema Phase III:
If duloxetine is shown to be clinically active



- 2-arm
- Double-blind
- Placebo-controlled
- Stratification
  - Male / Female
  - CAPOX / FOLFOXm

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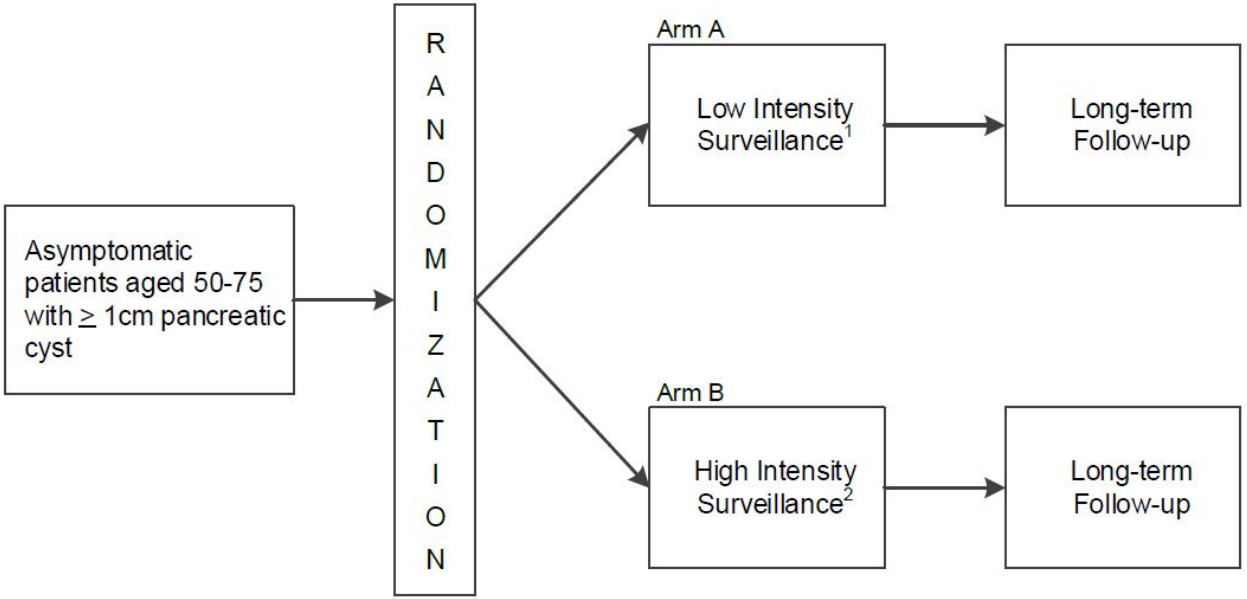
EA2185

Schema



Accrual: n = 4606

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Developing NRG NCORP Trials

Study No.	Disease	Comments
NRG-CC2047 (concept)	Gynecologic Cancer Therapy: The Vaginal Microbiome and Patient Symptom Experience	R01 submitted July 2021
NRG-CC2046 (concept)	Impact of Sentinel Lymph Node Mapping on Patient Reported Lower Extremity Limb Dysfunction in Endometrial Cancer	Pending final DCP review

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Concepts in Development

Concept	Disease	Comments
Improving Outcomes for Younger Breast Ca Survivors: Rand. Phase III Trial Testing the Efficacy of Remote Delivery of Mindfulness Awareness Practices in the NCORP	Breast	NRG NCORP review July 2021
Rand., Blinded, Placebo Controlled Phase 2 Trial of Concurrent ChemoRT w/ and w/out the BMX-001 in Patients with H&N Cancer	Head & Neck	
Endometrial cancer prevention in women with obesity with the levonorgestrel-releasing intrauterine system	Gyn/Endometrial	Developed from pre-LOI from
Stereotactic Pelvic Radiotherapy in Uterine Cancers (SPARTACUS) III	Uterine	
Ph III trial to evaluate limb cryocompression for prevention of paclitaxel-induced peripheral neuropathy	Breast & Gyn	Collaborative NCORP RB concept
Preoperative RT to Improve Cosmetic Outcomes in Breast Ca Pts	Breast	

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Resources for Concept Development

- NRG NCORP Website
  - https://www.nrgoncology.org/Scientific-Program/NRG-NCORP-Research-Base
  - Slide Deck Orientation: Click link under “Learn more about opportunities and working with NRG NCORP”
- CPC Concept Development Form
  - https://www.nrgoncology.org/Scientific-Program/NRG-NCORP-Research-Base/NCORP-Resources
- CPC Pre-LOI Form
  - Contact Erica Field, fielde@nrgoncology.org

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NCORP CPC Contact Information

Cancer Control and Symptom Management

Chair: Lisa Kachnic, MD, FASTRO;
lak2187@cumc.columbia.edu

Vice-Chair: Debra Barton, PhD;
debbartn@med.umich.edu

Cancer Prevention

Chair: Warner Huh, MD

whuh@uabmc.edu

Vice-Chair: Julie Bauman, MD;
jebauman@email.arizona.edu

Budgets/Other NCORP Questions

Erica Field, NCORP Administrator;
fielde@nrgoncology.org

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One year follow up of NRG Oncology CC001

Sunjay Shah, MD
Department of Radiation Oncology
Helen F. Graham Cancer and Research Center
Christiana Care Health System

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NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

One year follow up of NRG Oncology CC001

Sunjay Shah, MD
Department of Radiation Oncology
Helen F. Graham Cancer and Research Center
Christiana Care Health System
Newark, DE

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Helen F. Graham Cancer Center & Research Institute
Cancer Research

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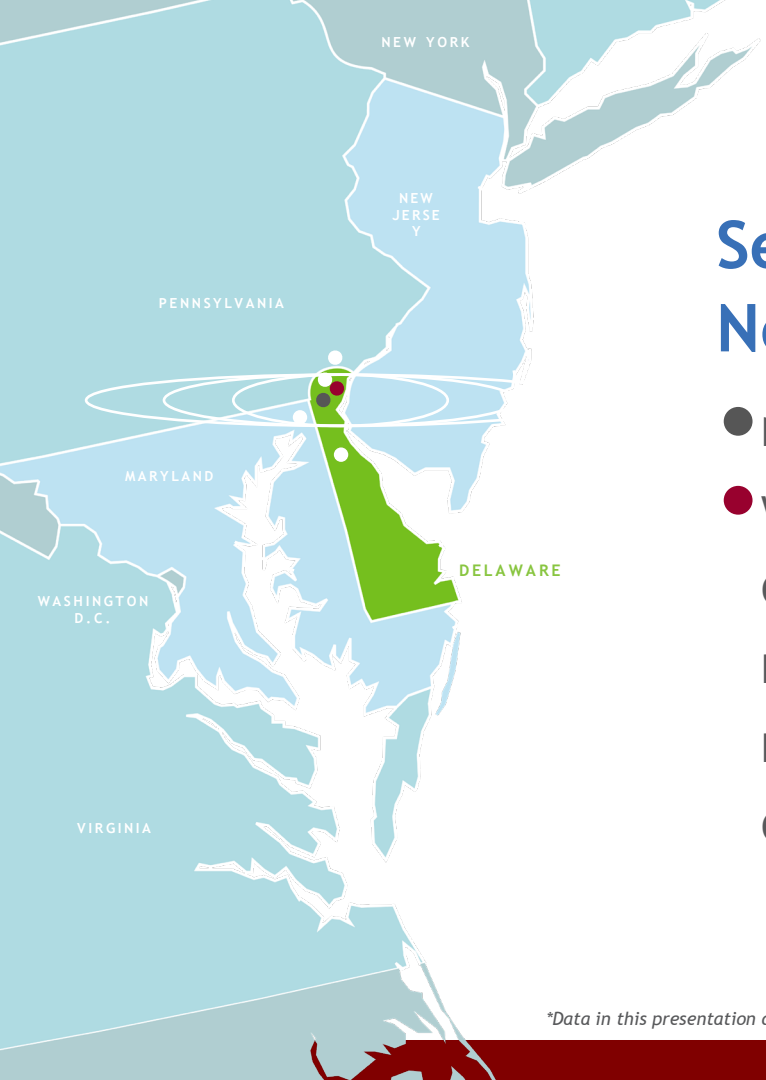


Serving Delaware, Pennsylvania, New Jersey and Maryland

- Newark Campus
- Wilmington Campus
- Concord Campus
- Beebe Health
- Beebe Health – South Coastal Campus
- Cecil County Campus – added Jan 2020

**Data in this presentation does not reflect the addition of Union Hospital and affiliates except where noted.*

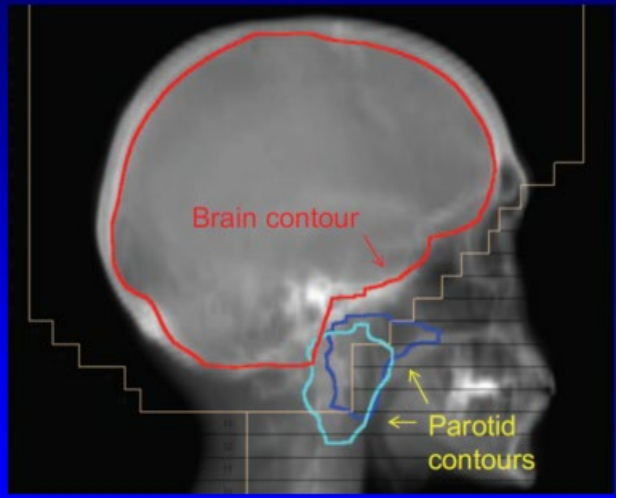
ChristianaCare

Brain mets are a major clinical problem

- Patients with brain metastases are a common clinical problem. 30-40% of lung cancer patients will develop brain metastases at some point.
- Patients present with severe neurological deficits. Chemotherapy has poor efficacy due to the blood/brain barrier.

Whole-Brain Radiation Therapy (WBRT)

- Logistically simple
- Little change in technique over decades
- Toxicity of WBRT (cognitive)
  - Need to decrease toxicity to improve therapeutic ratio of WBRT

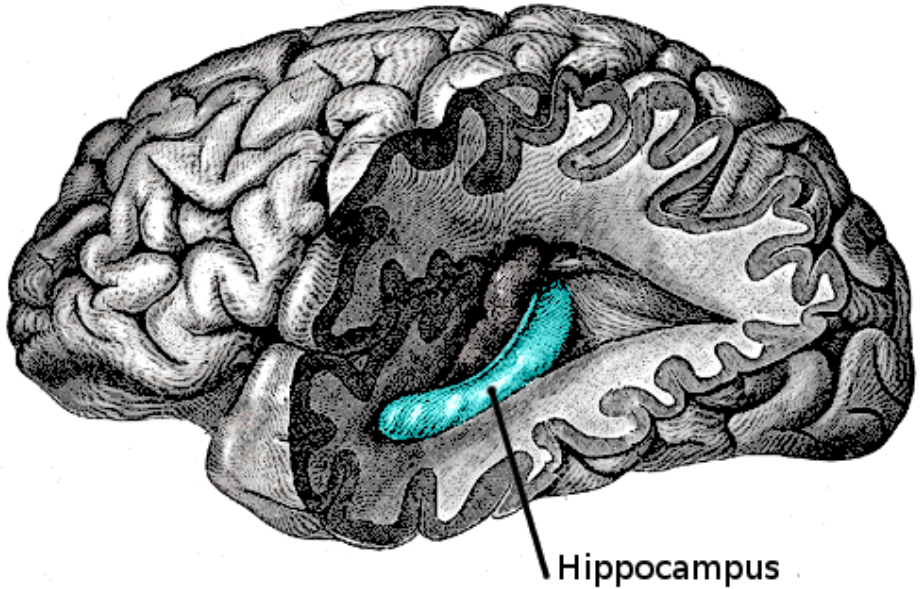


Wang JAMA Onc 2018

The trial has a strong and appealing scientific rationale

- Previous clinical trials had demonstrated a specific early decrease in short term memory in patients receiving whole brain XRT as opposed to executive and fine motor function.
- The hippocampi are the key parts of the limbic system involved with forming episodic and spatial memories. They are located in the medial temporal lobes of the brain.

Hippocampus



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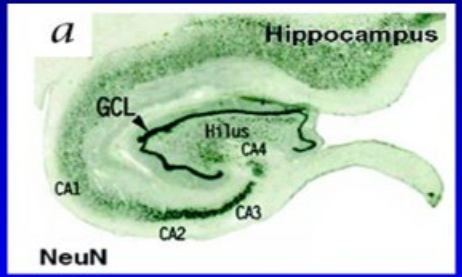
Pathophysiology

- Hippocampus primary site adult neurogenesis
  - Critical for learning and memory
- Hippocampus most sensitive to RT injury

Monje, Curr Op Neuro 2003; Laack, Sem Rad Onc, 2004

Hippocampal Physiology

- Generation of new hippocampal neurons arises from neural stem cells located in the subgranular layer of the hippocampus.
- Hippocampal neurogenesis vital to memory-related function
- 97% reduction in new neurons 2 months after cranial RT



Gondi V, Tome WA, M Mehta, Radiother Oncol 2010
Monje, M et al. Nat Med 2002;8(9):955-962

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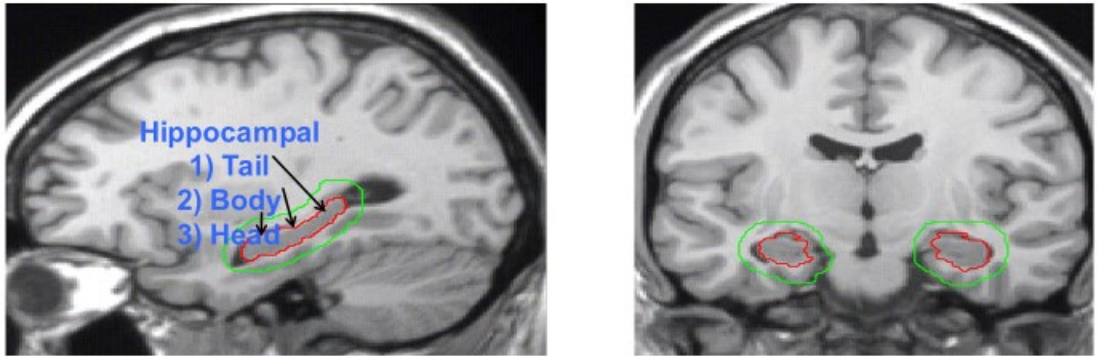
Anatomy of the Hippocampus



Red: Hippocampus **Green: Hippocampal Avoidance Zone**

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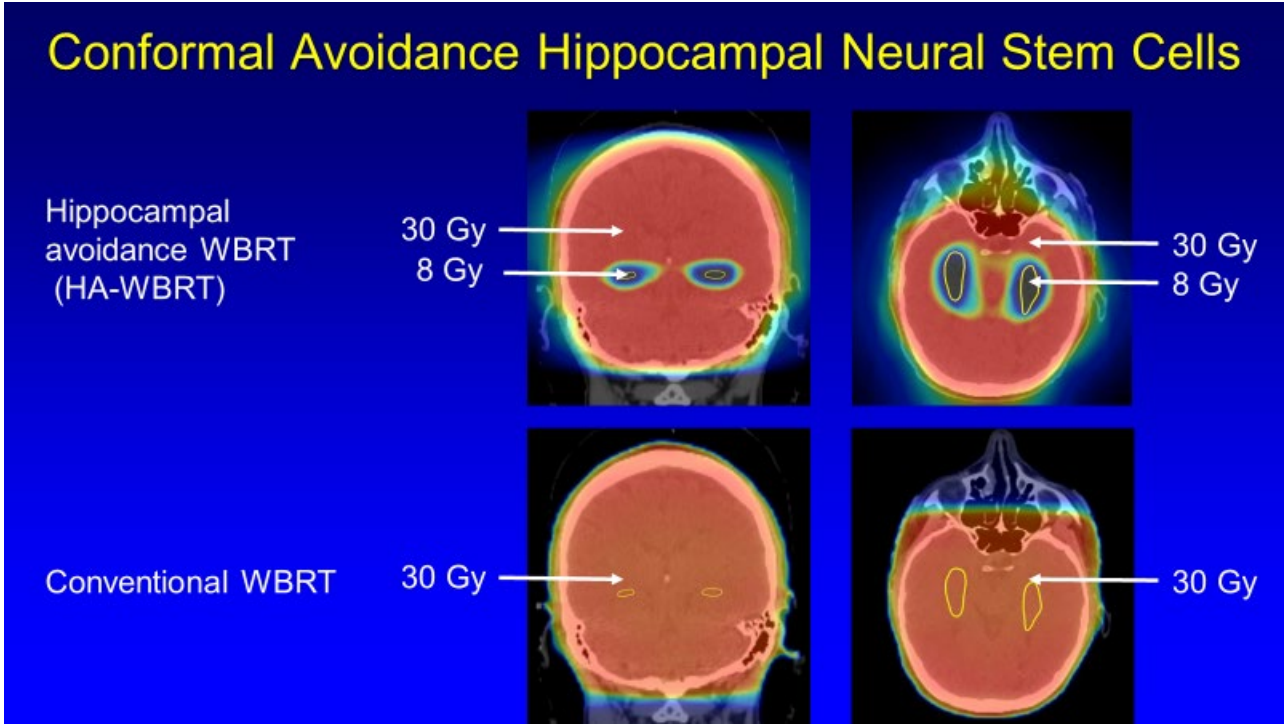
Conformal Avoidance Hippocampal Neural Stem Cells



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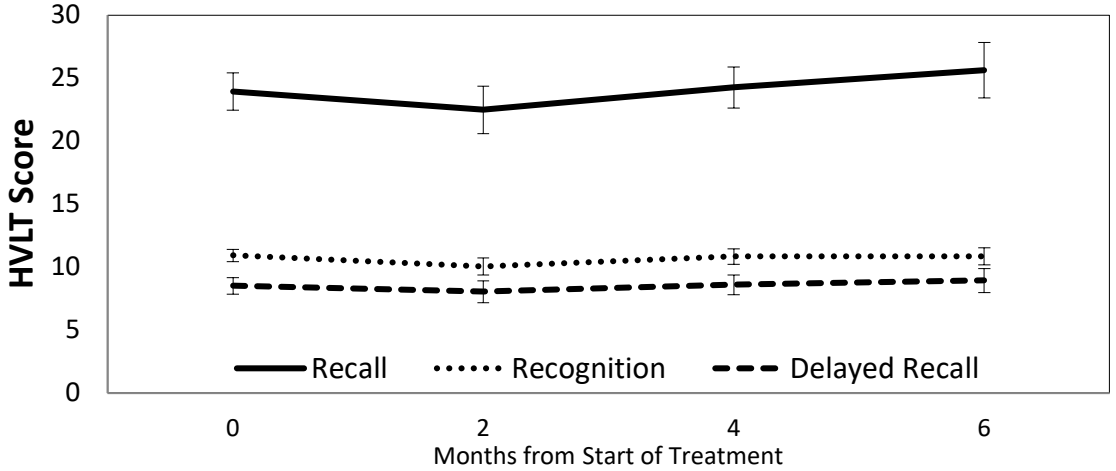
RTOG 0933

- Single-arm phase II trial of HA-WBRT (30 Gy in 10 fractions)
  - Credentialing and central review of hippocampal contouring and IMRT planning



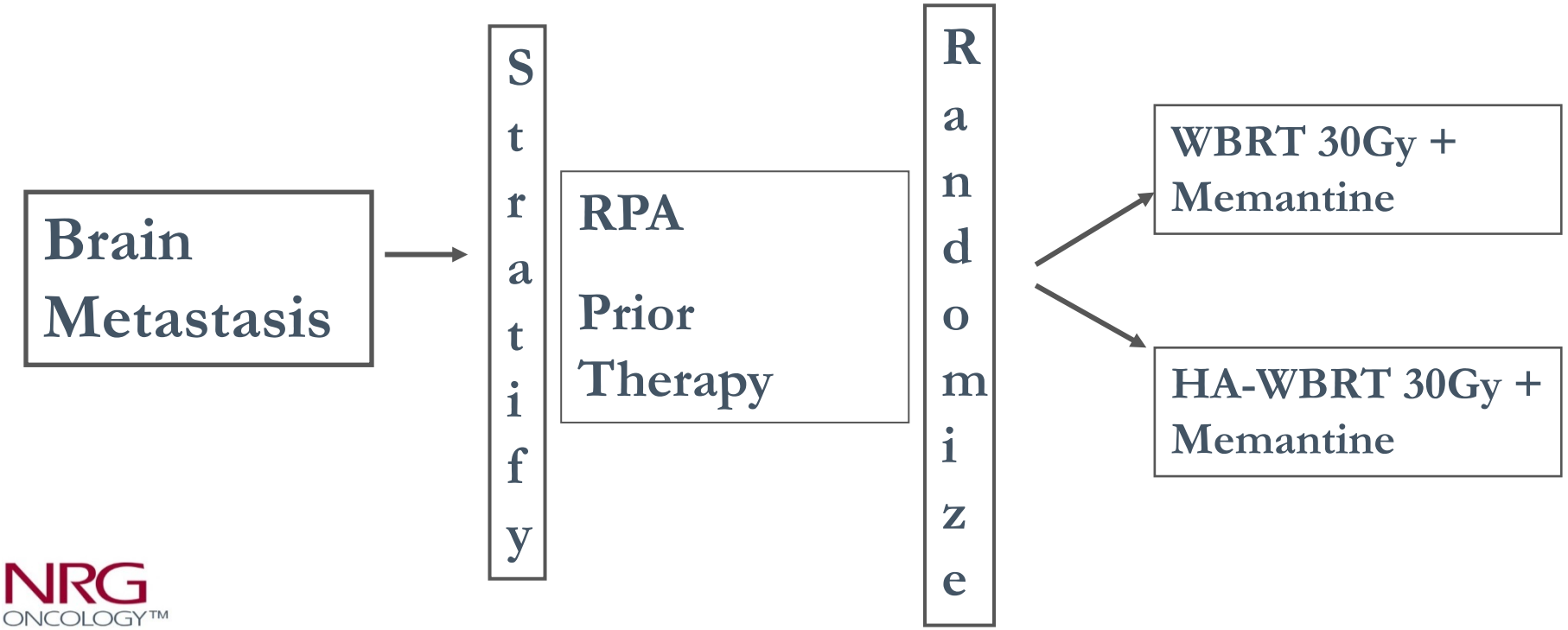
- **Mean decline in HVLT-Delayed Recall from baseline to 4 months:7.0% (95% CI: -4.7-18.7%)**
- Significantly less compared to historical control: 30% (*p*=0.0003)

Need phase III data for level I evidence

Gondi et al. JCO 2014

NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain metastases 5mm outside hippocampus; KPS≥70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing



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Baseline Characteristics

518 randomized patients

Baseline	WBRT+Mem n=257	HA-WBRT+Mem n=261	*p* value
Age	Median 61	Median 62	0.66
RPA class	Class I: 14.8% Class II: 85.2%	Class I: 12.6% Class II: 87.4%	0.48
Neurologic symptoms	None: 46.3% Minor: 33.5%	None: 43.3% Minor: 35.2%	0.83
Primary tumor	Lung 58.8% Breast 17.5%	Lung 59.8% Breast 19.5%	0.81
KPS	70: 20.6% 80: 29.2% 90-100: 50.2%	70: 18.4% 80: 31.0% 90-100: 50.6%	0.38

No differences in baseline patient characteristics, including cognitive function and patient-reported symptom burden

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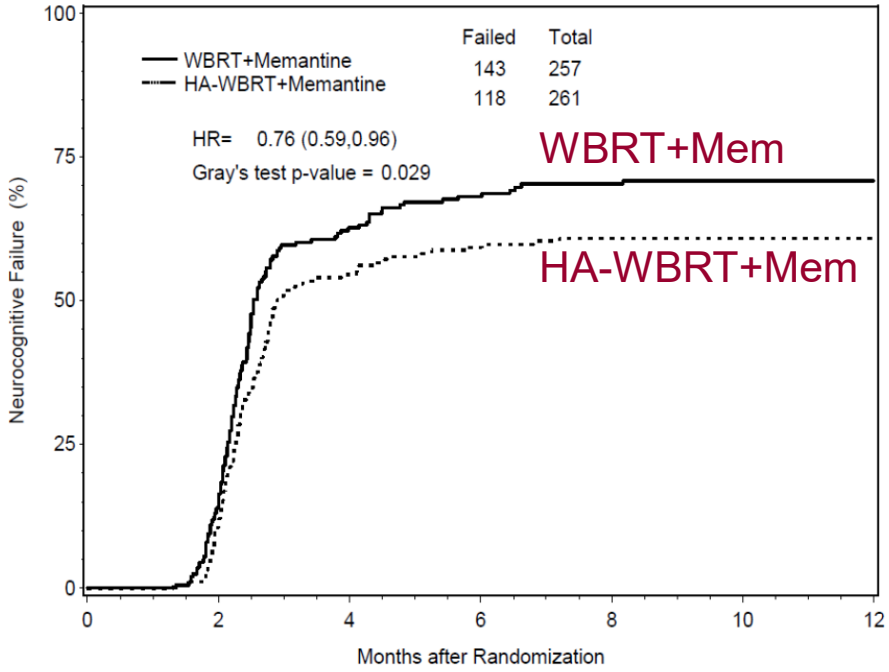
Primary Endpoint

- Hippocampal avoidance <u>prevents cognitive function failure</u>
  - Hazard ratio = 0.756 p=0.029
  - Separation of the curves starting at 3 months and maintained through the follow-up period



Median follow-up for alive patients: **12.1 months**

Cognition Domains at 6 Months

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)

Deterioration at 6 months:

Cognitive Domain	WBRT +Mem n=77	HA-WBRT +Mem n=61	*p*
HVLT-R Total Recall	26.8%	14.7%	0.07
HVLT-R Delayed Recall	30.0%	20.6%	0.19
HVLT-R Recognition	**36.3%**	**17.6%**	**0.011**
Trail Making Test Part A	28.0%	17.6%	0.13
Trail Making Test Part B	35.9%	23.9%	0.12
Controlled Oral Word Association	6.2%	11.8%	0.23

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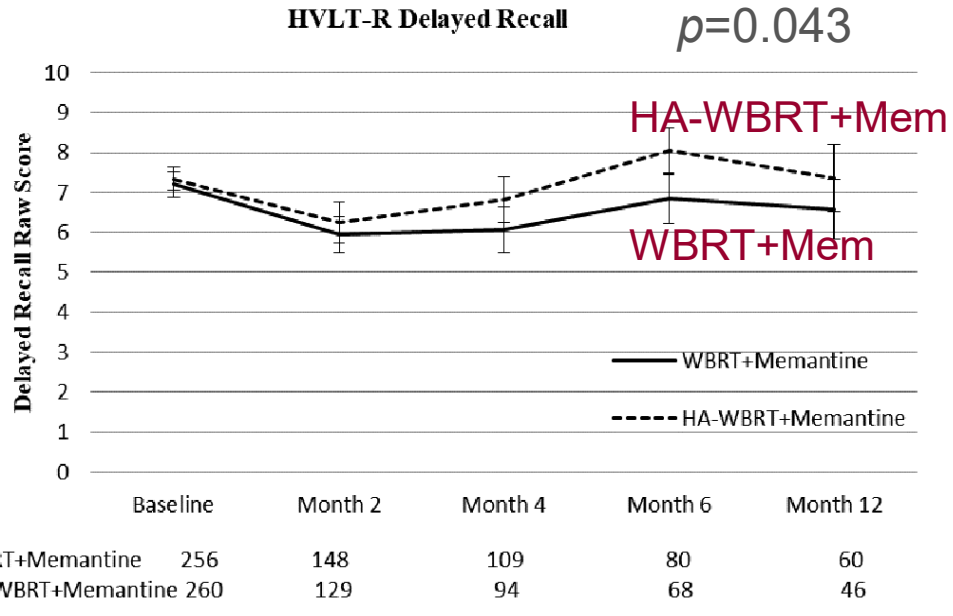
Median follow-up for alive patients: **12.1 months**

Cognition Domains Over Time

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)
- Hippocampal avoidance preserves all learning and memory domains over time
  - HVLT-R total recall, delayed recall and recognition

Mixed effects models using multiple imputation:



Higher score indicates better performance

Median follow-up for alive patients: **12.1 months**

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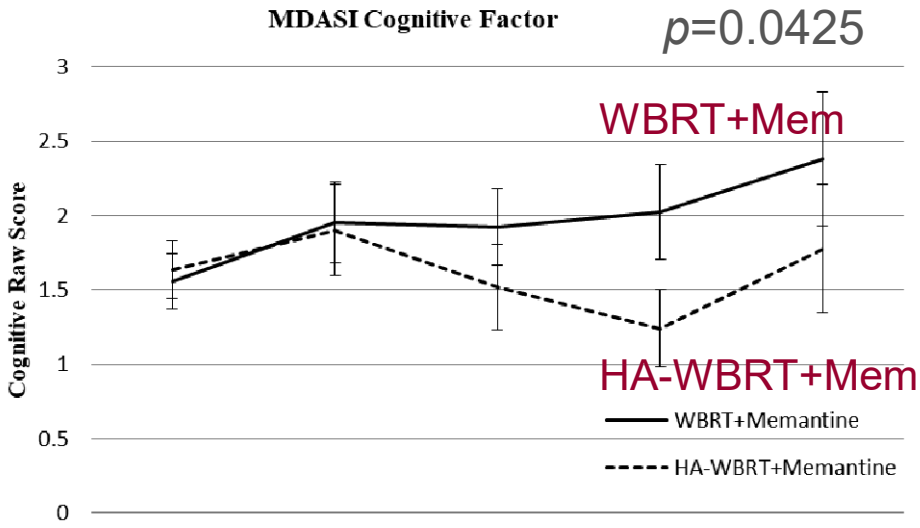
Patient-Reported Outcomes

- Hippocampal avoidance preserves patient-reported symptoms at 6 months:
  - Neurologic symptom burden
  - Interference of neurologic symptoms in daily activities
- Hippocampal avoidance preserves patient-reported cognitive factor over time:
  - Hippocampal avoidance associated with less problems remembering things at 6 months (p=0.016)

Mixed effects models using multiple imputation:



Higher score indicates more symptoms

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Median follow-up for alive patients: **12.1 months**

Survival

Toxicity	WBRT+Mem n=257	HA-WBRT+Mem n=261	*p* value
Intracranial Progression-Free Survival	Median: 5.3 months 95% CI: 4.7-6.0	Median: 5.0 months 95% CI: 4.4-6.2	**0.076**
	HR = 1.20 95% CI: 0.98-1.47		
Overall Survival	Median: 7.6 months 95% CI: 5.8-10.1	Median: 6.3 months 95% CI: 4.0-7.7	**0.242**
	HR = 1.14 95% CI: 0.91-1.43		

No significant differences in intracranial PFS or overall survival

HA region relapses:

HA-WBRT+Mem 11 WBRT+Mem 17

Median follow-up for alive patients: **12.1 months**

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NRG CC001: Conclusions

- Hippocampal sparing during WBRT plus memantine for brain metastases preserves cognitive function and patient-reported symptoms

  - Similar toxicity, **intracranial PFS and overall survival** outcomes
  - Benefits in executive functioning at 4 mos and learning and memory at 6 mos
  - Better patient-reported cognition, symptom interference, fatigue, difficulty speaking, and problems remembering things at 6 months

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Brown, Gondi et al JCO 2020

Conclusions

NCCN Guidelines Version 1.2019
Central Nervous System Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Brain Metastases

- **WBRT: Doses vary between 20 and 40 Gy delivered in 5–20 fractions.**
  - **The standard regimens include 30 Gy in 10 fractions or 37.5 Gy in 15 fractions.**
  - **Nevertheless, 20 Gy in 5 fractions is a good option for patients with poor predicted prognosis.[19]**
  - **For patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.[20]**
  - **For patients with a better prognosis (4 months or greater), consider hippocampal-sparing WBRT.[21-22]**

For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.

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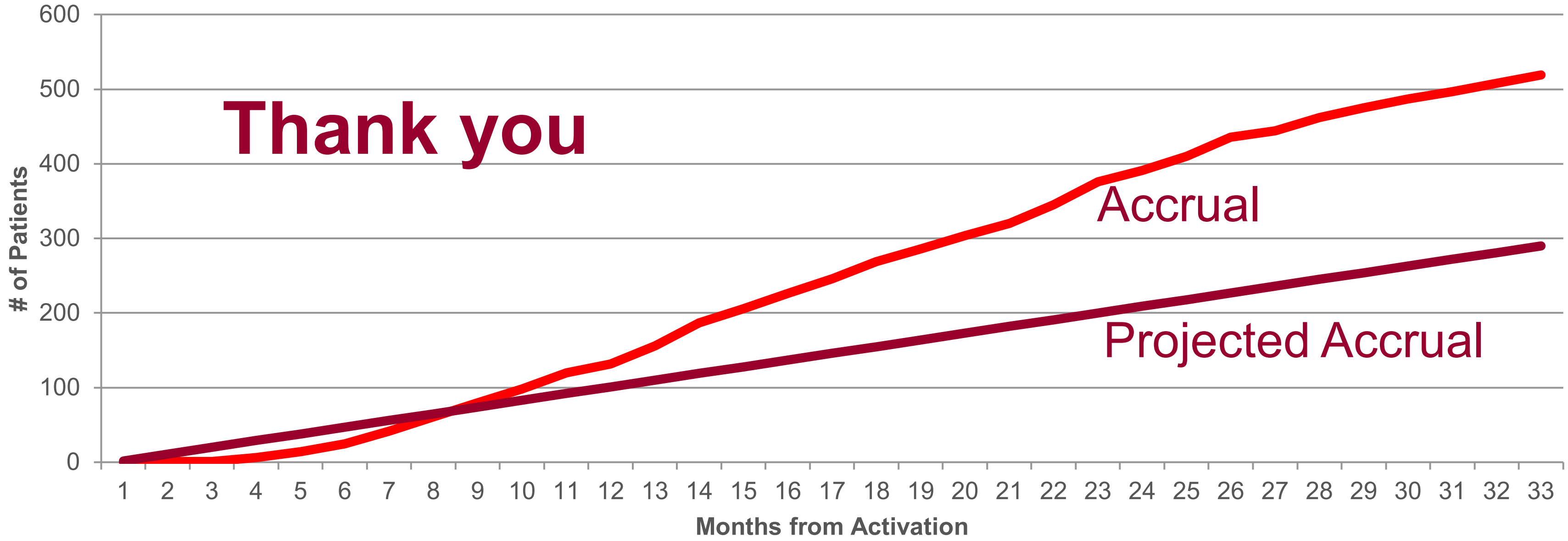
NRG CC001 Accrual

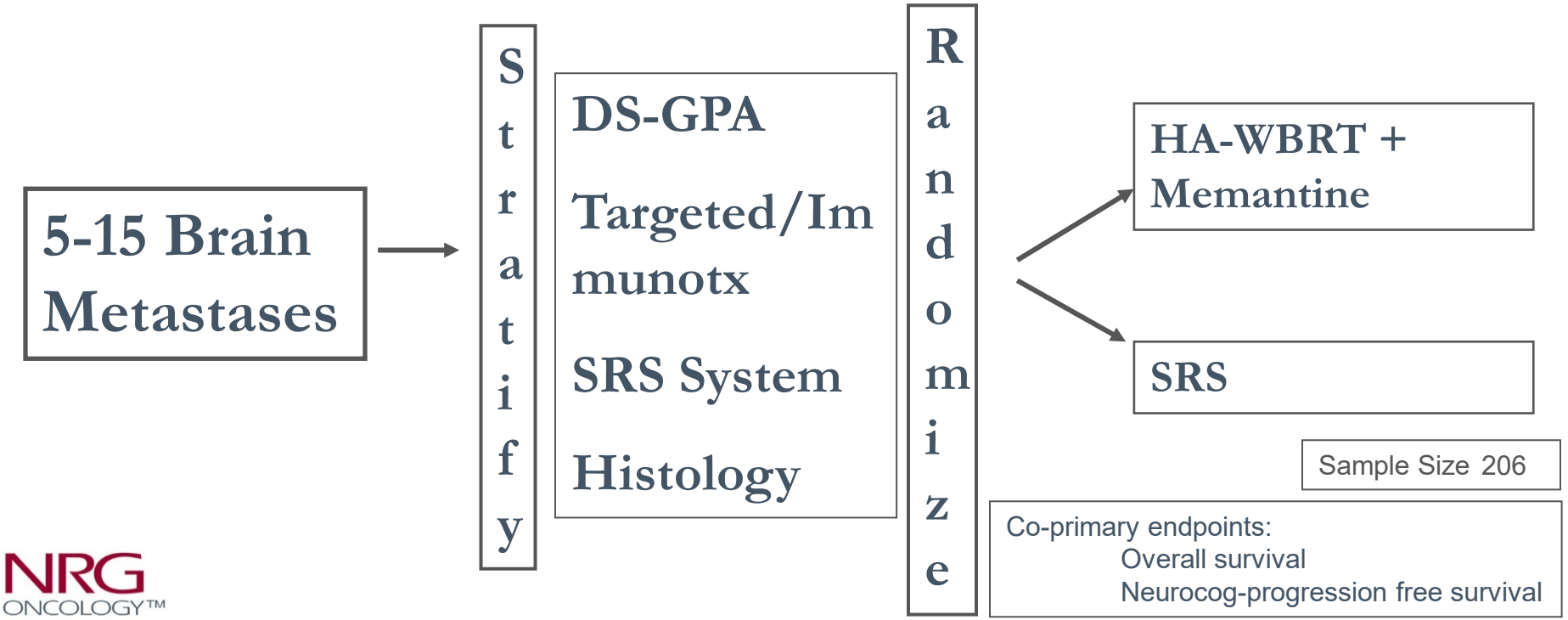


Community sites can develop safe approaches to deliver WBRT

Accrual 16 pts/month Completed 2 years earlier than projected

CCTG CE.7: Phase III Trial Stereotactic Radiosurgery versus Hippocampal Avoidant WBRT+memantine for 5-15 Brain Metastases

Basic Eligibility: 5-15 brain mets; largest met <2.5cm; total brain met vol ≤30cc



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RTOG 1203

Ann Klopp, MD, PhD
Associate Professor
Director of Radiation Oncology Gynecological Services
Center Medical Director, COVID Vaccine Clinic The University of Texas MD Anderson Cancer Center

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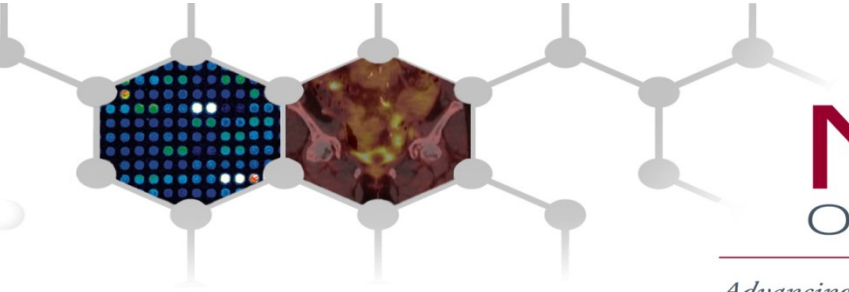

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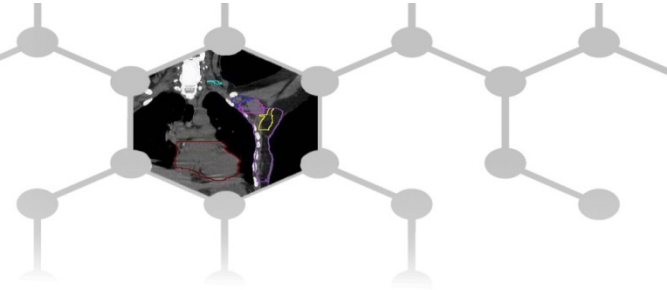

IMRT improves late toxicity compared to conventional RT: An update on NRG Oncology-RTOG 1203

Anamaria Yeung, MD, Stephanie Pugh, PhD, Ann Klopp, MD, PhD, Karen Gil, PhD, Lari Wenzel, PhD, Shannon N. Westin, MD, MPH, Andre Konski, MD, MBA, MA, FACR, J. Spencer Thompson, MD, Desiree E. Doncals, MD, Guilherme H.C. Cantuaria, MD, David P. D'Souza, MD, Amy Chang, MD, Vijayananda Kundapur, MD, Dasarahally S. Mohan, MD, Michael L. Haas, MD, Yong Bae Kim, MD, Catherine L. Ferguson, MD, Lisa A. Kachnic, MD, Deborah Bruner, PhD

ASTRO 2019
September 17, 2019

Disclosures

- I have no disclosures to report.

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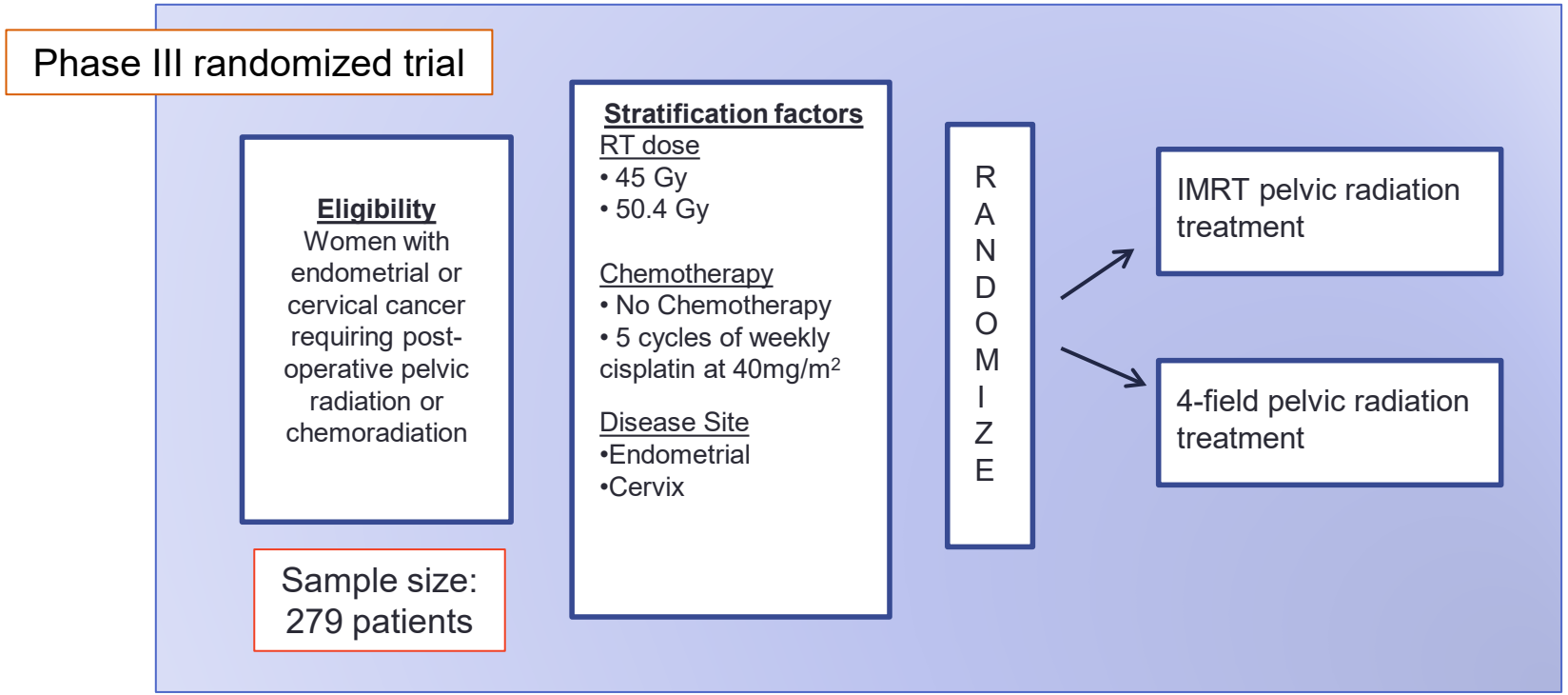
NRG Oncology RTOG 1203 Schema



Objectives

Primary Objective:

- To determine if **acute GI toxicity** is reduced with IMRT in week 5 of RT using patient reported measure of toxicity (EPIC Bowel)

Secondary Objectives:

- Acute urinary toxicity (EPIC tool)
- Quality of life (FACT-G)
- LRC, DFS, OS
- Validate EPIC in women
- Health utilities analysis

Median f/u for all patients: 37.8 months

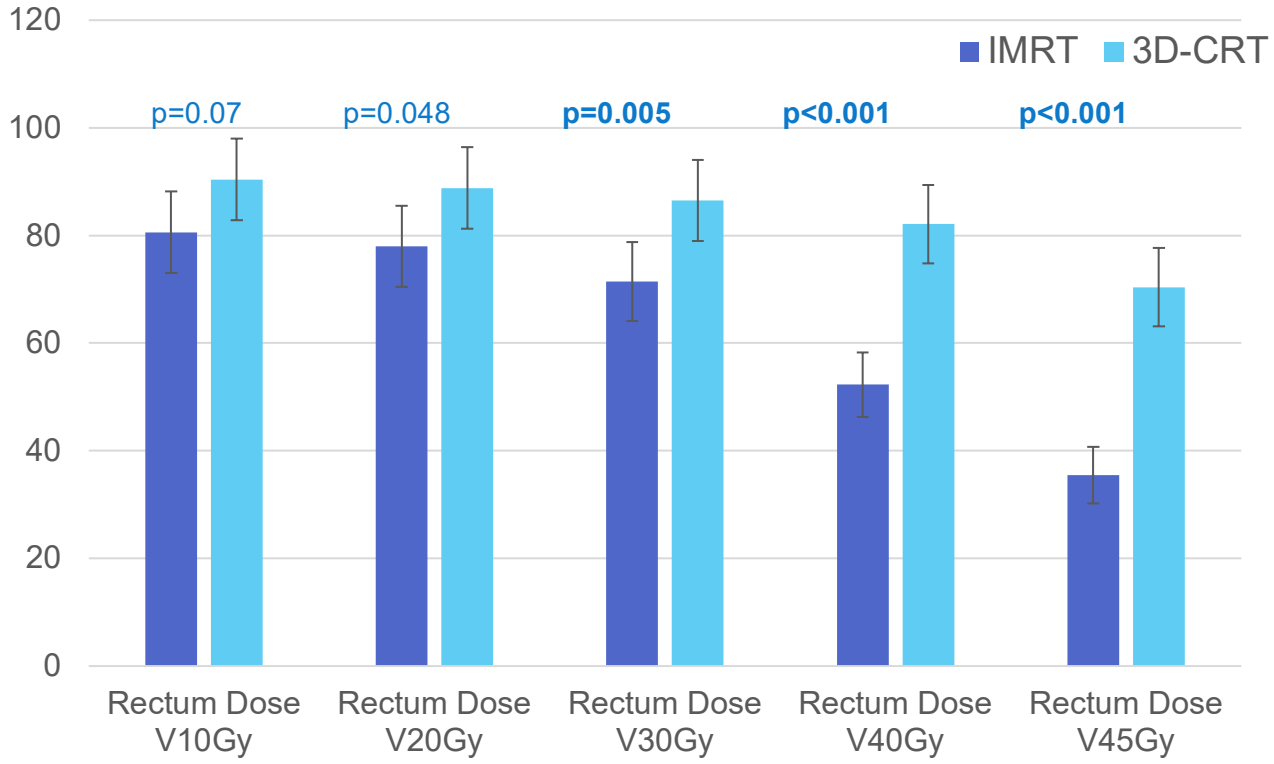
Time Point	Purpose
Before RT	Baseline
3 weeks after RT start	Compare early acute toxicity
End of RT (5 weeks after RT start)	Maximum difference in acute toxicity
4-6 weeks after RT	Compare resolution of acute toxicity
1 year from the start of RT	Early chronic toxicity
3 years from the start of RT	Long term toxicity

Disease Outcomes

- There were no differences between arms.

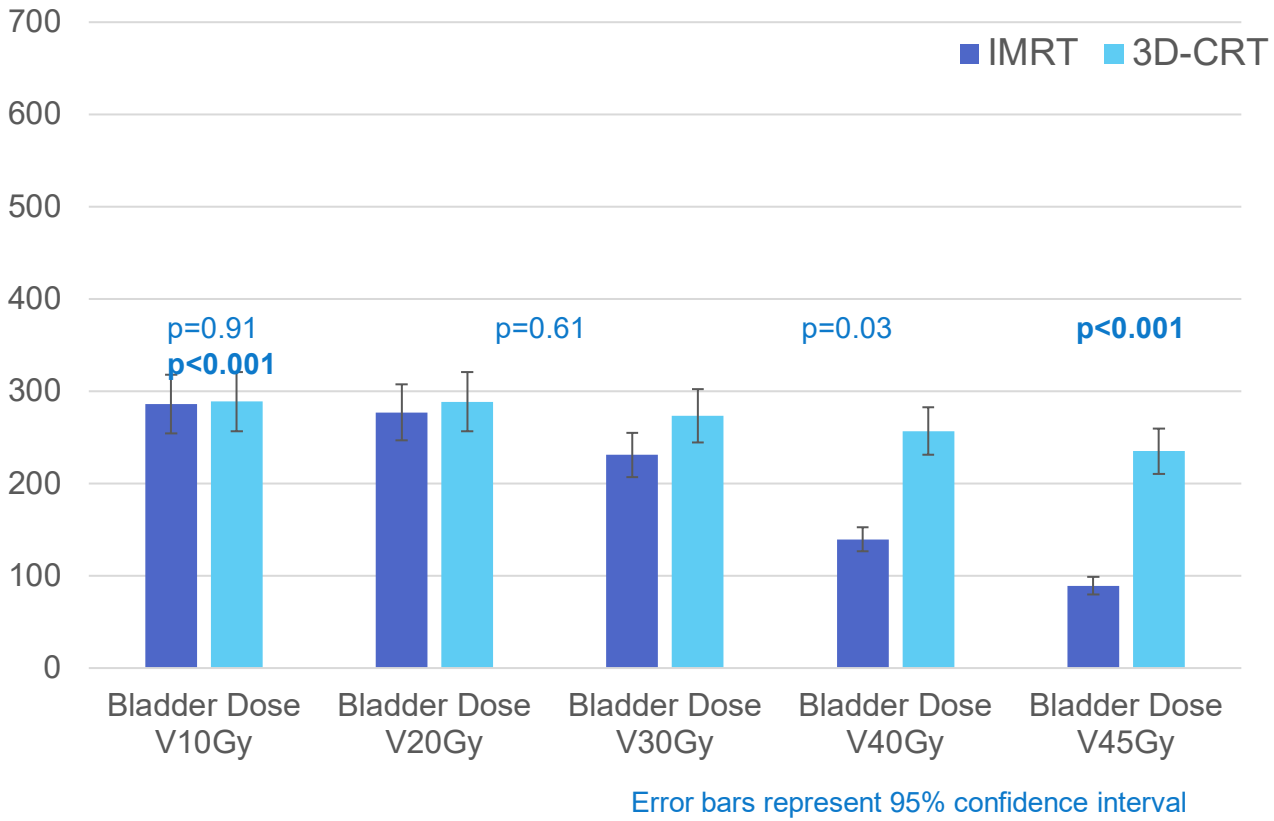
	2yr LRF	2yr DFS	2yr OS
IMRT	2.6%	89.1%	95.1%
4 Field	1.4%	86.1%	99.3%
HR (95% CI)	0.82 (0.20, 3.27)	1.39 (0.82, 2.35)	0.76 (0.32, 1.79)
p-value	0.81 (Gray's test)	0.21 (log-rank)	0.53 (log-rank)

Results: Mean Rectum Doses by Treatment



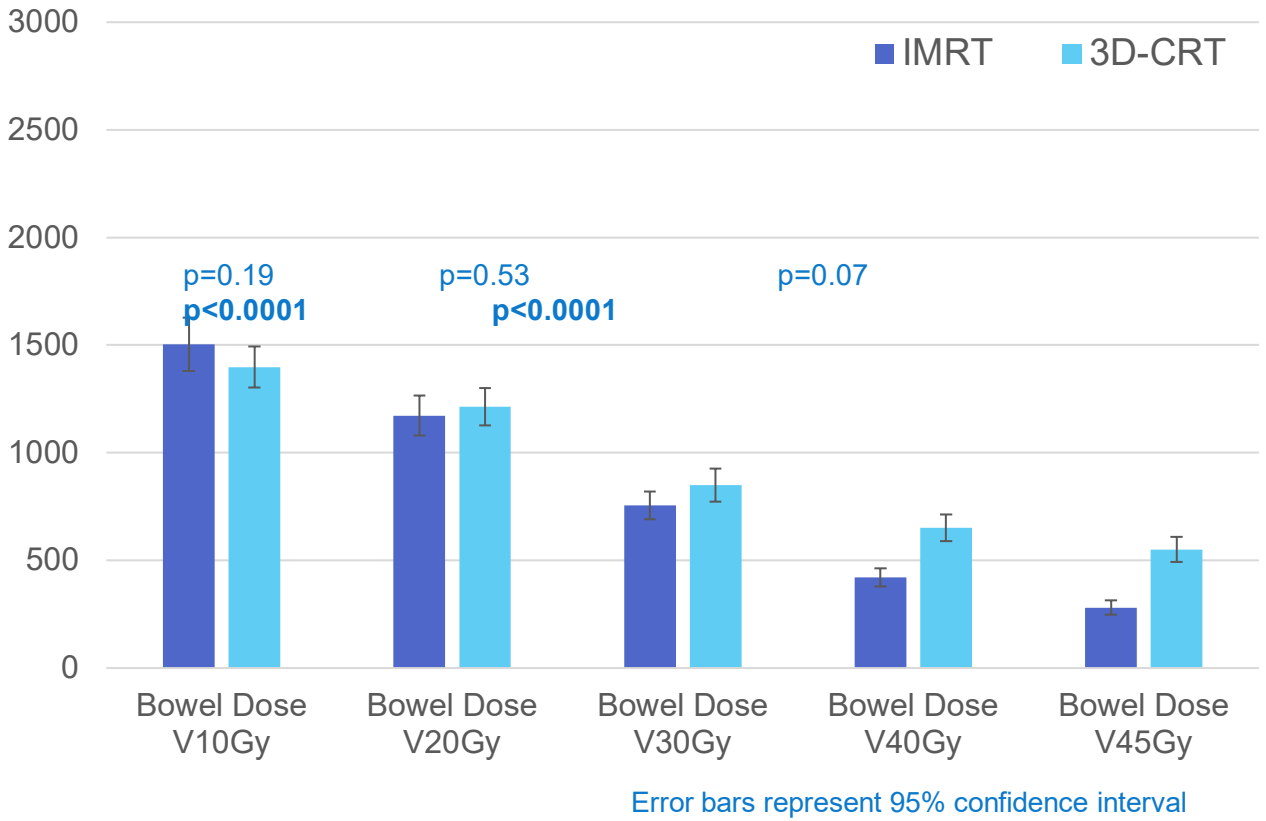
Error bars represent 95% confidence interval

Results: Mean Bladder Doses by Treatment

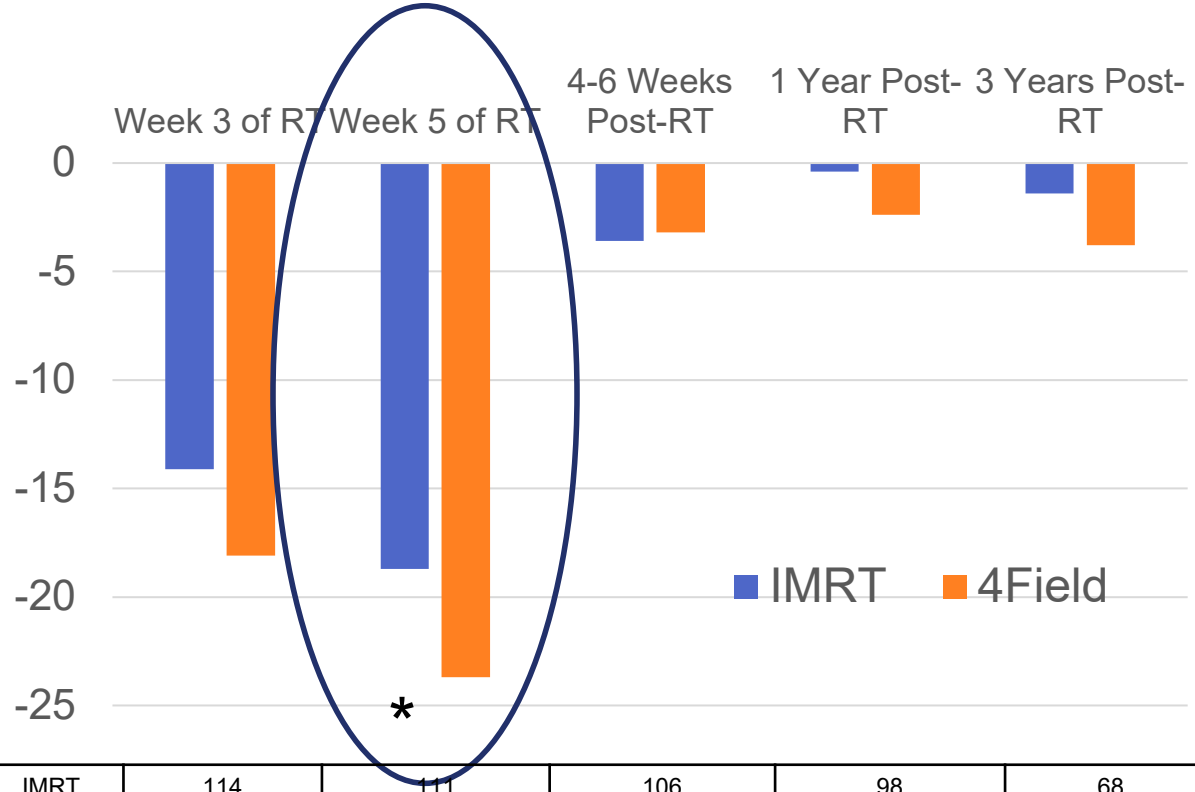


Error bars represent 95% confidence interval

Results: Mean Bowel Dose by Treatment



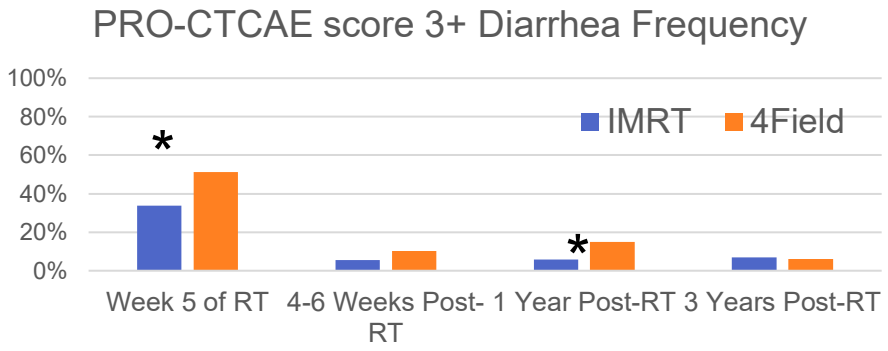
Patient-Reported Bowel Toxicity (EPIC)

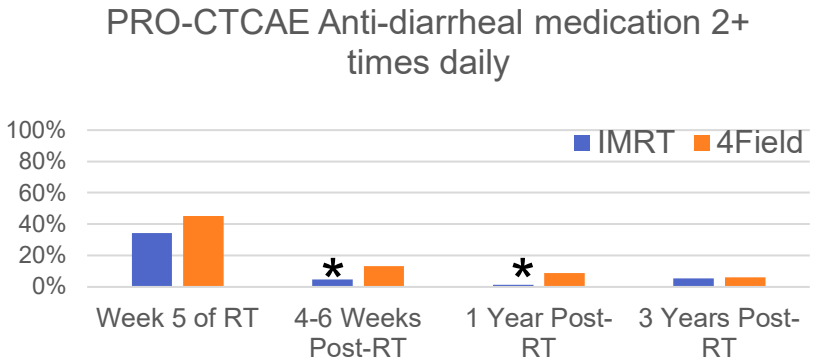


IMRT	114	111	106	98	68
4Field	134	130	131	114	79

* $p < 0.05$

Patient-Reported Diarrhea (PRO-CTCAE)

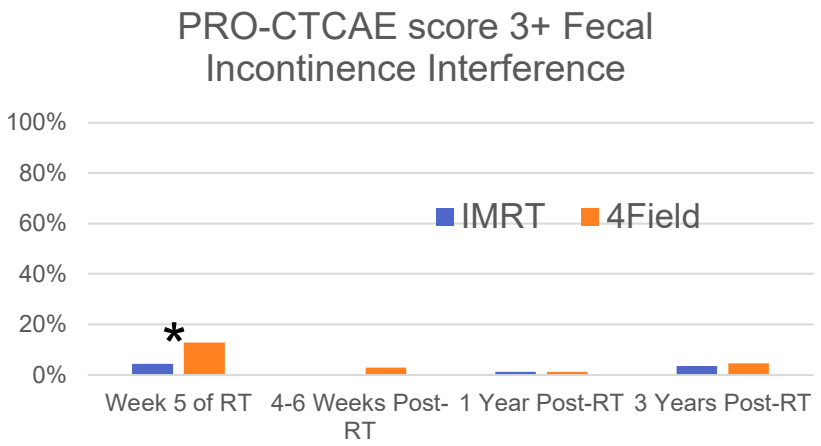


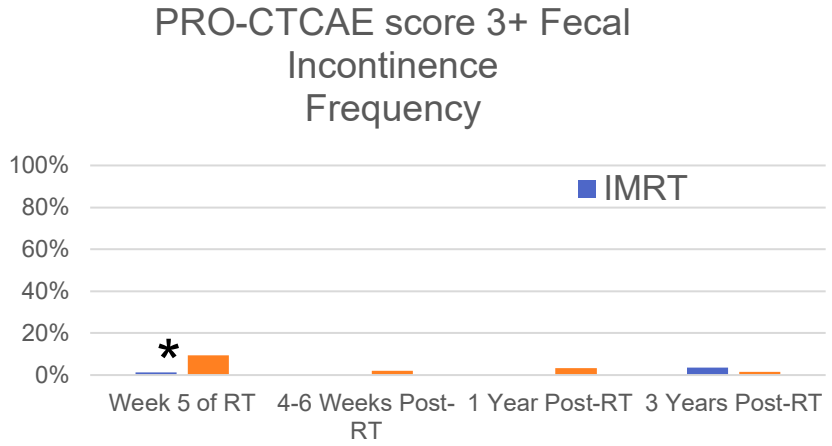


IMRT	92	88	87	58
4Field	109	108	93	66

* $p < 0.05$

Patient-Reported Fecal Incontinence (PRO-CTCAE)

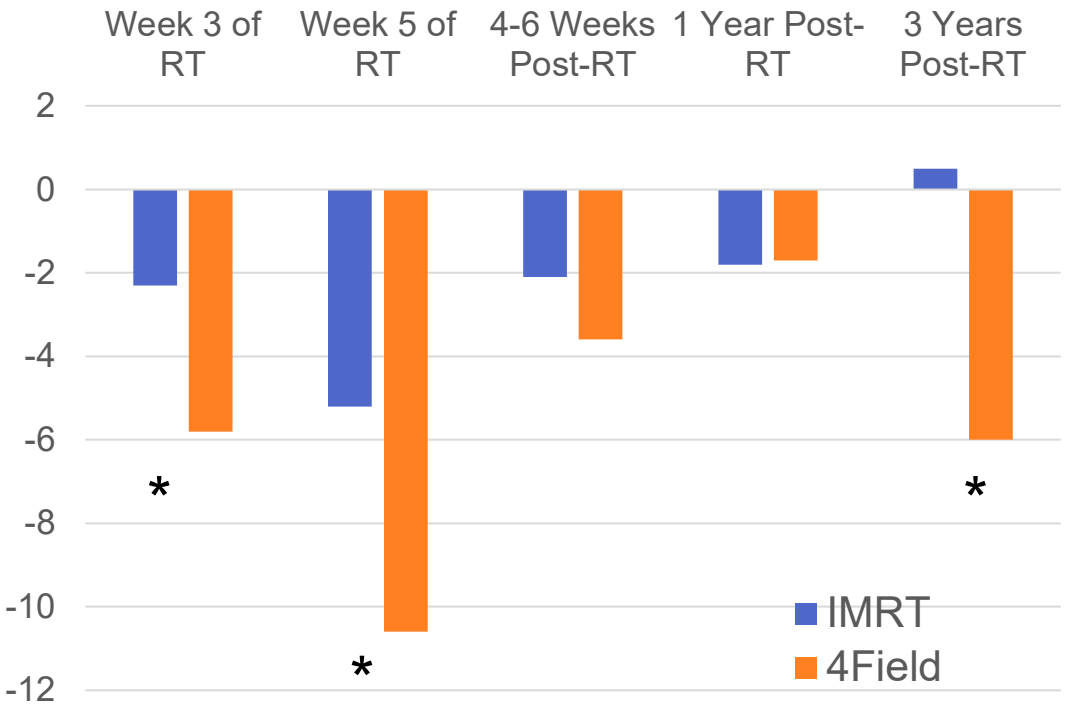




IMRT	92	88	87	58
4Field	109	108	93	66

* $p < 0.05$

Patient-Reported Urinary Toxicity (EPIC)



IMRT	114	111	106	98	68
4Field	134	130	131	114	78

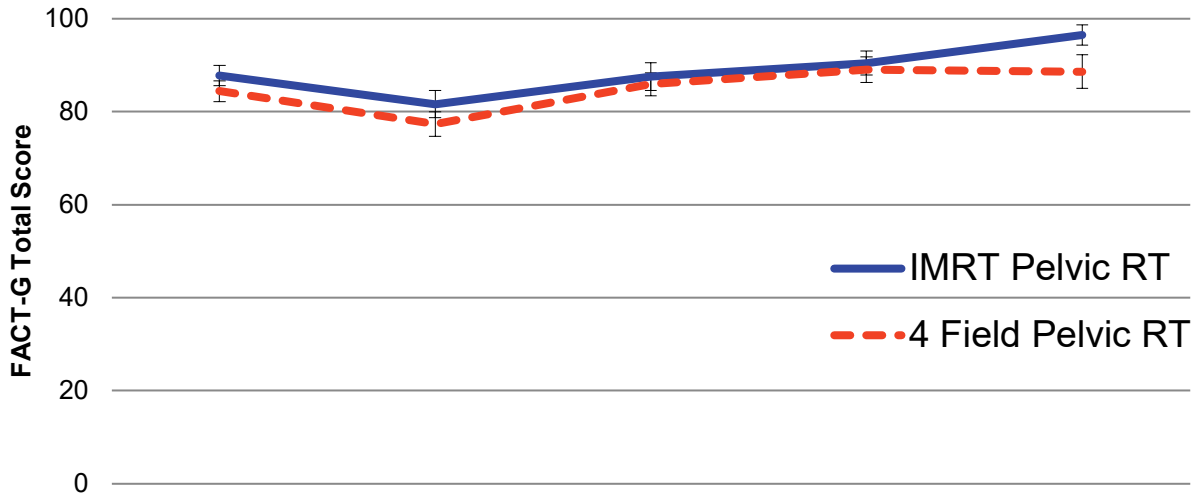
* $p < 0.05$

Physician-reported toxicity (CTCAE v4)

- No difference between arms

	Acute Toxicity Grade 2+		Late Toxicity Grade 2+	
	GI	**GU**	**GI**	**GU**
IMRT	26.4%	4.6%	11.2%	0
4 Field	21.5%	6.0%	11.8%	0
p value	0.35	0.60	0.88	N/A

Quality of Life – FACT-G Total Score



IMRT	107	91	89	86
56				
4Field RT	124	110	111	94

Conclusions

- In comparison with 3DCRT, IMRT reduces patient-reported:
  - Acute GI adverse events (EPIC Bowel and PRO-CTCAE diarrhea and fecal incontinence at 5 wks of RT)
  - Acute urinary adverse events (EPIC Urinary at 5 wks of RT)
  - **Late GI adverse events (PRO-CTCAE diarrhea at 1 year post-RT)**
  - **Late urinary adverse events (EPIC Urinary at 3 years post-RT)**

- No difference in disease outcomes at 2 years.

Acknowledgments…

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Questions

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GOG 0273 Secondary Endpoint

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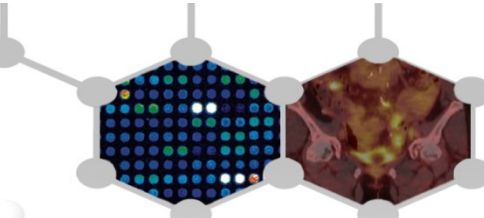

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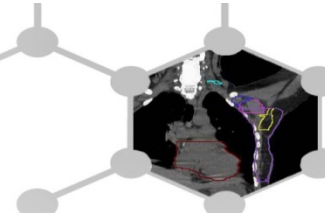

GERIATRIC ASSESSMENT AND OUTCOMES WITH CARBOPLATIN AND WEEKLY LOW-DOSE PACLITAXEL IN ELDERLY WOMEN WITH OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER: A GYNECOLOGIC ONCOLOGY GROUP STUDY (GOG273, Arm 3).

William Tew, Helen Huang, Vivian Von Gruenigen, Arti Hurria, Thomas Herzog, Lisa Landrum, Ritu Salani, Shashikant Lele, Michael Pearl, Angeles Alvarez Secord, James Fiorica, Tina Rizack, William E. Richards, Gini Fleming

1Dept of Medicine, Gynecologic Medical Oncology Service, Memorial Sloan Kettering Cancer Center, NY, 2GOG Statistics and Data Center, Buffalo, NY, 3Summa Akron City Hospital, Akron, OH, 4City of Hope, Duarte, CA, 5University of Cincinnati Cancer Institute, Cincinnati, OH, 6University of Oklahoma, OK, 7The Ohio State University Wexner Medical Center, OH, 8Roswell Park Cancer Institute, Buffalo, NY, 9Stony Brook University Hospital, Stony Brook, NY, 10Duke Cancer Center, NC, 11Indiana University, Bloomington, 12Women and Infants Hospital Rhode Island, RI, 13Candler Hospital, GA, 14University of Chicago, Chicago, IL , United States

Disclosures

- No conflicts of interest needed to disclose

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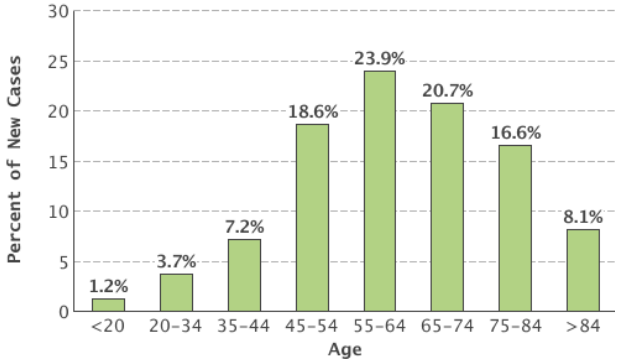
Ovarian Cancer in Older Adult



- **Median Age = 64yo;**
  - One-third are 70yo or older.
- **Older women with ovarian cancer:**
  - 2-fold increased death risk.
    - Higher co-morbidities
    - Less likely to undergo complete staging surgery and receive standard chemotherapy
    - Delay in diagnosis and treatment
    - Higher toxicity to treatments
    - Different biology

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GOG Upfront trials

Trial: Platinum-based upfront tx	Age >60	Age >70 (30% US OvCa population)	Age >80
GOG 273 – Arm1/2**	100%	100%	26%
GOG 262	55%	21%	4%
GOG 218	50%	18%	2%
GOG 172	38%	11%	1%

Development of age-specific trials **

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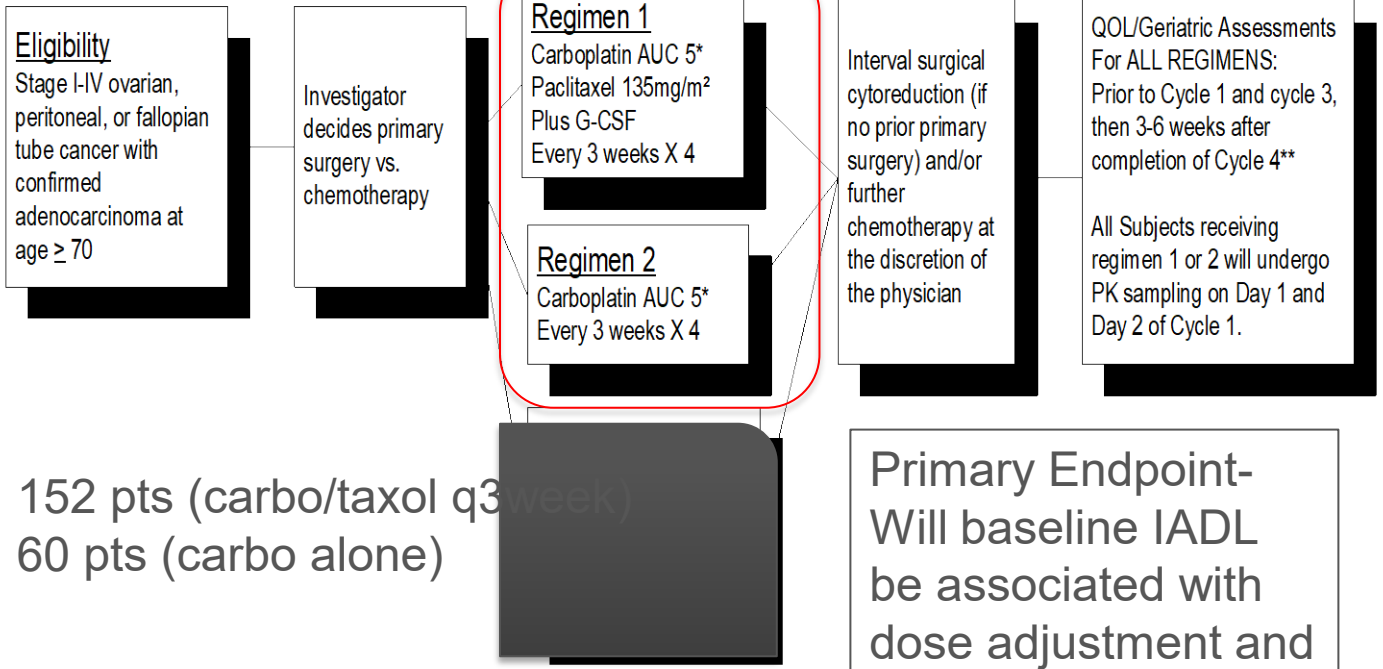
GOG 273

This is a prospective observational study, not a comparison of treatment regimens.



152 pts (carbo/taxol q3 week)
60 pts (carbo alone)

Primary Endpoint-
Will baseline IADL be associated with dose adjustment and delays

Once Regimen I and 2 complete accrual, these two treatments arms will be closed
*Patients for whom the physician deems a carboplatin dose of AUC 5 to be unsafe, may be given an AUC of 4.
**For patients unable to complete 4 cycles, perform QOL/geriatric assessments at 12-15 weeks after initiating study treatment.

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GOG 273 Arm I and II: Conclusions

Baseline IADL was associated with:

- Chemo regimen choice
- Chemo completion regardless of dose delay/adjustments
- Grade 3+ toxicity
- Overall survival (in CP group only).

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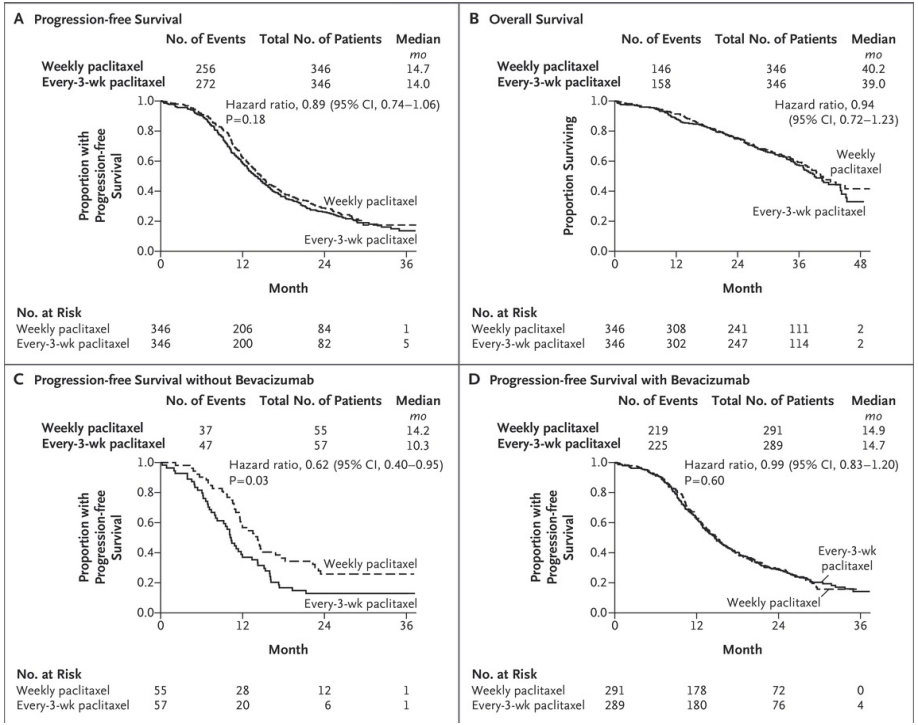
VonGuenigen, Huang, Beumer, Lankes, Tew, Herzog, Hurria et al, Gyn Oncol, 2016

Compare Weekly dd Paclitaxel versus q3 week Paclitaxel, Combined w/ Carboplatin q3week (BV optional)



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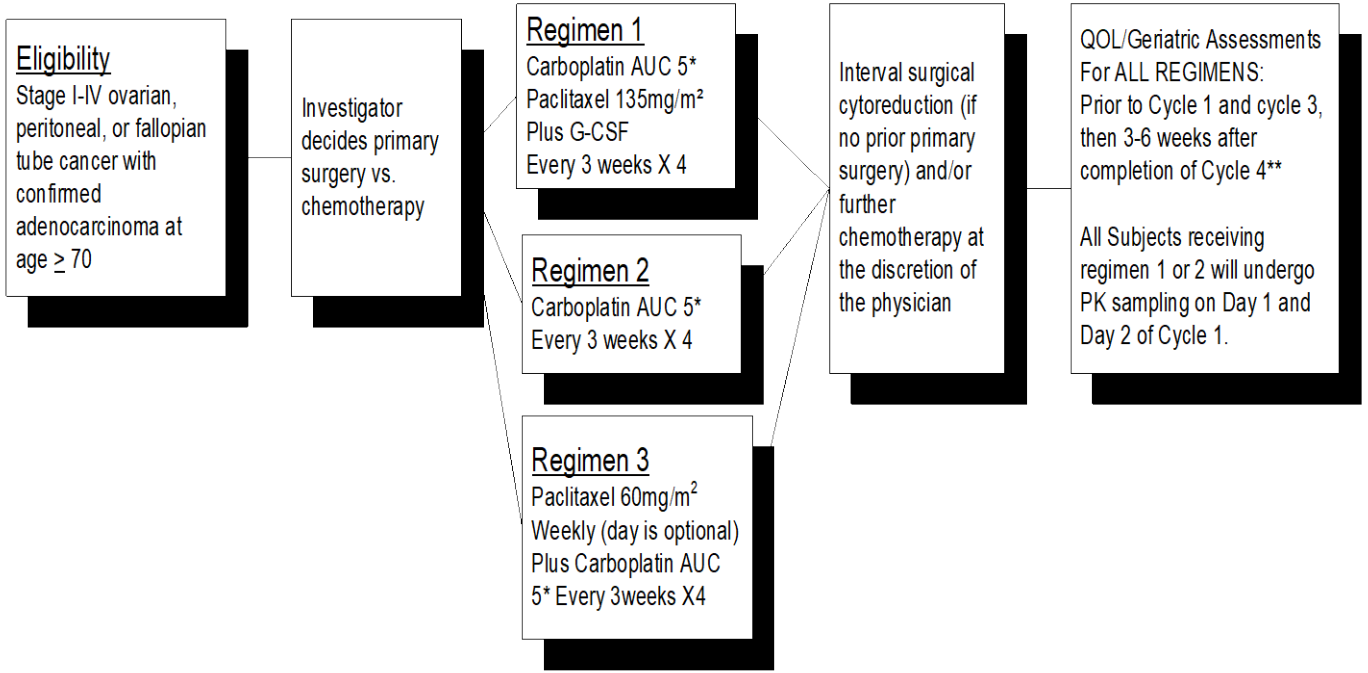
Chan JK et al. N Engl J Med 2016;374:738-748.

GOG 273

This is a prospective observational study, not a comparison of treatment regimens.
All patients entered after 8/12/2013 will receive Regiment 3 treatment.



Once Regimen I and 2 complete accrual, these two treatments arms will be closed. Regimen 3 will open as a single arm study

*Patients for whom the physician deems a carboplatin dose of AUC 5 to be unsafe, may be given an AUC of 4.

**For patients unable to complete 4 cycles, perform QOL/geriatric assessments at 12-15 weeks after initiating study treatment.

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GOG 273 Arm 3

Primary Objective:

- Explore the association between a baseline Geriatric Risk Score (GRS) and the patient's ability to complete 4 cycles of carboplatin q3week and paclitaxel qweek without dose reduction or >7-day treatment delays.

- To estimate the percentage of patients who are able to complete 4 cycles of chemotherapy.

Secondary Objectives:

- Explore reasons for treatment delays and dose reductions

- Explore whether age, baseline scores on geriatric measures (function, nutrition, comorbidity) and QOL are correlated with completed 4 cycles of chemotherapy.

- Describe chemotherapy toxicities.

- Describe QOL and other patient reported outcomes over time.

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GA Measures (via Arm 1 and 2)

- Instrumental Activities of Daily Living (IADL) (7 items).
- Activities of Daily Living (ADL) (10 items).
- FACT-O (38 items). The FACT-O score ranges 0-152 with a larger score indicating better QOL.
- FACT/GOG-Ntx4 subscale (4 items). The Ntx score ranges 0-16 with a larger score indicating worse neurotoxicity.
- Social Activities (4 items). The social activities score ranges 0-100 with a larger score indicating less limited in social activities.

Geriatric Risk Score (Arm 3)

Risk Factor	Score
Age >=72	2
Need for assistance in taking medications from (item from IADL).	1
Limited in walking one block (item from ADL).	2
Decreased social activity at least sometimes due to health/emotional problem (item from social activity survey).	1
Number of falls in the last 6 months ≥ 1.	3
Fair or worse Hearing.	2
Hemoglobin <10 g/dl.	3
Creatinine clearance <34 ml/min.	3
Standard chemotherapy	2
Total	19

2 items removed from CARG score – cancer type and multi/single chemo regimen

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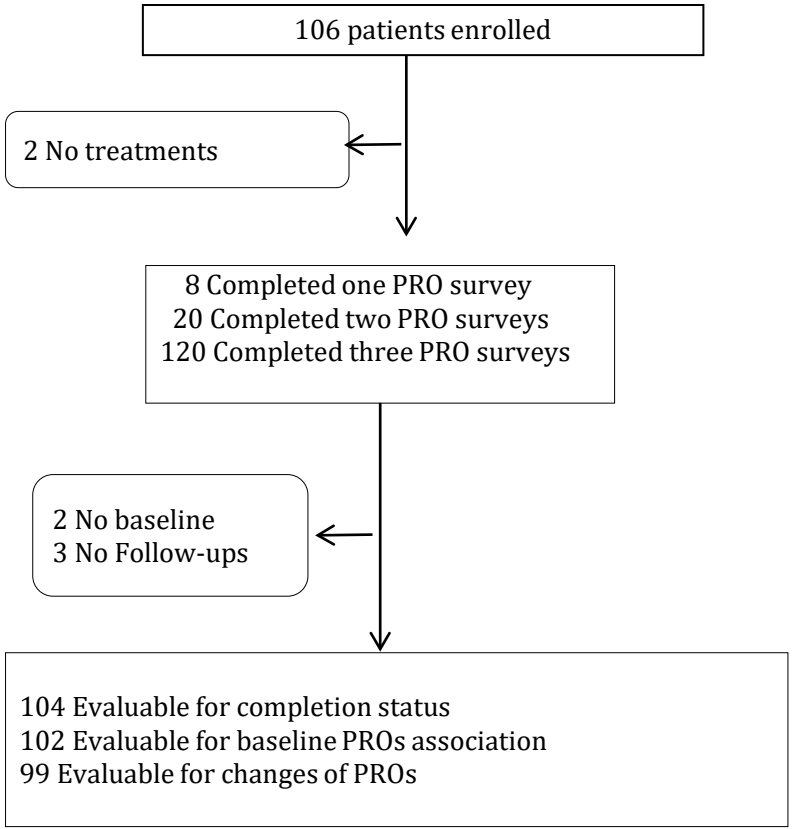
Hurria, Tew et al, CARG Toxicity Score, JCO, Sept 2011
Validation study, JCO, August 2016


106 patients enrolled
2 No treatments
8 Completed one PRO survey
20 Completed two PRO surveys
120 Completed three PRO surveys
2 No baseline
3 No Follow-ups
104 Evaluable for completion status
102 Evaluable for baseline PROs association
99 Evaluable for changes of PROs

Median age = 78yo (70-92)

Characteristic	Category	No.	%
Age categories	70-74	31	30
	75-79	34	33
	80-84	24	23
	≥85	15	14
Race	Non Hispanic Black	5	5
	Non Hispanic White	94	90
	Other	5	5
Performance Status	0	33	32
	1	55	53
	2	15	14
	3	1	1
Stage	I	10	10
	II	9	9
	III	69	66
	IV	16	15
Neoajuvent Chemo	No	76	73
	Yes	28	27
Chemotherapy	Reduced (Taxel<60 at d1/d8 or auc<5)	17	16
	Standard (proposed in study)	87	84
Starting Carbo AUC	4	13	13
	5	89	86
	6	2	2

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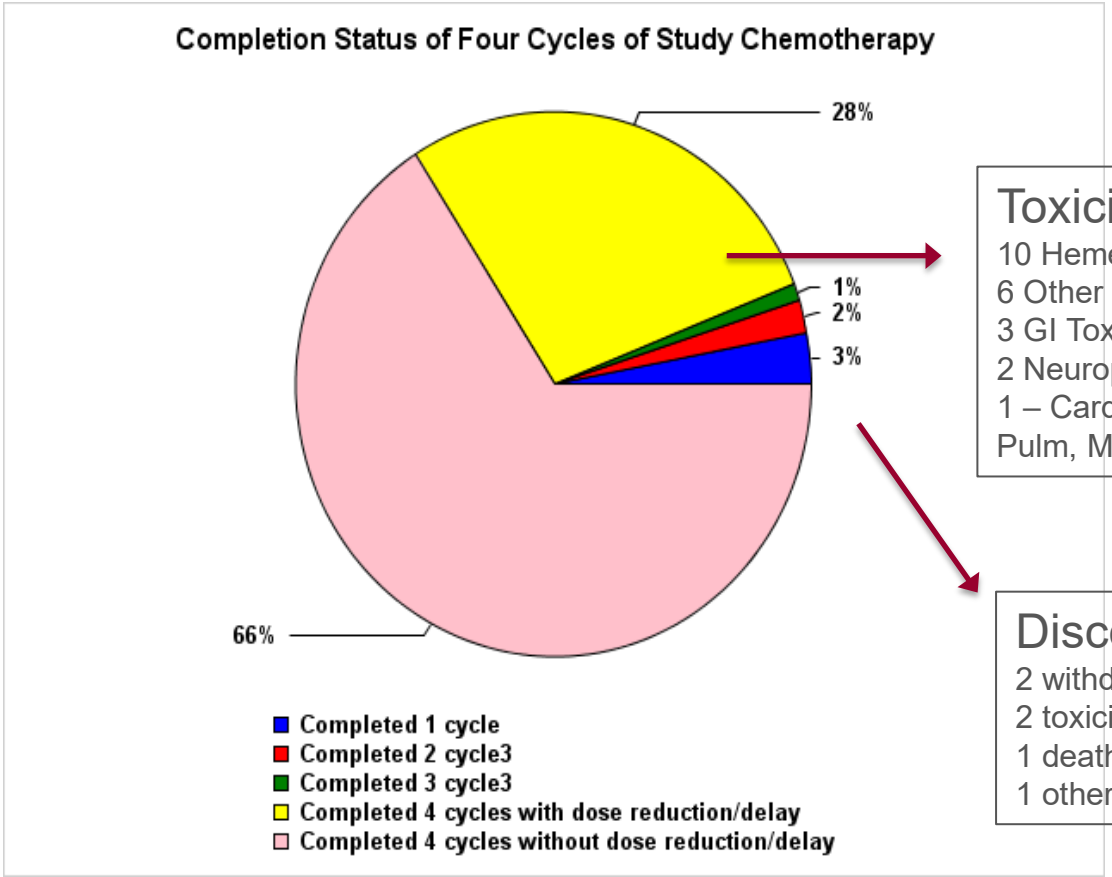

Toxicity (n=28):

10 Heme
6 Other
3 GI Toxicity
2 Neuropathy
1 – Cardiac, Allergy, Pulm, Musc-Skel

Discontinuation:

2 withdrew,
2 toxicity
1 death, cancer
1 other, comorbid

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AE	N (%)	AE	N (%)
Neutropenia	35 (35%)	Hyponatremia	5 (5%)
Anemia	18 (17%)	Dehydration	5 (5%)
Fatigue	9 (9%)	Hyperglycemia	4 (4%)
Hypertension	9 (9%)	Hypotension	3 (3%)
Nausea	8 (8%)	Lung Infection	3 (3%)
Vomit	7 (7%)	Dyspnea	3 (3%)
Hypokalemia	7 (7%)	Sepsis	2 (2%)
Diarrhea	6 (6%)	Ab pain	2 (2%)
Thrombocytopenia	6 (6%)	Neutropenic Fever	2 (2%)
Thromboembolic event	6 (6%)	Hypoalbuminemia	2 (2%)
Urinary Tract infection	6 (6%)	Neuropathy	1 (1%)
Syncope	5 (5%)	Other AEs	1 (1%)

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Baseline GRS:

Risk Factor	Yes	No	unknown
Age >=72	89 (86%)	15 (14%)	0
Need for assistance in taking medications	7 (7%)	94 (90%)	3 (3%)
Limited in walking one block	56 (54%)	44 (42%)	4 (4%)
Decreased social activity at least sometimes due to health/emotional problem	63 (61%)	37 (36%)	4 (4%)
Number of falls in the last 6 months ≥ 1.	15 (14%)	89 (86%)	0
Fair or worse Hearing.	18 (17%)	86 (83%)	0
Hemoglobin <10 g/dl.	9 (9%)	95 (91%)	0
Creatinine clearance <34 ml/min.	11 (11%)	93 (89%)	0
Standard chemotherapy	87(84%)	17(16%)	0

*Completed in 98 patients (all 9 questions answered).

**Standard chemo defined as carbo (AUC 5) and Weekly paclitaxel (60mg/m2)

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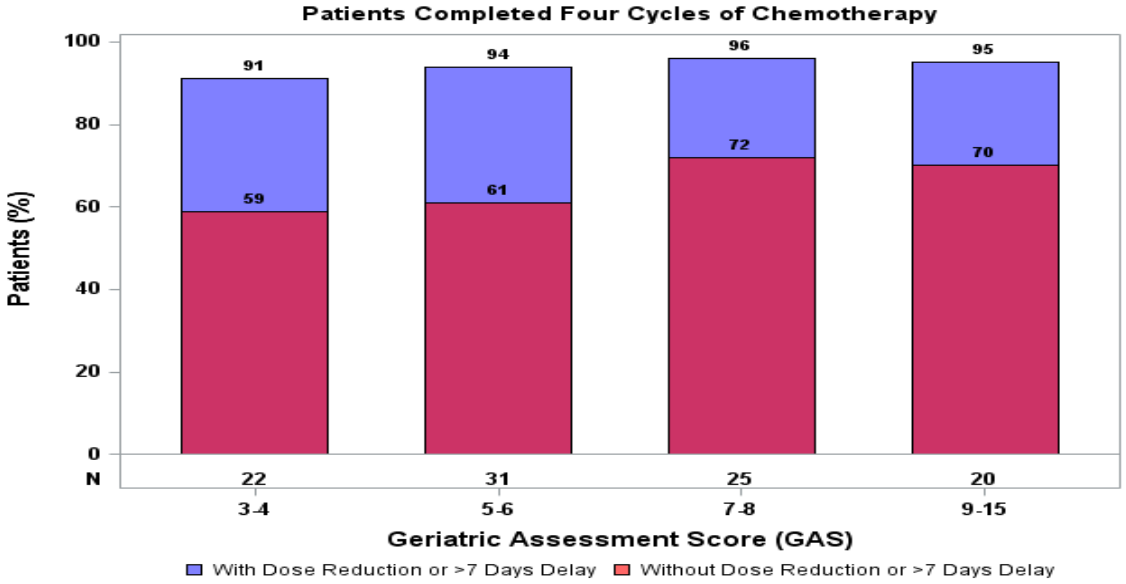

- Mean GRS was 6.5, median was 6 (range 3-15)
- No association with GRS and ability to complete 4 cycles of chemo
- Odds ratio 1.12 (95% 0.093 – 1.34; p=0.23) without dose adjustment
- Odds ratio 1.14 (95%: 0.78 – 1.68; p=0.5) with dose adjustment

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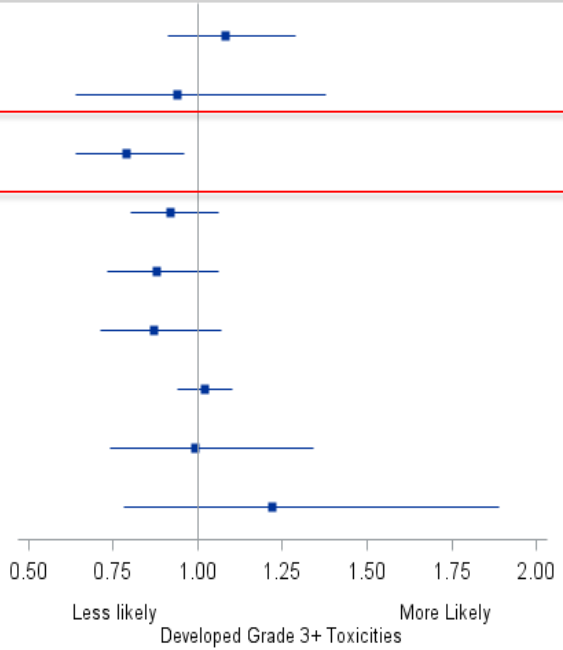
Association of GA variables with Grade 3+ Toxicity

Geriatric Measures	Odd Ratio	Unit	95% CI	P Value
Geriatric Assessment Score	1.08	1 point		0.393
Age	0.94	5 years		0.739
IADL	0.79	1 point		0.019
ADL	0.92	10 points		0.261
Social Activities	0.88	10 points		0.168
FACT-O	0.87	10 points		0.176
BMI	1.02	1 point		0.644
Weightloss within 6 Months(%)	0.99	5%		0.954
Comorbidity(N)	1.22	1 point		0.381



A larger scores indicates more independent or better QOL in IADL, ADL, Social Activities, and FACT-O

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PRO Measures	Baseline Mean(SD)	Pre-cycle 3 Mean(SD)	3~6 weeks post cycle 4 Mean(SD)	p-value
IADL	11.7(2.4)	12.0(2.1)	11.9(2.4)	0.47
ADL	42.1(28.2)	49.5(25.9)	48.7(24.4)	0.042
Social Activities	50.6(23.4)	57.5(21.4)	58.1(20.2)	0.002
FACT-O	112.8(21.3)	119.5(18.2)	119.1(17.3)	0.004
FACT/GOG-Ntx subscale	14.2(2.9)	14.0(2.8)	13.2(3.5)	0.011

Conclusions

- Carboplatin (AUC 5) and weekly paclitaxel (60mg/m2) is well tolerated.
- Despite ~65% G3+ tox rate, almost all completed 4 cycles of treatment
  - 66% without dose reduction or more than 7-day delays
  - 29% with dose adjustments
- Geriatric risk score was not associated with dose reduction / delays.
- Limitations:
  - CARG risk score was developed to predict grade 3-5 toxicity.
  - All study patients started at low doses of chemotherapy.
  - Older but fit (85% PS 0-1) patient population.
  - We stopped at 4 cycles – not 6 cycles – to include NACT patients who would undergo interval surgery.
- As in GOG 273 Arm 1 and 2, IADL remains an important and is associated with chemotherapy toxicity.
- Quality of life, ADLs, neuropathy and social activity improved over time.

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Questions

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