


WHEN MORE ISN'T BETTER: LESSONS IN DE-ADOPTION OF MULTI-MODALITY THERAPY FOR LOW RISK BREAST CANCER

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OBJECTIVES

- ▶ Review historical paradigm for tri-modality therapy of breast cancer
 - ▶ Highlight recent data suggesting de-escalation in older patients
 - ▶ Present data on real-world adoption and effectiveness
 - ▶ Discuss implications for de-adoption of preference-sensitive treatment alternatives
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HOW TO TREAT BREAST CANCER IN THREE (OR FOUR) EASY STEPS


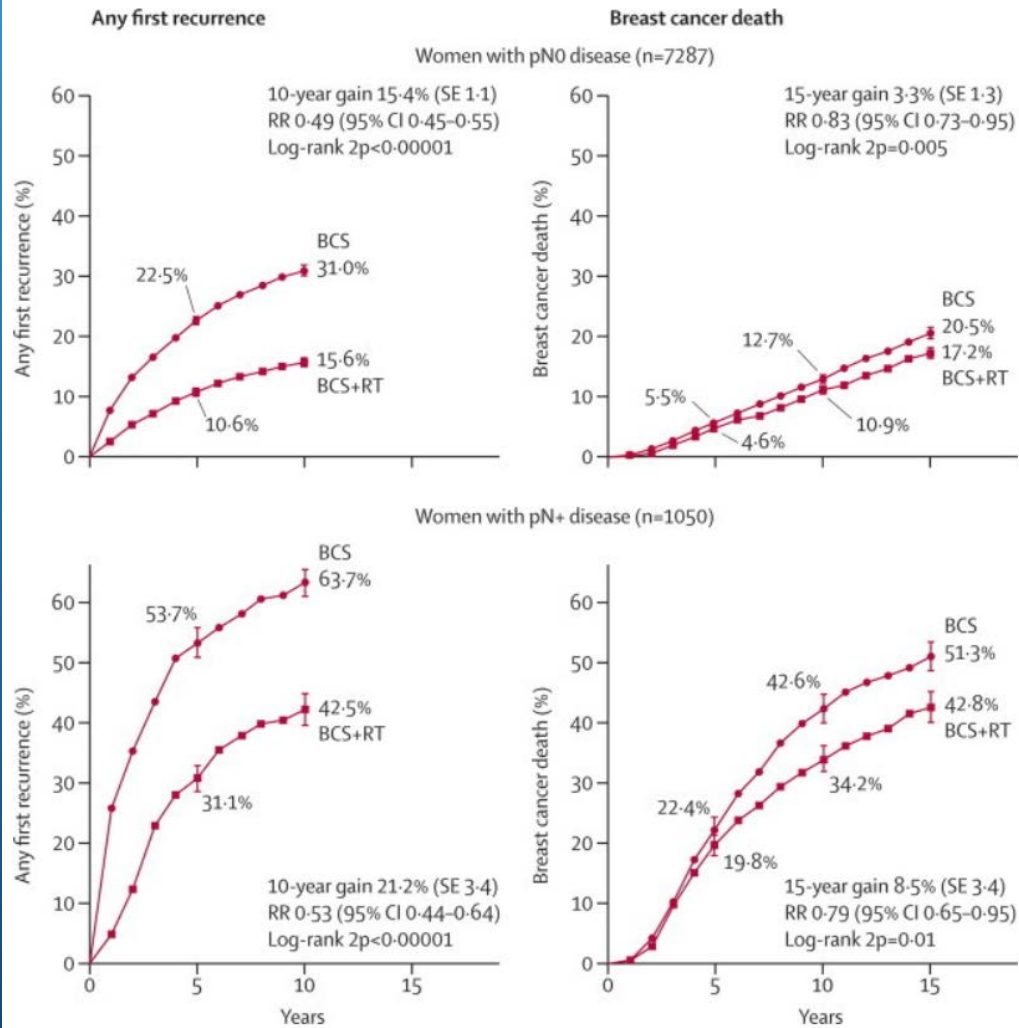
- ▶ **Step 1:** surgical removal (lumpectomy or mastectomy)
 - ▶ **Step 2:** chemotherapy if moderate/high recurrence risk
 - ▶ **Step 3:** radiation if indicated (lumpectomy or high risk)
 - ▶ **Step 4:** endocrine therapy if hormone receptor positive
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Figure 2



GAINS FROM POST-LUMPECTOMY RADIATION ARE REAL BUT MODEST


BENEFITS OF POST-LUMPECTOMY RADIATION

- ▶ Lower rate of in-breast recurrence (14% versus 39%)
- ▶ Reduction of risk for breast cancer death in a stage-dependent fashion (3.3% at 15 years if node negative, 8.5% if node-positive)
- ▶ In the real world, selection for radiation has been related less to risk than to access (lower rates of radiation and less timely radiation in vulnerable populations)


WHICH PATIENTS MAY BE ABLE TO ELIMINATE RADIATION?

- ▶ Earliest stage tumors
- ▶ Receptor phenotype with longest time to recurrence (+/+/-)
- ▶ Patients with shorter overall survival/greater competing co-morbidities
- ▶ In one randomized trial of women with <1cm tumors, in-breast tumor recurrence was 16.5% with TAM, 9.3% with XRT and placebo, and 2.8% with XRT and TAM.

CALGB 9343 TRIAL

- ▶ Women 70+ with stage I (T1N0) HR+ breast cancer, n=638
 - ▶ Randomized to lumpectomy +/- radiation (all got endocrine therapy)
 - ▶ Conducted 1994-1999
 - ▶ Initial results published 2004, 12 year follow-up
 - ▶ At 5 years: 1% locoregional recurrence in RT group, 4% in no RT
 - ▶ At 12 years: 3% vs 10%
 - ▶ No differences in distant metastases or overall survival
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PRIME II TRIAL

- ▶ Confirmatory trial published in 2015 (conducted 2003-2009)
 - ▶ Extended criteria to women age 65+ and tumors up to 3 cm, n = 1326
 - ▶ Similar, low rates of in breast recurrence at 5 years
 - ▶ No differences in regional or distant recurrences
 - ▶ Most deaths (36/40 in one arm, 41/49 in the other) were not related to breast cancer
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UNC MEDICARE STUDY

- ▶ Retrospective cohort study combining patients from SEER-Medicare and NC Medicare (~31% of US population)
- ▶ Has practice regarding radiation changed in older women who fit “Hughes criteria” in the past decade?
- ▶ Does the real world experience confirm findings of clinical trials in a more diverse, less healthy population?
- ▶ Is RT alone (as opposed to RT + ET or ET alone) a viable option for women in this low-risk group?


UNC Collaborators: Tim Zagar, Stephanie Wheeler, Anne Marie Meyer, Chris Baggett, Zhou Xi

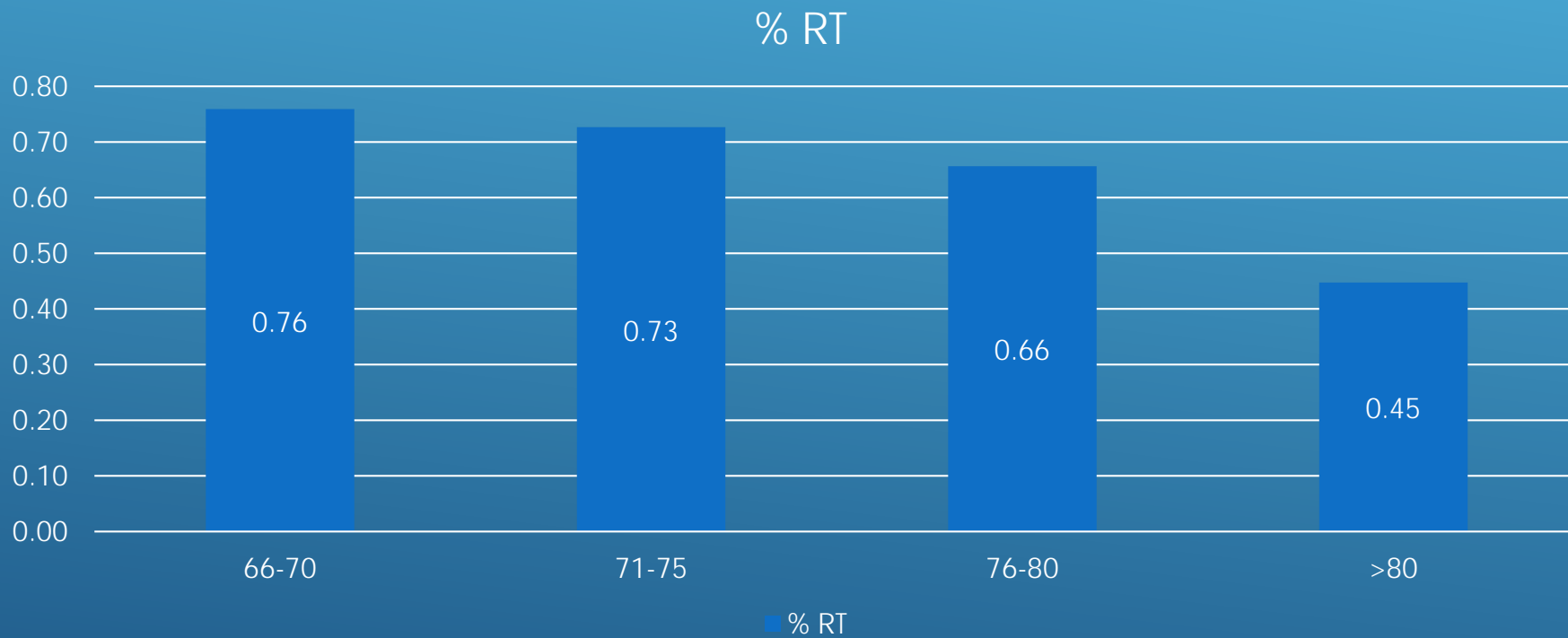
Funding: American Society for Radiation Oncology (ASTRO)

STUDY DESIGN

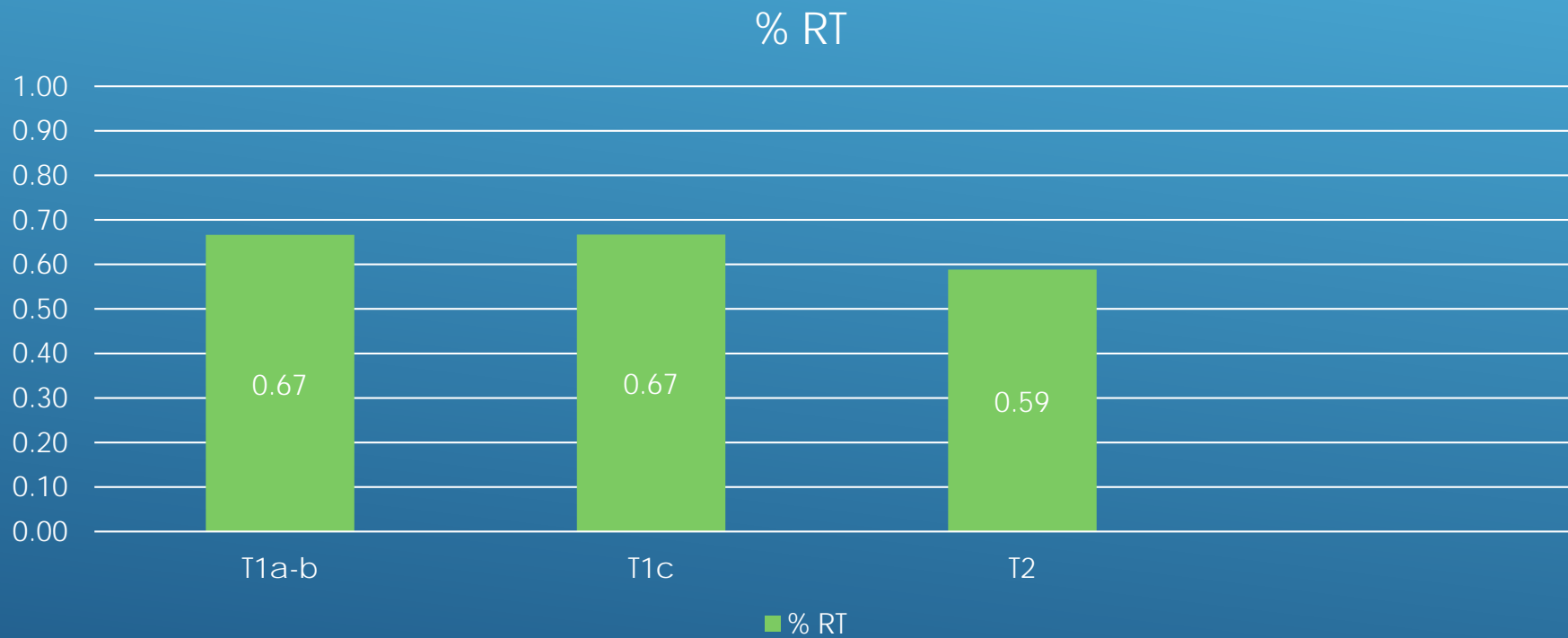
- ▶ ER/PR+ breast cancer diagnosed 2007-2011 at age 66 or older
 - ▶ Received definitive breast conserving surgery
 - ▶ Enrolled in eligible insurance plan months -12 to +12
 - ▶ Final sample size = 10,204
 - ▶ Four study arms: (1) no adjuvant therapy (2) RT alone (3) ET alone (4) RT+ET
 - ▶ Recurrence assessed by a registry/claims algorithm; patients must complete 12 months without recurrence
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PART 1: PATTERNS OF CARE

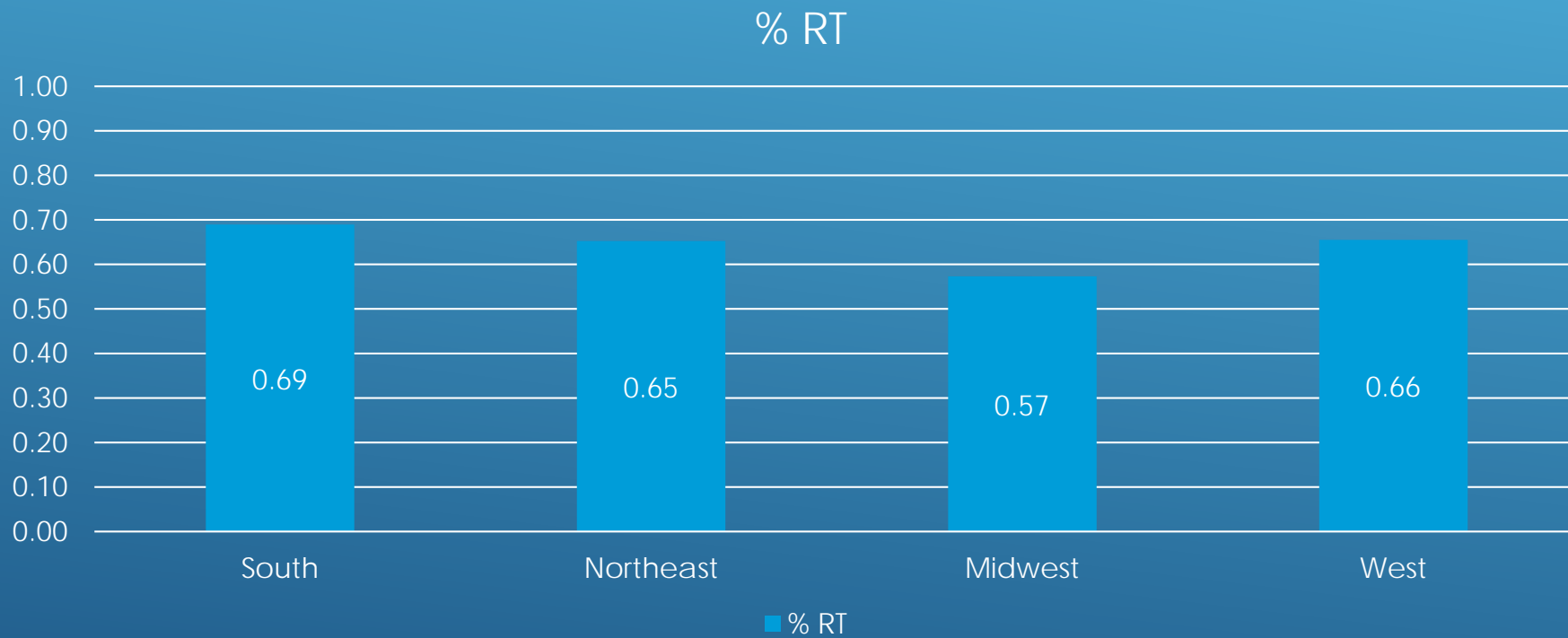
- ▶ Patients grouped into “RT” (with or without ET) versus “no RT” (surgery alone or ET alone)
 - ▶ Outcome: receipt of radiation
 - ▶ Frailty index (predicting dependence in activities of daily living) and comorbidity examined
 - ▶ Also controlled for race, geographic region and disease characteristics
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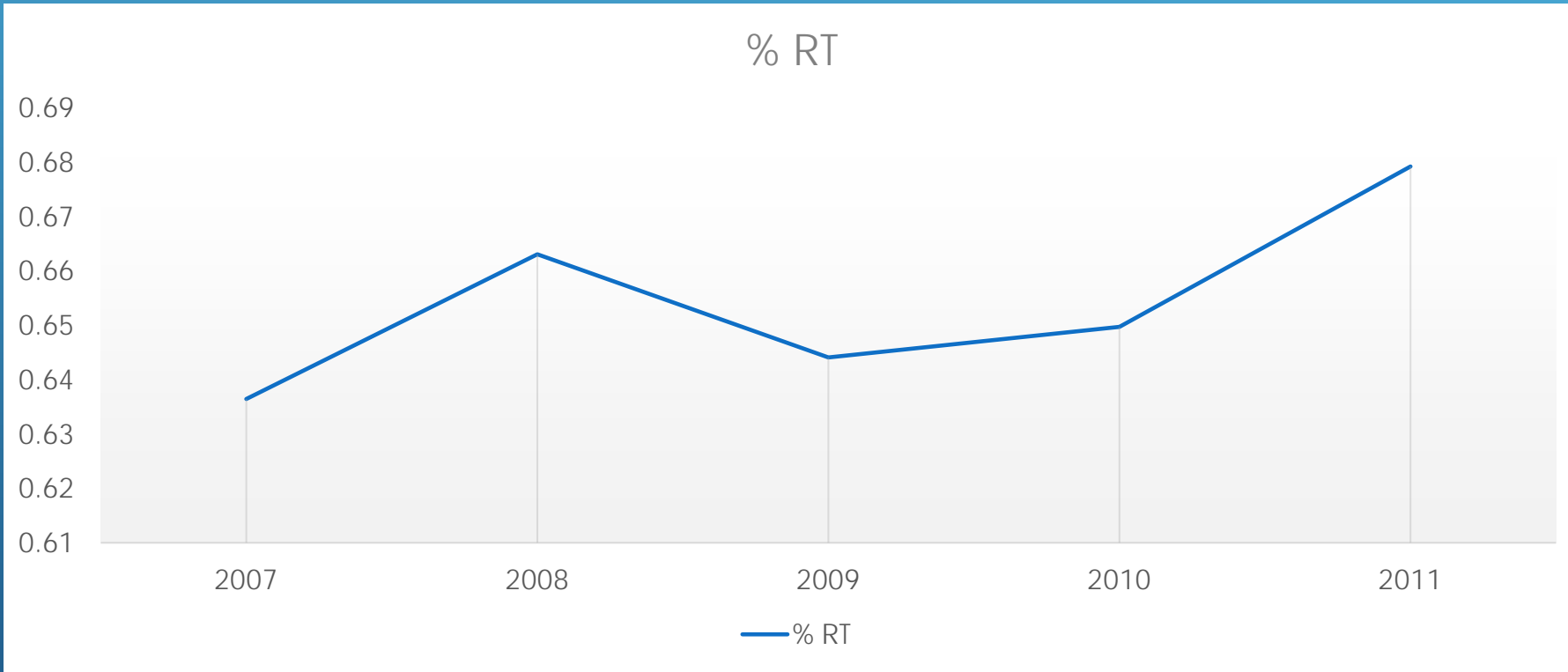
RADIATION USE BY AGE



RADIATION USE BY TUMOR SIZE



RADIATION USE BY GEOGRAPHY

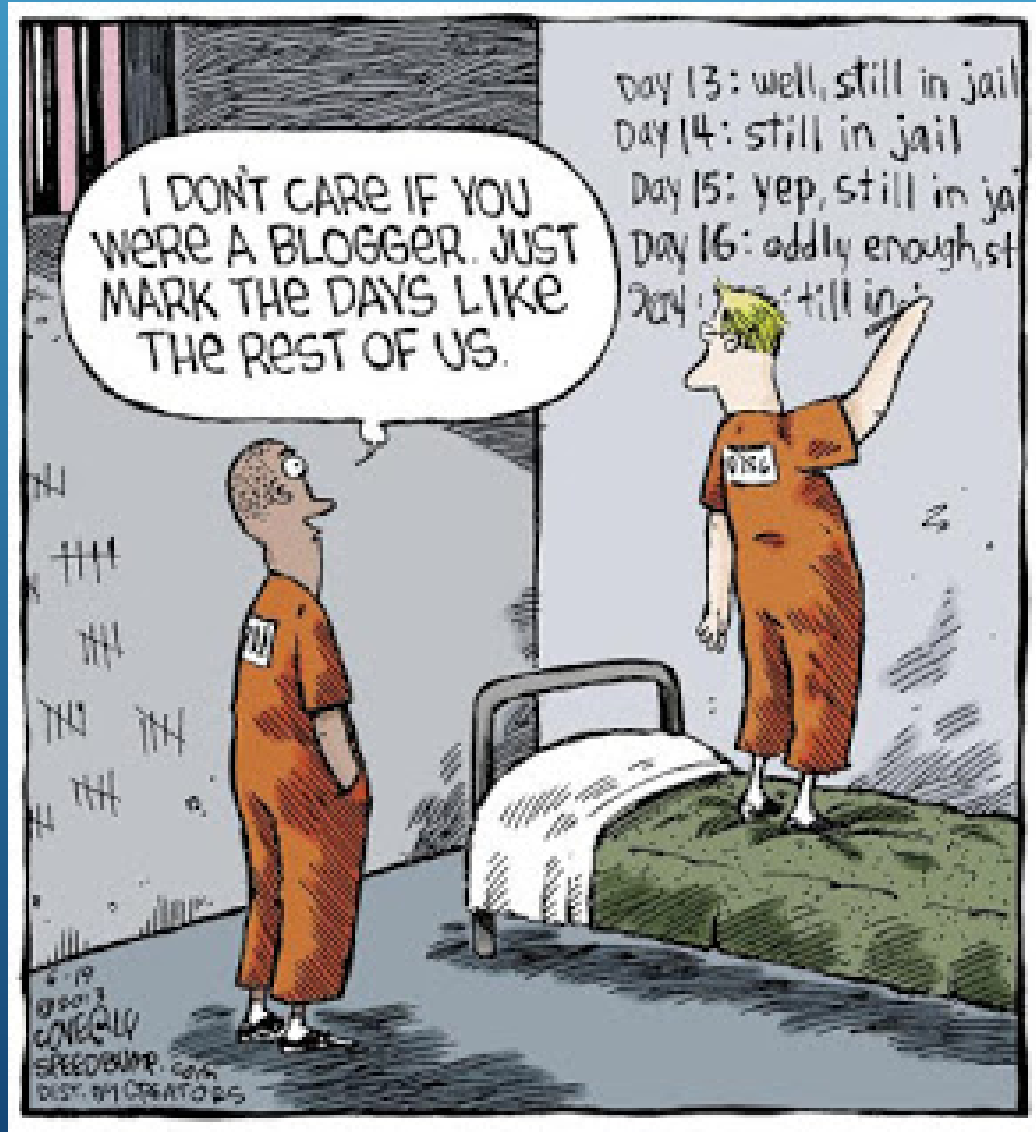


Hughes 5 year

TRENDS IN RADIATION USE OVER TIME

Hughes 12 yr

PRIME II




OLD HABITS CAN BE
HARD TO BREAK,
EVEN WHEN THE
SETTING CALLS FOR IT

Table 2 Association between Variables and Radiation without Weighting (1=Radiation, 0=No Radiation)

Variables	Levels	Adjusted without Frailty Index			Adjusted without Age at diagnosis		
		OR	95% CI	P-value	OR	95% CI	P-value
Race/Ethnicity	Non-Hispanic White	1.00	-	-	1.00	-	-
	Other	0.95	(0.83 - 1.08)	0.4019	0.96	(0.85 - 1.10)	0.5650
Frailty Index Quartile	Quartile 1: <25%	-	-	-	1.00	-	-
	Quartile 2: 25%-<50%	-	-	-	1.00	(0.90 - 1.13)	0.9346
	Quartile 3: 50%-<75%	0.78	(0.70 - 0.87)	<.0001	0.78	(0.70 - 0.87)	<.0001
	Quartile 4: >=75%	0.83	(0.73 - 0.95)	0.0049	0.83	(0.73 - 0.95)	0.0049
NCI Combined Comorbidity Index	0	1.00	-	-	1.00	-	-
	1+	0.89	(0.82 - 0.97)	0.0104	0.80	(0.73 - 0.87)	<.0001
Region, U.S. Census Bureau	West	0.85	(0.77 - 0.95)	0.0031	0.85	(0.77 - 0.94)	0.0017
	Midwest	0.62	(0.53 - 0.72)	<.0001	0.60	(0.52 - 0.69)	<.0001
	Northeast	0.93	(0.82 - 1.06)	0.2707	0.84	(0.75 - 0.95)	0.0048
	South	1.00	-	-	1.00	-	-
Tumor grade	Well differentiated	1.00	-	-	1.00	-	-
	Moderately differentiated	1.02	(0.93 - 1.12)	0.6522	1.00	(0.92 - 1.10)	0.9413
	Poorly differentiated	1.01	(0.88 - 1.15)	0.9320	0.95	(0.83 - 1.08)	0.4430
Ajcc T	T1a-b	1.00	-	-	1.00	-	-
	T1c	1.08	(0.98 - 1.18)	0.1256	1.01	(0.92 - 1.10)	0.9068
	T2	0.86	(0.76 - 0.98)	0.0236	0.73	(0.64 - 0.83)	<.0001
Year of Diagnosis	2007	1.00	-	-	1.00	-	-
	2008	1.09	(0.95 - 1.26)	0.2111	1.12	(0.97 - 1.28)	0.1139
	2009	1.02	(0.89 - 1.16)	0.8168	1.03	(0.91 - 1.18)	0.6251
	2010	1.03	(0.90 - 1.17)	0.7147	1.07	(0.93 - 1.22)	0.3384
	2011	1.18	(1.03 - 1.34)	0.0154	1.22	(1.08 - 1.39)	0.0020
Age at Diagnosis	66-70 yr	1.00	-	-	-	-	-
	71-75 yr	0.86	(0.76 - 0.97)	0.0132	-	-	-
	76-80 yr	0.62	(0.55 - 0.70)	<.0001	-	-	-
	>80 yr	0.26	(0.24 - 0.30)	<.0001	-	-	-

MULTIVARIABLE PREDICTORS OF RT USE

PART 2: COMPARATIVE EFFECTIVENESS OF TREATMENT OPTIONS

- ▶ 3 category exposure: RT only, ET only, RT + ET (patients with no tx after surgery were removed); n=9096
 - ▶ Propensity score weighting with stabilized IPTW (matching as a sensitivity analysis)
 - ▶ Outcome: recurrence free survival; censoring for death without recurrence and end of follow-up
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Variables	Levels	HR	95% CI	P-value
Treatment	RT+ET	0.629	(0.51 - 0.77)	<.0001
	RT only	0.799	(0.66 - 0.96)	0.0190
Race/Ethnicity	Non-Hispanic White	1.000		.
	Other	1.066	(0.82 - 1.39)	0.6364
Frailty Index Quartile	Quartile 1: <25%	1.000		.
	Quartile 2: 25%-<50%	0.938	(0.74 - 1.19)	0.5943
	Quartile 3: 50%-<75%	1.068	(0.81 - 1.40)	0.6342
	Quartile 4: >=75%	0.999	(0.79 - 1.26)	0.9955
NCI Combined Comorbidity Index	0	1.000		.
12 Months prior to Diagnosis	1+	1.242	(1.05 - 1.47)	0.0102
Region, U.S. Census Bureau	West	1.000		.
	Midwest	0.852	(0.63 - 1.15)	0.2901
	Northeast	1.055	(0.85 - 1.31)	0.6262
	South	1.049	(0.86 - 1.28)	0.6332
Tumor grade	Well differentiated	1.000		.
	Moderately differentiated	1.206	(1.01 - 1.44)	0.0412
	Poorly differentiated	1.398	(1.09 - 1.78)	0.0072
Ajcc T	T1a-b	1.000		.
	T1c	1.101	(0.93 - 1.31)	0.2762
	T2	1.253	(0.96 - 1.63)	0.0968
Year of Diagnosis	2007	1.000		.
	2008	1.116	(0.90 - 1.39)	0.3229
	2009	0.978	(0.77 - 1.24)	0.8541
	2010	0.780	(0.59 - 1.03)	0.0842

PS-ADJUSTED MODEL
OF ASSOCIATION
BETWEEN TREATMENT
ARM AND
RECURRENCE FREE
SURVIVAL


MOST COHORT DEATHS ARE NOT DUE TO BREAST CANCER

Cause of Death	RT alone N=2046	ET alone N=2407	RT+ET N=4643	PRIME ET alone (n=668)	PRIME ET + RT (n=658)
Breast CA	19 (8.5%)	31 (8.6%)	11 (3.9%)	8 (16%)	4 (10%)
Other CA	18	35	29	n/a	n/a
Non-cancer	96	125	101	41	36
Unknown	91	167	135	n/a	n/a
All Deaths	224	358	276	49	40

ADHERENCE AND TREATMENT ASSIGNMENT

- ▶ Non-adherence (PDC<80%) was common, slightly more so in radiated patients: 37% in ET only and 39% in ET + RT (p=0.026)
 - ▶ Sensitivity analyses will evaluate relative effectiveness of ET-containing arms in adherent vs non-adherent patients
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FACTORS CONTRIBUTING TO PRACTICE INTRANSIGENCE


- ▶ Preference-sensitive decision
 - ▶ Perverse payment incentives
 - ▶ De-adoption is always an uphill battle
 - ▶ You can tell cars they're too old to fix...it's hard to tell people
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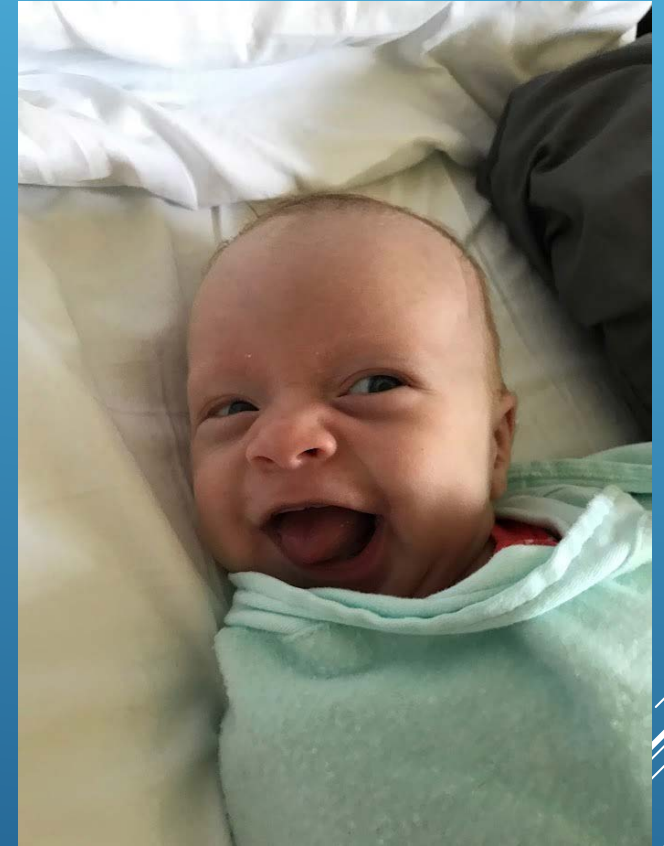
WHAT PROBABLY WON'T HELP

- ▶ Changes to payment policy/insurance restrictions
- ▶ Fuzzy and vague guidelines
- ▶ Implications that radiation oncologists are evil geniuses



WHAT MIGHT HELP

- ▶ Promoting awareness that current practice patterns are NOT stratifying radiation by risk, but most likely by access
 - ▶ Data on patient preferences and PROs as measures of harm
 - ▶ Time (latest trial data are recent)
 - ▶ Development of guidelines with concrete thresholds (below 1cm?)
 - ▶ A broader view of de-escalation – RT alone may be a viable option (and a lot of patients are voting on ET with their feet)
- 



THE BIG PICTURE: SOMETIMES IT'S HARD TO QUIT DOING STUFF...BUT THE TIPPING POINT WILL COME EVENTUALLY.

Tim Zagar

Larry Marks

Stephanie Wheeler

Jason Rotter

Chris Baggett

Anne Marie Meyer

Zhou Xi



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