Chill out!
Take 2 aspirin.
Call me in the morning.

Anurag K. Singh MD
Professor
Director of Radiation Research
Co-Leader, Cell Stress and Biophysical Therapy Program
Associate Dean Graduate Medical Education For Research
Roswell Park Comprehensive Cancer Center
August 9, 2019

Outline

- **Chill Out**
  - **Beta-blockers, RT, and Immunity**
    - **Esophageal Cancer**
  - **Patient stress maybe bad**
  - **Reduce patient stress**
- **Take "Two" Aspirin**
  - **H&N**
  - **Rectal**
- **Call Me in the Morning**
  - **Circadian Rhythm**

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Outline

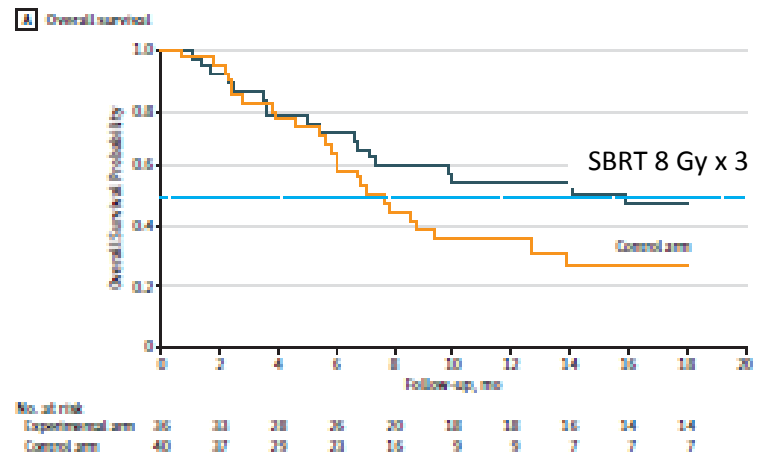- **Chill Out**
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Pembro +/- RT NSCLC. **Secondary analysis**
Shaveridan et al. Lancet Oncol. 2017.
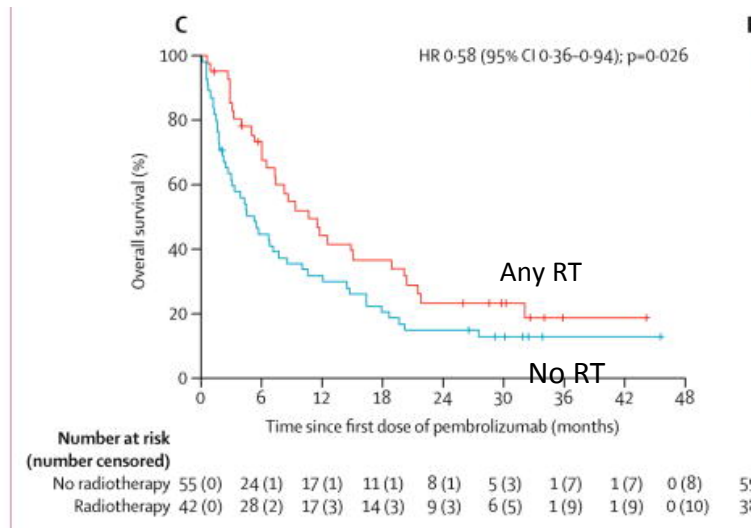
Pembro +/- SBRT NSCLC. Phase 2
Theelen et al. JAMA Oncol. 2019.

Beta-blockers + RT= Abscopal   (Repasky)

CT26   6 Gy x 1

Tumor measurements
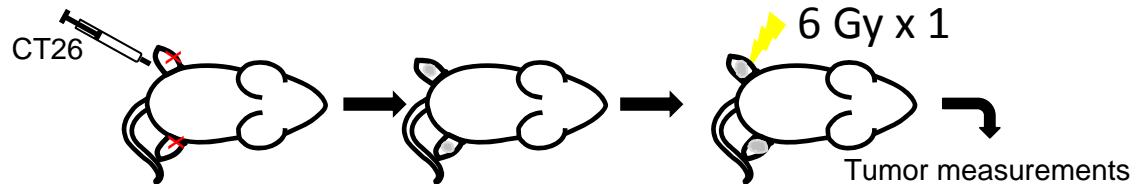
Analogous data:
1. Celebrex, Aspirin

Irradiated Tumor

- ▲ PBS
- ▼ Prop
- ◆ PBS+ Rad
- ✚ Prop + Rad

Tumor volume (mm³)

Days Post Radiation

*
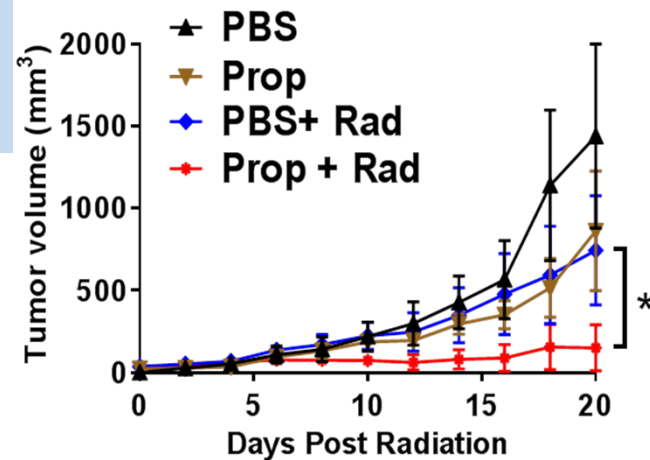
Distant Tumor (Non-irradiated)

- ▲ PBS
- ▼ Prop
- ◆ PBS+ Rad
- ✚ Prop + Rad

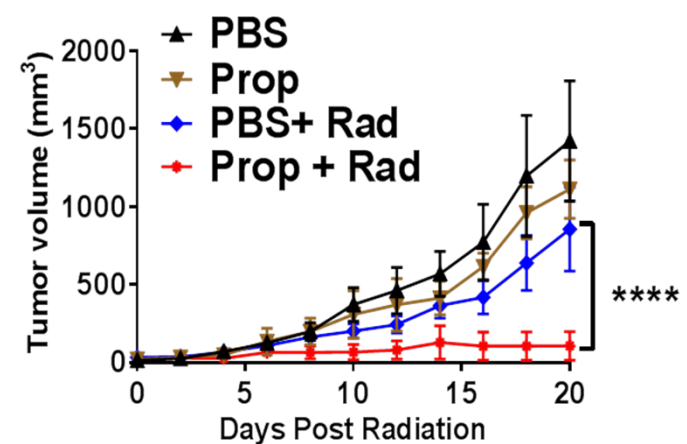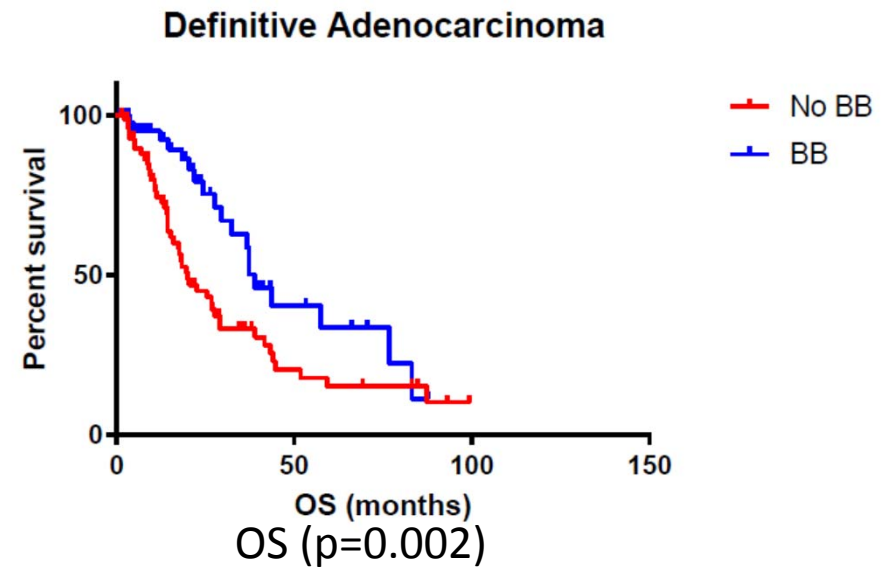Tumor volume (mm³)
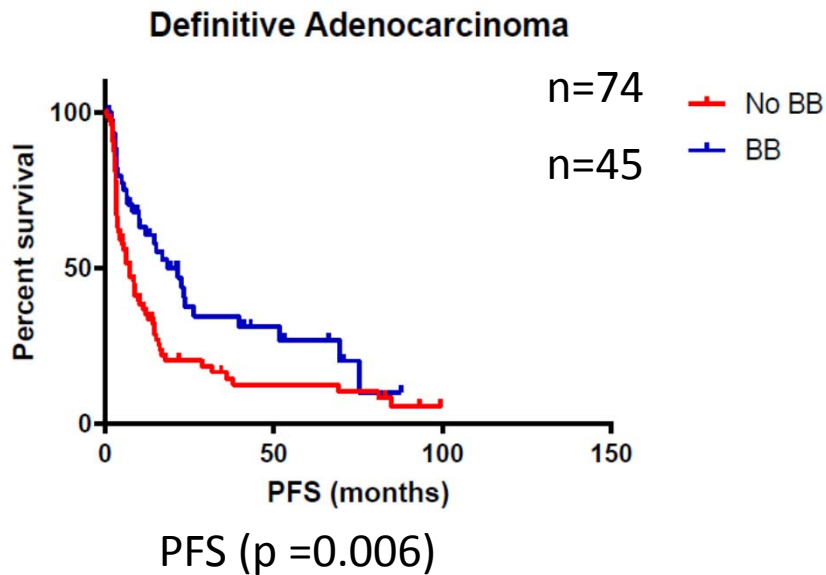
Days Post Radiation

****

Fig 4. B-blockers improve response of both irradiated tumor and distant (abscopal) tumor. Ct26 tumors. Irradiated tumor was received 6Gy on Day 0. *p<0.05, ****p<0.0001
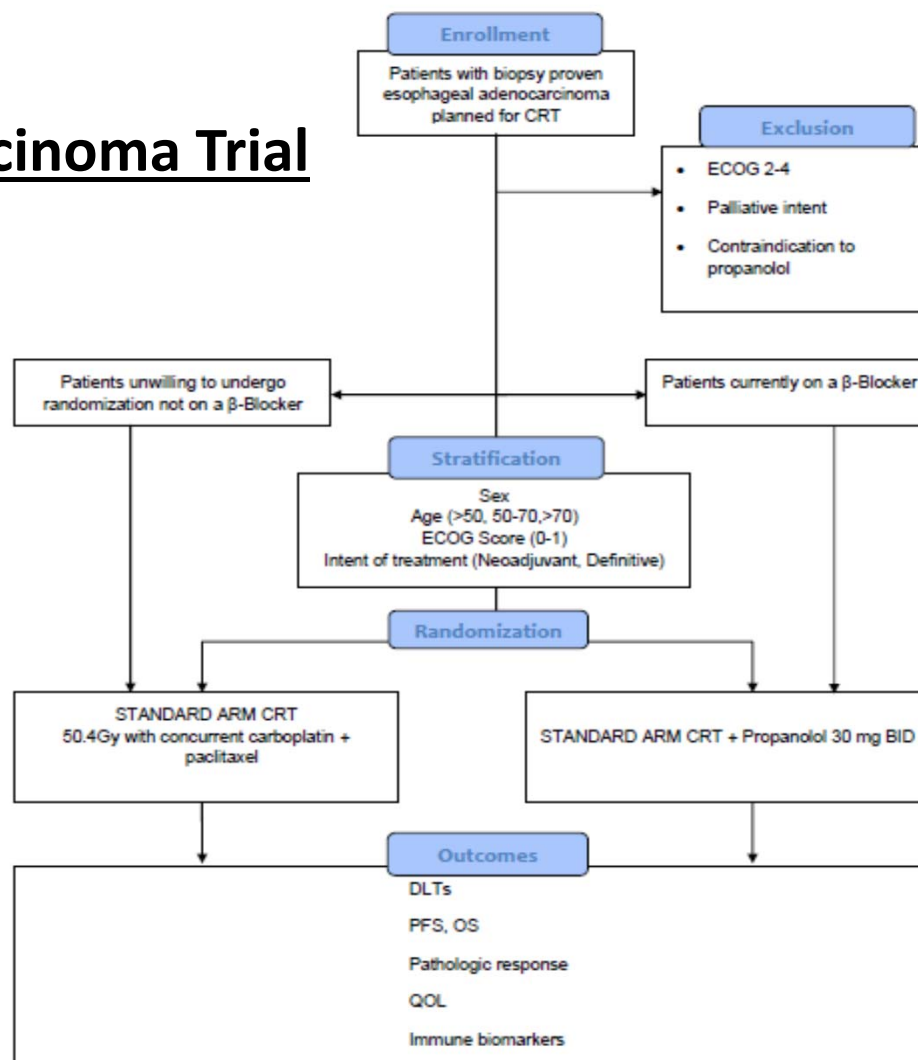
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Beta-adrenergic Stress is Bad for you:
Esophageal Adenocarcinoma ChemoRT Only

PFS (p =0.006)

OS (p=0.002)

Farrugia, Singh

Esophageal Adenocarcinoma Trial
CRT +/- Propranolol

Enrollment
Patients with biopsy proven esophageal adenocarcinoma planned for CRT

Exclusion
- ECOG 2-4
- Palliative intent
- Contraindication to propanolol

Patients unwilling to undergo randomization not on a β-Blocker

Patients currently on a β-Blocker

Stratification
Sex
Age (>50, 50-70,>70)
ECOG Score (0-1)
Intent of treatment (Neoadjuvant, Definitive)

Randomization

STANDARD ARM CRT
50.4Gy with concurrent carboplatin + paclitaxel

STANDARD ARM CRT + Propanolol 30 mg BID

Outcomes
DLTs
PFS, OS
Pathologic response
QOL
Immune biomarkers

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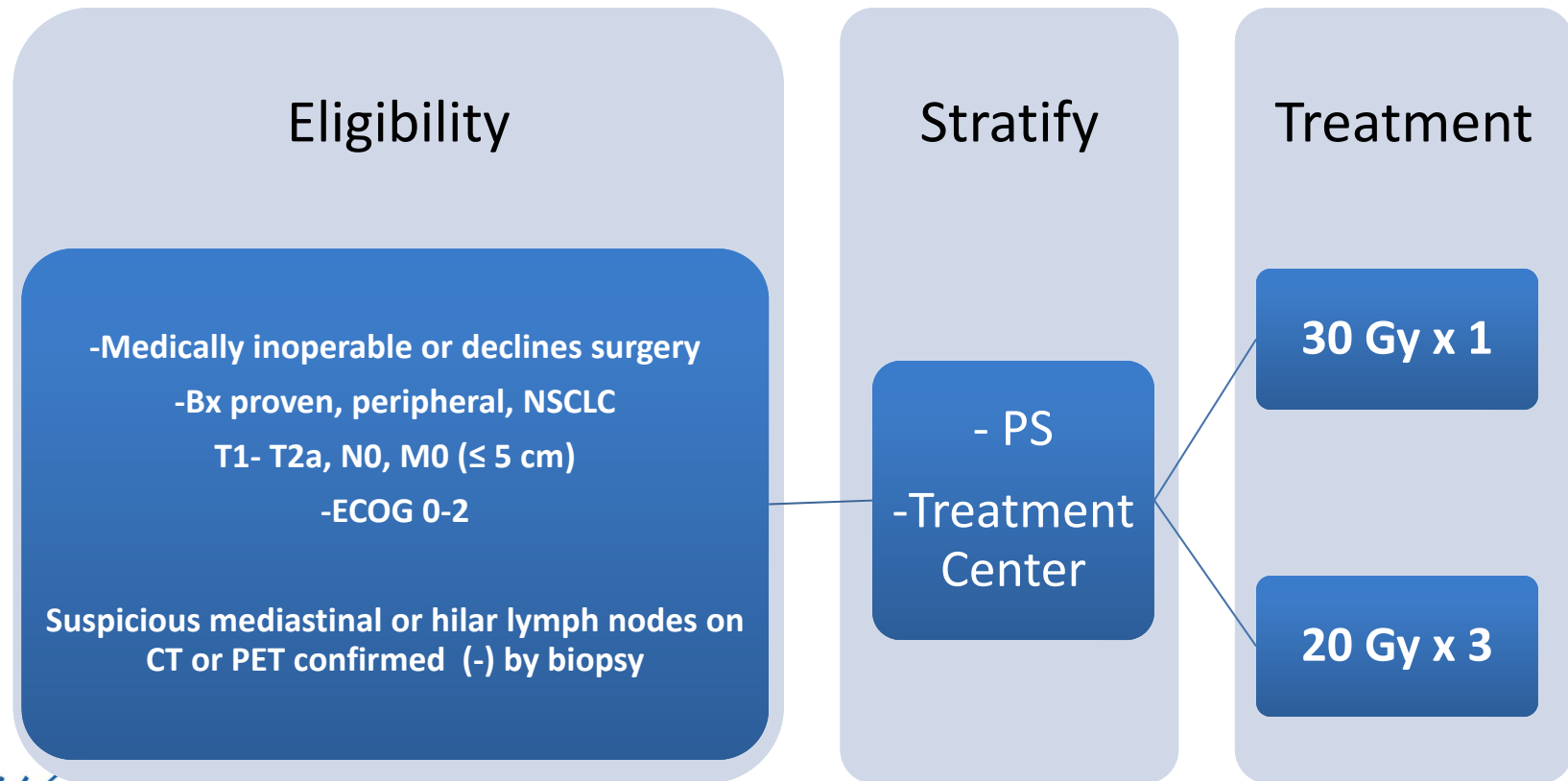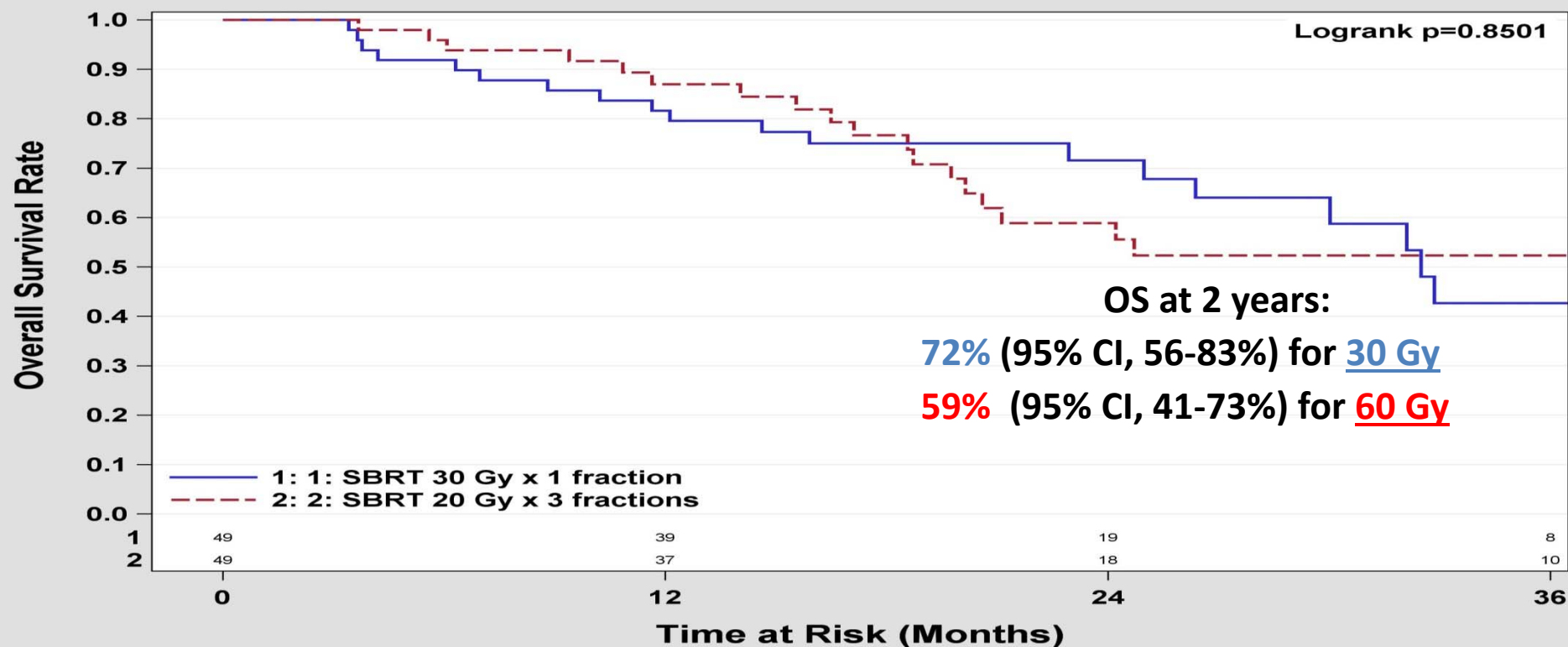
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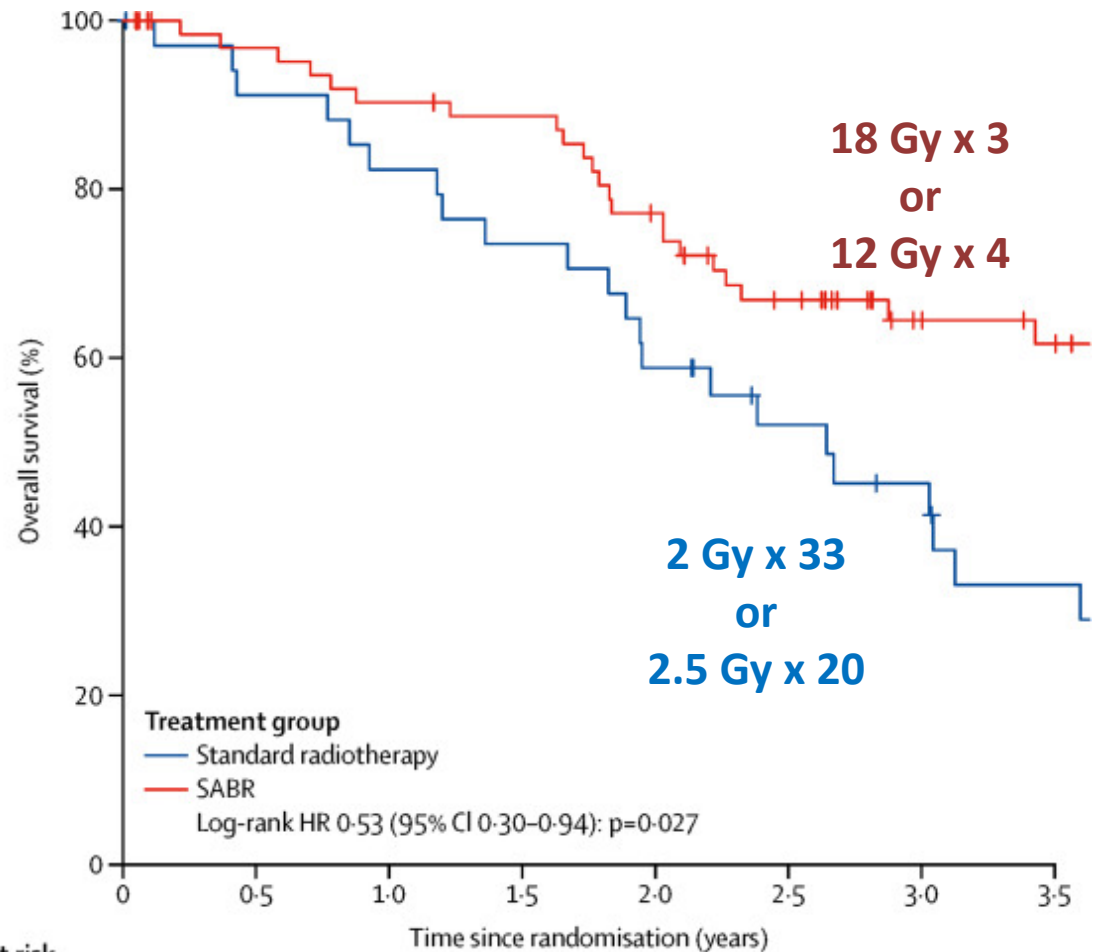
I 124407 (Roswell, Cleveland Clinic, Upstate)

Eligibility

-Medically inoperable or declines surgery

-Bx proven, peripheral, NSCLC

T1- T2a, N0, M0 (≤ 5 cm)

-ECOG 0-2

Suspicious mediastinal or hilar lymph nodes on CT or PET confirmed (-) by biopsy

Stratify

- PS

-Treatment Center

Treatment

30 Gy x 1

20 Gy x 3

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Singh et al. Int Jn Radiat Oncol Phys. 2019 In press.

CHISEL Trial

Ball et al. Lancet Oncology. 2019.

Overall survival (%) vs Time since randomisation (years)

18 Gy x 3 or 12 Gy x 4

2 Gy x 33 or 2.5 Gy x 20

Treatment group
— Standard radiotherapy
— SABR
Log-rank HR 0·53 (95% CI 0·30–0·94): p=0·027

Number at risk (number censored)							
Standard radiotherapy	35 (0)	31 (1)	28 (1)	25 (1)	20 (1)	15 (4)	12 (5)	8 (6)
SABR	66 (0)	60 (4)	56 (4)	54 (5)	46 (6)	37 (9)	25 (20)	22 (22)

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Increase in Financial Burden Worsens Survivals
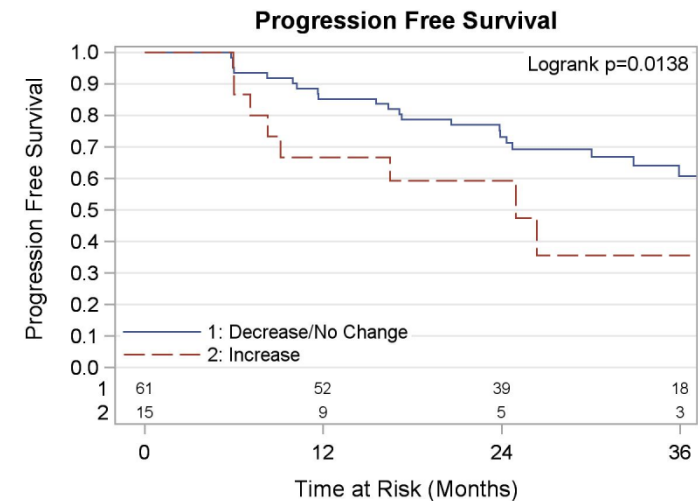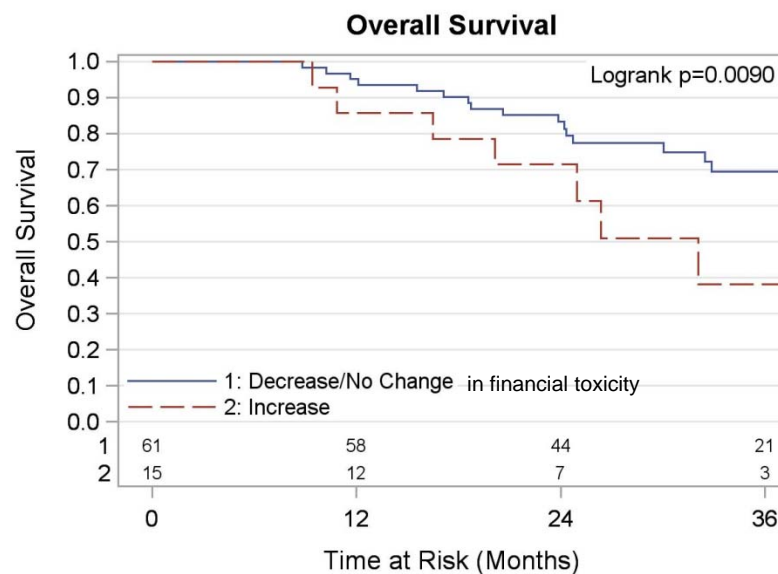
On multivariate analysis, increase in financial problems was the only significant predictor of overall survival.

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The effect of time between diagnosis and initiation of treatment on outcomes in patients with head and neck squamous cell carcinoma

Luke H. DeGraaff[a], Alexis J. Platek[a], Austin J. Iovoli[a], Kimberly E. Wooten[b], Hassan Arshad[b], Vishal Gupta[b], Ryan P. McSpadden[b], Moni Abraham Kuriakose[b], Wesley L. Hicks Jr[b], Mary E. Platek[c,d], Anurag K. Singh[d,*]

[a] Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, United States
[b] Department of Head and Neck Surgery/Plastic and Reconstructive Surgery, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States
[c] Department of Dietetics, D'Youville, Buffalo, NY, United States
[d] Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buff
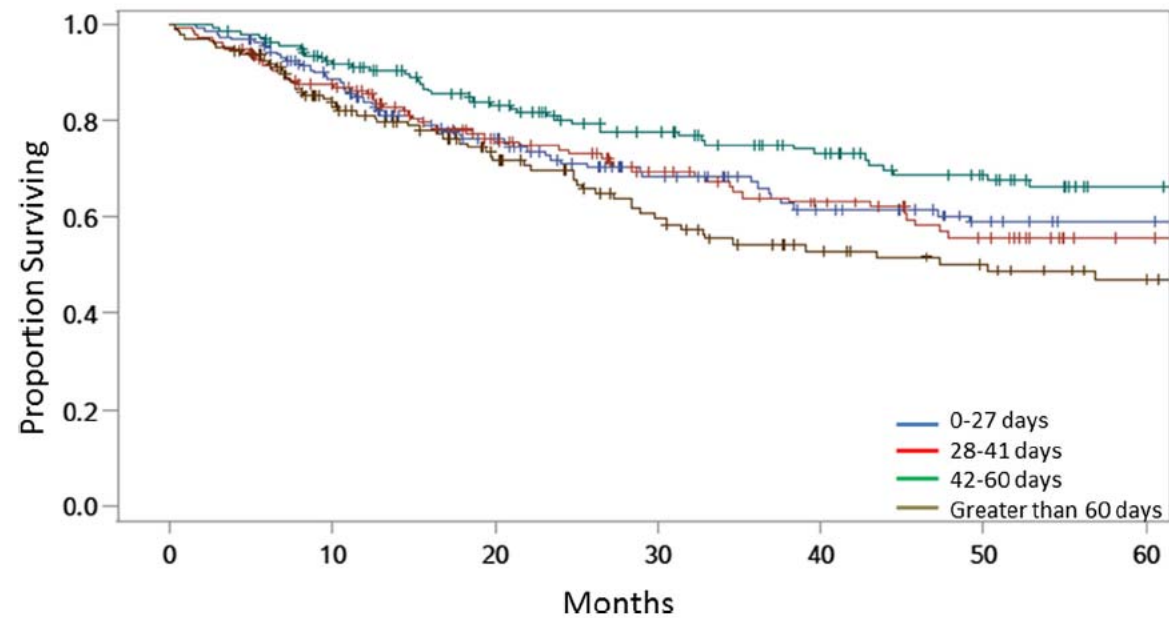
Fig. 1. Kaplan Meier overall survival of squamous cell carcinoma of the head and neck from stratified by treatment initiation time; 0–27 days, 28–41 days, 42–60 days, and greater than 60 days. Patients with 42–60 days before treatment initiation exhibited the best overall survival (n = 633, p = 0.02).

Routine surveillance scanning in HNSCC: Lung screening CT scans have value but head and neck scans do not

Austin J. Iovoli[a], Alexis J. Platek[a], Luke Degraaff[a], Chong Wang[b], William D. Duncan[b], Kimberly E. Wooten[c], Hassan Arshad[c], Vishal Gupta[c], Moni A. Kuriakose[c], Wesley L. Hicks Jr.[c], Mary E. Platek[d,e], Anurag K. Singh[e,*]
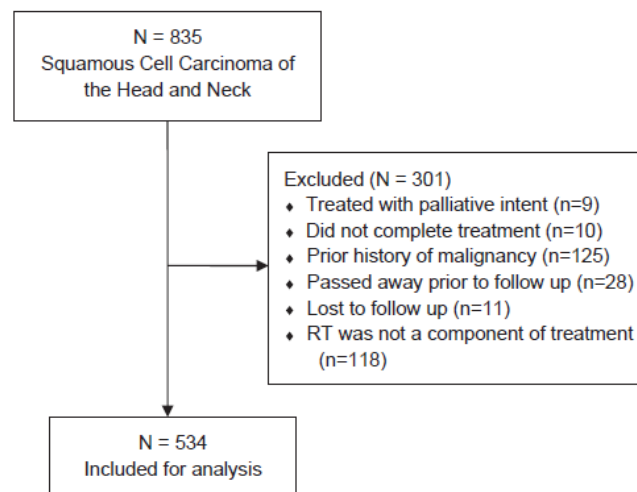
Fig. 1. CONSORT diagram for patient selection criteria.
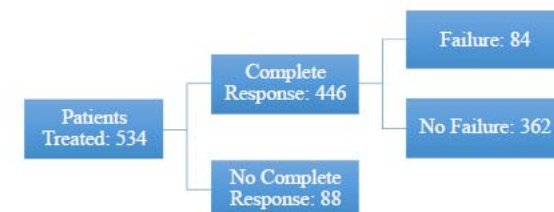

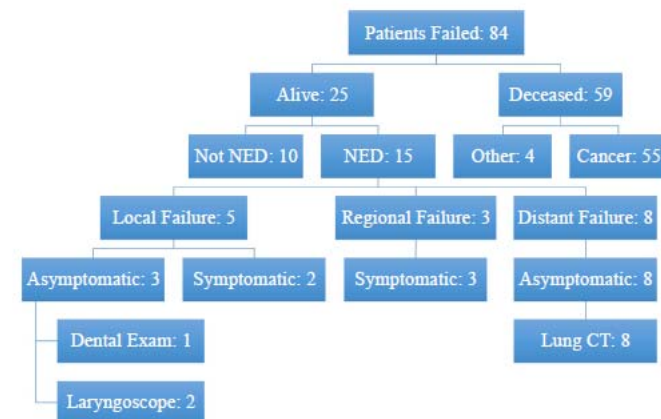Fig. 2. Response to treatment and failure rate of the overall cohort.

Fig. 3. Outcomes for patients with a complete response to treatment who subsequently failed. Patients with recurrence were categorized as symptomatic or asymptomatic at the time of failure. Asymptomatic patients were further subdivided based on the screening method used to detect recurrence. One patient was successfully salvaged for both local and distant failure.

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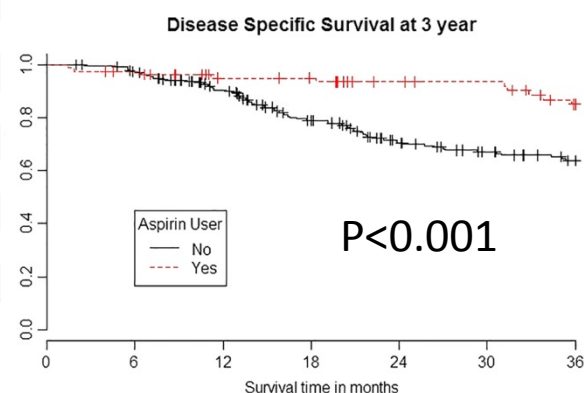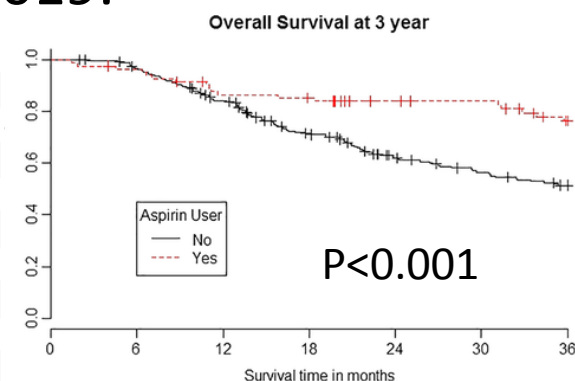 - **Circadian Rhythm**

# VA H&N Cancer: Post Diagnosis Aspirin Use
Lumley et al. Head Neck. 2019.

TABLE 1 Clinical-pathologic characteristics of aspirin users and nonaspirin users after HNC diagnosis

Characteristics	Aspirin users $N = 84$ (%)	Non-aspirin users $N = 245$ (%)	P-value
Age	66.3 ± 9.3	61.8 ± 8.6	<.0001*
Sex			
Male	84 (100.0)	242 (98.8)	.5731
Female	0 (0.0)	3 (1.2)	
Race/ethnicity[a]			
Caucasian	22 (26.8)	88 (37.8)	.1200
African American	58 (70.7)	143 (61.4)	
Other	2 (2.4)	2 (0.9)	
Tobacco use[b]			
Never	8 (9.5)	13 (5.4)	.092
Former	23 (27.4)	47 (19.4)	
Current	53 (63.1)	182 (75.2)	
Alcohol use[c]			
Never	17 (20.5)	23 (9.7)	.0368*
Former	15 (18.1)	49 (20.6)	
Current	51 (61.5)	166 (69.8)	
Treatment type			
Surgery alone	23 (27.4)	42 (17.1)	.1012
RT alone	37 (44.1)	113 (46.1)	
Surgery + RT	24 (28.6)	90 (36.7)	

Primary site			
Oral cavity	15 (17.9)	47 (19.2)	
Oropharynx	29 (34.5)	114 (46.5)	.1386
Larynx	35 (41.7)	70 (28.6)	
Hypopharynx	5 (6.0)	14 (5.7)	
TNM stage			
I	29 (34.5)	32 (13.1)	
II	13 (15.5)	31 (12.7)	<.0001*
III	18 (21.4)	46 (18.8)	
IV	24 (28.6)	136 (55.5)	
N class			
N0	59 (70.2)	101 (41.2)	
N1	13 (15.5)	37 (15.1)	<.0001*
N2	12 (14.3)	99 (40.4)	
N3	0 (0.0)	8 (3.3)	
T class[d]			
T1	33 (39.3)	52 (21.6)	
T2	22 (26.2)	76 (31.0)	.010*
T3	13 (15.5)	62 (25.3)	
T4	16 (19.0)	54 (22.0)	

Overall Survival at 3 year

P<0.001

Disease Specific Survival at 3 year

P<0.001

Treatment benefit of regular NSAID exposure for DSS and OS. (A) Model-predicted DSS probability indicates no survival difference between regular users (Yes, blue) versus never or occasional users (No,

Matthew L. Hedberg et al. J Exp Med 2019;216:419-427
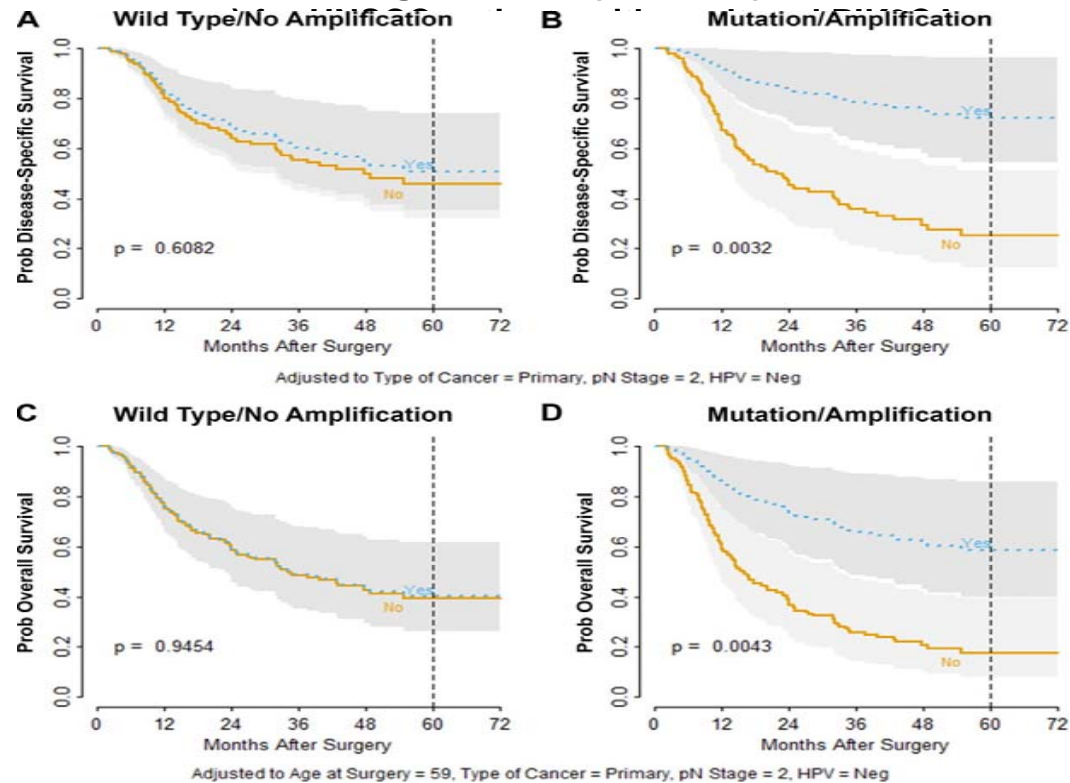
NSAIDs and Roswell H&N

- N=459
- 2005-2017 HNSCC treated with chemoRT

Local Failure: NSAIDs and Roswell H&N

Variable	N	Total Failures	NSAID negative	NSAID positive	chi square p-value	Fischer's exact
Total	459	10.9%	7.4%	3.5%	0.075	0.096
Primary Site						
Oral Cavity	29	31.0%	20.7%	10.3%	0.73	1.0
Oropharynx	249	6.8%	4.0%	2.8%	0.55	0.62
Hypopharynx	43	21.0%	16.3%	4.7%	0.8	1.0
Nasopharynx	17	11.8%	11.8%	(0/0) 0%	0.21	0.49
Larynx	119	16.0%	11.8%	4.2%	0.33	0.44
Non-Oropharynx	228	16.6%	11.7%	4.9%	0.23	
Current Smoker	115	17.4%	12.2%	5.2%	0.12	0.80
Former Smoker	242	11.0%	7.4%	3.3%	0.047	0.06
Never Smoker	102	3.9%	2.0%	2.0%	0.71	
Current or Former Smoker	357	12.9%	9.0%	3.9%	0.039	0.04

Survival: NSAIDs and Roswell H&N

- Factors associated with worse OS:
    - T stage (p=0.006)
    - Overall stage (p=0.022)
    - Smoking status (<0.001)
   - Oral cavity primary (0.02)
    - No NSAID (p=0.015)

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
DSS	1.22 (0.71-2.09)	0.48	0.98 (0.91-1.04)	0.47
OS	0.62 (0.42-0.91)	**0.015**	0.90 (0.83-0.98)	**0.018**

*adjusted for age, stage, gender, primary tumor site, HPV status, diabetes mellitus, stroke, hyperlipidemia (all alpha<0.21 on univariate)

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Cancer-Specific Survival: NSAIDs and Roswell H&N

Log rank=0.51
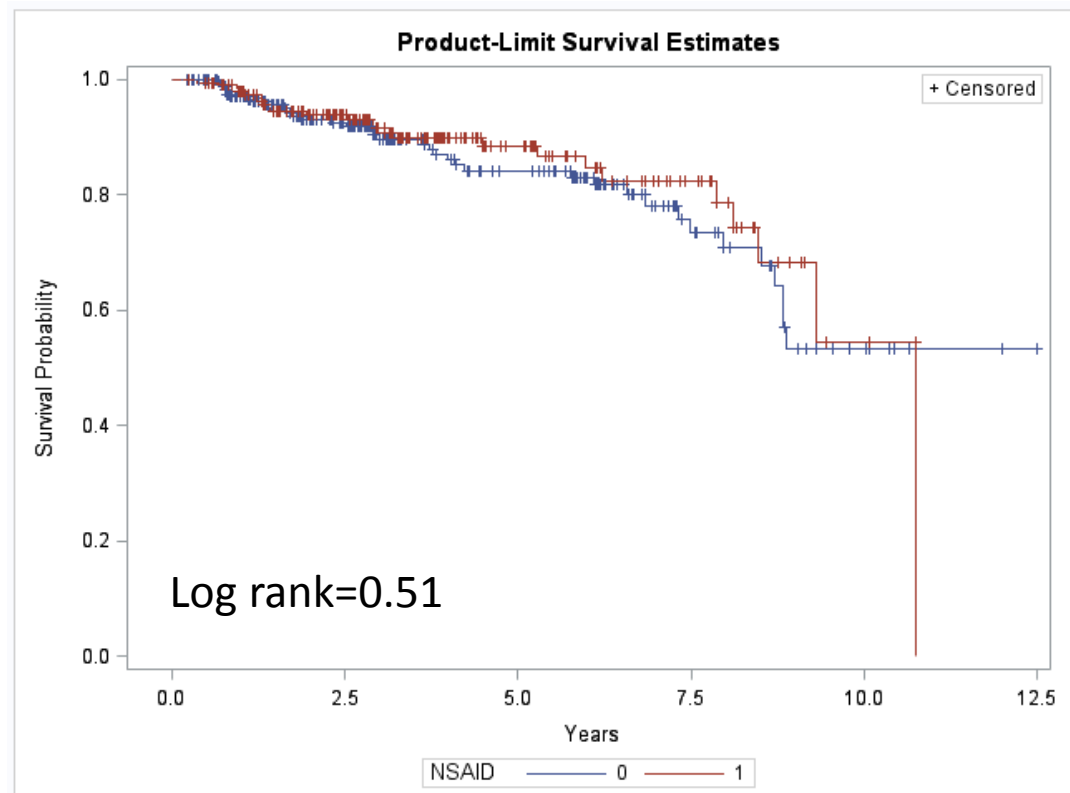
Overall Survival: NSAIDs & Roswell H&N
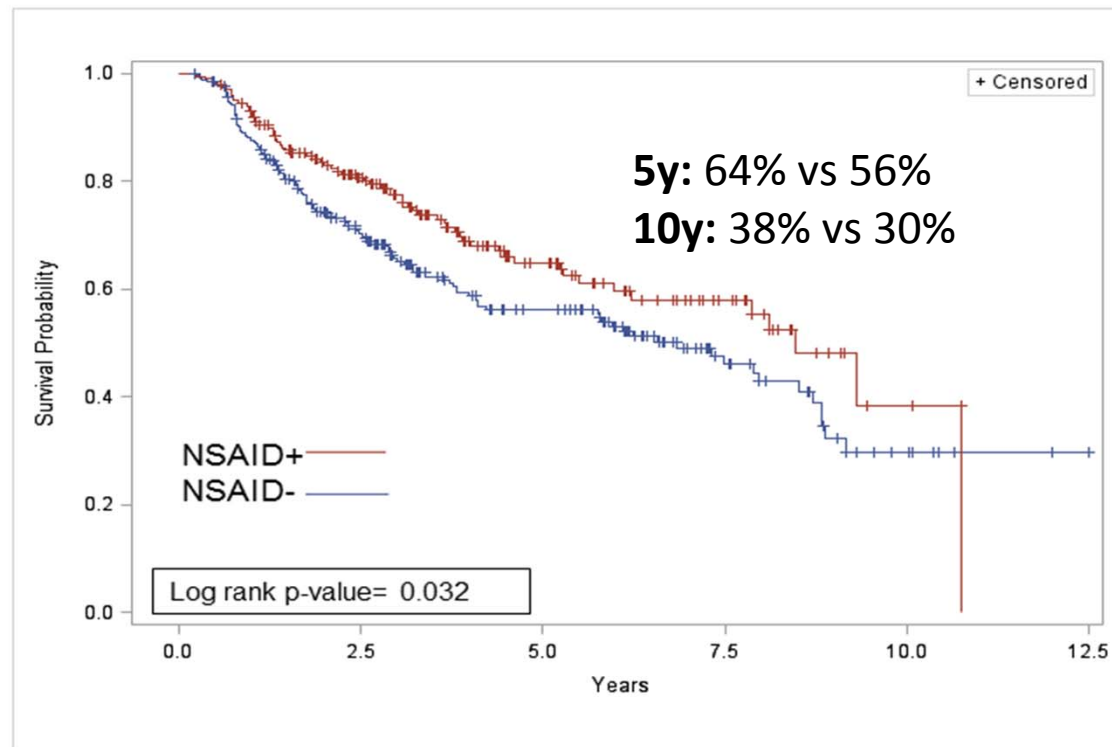
5y: 64% vs 56%
10y: 38% vs 30%

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Rectal Cancer and Aspirin: Roswell Park

N=153
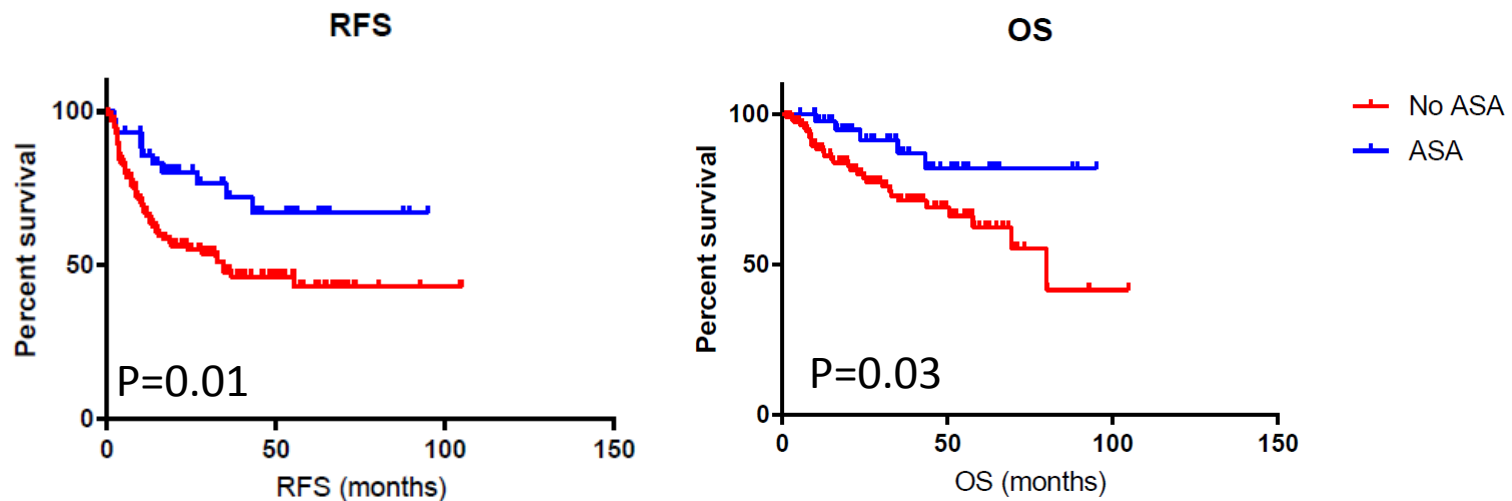
Farrugia, Singh

Possibilities with Rectal Specimens

- PIK3 kinase?

- ~20% of rectal ca pts PIK3A mut Of ~1000pts
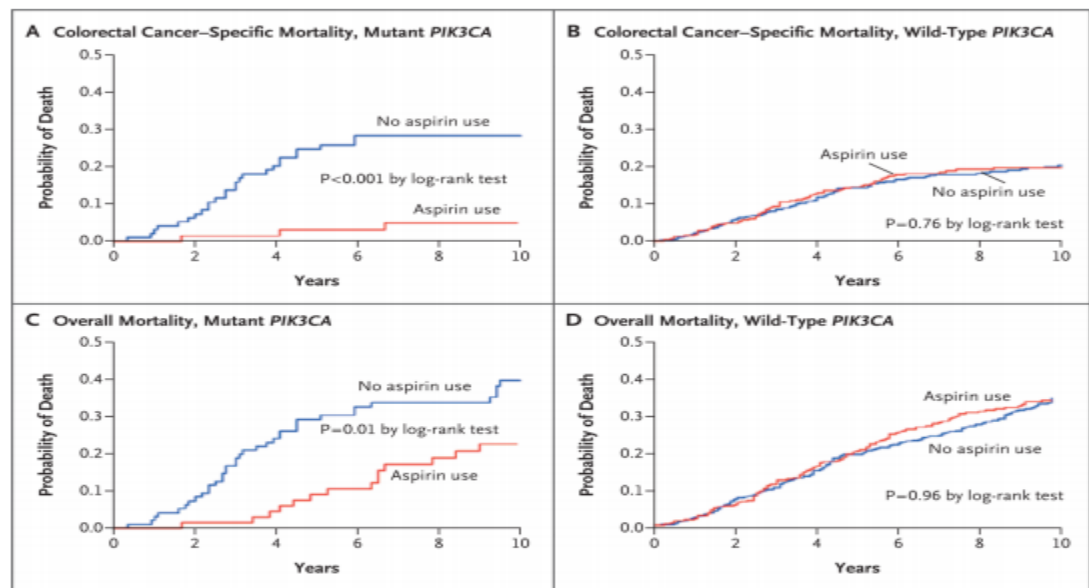
Figure 1. Mortality among Patients with Colorectal Cancer, According to Regular Use or Nonuse of Aspirin after Diagnosis and *PIK3CA* Mutation Status
Panels A and B show colorectal cancer–specific mortality among patients with mutant-*PIK3CA* tumors and those with wild-type *PIK3CA* tumors, respectively, and Panels C and D show overall mortality in the respective subgroups of patients.

Liao et al. NEJM 2012

Master Aspirin, Propranolol Rectal Trial

15 Patient pilot trials
Primary Endpoint:
Tolerance
Secondary: Complete
Response, Immune
Analyses
Tertiary: Local Control/OS

Eligible

Rectal Cancer Patients getting standard ChemoRT

Stratify

Not Eligible for aspirin
Note: if on beta-blockers

Eligible for Aspirin
Note: if on beta-blockers

Treatment

Nothing

Propranolol

Baby Aspirin

High Dose Aspirin

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Time of Radiotherapy and mucositis in H&N cancer patients (Anurag Singh, Williams Duncan, Alan Hutson)

Author, year	Sample size	Treat time	Primary Endpoint	Results
Goyal, et al. 2009	88 + 89	8-11 am vs. 3-6 pm	III/IV mucositis	26% vs. 38% at 7th week; p=0.08
Bjarnason, et al. 2008	101 + 101	8-10 am vs. 4-6 pm	RTOG grade 3+ mucositis	52.9% vs. 62.4%; p=0.17
	111 patients with dosage ≥ 66 Gy			44.6% vs. 67.3%; p=0.03
	53 smokers			42.9% vs. 76%; p=0.04

Limitations: Not statistical significant for each single study

Patients are not representative (healthier, no sleep issue)

No information for treatment time of early afternoon and late morning
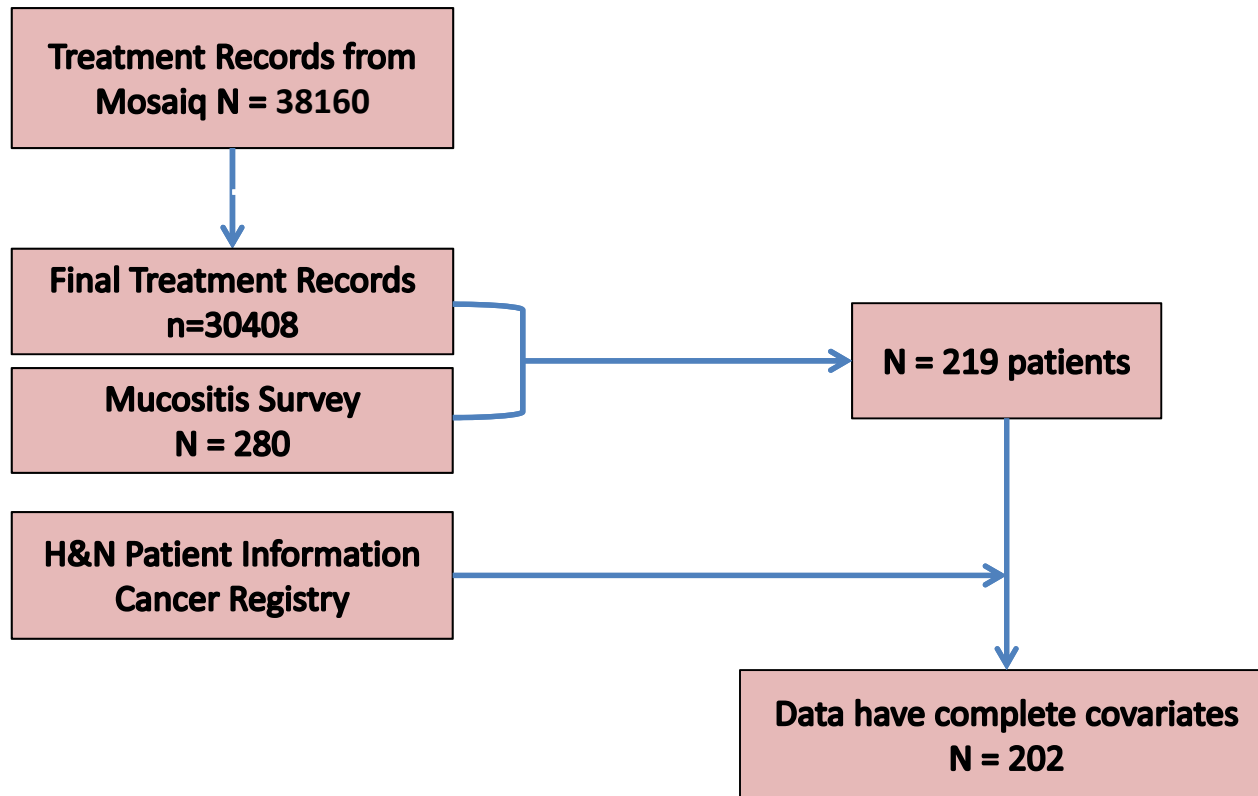
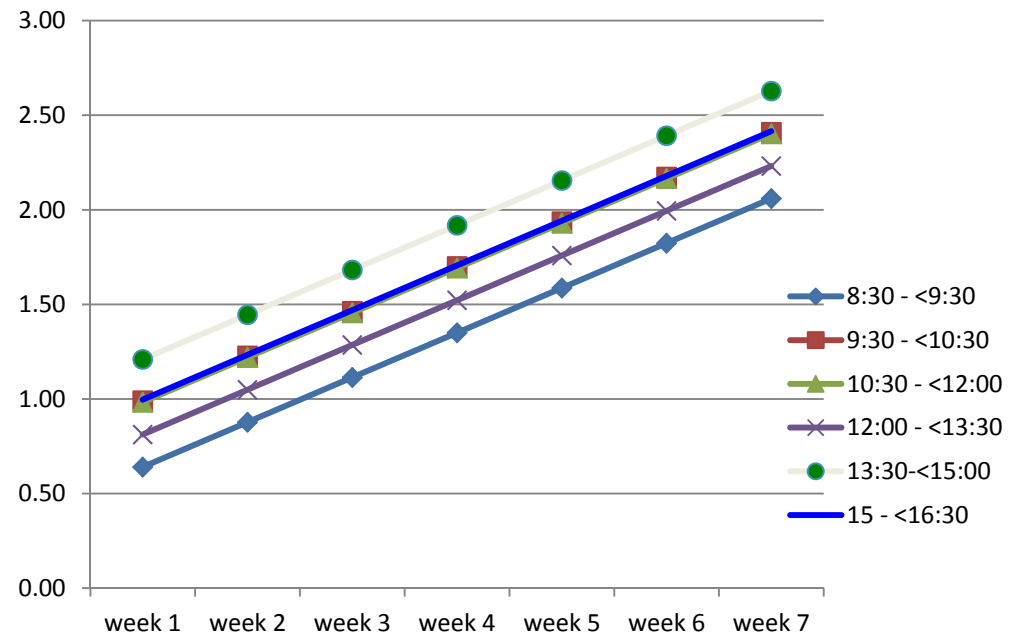# Average Maximum soreness quality by time category (n=219)
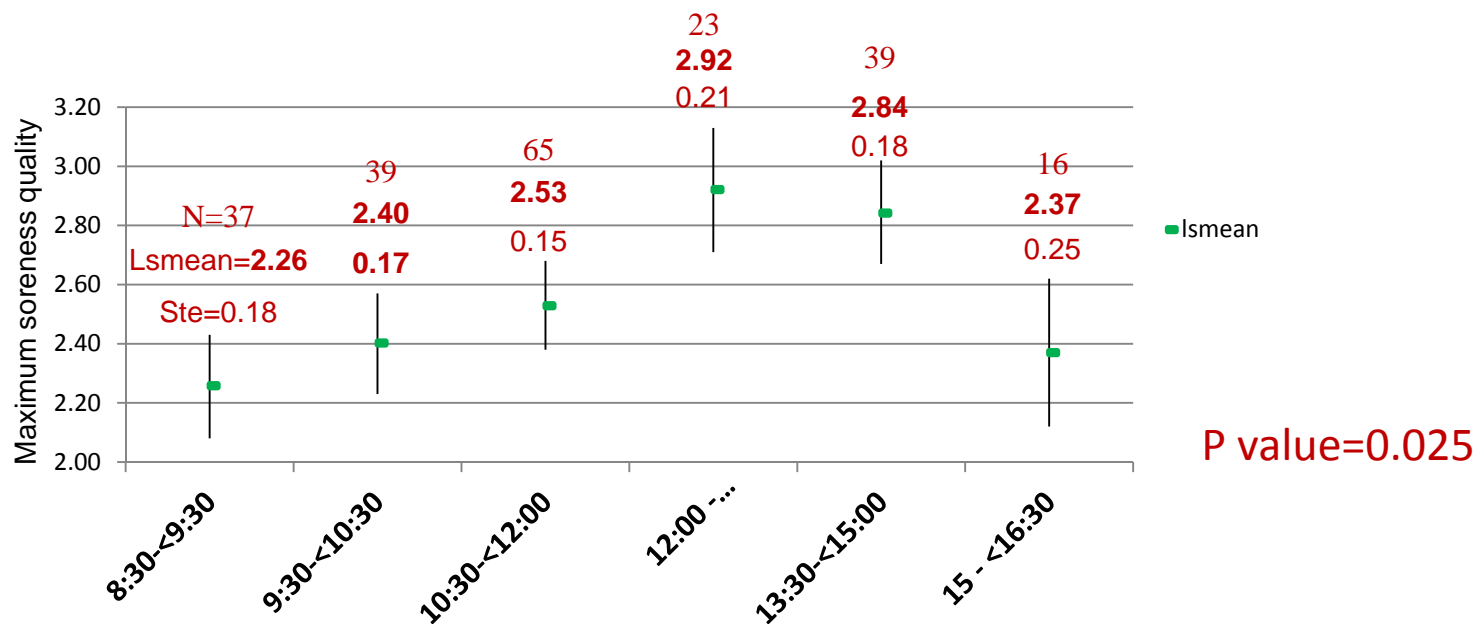
LSmeans (marginal average score adjusting for other factors) were obtained from **GLM model** with maximum soreness score as dependent variable (0, 1, 2, 3, 4; continuous), time category as categorical. Covariates: cancer site, smoking at diagnosis, age at radiotherapy, week of mucositis, type of radiotherapy

Predicted average soreness quality score using Mixed model (n=1278 records)

Average Lsmean by time category

	N	LSmean	Ste	P
8:30 - <9:30	231	1.36	0.20	0.001
9:30 - <10:30	231	1.72	0.20	
10:30 - <12:00	381	1.69	0.19	
12:00 - <13:30	**120**	1.58	0.20	
13:30-<15:00	218	1.93	0.18	
15 - <16:30	**97**	1.73	0.22	

Lsmean for each survey week by time category

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