Chill out!
Take 2 aspirin.
Call me in the morning.
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
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
Pembro +/- RT NSCLC. Secondary analysis

Pembro +/- SBRT NSCLC. Phase 2
Theelen et al. JAMA Oncol. 2019.
Beta-blockers + RT = Abscopal (Repasky)

Analogous data: 1. Celebrex, Aspirin
Beta-adrenergic Stress is Bad for you:
Esophageal Adenocarcinoma ChemoRT Only

Farrugia, Singh
Esophageal Adenocarcinoma Trial
CRT +/- Propranolol
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
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
OS at 2 years:

72% (95% CI, 56-83%) for 30 Gy
59% (95% CI, 41-73%) for 60 Gy

CHISEL Trial

18 Gy x 3
or
12 Gy x 4

2 Gy x 33
or
2.5 Gy x 20

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)
Increase in Financial Burden Worsens Survivals

On multivariate analysis, increase in financial problems was the only significant predictor of overall survival.
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
The effect of time between diagnosis and initiation of treatment on outcomes in patients with head and neck squamous cell carcinoma


*School of Medicine and Biomedical Sciences, University of New York, United States
1 Department of Head and Neck Surgery, Plastic and Reconstructive Surgery, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States
2 Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

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\textsuperscript{a}, Alexis J. Platek\textsuperscript{a}, Luke Degraaff\textsuperscript{b}, Chong Wang\textsuperscript{b}, William D. Duncan\textsuperscript{b}, Kimberly E. Wooten\textsuperscript{c}, Hassan Arshad\textsuperscript{d}, Vishal Gupta\textsuperscript{d}, Moni A. Kuriakose\textsuperscript{e}, Wesley L. Hicks Jr.\textsuperscript{e}, Mary E. Platek\textsuperscript{a,}\textsuperscript{e}, Anurag K. Singh\textsuperscript{a,}\textsuperscript{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.
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
VA H&N Cancer: Post Diagnosis Aspirin Use

### Table 1: Clinical-pathologic characteristics of aspirin users and non-aspirin users after HNC diagnosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aspirin users</th>
<th>Non-aspirin users</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.3 ± 9.3</td>
<td>61.3 ± 8.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84 (100.0)</td>
<td>242 (98.8)</td>
<td>.5731</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0.0)</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>22 (26.8)</td>
<td>88 (37.8)</td>
<td>.1200</td>
</tr>
<tr>
<td>African American</td>
<td>58 (70.7)</td>
<td>143 (61.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.4)</td>
<td>2 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Tobacco use^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>8 (9.5)</td>
<td>13 (5.4)</td>
<td>.092</td>
</tr>
<tr>
<td>Former</td>
<td>23 (27.4)</td>
<td>47 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>53 (63.1)</td>
<td>182 (75.2)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17 (20.5)</td>
<td>23 (9.7)</td>
<td>.0687</td>
</tr>
<tr>
<td>Former</td>
<td>15 (18.1)</td>
<td>49 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>51 (61.5)</td>
<td>166 (69.8)</td>
<td></td>
</tr>
<tr>
<td>Treatment type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>23 (27.4)</td>
<td>42 (17.1)</td>
<td>.1012</td>
</tr>
<tr>
<td>RT alone</td>
<td>37 (44.1)</td>
<td>113 (48.1)</td>
<td></td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>24 (28.6)</td>
<td>90 (36.7)</td>
<td></td>
</tr>
</tbody>
</table>

### Primary site

<table>
<thead>
<tr>
<th>Site</th>
<th>No Aspirin</th>
<th>Aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>15 (17.9)</td>
<td>47 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>29 (34.5)</td>
<td>114 (46.5)</td>
<td>.1386</td>
</tr>
<tr>
<td>Larynx</td>
<td>35 (41.7)</td>
<td>70 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>5 (6.0)</td>
<td>14 (5.7)</td>
<td></td>
</tr>
</tbody>
</table>

### TNM stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>No Aspirin</th>
<th>Aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>29 (34.5)</td>
<td>32 (13.1)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13 (15.5)</td>
<td>31 (12.7)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>III</td>
<td>18 (21.4)</td>
<td>46 (18.8)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>24 (28.6)</td>
<td>136 (55.5)</td>
<td></td>
</tr>
</tbody>
</table>

### N class

<table>
<thead>
<tr>
<th>Class</th>
<th>No Aspirin</th>
<th>Aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>59 (70.2)</td>
<td>101 (41.2)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>13 (15.5)</td>
<td>37 (15.1)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>N2</td>
<td>12 (14.3)</td>
<td>99 (40.4)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>0 (0.0)</td>
<td>8 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>

### T class

<table>
<thead>
<tr>
<th>Class</th>
<th>No Aspirin</th>
<th>Aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>33 (39.3)</td>
<td>52 (21.6)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>22 (26.2)</td>
<td>76 (31.0)</td>
<td>.010*</td>
</tr>
<tr>
<td>T3</td>
<td>13 (15.5)</td>
<td>62 (25.3)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>16 (19.0)</td>
<td>54 (22.0)</td>
<td></td>
</tr>
</tbody>
</table>
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, orange) for HNSCC patients with unaltered PIK3CA.

NSAIDs and Roswell H&N

• N=459
• 2005-2017 HNSCC treated with chemoRT
## Local Failure: NSAIDs and Roswell H&N

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

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>DSS</td>
<td>1.22 (0.71-2.09)</td>
<td>0.48</td>
</tr>
<tr>
<td>OS</td>
<td>0.62 (0.42-0.91)</td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>0.98 (0.91-1.04)</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>0.90 (0.83-0.98)</td>
<td><strong>0.018</strong></td>
</tr>
</tbody>
</table>

*adjusted for age, stage, gender, primary tumor site, HPV status, diabetes mellitus, stroke, hyperlipidemia (all alpha<0.21 on univariate)
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%
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
Rectal Cancer and Aspirin: Roswell Park

N=153

RFS

P=0.01

OS

P=0.03

Farrugia, Singh
Possibilities with Rectal Specimens

- PIK3 kinase?
- ~20% of rectal ca pts PIK3A mut
- Of ~1000pts

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
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
Both acute response and late side effects of chemotherapy and radiation are modulated by the circadian clock; disrupted circadian rhythms may impair therapeutic efficacy.

Clinical Potential

- Identifying circadian markers of sensitivity to radiation in cancer patients
- Search for pharmacological modulators of circadian function

New provocative question grant awarded in July, 2018 (R21 CA227375)
Time of Radiotherapy and mucositis in H&N cancer patients (Anurag Singh, Williams Duncan, Alan Hutson)

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

**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
Thanks William Duncan Yingdong, Austin Miller
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)

<table>
<thead>
<tr>
<th>Time Category</th>
<th>N</th>
<th>Lsmean</th>
<th>Ste</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 - &lt;9:30</td>
<td>231</td>
<td>1.36</td>
<td>0.20</td>
<td>0.001</td>
</tr>
<tr>
<td>9:30 - &lt;10:30</td>
<td>231</td>
<td>1.72</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>10:30 - &lt;12:00</td>
<td>381</td>
<td>1.69</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>12:00 - &lt;13:30</td>
<td>120</td>
<td>1.58</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>13:30 - &lt;15:00</td>
<td>218</td>
<td>1.93</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>15 - &lt;16:30</td>
<td>97</td>
<td>1.73</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>
Assessing Single-fraction SBRT versus Standard palliative Radiation In patients with metastatic Disease (ASTEROID)

-300 pts eligible /yr
-Banking with DBBR

Enrollment

All Patients with (non-CNS) metastatic disease eligible for radiation therapy

Stratification

Patients unable or unwilling to undergo randomization

Physicians unwilling to randomize patients

Sex
- Age (<50, 50-70, >70)
- Years since diagnosis (<1, 1-3, >3)
- Treatment site (osseous vs non-osseous)
- Number of metastases (<, ≥5)
- Tumor Histology
- ECOG score (0, 1, 2, 3-4)
- Frailty Index (non-frail, pre-frail, frail)
- Current Systemic Therapy (yes/no)
- Brief Pain Inventory, Question 3 (<5, >5)
- Morphine equivalents (<60, ≥60)

Randomization

STANDARD ARM (Physician Preference)
3 Gy x 10
8 Gy x 1
4Gy x 5-6
5-10 Gy x 3-5

SBRT
16-26 Gy x 1 fx

Outcomes

Primary Outcomes: Pain Relief, QOL
Secondary Outcomes: OS
Exploratory Outcomes: Immune Biomarkers, Toxicity, Frailty Index, Cognitive function, Pain Catastrophizing Index, Circadian Rhythm Effects