Review of time to treatment for head and neck cancer patients at a rural Maine cancer center

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3/21/2019 | Adam Curtis, MS
Part I:
Review of Head and Neck Cancers

- 2018 Quality Initiative at Northern Light Cancer Inst.
- Cases Diagnosed between 2013-2017
- Received Treatment at Northern Light Health/EMMC
- Oral, Oropharyngeal, Laryngeal, and Hypopharyngeal squamous cell carcinoma
- Nasopharyngeal cancers excluded
Head and Neck Cancers: 2013-2017

n=296

- Oropharynx: 99 (33.5%)
- Larynx: 92 (31.1%)
- Hypopharynx: 13 (4.4%)
- Oral: 82 (27.7%)
- NOS: 10 (3.4%)

n=296
Head and Neck Cancers: 2013-2017

First Treatment by Primary Tumor Site

<table>
<thead>
<tr>
<th>Tumor Primary Site</th>
<th>Oral (n=81)</th>
<th>Oropharynx (n=96)</th>
<th>Larynx (n=92)</th>
<th>All (n=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo/Radiation</td>
<td>14 (17.3%)</td>
<td>62 (64.6%)</td>
<td>29 (31.5%)</td>
<td>105 (39.0%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (7.4%)</td>
<td>28 (29.2%)</td>
<td>13 (14.1%)</td>
<td>95 (35.3%)</td>
</tr>
<tr>
<td>Radiation Only</td>
<td>7 (8.6%)</td>
<td>3 (3.1%)</td>
<td>9 (9.8%)</td>
<td>50 (18.6%)</td>
</tr>
<tr>
<td>No Treatment</td>
<td>3 (3.1%)</td>
<td>3 (3.1%)</td>
<td>19 (7.1%)</td>
<td>19 (7.1%)</td>
</tr>
</tbody>
</table>

*4 Patients received chemo only n=269
Head and Neck Cancers: 2013-2017

Stage at Diagnosis

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>2.0%</td>
</tr>
<tr>
<td>I</td>
<td>53</td>
<td>17.9%</td>
</tr>
<tr>
<td>II</td>
<td>44</td>
<td>14.9%</td>
</tr>
<tr>
<td>III</td>
<td>50</td>
<td>16.9%</td>
</tr>
<tr>
<td>IV a</td>
<td>129</td>
<td>43.6%</td>
</tr>
<tr>
<td>IV b</td>
<td>6</td>
<td>2.0%</td>
</tr>
<tr>
<td>IV c</td>
<td>6</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

* 2 patients not staged
n=294

Chemo/Radiation
Surgery
Radiotherapy Only
No Treatment

*Head and Neck Cancer Time To Treatment*
Head and Neck Cancers: 2013-2017

First Treatment by Stage

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Percent of Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-I</td>
<td></td>
</tr>
<tr>
<td>n=59</td>
<td></td>
</tr>
<tr>
<td>Chemo/Radiation</td>
<td>1.7%</td>
</tr>
<tr>
<td>Surgery</td>
<td>49.2%</td>
</tr>
<tr>
<td>Radiation Only</td>
<td>40.7%</td>
</tr>
<tr>
<td>No Treatment</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
</tr>
<tr>
<td>n=44</td>
<td></td>
</tr>
<tr>
<td>Chemo/Radiation</td>
<td>13.6%</td>
</tr>
<tr>
<td>Surgery</td>
<td>29.5%</td>
</tr>
<tr>
<td>Radiation Only</td>
<td>29%</td>
</tr>
<tr>
<td>No Treatment</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
</tr>
<tr>
<td>n=49</td>
<td></td>
</tr>
<tr>
<td>Chemo/Radiation</td>
<td>6.1%</td>
</tr>
<tr>
<td>Surgery</td>
<td>45.5%</td>
</tr>
<tr>
<td>Radiation Only</td>
<td>28.6%</td>
</tr>
<tr>
<td>No Treatment</td>
<td>11.4%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>n=138</td>
<td></td>
</tr>
<tr>
<td>Chemo/Radiation</td>
<td>3.6%</td>
</tr>
<tr>
<td>Surgery</td>
<td>58%</td>
</tr>
<tr>
<td>Radiation Only</td>
<td>5.8%</td>
</tr>
<tr>
<td>No Treatment</td>
<td>45%</td>
</tr>
</tbody>
</table>

*2 Patients not staged
*4 Patients received chemo only
n=290
Part II: Time to Treatment

- Median time from biopsy to first treatment. (Patients not receiving a biopsy were excluded).

- Patients were categorized by first treatment modality, even if they had subsequent additional treatment.
Why is Time to Treatment Important?

- **Jensen et al., Denmark (2007), Radiotherapy and Oncology:**
  
  n=61 radiotherapy patients that had a diagnostic and treatment scan MRI or CT
  
  28 days: Median interval between scans
  
  • 62% tumors had measurable volume increase (49% median volume increase)
  • 20% developed lymph node metastasis
  • 16% progressed in TNM classification

  99 days: Tumor volume doubling time: fastest tumors: 30 days

- **Fujima et al., Japan (2017), Oncotarget:**
  
  n=55 patients that had a diagnostic and treatment scan (MRI or CT)
  
  34 days: Median interval between scans
  
  • 34% median increase in tumor diameter

- **Xiao et al., Cleveland Clinic/Case Western (2018), Cancer:**
  
  • 12.1% T upstaged, n=60,194 (NCDB)
  • 18.6% N upstaged, n=51,380 (NCDB)
  • 17.4% Stage upstaged, n=52,980 (NCDB)
  • Any upstaging predicted increased mortality
  • TTT predicted mortality after 70 days
# Head and Neck Cancer Time to Treatment Studies:

## United States

<table>
<thead>
<tr>
<th>Study</th>
<th>Year/Journal</th>
<th>Facility</th>
<th>Sample Size</th>
<th>Years of Dx</th>
<th>Source</th>
<th>Median TTT</th>
<th>Delay Threshold Tested</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Murphy et al.</td>
<td>2015 Cancer</td>
<td>Fox-Chase</td>
<td>274,630</td>
<td>1998-2011</td>
<td>NCDB</td>
<td>26 days</td>
<td>N/A</td>
<td>Increasing TTT 1998-2011 for all conditions</td>
</tr>
<tr>
<td>2. Murphy et al.</td>
<td>2016 JCO</td>
<td>Fox-Chase</td>
<td>51,655</td>
<td>2003-2005</td>
<td>NCDB</td>
<td>26 days</td>
<td>&gt;67 days</td>
<td>Decreased OS with higher TTT</td>
</tr>
<tr>
<td>3. Cheraghlou et al.</td>
<td>2017 Laryngoscope</td>
<td>Yale</td>
<td>5,627</td>
<td>2004-2012</td>
<td>NCDB</td>
<td>N/A</td>
<td>&gt;100 days</td>
<td>&gt;100 = decreased OS 1% of cases &gt;100 days (56)</td>
</tr>
<tr>
<td>4. Fujiwara et al.</td>
<td>2017 Head and Neck</td>
<td>Yale</td>
<td>4,868</td>
<td>1998-2011</td>
<td>NCDB</td>
<td>30 days</td>
<td>&gt;45 days</td>
<td>25% cases &gt;45 days No OS association</td>
</tr>
<tr>
<td>5. Sharma et al.</td>
<td>2016 Oral Oncology</td>
<td>UPenn</td>
<td>6,606</td>
<td>2003-2006</td>
<td>NCDB</td>
<td>N/A</td>
<td>&gt;30 days</td>
<td>&gt;30 days = decreased OS</td>
</tr>
<tr>
<td>7. Bilimoria et al.</td>
<td>2011 Annals of Surgery</td>
<td>Northwestern</td>
<td>1,228,071</td>
<td>1995-2005</td>
<td>NCDB</td>
<td>N/A</td>
<td>N/A</td>
<td>TTT increased for all cancers, all categories over time</td>
</tr>
</tbody>
</table>
### Head and Neck Cancer Time to Treatment Studies:

#### International

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Year</th>
<th>Facility/Country</th>
<th>Sample Size</th>
<th>Years of Dx</th>
<th>Source</th>
<th>Median TTT</th>
<th>Delay Threshold</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Polesel et al.</td>
<td>2017 Oral Oncology</td>
<td>Italy</td>
<td>1,616</td>
<td>2003-2009</td>
<td>Regional Cancer Registry</td>
<td>28 days</td>
<td>&gt;90 days</td>
<td>Decreased OS with increased TTT, Significant &gt;90 days, Increased &lt;45 days</td>
</tr>
<tr>
<td>2. Van Harten et al.</td>
<td>2014 Oral Oncology</td>
<td>Netherlands</td>
<td>2,493</td>
<td>1990-2011</td>
<td>Netherlands Cancer Registry</td>
<td>37 days</td>
<td>N/A</td>
<td>Decreased OS with increased TTT, Longer TTT: men, oropharynx, stage IV, CR</td>
</tr>
<tr>
<td>5. Tsai et al.</td>
<td>2017 PLoS One</td>
<td>Taiwan</td>
<td>21,263</td>
<td>2004-2010</td>
<td>Nat. Health Ins. Database, China</td>
<td>&lt;30 days (85.5%), &gt;120 days (2.7%)</td>
<td>N/A</td>
<td>Decreased OS &gt;120 days</td>
</tr>
<tr>
<td>6. Liao et al.</td>
<td>2017 Euro J. Cancer</td>
<td>Taiwan</td>
<td>18,677</td>
<td>2004-2010</td>
<td>Nat. Health Ins. Database, China</td>
<td>&lt;20 days (57%), 21-45 days (34%), 46-90 days (6%), &gt;91 days: (3%)</td>
<td>N/A</td>
<td>Decreased OS with increasing TTT, even after 20 days</td>
</tr>
<tr>
<td>7. Chiou et al.</td>
<td>2016 Medicine</td>
<td>Taiwan</td>
<td>2,703</td>
<td>2007-?</td>
<td>Nat. Health Ins. Database, China</td>
<td>22.45 days (mean)</td>
<td>N/A</td>
<td>Lower likelihood for delays if: higher income, higher Charleson, young age</td>
</tr>
</tbody>
</table>
*7 out of 9 studies measuring outcome, revealed a correlation between decreased overall survival and longer time to treatment, one after only 20 days. (2 showed no association)

*Time to Treatment has generally increased over time in recent years

- **Murphy et al., Fox-Chase (2015), Cancer:**
  Time to treatment (TTT), for **head and neck** cancers in the US, has increased continually over time regardless of stage, treatment modality, or site from 1998-2011. *(n=274,630, NCDB)*

- **Billmoria et al., Northwestern (2011), Radiotherapy and Oncology:**
  Time to treatment (US) has increased continually for **all cancers**, all conditions, from 1995 to 2005. *(n=1.2 million, NCDB)*
Head and Neck Cancer is difficult to treat and requires coordination of multiple factors

(Example Timeline)

Rising time to treatment (TTT) reflects the increased use of sophisticated diagnostic and therapeutic techniques.
Two Definitive Studies by Murphy et al., Fox Chase Cancer Center, Philadelphia, PA
For Comparison

Murphy et al., Cancer, 2015
Increasing Time to Treatment Initiation for Head and Neck Cancer: An Analysis of the National Cancer Database

Colin T. Murphy, MD, Thomas J. Galloway, MD, Elizabeth A. Handorf, PhD, Lora Wang, MD, Raneen Mehra, MD, Douglas B. Flicker, MD; and John A. Ridge, MD PhD

BACKGROUND: The objective of this study was to identify trends and predictors of the time to treatment initiation (TTT) for patients with head and neck squamous cell carcinoma (HNSSC). METHODS: The National Cancer Database (NCDB) was reviewed for the following head and neck cancer sites: oral tongue, oropharynx, larynx, and hypopharynx. TTT was defined as the number of days from diagnosis to the initiation of definitive treatment and was measured according to covariates. Significant differences in the median TTT across each covariate were measured using the Kruskal-Wallis test, and the Spearman test was used to measure trends within covariates. For multivariate analysis, a zero-inflated, negative, binomial regression model was used to estimate the expected TTT, which was based on the number of days from diagnosis to treatment initiation.

Purpose: Characterize TTT for U.S. Patients

Med TTT: 26 Days

Source: National Cancer Database
n=274,630

Purpose: Determine critical TTT thresholds by studying outcomes

Principle Finding: TTT increased for all conditions: 1998-2011

Murphy et al., JCO, 2016
Survival Impact of Increasing Time to Treatment Initiation for Patients With Head and Neck Cancer in the United States

Colin T. Murphy, Thomas J. Galloway, Elizabeth A. Handorf, Brian L. Egleson, Lora S. Wang, Raneen Mehra, Douglas B. Flicker, and John A. Riddle

Source: National Cancer Database
n=51,655

Purpose: Determine critical TTT thresholds by studying outcomes

Principle Finding: Threshold: 67 days
Head and Neck Cancer: 2013-2017
Time to Treatment: First Treatment Type by Year

Median Days Biopsy to First Treatment

- **2013**
  - CR: n=28
  - R: n=10
  - S: n=15

- **2014**
  - CR: n=24
  - R: n=11
  - S: n=15

- **2015**
  - CR: n=20
  - R: n=14
  - S: n=25

- **2016**
  - CR: n=28
  - R: n=11
  - S: n=20

- **2017**
  - CR: n=17
  - R: n=6
  - S: n=21

*Error bars represent inter-quartile range

Total Patients: 296
Patients Rec. Biopsy: 287
Chemo Only: 2
No Treatment: 20
n=265
Head and Neck Cancer: 2013-2017
Comparison to Murphy et al., Cancer, 2015

Approximate time of widespread implementation of PET-CT for H&N Cancers

Median Days: Biopsy to First Treatment

- Murphy et al., Cancer, 2015
  n=274,630: 1998-2011
- Northern Light Cancer Inst.
  n=265: 2013-2017
Head and Neck Cancer: 2013-2017
Time to Treatment: Comparison to Murphy et al., Cancer, 2015

First Treatment Modality

Median Days: Biopsy to First Treatment

- **Murphy et al., Cancer, 2015**
  - All: 26
  - Chemo/Radiation: 38
  - Radiation: 40
  - Surgery: 17

- **Northern Light Cancer Inst.**
  - All: 42.5
  - Chemo/Radiation: 40
  - Radiation: 34
  - Surgery: 34

* Error bars represent inter-quartile range
*χ² test p<0.05

Total Patients: 296
- Rec. Biopsy: 287
- Chemo Only: 2
- No Treatment: 20

n=265
Head and Neck Cancer: 2013-2017
Time to Treatment: Comparison to Murphy et al., Cancer, 2015

Primary Tumor Site

- Larynx
  - Median Days: 23
  - Total Patients: 114,144 / 80

- Oral
  - Median Days: 29
  - Total Patients: 80,971 / 72

- Oropharynx
  - Median Days: 27
  - Total Patients: 60,328 / 91

- Hypopharynx
  - Median Days: 29
  - Total Patients: 19,124 / 12

*χ² test p<0.05

Error bars represent inter-quartile range

Total Patients: 296
Patients Rec. Biopsy: 287
Chemo Only: 2
No Treatment: 20
Site not Specified: 10

n=255
Head and Neck Cancer: 2013-2017
Time to Treatment:
Comparison to Murphy et al., Cancer, 2015

Stage at Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median Days: Biopsy to First Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20 (n=59,245 / 50)</td>
</tr>
<tr>
<td>II</td>
<td>25 (n=37,514 / 38)</td>
</tr>
<tr>
<td>III</td>
<td>28 (n=49,650 / 47)</td>
</tr>
<tr>
<td>IV</td>
<td>29 (n=101,106 / 130)</td>
</tr>
</tbody>
</table>

Error bars represent inter-quartile range

*χ² test p<0.05

Murphy et al., Cancer, 2015
n=247,515: 1998-2011

Northern Light Cancer Inst.
n=265: 2013-2017

Total Patients: 296
Patients Rec. Biopsy: 287
Chemo Only: 2
No Treatment: 20
n=265
How Long is Too Long?

![Graph showing the relationship between time to treatment (TTI) and hazard ratio of mortality.](image)

- **Hazard Ratio of Mortality**
  - **Reference, HR = 1**
  - **HR vs TTI = 0 d**

- **Time to Treatment (TTI)**
  - **0 d**
  - **67 Days**

- **Hazard Ratio of Mortality**
  - **1.0**
  - **1.2**
  - **1.4**
  - **1.6**
  - **1.8**
  - **2.0**

- **n=51,655**
  - **2003-2005**

---

**Fig 2.** Adjusted hazard ratio (HR) of overall mortality according to time to treatment initiation (TTI) as a continuous variable by using restricted cubic splines with seven knots. The reference equals 1 at a TTI of 0 days. The restricted cubic spline allows for a nonlinear relationship of TTI with the log HR of mortality, estimated from the full Cox regression model adjusted for all covariates. The knots define change points where the cubic function can change. We found that the HR of death with respect to a TTI of zero decreased to a HR of less than 1 and then crossed the HR equivalent to 1 close to day 67, which was the cut point found in the recursive partitioning analysis. With a TTI greater than 67, the HR increased substantially.
Head and Neck Cancers: 2013-2017
Time to Treatment:
Murphy et al., Journal of Clinical Oncology, 2016

Murphy et al. JCO, 2016
n=51,655
Northern Light Cancer Inst.
n=265

Percent of Patients

Time to Treatment (Median Days from Biopsy)

0-30 Days
31-52 Days
53-67 Days
>67 Days
Head and Neck Cancer: 2013-2017
Comparison to Murphy et al., Cancer, 2015

Approximate time of widespread implementation of PET-CT for H&N Cancers

Median Days: Biopsy to First Treatment

- **Murphy et al., Cancer, 2015**
  - n=274,630: 1998-2011

- **Northern Light Cancer Inst.**
  - n=265: 2013-2017

Head and Neck Cancer Time To Treatment | 3/21/2019 | 21
Conclusions

- 296 cases of Head and neck cancer were treated at Northern Light Cancer Inst. from 2013-2017 (~59 per year).

- Time to treatment (TTT) did not differ based on stage, or primary site.

- Patients that received surgery had a shorter TTT compared to radiation. This is likely due to additional time needed for dental clearance, and additional preparation inherent in radiotherapy.

- Median TTT was approximately 12 days longer, on average, for NLCI patients compared with Murphy et al, 2015, however consideration must be given to the fact that the Murphy data is from 1998-2011 and when extrapolated to the present time is comparable to our values.

- Most (49.8%) NLCI patients were treated between 31-52 days, whereas Murphy et al., 2016, found the majority (59.5%) of patients received treatment within 30 days.

- Only 10.6% (28) of NLCI patients exceeded the 67 day critical TTT threshold determined by Murphy et al., 2016. This percentage was comparable to the findings of the Murphy study, in spite of the difference in time periods between the two data sets.
Next Steps:

- In depth analysis of the cases that exceeded 52 days to determine reasons for delay in those cases.

- Correlate patient outcomes with time to treatment.

- Efforts to streamline patient care and reduce time to treatment:
  - Patient navigation
  - Coordination with dental care for RT patients
  - Identification of timeline “bottlenecks”
Thank you

Questions?