

# ASSOCIATION BETWEEN INITIAL TREATMENT AND SUBSEQUENT PRIMARIES IN HODGKIN'S LYMPHOMA PATIENTS

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# What is Hodgkin's Lymphoma?

- Hodgkin's Lymphoma is a type of cancer in the lymphatic system
- The lymphatic system is a piece of the immune system which transports fluids through the human body
  - Within the lymphatic system are B cells and T cells
  - B cells are responsible for creating antibodies and storing pathogen information
  - T cells hunt and kill infected cells, as well as sends cytokines to alert the immune system of a foreign object
- Most cases of Hodgkin's Lymphoma begin when B cells are compromised

# Classic Hodgkin's Lymphoma Vs. NLPHD

- About 95% of Hodgkin's Lymphoma in developed countries is Classic Hodgkin's Lymphoma
  - The carcinogenic cells are classified as Reed-Sternberg cells. These are large and abnormal B cells
- Nodular Lymphocyte Predominant Hodgkin's Disease (NLPHD) takes up the other 5%
  - The cells are very large, often called popcorn cells, and are variants of the Reed-Sternberg cells

# What are the Known Risk Factors?

- Mononucleosis- Those who have had mononucleosis have greater risk because of their prior exposure to the Epstein-Barr virus (EBV)
- Age- Crockett and Lunning (2014) stated the most common age ranges of occurrence are 15-30 and over 50 years
- Gender- Crockett and Lunning (2014) also claim the disease is more prevalent in men than women
- HIV- The risk is increased for HIV positive subjects

# Importance of Hodgkin's Lymphoma Research

- The National Institute of Health determined that “In 2016, it is estimated that there will be 8,500 new cases of Hodgkin's Lymphoma and an estimated 1,120 people will die of this disease” (2016) in the United States
- Cancer Research UK stated “0.5% of cancer cases diagnosed in adults in 2012 were Hodgkin Lymphoma (Worldwide). This is 65,950 cases” (2014)

# Problem

- It is believed that Chemotherapy and/or Radiation may be associated with secondary malignancies (cancer recurrences)
- There is also the belief that radiating an organ may be associated with surrounding organ failures or may be associated with carcinogenic states

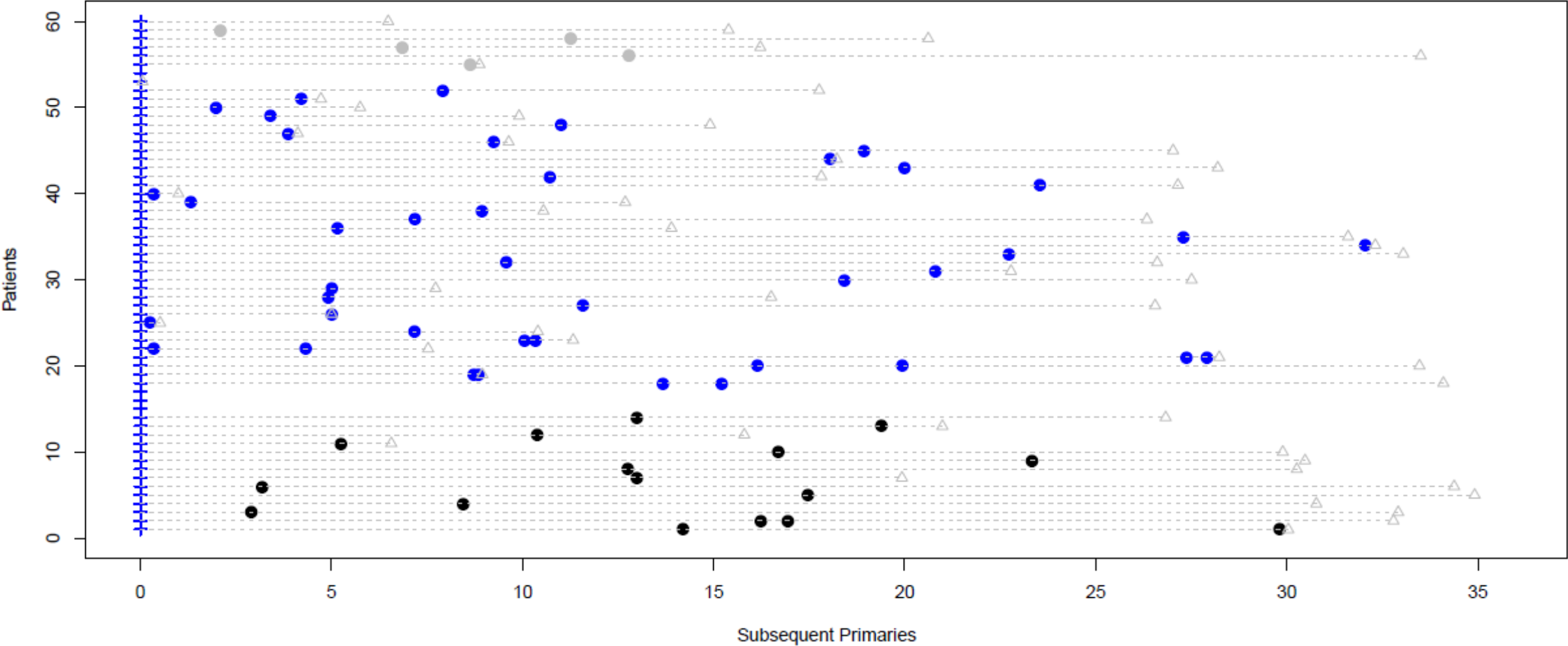
# Questions

- How does Initial Treatment affect subsequent primaries in Hodgkin's Lymphoma patients?
- What are contributing prognostic factors associated with developing subsequent primaries?

# Information About our Dataset

- Our database is the oncology registry at the University of Iowa
- There were 518 patients considered in this study
- The age of diagnosis ranged from 3 to 90 years of age
- 296 males and 222 females were involved
- 463 people did not have a recurrence, 47 people had a single recurrence, and 8 people developed two recurrences
- The treatments were categorized as Chemotherapy, Radiation, and combinations of these treatments

# Cancer Recurrences





# General Treatments for Hodgkin's Lymphoma

## Chemotherapy

- Kills cells and prevents the division of rapidly dividing cells
- Can be administered orally or through an IV

## Radiation

- External Radiation is performed by a medical device outside the body that sends radiation to the carcinogenic cells

## Combination of Chemotherapy and Radiation



# Question

- Which methods will we use to assess the association between occurrences and Initial Treatment groups, or other prognostic factors?

# Answer

- We will use an adaptation of the Cox Proportional Hazards Model

# Cox Proportional Hazards Model

- The Cox Proportional Hazards Model is a method used to analyze the likelihood of an event happening as a function of prognostic factors and the amount of time elapsed

$$\log \left\{ \frac{h_i(t)}{h_0(t)} \right\} = \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi} \Leftrightarrow \frac{h_i(t)}{h_0(t)} = e^{(\beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi})} \quad (1)$$

- The hazard function is the probability of this certain event happening within a short time frame, given that the individual has survived treatment up to that point

$$h(t) = \lim_{\delta t \rightarrow 0} \left\{ \frac{P(t \leq T < t + \delta t | T \geq t)}{\delta t} \right\} \quad (2)$$

- The baseline hazard is when no covariates are taken into account

$$h_0(t)$$

# Outcome

- (Gap Time, Event Indicator)

## Predictors or Prognostic Factors

- Initial Treatment
- Follow-Up Treatment
- Age
- Gender

# How does Initial Treatment Affect the Hazard of Recurrence?

- The Initial Treatment groups are: Chemotherapy(Chm)—Radiation(RT)—Chm&RT
- We start by analyzing an univariate CPH model adaptation with response variable being the time to recurrence and covariate being Initial Treatment group where the baseline for comparison is Chm&RT

## Results

- Chm alone when compared to Chm&RT shows a very statistically significant difference with a higher hazard of recurrence
- RT when contrasted to Chm&RT shows a slight significance with approximately 3 times the hazard of recurrence

	Coef	Exp(coef)	Se(coef)	z	Pr(>  z )
Chm	1.30	3.67	0.47	2.74	0.00613
RT	1.02	2.76	0.52	1.97	0.04868
Chm&RT	-	-	-	-	-

# How does Follow-Up Treatment Affect the Hazard of Recurrence?

- The Follow-Up Treatment groups are: Chm—RT—Chm&RT—Other Treatments
- We chose Chm&RT as the baseline for these groups

## Results

- There is marginally significant evidence that Chm has a larger hazard than baseline
- RT and the Other Treatments do not show statistical significance in this study

	Coef	Exp(coef)	Se(coef)	Z	Pr(>  z )
Chm	0.95	2.59	0.486	1.96	0.0506
RT	0.43	1.53	0.542	0.79	0.4326
Other Treatments	0.86	2.36	0.510	1.68	0.0925
Chm&RT	-	-	-	-	-

# How does Age Affect the Hazard of Recurrence?

- We first compare Age as a single group

## Results

- Each year that passes, the hazard of recurrence multiplies by approximately 1.04
  - This may not sound alarming at first, but this could accumulate over a large period of time

	Coef	Exp(coef)	Se(coef)	z	Pr(>  z )
Age	0.04	1.04	0.007	6.14	8.3e-10



# Categorizing Age

- Crockett and Lunning (2014) claimed that Hodgkin's Lymphoma is most common in two Age groups:
  - 15-30 years of age
  - Over 50 years of age
- We wanted to categorize age into Age groups to assess their effect on the hazard of recurrence

# How does Categorizing Age Affect the Hazard of Recurrence?

- We chose the baseline hazard for Age to be the youngest group

## Results

- There is no statistical significance for the 15-30 age group
- When 31-49 year olds are compared to the baseline, the hazard of recurrence increases
- The group of 50 years and older have over 20 times the hazard of recurrence compared to baseline

	Coef	Exp(coef)	Se(coef)	z	Pr(>  z )
15-30	1.17	3.23	1.031	1.14	0.25513
31-49	2.45	11.58	1.017	2.41	0.01606
50 and Older	3.04	20.92	1.037	2.93	0.00336
14 and Younger	-	-	-	-	-

# How does Gender Affect the Hazard of Recurrence?

- We chose the baseline hazard to be male

## Results

- Being female is marginally significant with a lower hazard of recurrence

	Coef	Exp(coef)	Se(coef)	z	Pr(>  z )
Female	-0.49	0.61	0.265	-1.86	0.0632
Male	-	-	-	-	-

# Question

- What is the joint effect of these prognostic factors on the hazard of recurrence?
- We explore this question by considering a multivariate Cox Proportional Hazards Model

# Multivariate Cox Proportional Hazards Model

- A multivariate CPHM approximates the hazard when all other factors are held fixed
- Chm alone as Initial Treatment multiplies the hazard by more than 11
- The effect of Initial Treatment being RT multiplies the hazard by nearly 20
- Ages 15-30 do not show any statistical significance

	Coef	Exp(coef)	Se(coef)	z	Pr(> z )
Initial Treatment: Chm	2.40	11.02	1.199	2.00	0.04547
Initial Treatment: RT	2.93	18.73	1.284	2.28	0.02253
Age: 15-30	1.08	2.95	1.035	1.05	0.29541
Age: 31-49	2.23	9.33	1.021	2.19	0.02869
Age: Over 50	2.80	16.43	1.042	2.69	0.00724
Gender	-0.50	0.61	0.286	-1.76	0.07903
Follow-Up Treatment: Chm	-1.72	0.18	1.213	-1.42	0.15517
Follow-up Treatment: RT	-2.35	0.09	1.319	-1.79	0.07423
Follow-up Treatment: Other Treatments	-1.58	0.21	1.196	-1.32	0.18656

# Multivariate Cox Proportional Hazards Model

- Patients between 31-49 years of age have an increase in the hazard of recurrence
- Those above the age of 50 have 16 times the hazard when compared to ages 14 and younger
- Gender is not statistically significant in this study
- The Follow-Up Treatment has no statistical significance as well but is worth adjusting for

	Coef	Exp(coef)	Se(coef)	z	Pr(> z )
Initial Treatment: Chm	2.40	11.02	1.199	2.00	0.04547
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Follow-up Treatment: Other Treatments	-1.58	0.21	1.196	-1.32	0.18656

# Problem

- Additional insights came to light after consulting with an expert in the field of Lymphoma, Dr. Brian K. Link. We were informed treatments have evolved over time. For example
  - Radiation was primarily used in the 80's since Chemotherapy was very toxic in that time period
  - Nowadays both treatments are widely used and well tolerated
- Therefore the monitoring period is worth adjusting for to reflect these underlying changes

# Solution

- We adjusted for the monitoring period in the Cox Proportional Hazards Model

# Adjusted Multivariate Cox Proportional Hazards Model

- When the Monitoring Period is adjusted for, Initial Treatment being Chm and Ages 31-49 lose their significance
- Initial Treatment being RT now shows a decrease in the hazard of recurrence
- Patients over the Age of 50 multiplies the hazard of recurrence by 12
- The Monitoring Period in this study is very significant

	Coef	Exp(coef)	Se(coef)	z	Pr(>  z )
Initial Treatment: Chm	-0.424	0.654	0.299	-1.42	0.1561
Initial Treatment: RT	-1.863	0.155	0.764	-2.44	0.0148
Age: 15-30	0.950	2.585	1.036	0.92	0.3592
Age: 31-49	1.861	6.432	1.028	1.81	0.0701
Age: Over 50	2.492	12.085	1.048	2.38	0.0175
Gender	-0.002	0.979	0.297	-0.07	0.9432
Follow-Up Treatment: Chm	0.603	1.828	0.501	1.21	0.2282
Follow-up Treatment: RT	0.644	1.904	0.548	1.18	0.2400
Follow-up Treatment: Other Treatments	0.209	1.232	0.527	0.40	0.6916
Monitoring Period	-3.076e-04	9.997e-01	5.681e-05	-5.41	6.15e-08



# Conclusion

- Before adjusting for the monitoring period, our findings suggested that the combination of Chemotherapy and Radiation was protective as Initial Treatment
  - Radiation alone was the most hazardous
- After factoring in expert opinion our findings are reversed. Our findings support that Radiation alone is the least hazardous as Initial Treatment

# Future Research

- Dr. Brian K. Link also suspects tumor stage and tumor size might determine the treatment administered. Thus, these variables might be associated with the hazard of recurrence
  - Unfortunately, our data did not contain an adequate amount of stages recorded, nor did it include tumor size
- Since medical treatments are constantly evolving, further research is needed to consider the year the patient was treated
- Further exploration must also be made to consider the frailty of the patient and the treatment they receive

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# Thank You

- Thank you for your time
- Are there any questions?