Prognostic Factors for T1 High Grade Bladder Cancer Recurrence and Estimation of Overall Survival between Induction Recurrence vs Cystectomy

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Outline

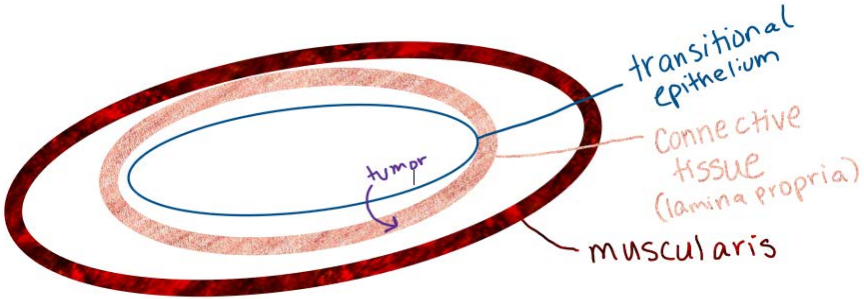
1. Bladder Cancer
    a. Risk factors
    b. Staging
    c. Treatment
2. Goals
    a. Recurrence
        i. What is recurrence?
        ii. What factors could help us predict recurrence?
    b. Will induction with recurrence have a survival advantage compared to cystectomy?
3. Methods
4. Results
5. Discussion/Conclusion

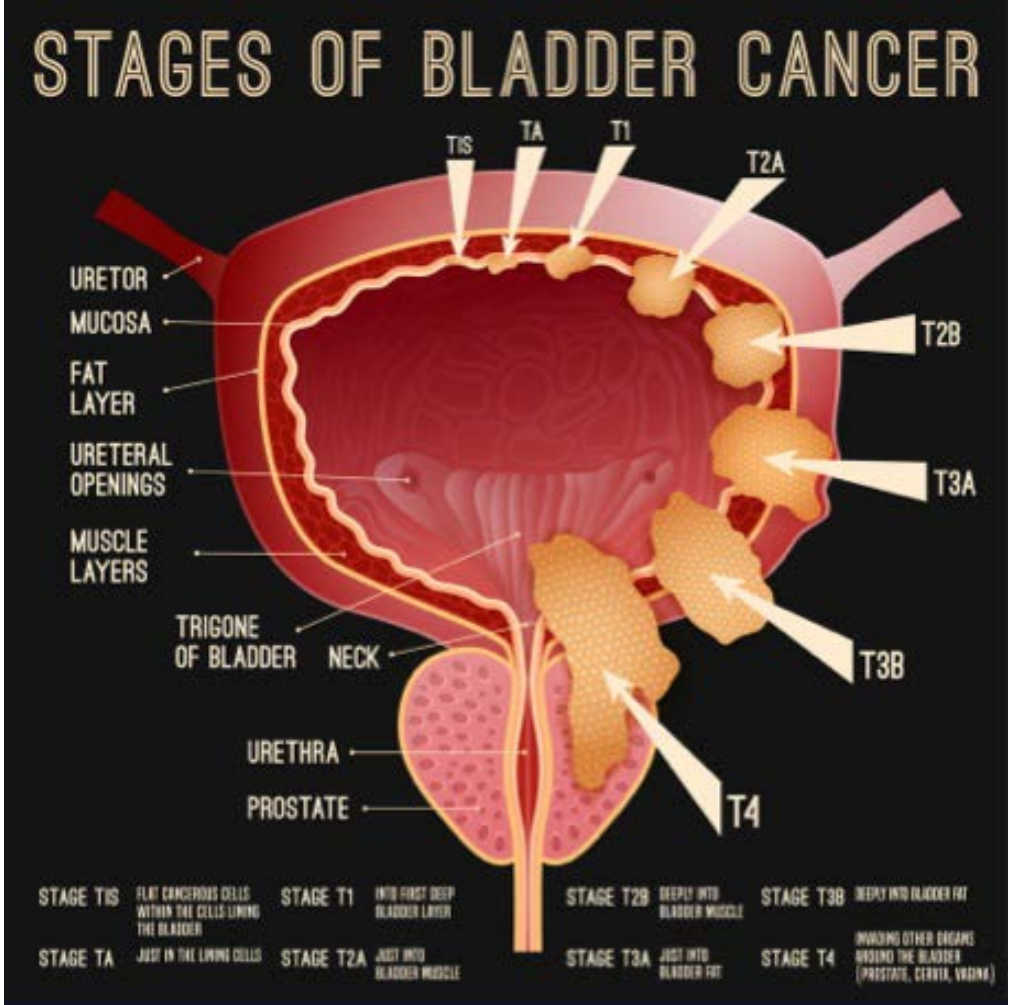
Bladder Cancer

What is bladder cancer?

Bladder Cancer: A tumor in the lining of the bladder that can spread to different layers including the mucosa, submucosa, and muscularis (muscular wall)

T1 Grade Bladder Cancer: The spread of the tumor penetrates into the connective tissue called the lamina propria which is between bladder lining and muscle. At this point, it has not reached the muscularis (cancer.net)




STAGES OF BLADDER CANCER
TIS
TA
T1
T2A
T2B
T3A
T3B
T4
URETOR
MUCOSA
FAT LAYER
URETERAL OPENINGS
MUSCLE LAYERS
TRIGONE OF BLADDER
NECK
URETHRA
PROSTATE
STAGE TIS FLAT CANCEROUS CELLS WITHIN THE CELLS LINING THE BLADDER
STAGE TA JUST IN THE LINING CELLS
STAGE T1 INTO FIRST DEEP BLADDER LAYER
STAGE T2A JUST INTO BLADDER MUSCLE
STAGE T2B DEEPLY INTO BLADDER MUSCLE
STAGE T3A JUST INTO BLADDER FAT
STAGE T3B DEEPLY INTO BLADDER FAT
STAGE T4 INVADING OTHER ORGANS AROUND THE BLADDER (PROSTATE, CERVIX, VAGINA)
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Recurrence

- Over a 10-year nationwide study, 72.1% of bladder cancer patients recurred (Chamie et al., 2013)
- According to the literature (Sylvester et al., 2006) , risk factors include:
    1. Age
    2. Prior treatment
    3. Number of tumors
    4. Highest grade of cancer
    5. Involvement of surrounding tissue
    6. Smoking status

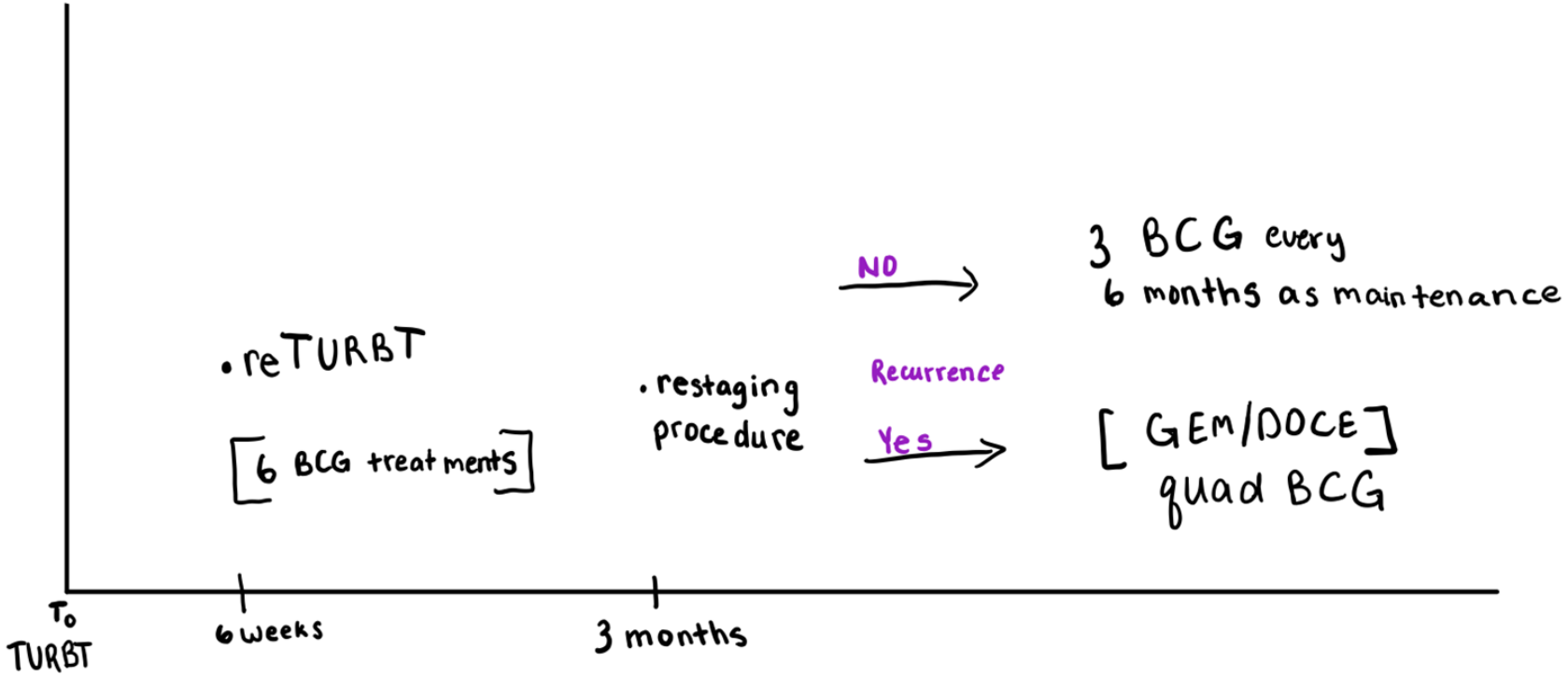
What are the treatment options?

1. Surgical
    a. Transurethral bladder tumor resection (TURBT)
    b. Radical cystectomy/lymph node dissection
2. Chemotherapy
    a. Intravesical
    b. Systemic
3. Immunotherapy
    a. Bacillus Calmette-Guerin Immunotherapy (BCG)
    b. Interferon & BCG
    c. Other regimens

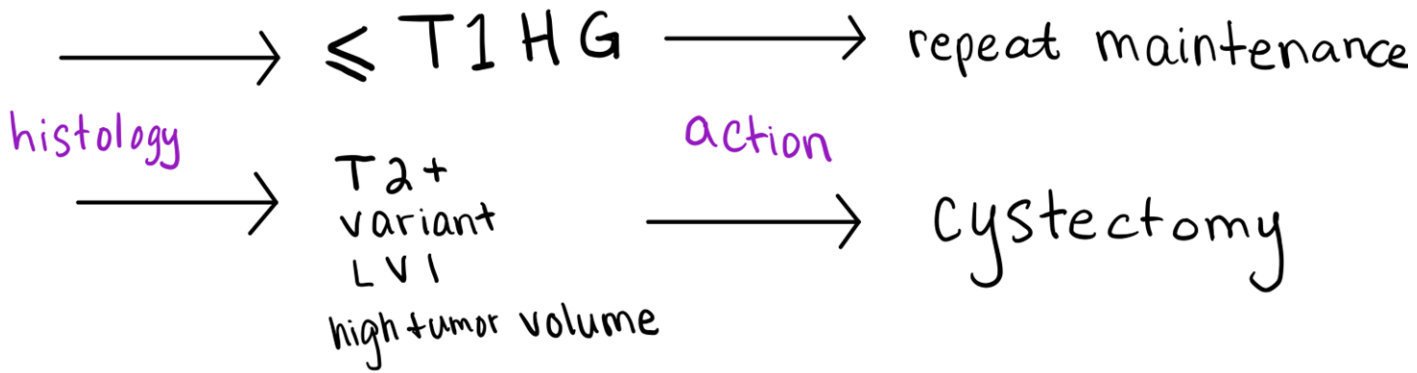
Induction Treatments under Study

1. BCG +/- Other
    - Any BCG containing regimen, including a full course, or switching to other regimen based on tolerability, IFN, quadBCG, or other modifications
1. Other
    - Non-BCG regimen, such as GEM/DOCE, Mitomycin, or Adriamycin
1. None
    - No induction treatment. Could be due to systemic chemotherapy, health concerns, age, or refusal of treatment

Bladder Cancer Management



Bladder Cancer Management



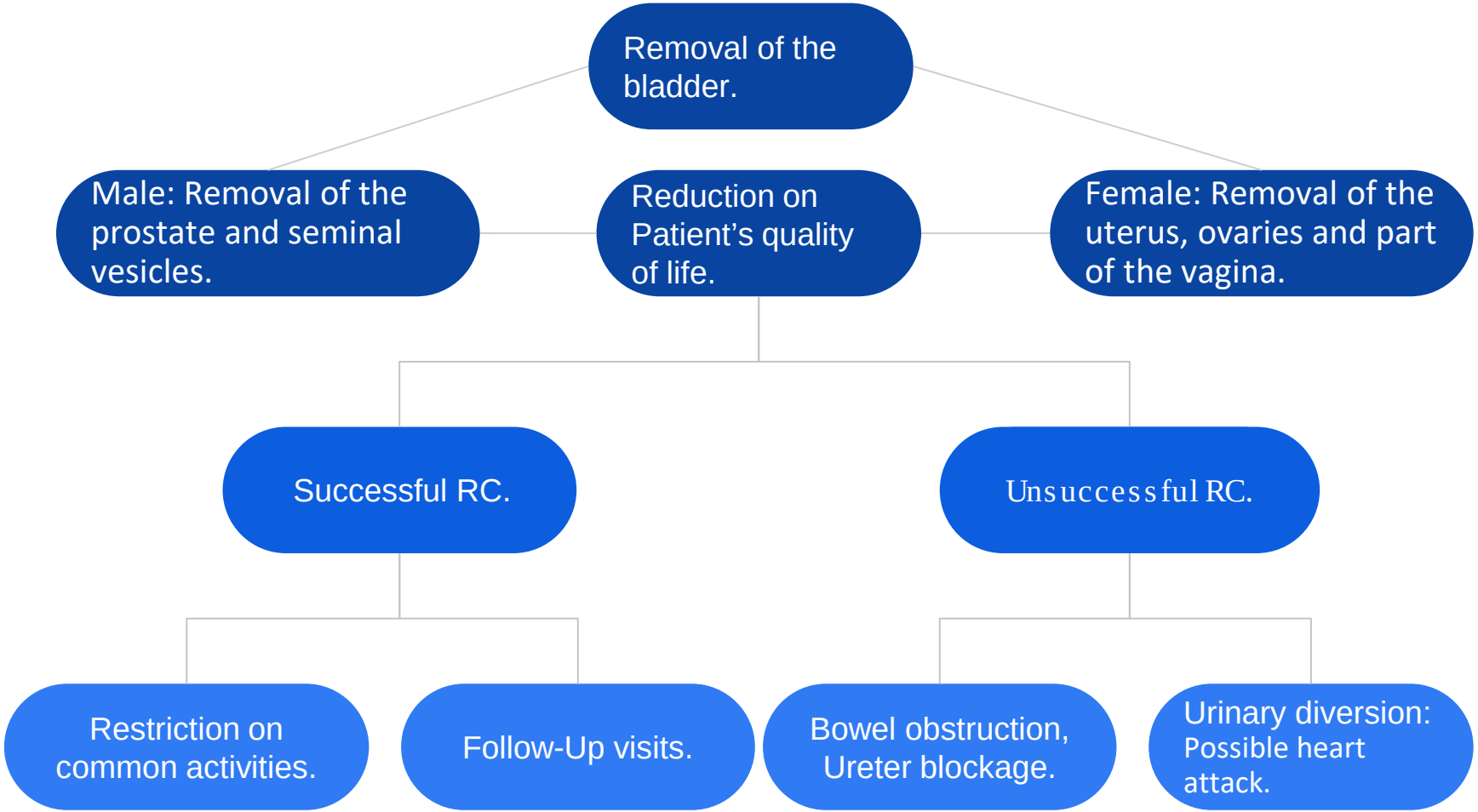
American Urological Association (AUA)

AUA

T1HG → induction → recur → cystectomy

→ induction → recur

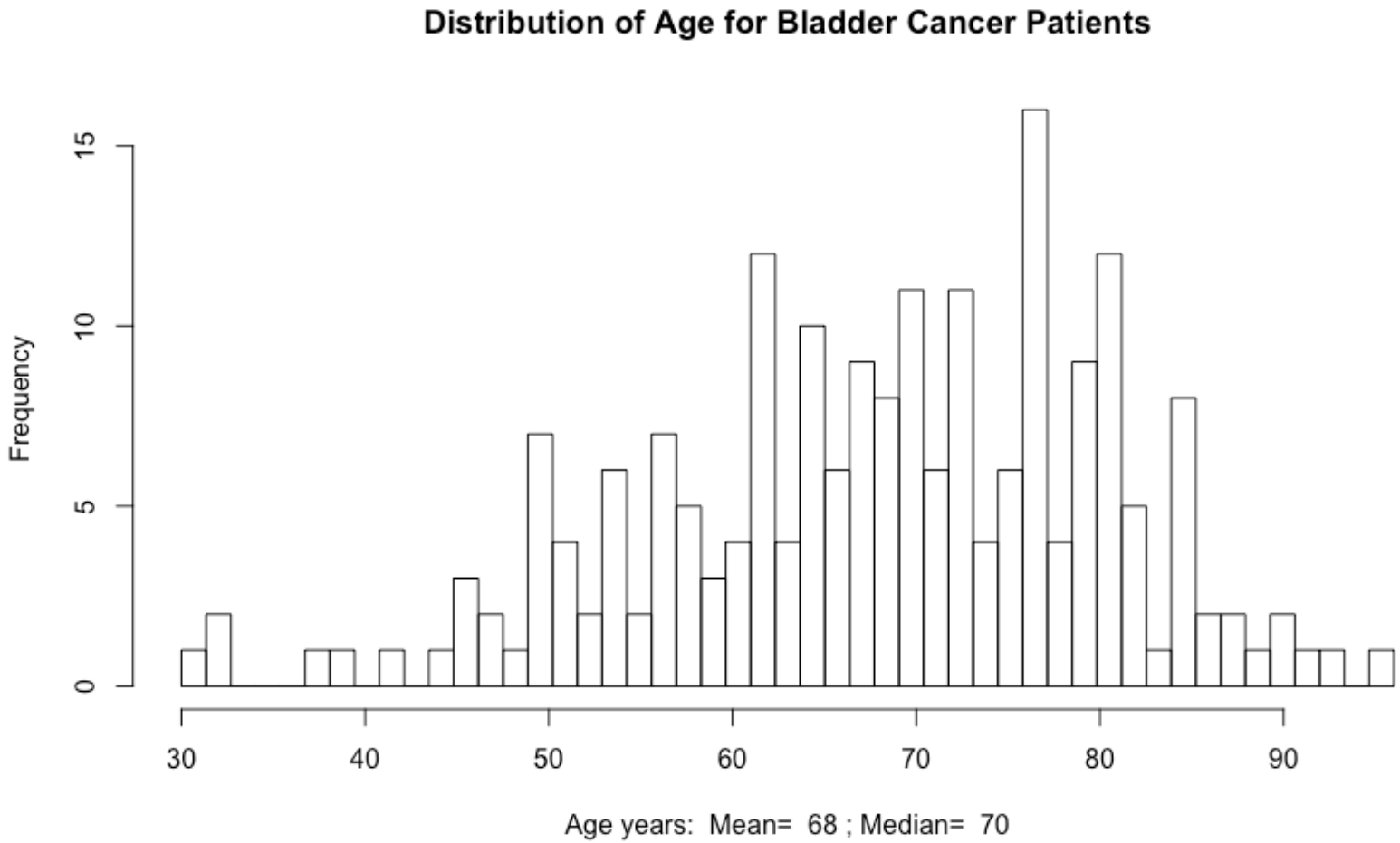
Cystectomy


Removal of the bladder.
Male: Removal of the prostate and seminal vesicles.
Reduction on Patient's quality of life.
Female: Removal of the uterus, ovaries and part of the vagina.
Successful RC.
Unsuccessful RC.
Restriction on common activities.
Follow-Up visits.
Bowel obstruction, Ureter blockage.
Urinary diversion: Possible heart attack.

The Population

Population Characteristics

Variable	Level	Frequency	%
Gender	Female	37	18.0%
	Male	168	82.0%
Marital Status	Married	153	74.6%
	Not Married	51	24.9%
	Missing	1	0.5%
Race	White	200	97.6%
	Black	4	2.0%
	Hispanic	1	0.5%
Smoking Status	Current	45	22.0%
	Former	118	57.6%
	Never	42	20.5%
Cystectomy Offered	No	125	61.0%
	Yes	80	39.0%
Cystectomy	No	185	90.2%
	Radical	20	9.8%
Vital Status	Alive	131	63.9%
	Dead	74	36.1%
Bladder Cancer Mortality	No	193	94.1%
	Yes	12	5.9%


Distribution of Age for Bladder Cancer Patients
Frequency
0
5
10
15
30
40
50
60
70
80
90
Age years: Mean= 68 ; Median= 70

Goals

Goal 1:

Determine which prognostic factors are associated with recurrence of bladder cancer over time

Goal 2:

Evaluate the effectiveness of continuing induction treatments versus varying types of cystectomies in cystectomy-eligible patients

To explore an association between a covariate and survival time (or the hazard of an event) one uses a Cox Proportional Hazards (CPH) Model

What then is the CPH Model?

Cox Proportional Hazards Model

The hazard of an event, λ, is influenced by a set of prognostic factors, X, that will increase or decrease hazard

According to Sir Cox,

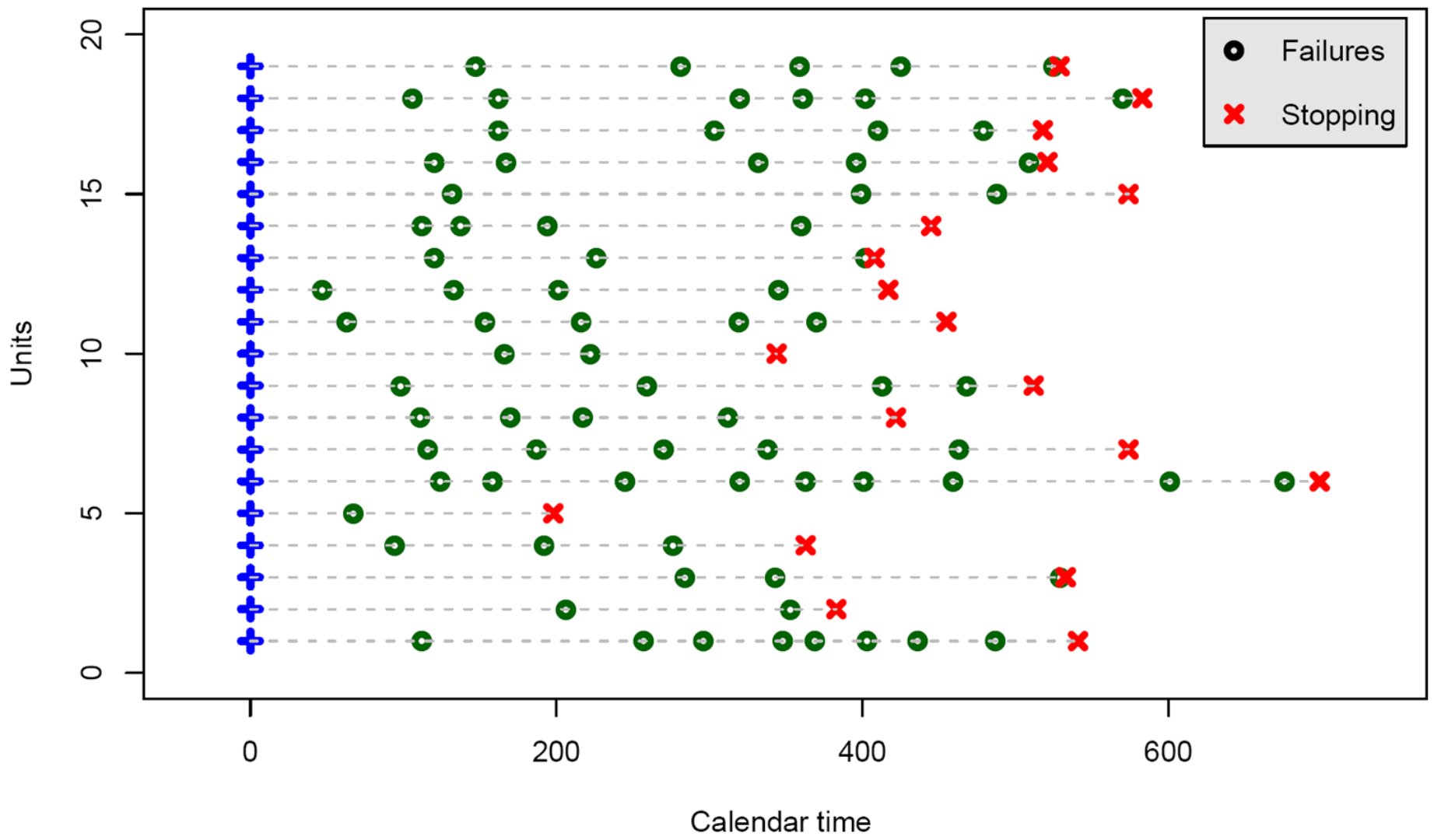
$$\lambda(t|X) = \lambda_0(t)e^{\beta X}$$

$\lambda_0(t)$ represents the baseline hazard which may be referred to as the force mortality or force vitality

This model holds for subjects that are observed for the occurrence of a single event

But in our setting, we are dealing with recurrence

Goal 1: Recurrence Modeling


Failures
Stopping
Units
0
5
10
15
20
0
200
400
600
Calendar time

Recurrent Events & PWP Model Proposal

Time intervals may change based on recurrence number because multiple events behave different from single events

This means the Cox model is not sufficient and must be adapted to accommodate multiple-failures

Therefore, it makes sense to assume the baseline hazard will change in time according to accumulation of events as well

Stratification is used based on prior number of events within subjects

Initially, everyone is at equal likelihood to experience the first event but the second event can only be experienced after the first event was experienced

This holds for each subsequent event

Prentice Williams Pearson (PWP) Model Proposal

The baseline hazard (λ_0) changes according to stratum (λ_{0s}) in order to account for the different recurrence count. We will have:

$$\lambda(t|X) = \lambda_{0s}(t)e^{\beta X} \qquad (1.)$$

$$\lambda(t|X) = \lambda_{0s}(t - t_k)e^{\beta X} \qquad (2.)$$

where (1.) accounts for the calendar time and (2.) accounts for the most recent failure (or gaptime)

PWP Model Proposal

If there is a possibility that X is a time varying covariate, then this can be written:

$$\lambda(t|X(t)) = \lambda_{0s}(t)e^{\beta X(t)}$$

$$\lambda(t|X(t)) = \lambda_{0s}(t - t_k)e^{\beta X(t)}$$

PWP Analysis

Variable	Specific Entry	Coefficient $(\hat{\beta})$	Risk Rate (e^$\hat{\beta}$)	95% CI	P-Value
Smoking Status	Former	0.5117	1.67	(1.0611,2.622)	0.027
	Never	0.219	1.24	(0.6458,2.400)	0.513
	Current	----------	----------	----------	----------
Age	Quantitative	0.015658	1.06	(1.002,1.03)	0.030
Time from last failure	6+ Months	-0.5033	0.60	(0.3344,1.093)	0.096
	<6 Months	----------	----------	----------	----------
Re-resection perfomed?	Yes	-0.2974	0.74	(0.5051,1.092)	0.131
	No	----------	----------	----------	----------
Urethra Involved?	Yes	0.3685	1.45	(0.7713,2.709)	0.250
	No	----------	----------	----------	----------
Induction Regimen	None	0.21073	1.23	(0.7858,1.940)	0.361
	Other	-0.01113	0.99	(0.6318,1.548)	0.961
	BCG	----------	----------	----------	----------
Worst Pathology	Ta-T1LG	-0.2104	0.81	(0.3731,1.760)	0.595
	T1HG-T2+	0.1823	1.20	(0.5772,2.495)	0.625
	Any CIS	----------	----------	----------	----------
Gender	Male	0.05276	1.05	(0.6594,1.685)	0.826
	Female	----------	----------	----------	----------

Goal 2: Induction vs. Cystectomy

Kaplan Meier Estimator

$$\widehat{S}(t) = \prod_{i:\, t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$

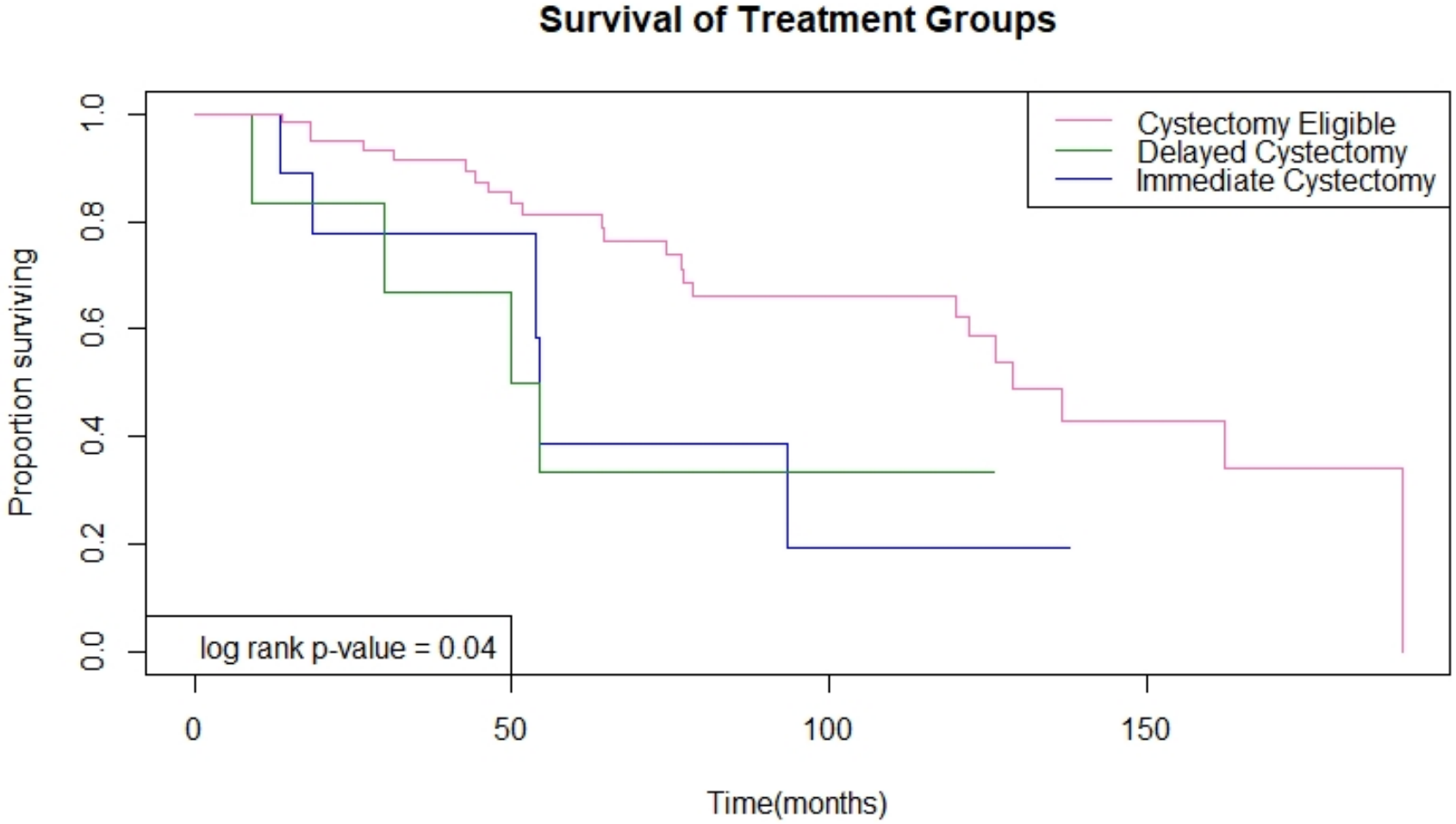
- A non-parametric estimator of the survival function
- Probability is recalculated any time an “event” occurs (Unconditional probability)
  - Risk set is reevaluated at each event time
- Product limit estimator
  - Survival Estimates are characterized as a non-increasing step function

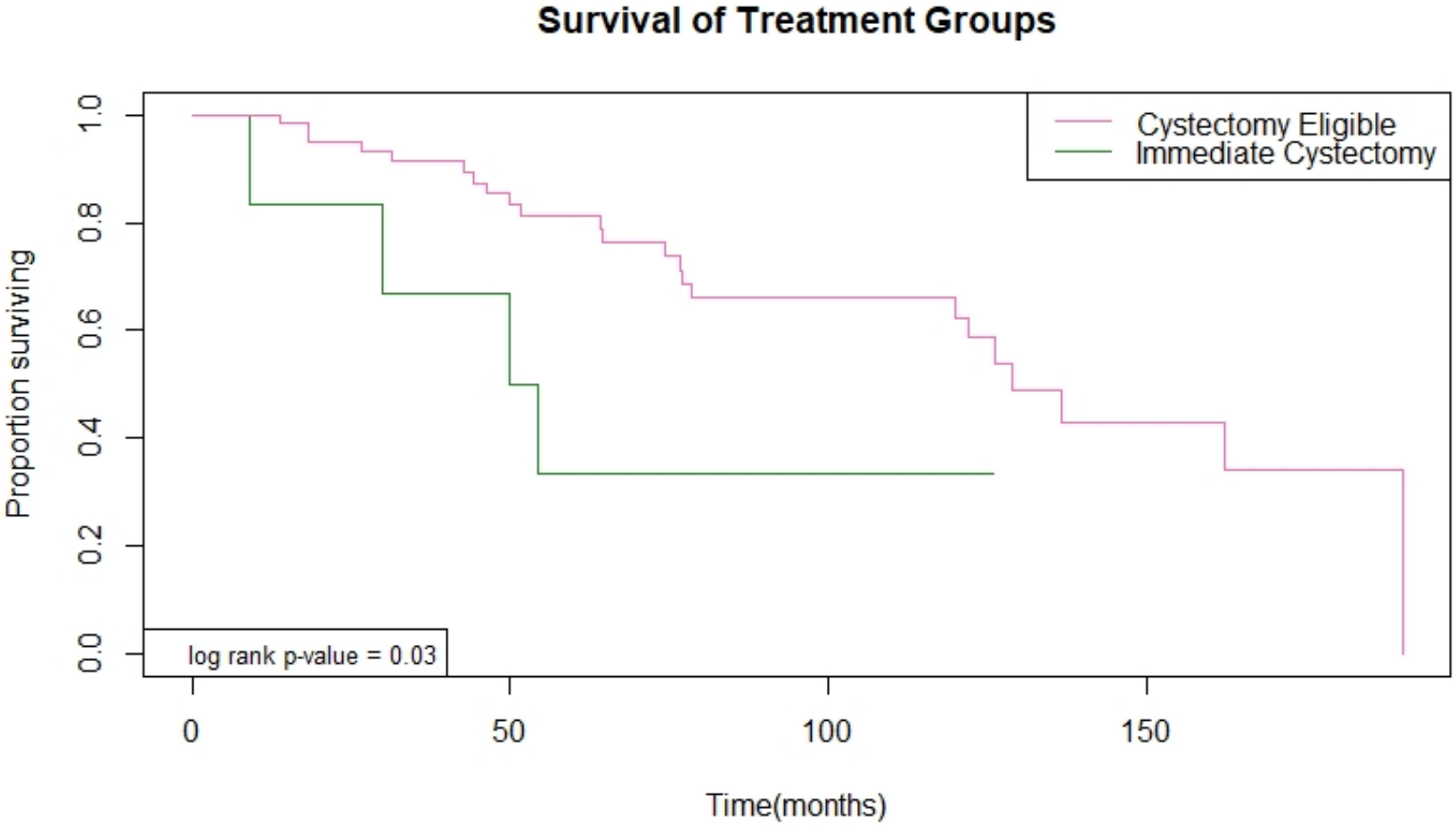
Kaplan Meier Estimation

Kaplan Meier was used to assess the overall survival among the people who were offered a cystectomy

Death was defined as the event in order to determine the rate of overall survival between groups who did or did not undergo cystectomy

The groups were separated according to cystectomy eligible (did not take the cystectomy) while the other two groups were immediate or delayed cystectomies


Survival of Treatment Groups
Cystectomy Eligible
Delayed Cystectomy
Immediate Cystectomy
log rank p-value = 0.04
Proportion surviving
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Time(months)


Survival of Treatment Groups
Cystectomy Eligible
Immediate Cystectomy
Proportion surviving
0.0
0.2
0.4
0.6
0.8
1.0
log rank p-value = 0.03
0
50
100
150
Time(months)

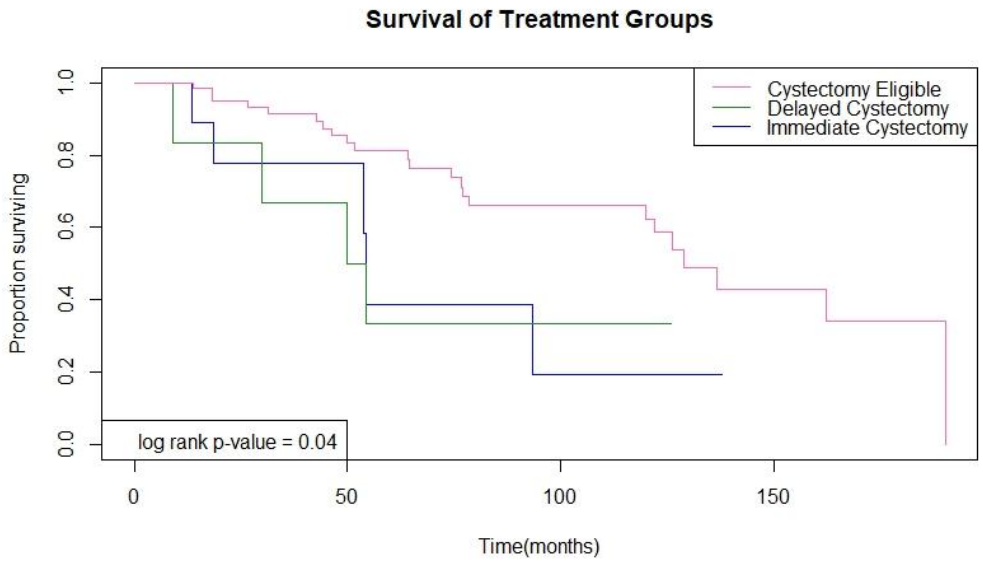
Discussion

Discussion of PWP Data

Variable	Specific Entry	Coefficient (β)	Risk Rate (e^β)	95% CI	P-Value
Smoking Status	Former	0.5117	1.67	(1.0611,2.622)	0.027
	Never	0.219	1.24	(0.6458,2.400)	0.513
	Current	----------	----------	----------	----------

	Smoking Status		
Recurrences	Never	Former	Current
1	42	118	45
2	14	54	15
3	10	40	**3**

- Nonsensical smoking results are from smoking status by recurrence numbers being so different
  - Potentially due to current smokers not living long enough to have 3+ recurrences
- Having only 3 current smokers in that group makes the hazard estimation impossible-- the estimated confidence interval is (0,0)



It is important to note that there was a selection bias on likelihood of success.

Even if this were adjusted for and the curves were the same, the quality of life will play a factor as well

Conclusion

Recommendations

Given that age is a factor that might increase chances of recurrence, likely due to frailty:

> However, their frailty might decrease cystectomy eligibility so it cannot be recommended to have cystectomy

Given that managing versus cystectomy has higher overall survival:

> AUA guidelines do not have to apply to all cases of recurrence

Future Work

- Broadening the study for more generalized applications by analyzing more data:
  - Race, occupation, or family history are more covariates to consider for this analysis
- Due to frequently missing essential data, more work has to be done to understand the kind of missing values. Predictive methods such as data imputation could potentially compensate for the missing data necessary for a broader study research
- Genetics behind varying responses to treatment

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Questions?