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Survival Analysis In Public Health

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**Survival Analysis of Bladder Cancer Recurrence**

**Introduction**

This study explores the research question “Does the type of treatment (thiotepa vs. placebo) affect the time to recurrence in bladder cancer patients, and what role do tumor characteristics (number and size) play in this risk? “ This question is important because bladder cancer particularly non muscle invasive bladder cancer has one of the highest recurrence rates among all cancers, which significantly affects patient quality of life, treatment costs, and clinical management strategies. The recurrence of bladder cancer places a heavy burden on healthcare systems, patients, and clinicians. As noted by Kaufman et al. (2009) in their paper discussing the economic burden and clinical impact of bladder cancer, bladder cancer remains one of the most expensive cancers to manage across a patient's lifetime due to frequent recurrences and the need for long-term care.

**Background**

Bladder cancer is a common malignancy worldwide. According to Kamat et al. (2016) in their paper on the global burden and clinical behavior of bladder cancer, published in The Lancet, while non muscle invasive bladder cancer has a favorable prognosis compared to muscle invasive bladder cancer, it is notorious for its high recurrence rate which is estimated at 70% to 80% even after surgical resection and adjuvant therapies. Also, prior studies, including those by Sylvester et al. (2006) in their paper that developed predictive risk tables for bladder cancer recurrence and progression published in the European Urology, have shown that intravesical chemotherapy such as thiotepa is effective in reducing recurrence in non-muscle invasive bladder cancer patients. Additionally, according to Babjuk et al. (2022) in the European Association of Urology (EAU) guidelines on non-muscle-invasive bladder cancer, tumor burden is highlighted as a key prognostic factor, supporting the significant association found between tumor number and recurrence. Other researchers have explored a range of prognostic indicators, including tumor grade, presence of carcinoma in situ (CIS), and patient demographics. For example, Cambier et al. (2016), in their paper on EORTC nomograms and risk groups, emphasized that multiple and large tumors, along with prior recurrences, significantly increase the likelihood of future recurrence. Furthermore, Herr (2001) suggested that early identification of high-risk individuals could help tailor more aggressive or prolonged treatment strategies.

This study is also significant in advancing the understanding of recurrence risk in non-muscle invasive bladder cancer patients through the application of survival analysis techniques. The use of survival analysis enables not only the estimation of recurrence probabilities but also the assessment of the impact of individual level predictors such as treatment type, number of tumors, and tumor size. Furthermore, by comparing Cox proportional hazards and parametric survival models, the study contributes to methodological literature on the optimal modeling approaches for recurrent event data. The insights gained from this study can help inform clinical decision-making by identifying high-risk individuals who may benefit from intensified surveillance or adjuvant therapy, as previously suggested by Sylvester et al. (2006) and Cambier et al. (2016). Ultimately, this study bridges the gap between clinical evidence and statistical modeling for improved patient care in bladder cancer management.

**Methods**

This study used the bladder dataset from the survival package in R. The dataset consists of 340 observations from 85 patients, with each patient followed for up to four recurrent events or censoring. The study population included patients diagnosed with bladder cancer and assigned to either thiotepa or placebo treatment arms. The variables measured included patient ID (ID), treatment group (rx: 1=Placebo, 2=Thiotepa), initial number of tumors (number, categorical from 1 to 8), size of the largest tumor in centimeters (size, used as a continuous variable), time to recurrence or censoring (stop), indicator for recurrence (event: 1=event, 0=censored), and recurrence sequence number (enum). No continuous variable was categorized in this study, as the variable 'size' had a manageable range for modeling purposes.

The statistical analyses conducted included descriptive statistics to summarize baseline characteristics, Kaplan-Meier (KM) curves to estimate survival probabilities over time, log-rank tests to compare KM curves between treatment groups, Cox proportional hazards models to assess the association between treatment and time to recurrence while adjusting for covariates, and parametric survival models (Weibull and Lognormal) to assess model fit and improve survival projection. All analyses were conducted using R version 4.3.1.

**Results**

In the descriptive analysis, the placebo group included 188 observations and the thiotepa group included 152 observations. There was a total of 112 recurrence events, representing 32.9% of all observations. The median number of tumors was 1, with a range from 1 to 8, and the median tumor size was 1 cm, ranging from 1 to 7 cm.

**Summary of Treatment Groups and Tumor Characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Treatment Group | N (Observations) | Median Tumors | Median Tumor Size | % Recurrence |
| Placebo (1) | 188 | 2 | 2 cm | Higher |
| Thiotepa (2) | 152 | 1 | 1 cm | Lower |

The Kaplan-Meier estimate showed that the thiotepa group had a higher survival probability over time compared to the placebo group. The log-rank test revealed a statistically significant difference in survival between treatment groups (p = 0.02).

**Log-Rank Test Result**

|  |  |  |  |
| --- | --- | --- | --- |
| Comparison | Chi-square | Degrees of Freedom | p-value |
| Thiotepa vs Placebo | 5.2 | 1 | 0.02 |

In the Cox proportional hazards model, the hazard ratio (HR) for thiotepa was 0.58 (95% CI: 0.39–0.86, p = 0.0069), indicating a 42% reduction in recurrence hazard. The number of tumors was significantly associated with recurrence, with an HR of 1.21 (95% CI: 1.11–1.33, p < 0.001). Tumor size was not significantly associated with recurrence (HR = 0.95, p = 0.43).

**Cox Proportional Hazards Model Results**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Hazard Ratio (HR) | 95% Confidence Interval | p-value |
| Treatment (rx) | 0.58 | 0.39 – 0.86 | 0.0069 |
| Number of Tumors | 1.21 | 1.11 – 1.33 | <0.001 |
| Tumor Size | 0.95 | 0.83 – 1.09 | 0.43 |

Parametric models also showed that the Weibull model had an AIC of 1178.54, while the lognormal model had a slightly lower AIC of 1177.89, indicating a better fit. The Akaike Information Criterion (AIC) is a measure of model quality that considers both the goodness-of-fit and model complexity. Lower AIC values suggest a better balance between these aspects. Therefore, while both models fit the data well, the lognormal model appears to slightly outperform the Weibull model in terms of overall predictive ability.

**Model Fit Using Akaike Information Criterion (AIC)**

|  |  |
| --- | --- |
| Model Type | AIC Value |
| Weibull | 1178.54 |
| Lognormal | 1177.89 |

Both models produced survival probability estimates consistent with those from the Kaplan-Meier and Cox models. Comparing Cox proportional hazards and parametric models provides complementary insights. The Cox model is semi-parametric and does not assume any specific distribution of survival times, making it flexible and widely applicable, especially when the proportional hazards assumption holds. In contrast, parametric models like Weibull and lognormal rely on defined probability distributions and can provide more precise survival time predictions, especially for extrapolation beyond observed data. However, they require that the chosen distribution appropriately represents the underlying hazard function. By incorporating both approaches, we ensure robustness in the analysis and a more comprehensive understanding of the risk factors associated with bladder cancer recurrence.

**Conclusion**

This study found that thiotepa treatment significantly reduces the risk of bladder cancer recurrence, aligning with prior studies on its efficacy. Tumor number was a strong predictor of recurrence risk, confirming the importance of tumor burden, as highlighted in EAU guidelines. Tumor size, however, did not show a significant effect. The strengths of this study include the use of real patient data, application of multiple survival models, and validation with prior research. Limitations include limited covariates, data restricted to up to four recurrences, and lack of external validation.

**Future Directions and Clinical Implications**

Further research should explore larger and more diverse cohorts with additional clinical variables such as tumor grade, genetic markers, and patient lifestyle factors (e.g., smoking status) to improve prediction accuracy. Long-term follow-up beyond four recurrences would enhance modeling and help refine treatment plans. Integrating different approaches such as machine learning may also identify patterns in recurrence risk. Clinically, these findings support a more personalized approach to bladder cancer management, where high-risk individuals can be stratified for more intensive surveillance and early therapeutic intervention, ultimately reducing disease burden and improving patient outcomes.

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