**Outcomes of adjuvant radiation in early-stage small cell lung cancer based on nodal involvement: Is there a role for adjuvant radiation in pN1 disease: An analysis of National Cancer Database**

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**Abstract**

**Purpose:**This study evaluates survival outcomes for patients with pathological N1 (pN1) small cell lung cancer (SCLC) who underwent definitive surgery, comparing the effectiveness of different adjuvant treatment strategies.

**Study Design:**A retrospective analysis was conducted on 659 patients from the National Cancer Database (2010–2020) using advanced survival analysis methods, including Kaplan-Meier curves, log-rank tests, Wilcoxon tests, multiple comparison tests, and Cox proportional hazards models.

**Findings:** Significant differences were observed in Age, Gender, Insurance Status, and Surgery Type across treatment groups. While the log-rank test showed no overall survival differences among all groups (p = 0.0553), the Wilcoxon test revealed significant early survival differences (p = 0.0288). Tukey multiple comparisons indicated that sequential treatment was significantly different from other treatments. Sequential treatment has the longest median survival time (1159.22 days) based on Kaplan-Meier estimates. In comparison, median survival times were lower for chemotherapy only (870.96 days), concurrent therapy (694.10 days), no adjuvant treatment (659.10 days), and radiation only (565.49 days). These results were supported by hazard ratios from the Cox proportional hazards model, which met all model assumptions.

**Introduction**

Small cell lung cancer (SCLC) is an aggressive malignancy strongly linked to smoking, characterized by rapid progression, high metastatic potential, and poor prognosis. It accounts for 14% of all lung cancer cases, with a five-year survival rate of only 25%, resulting in over 130,000 deaths annually in the United States. Pathological N1 (pN1) disease, defined by regional lymph node involvement, represents an early-stage subgroup of SCLC with uncertain treatment outcomes. While adjuvant chemoradiation is standard for advanced pN2 disease, there is no clear consensus on optimal adjuvant therapy for pN1 cases, particularly regarding the role of radiation therapy.

This study evaluates survival outcomes for pN1 SCLC patients treated with different adjuvant strategies: sequential therapy (radiation after 90 days of chemotherapy), concurrent therapy (radiation within 90 days of chemotherapy), chemotherapy only, radiation only, and no adjuvant treatment. Using data from the National Cancer Database (NCDB) and advanced survival analysis methods, this research aims to identify the most effective approach to improving survival in this understudied subgroup.

**Data Description**

This study analyzed 659 patients with pathological N1 (pN1) small cell lung cancer (SCLC) from 3.3 million [National Cancer Database](https://training.seer.cancer.gov/operations/standards/setters/ncdb.html) (NCDB) records.

**Patients met the following criteria**:

1. Diagnosed between 2010 and 2020
2. Underwent definitive surgery
3. Diagnosed with pN1 disease
4. No distant metastases or Stage IV disease
5. Survived at least 30 days post-surgery

**Patient Characteristics and Variables**:

* Age
* Gender
* Insurance Status
* Surgery Type
* Treatment Type
* Vital Status
* Survival Time

**Treatment Type Categories:**

1. Sequential: Radiation administered more than 90 days after chemotherapy.
2. Concurrent: Radiation administered within 90 days of chemotherapy.
3. Chemotherapy Only: Chemotherapy without radiation.
4. Radiation Only: Radiation without chemotherapy.
5. None: No radiation or chemotherapy.

**Variable Selection**

The variables above were chosen based on their statistical significance in ANOVA and chi-squared tests of independence. This ensures the study focuses on treatment type while accounting for key confounding factors, improving the reliability of the survival model.

**Survival Time Definition**

Survival Time is the number of days from diagnosis to either the last contact or death.

* If a patient is alive, survival time ends at the last contact date.
* If a patient is deceased, survival time ends at the date of death.

The analysis incorporates censored data (patients alive at last contact), using survival modeling methods that effectively handle time-to-event outcomes.

**Appendix**

The **Appendix A** contains a frequency table summarizing patient data by treatment type. It provides the distribution of patient characteristics, including Age, Gender, Insurance Status, Surgery Type, and Vital Status, across the five treatment categories. Additional details, including p-values from ANOVA and chi-squared tests, validate the selection of variables and support the robustness of the statistical analysis.

**Statistical Method**

Kaplan-Meier survival curves were used to visualize survival trends and estimate median survival times for each treatment group. These curves also helped assess potential violations of the proportional hazards (PH) assumption required for Cox proportional hazards models. Survival distributions among treatment groups were compared using the log-rank test, and early survival differences were evaluated using the Wilcoxon test. Tukey’s method was applied for multiple comparisons to identify significant differences between treatment groups.

A Cox proportional hazards model provided a detailed analysis by comparing treatment groups through hazard ratios, quantifying the relative risk of death. The model was adjusted for key confounders to enhance accuracy. Assumptions of the Cox model, including proportional hazards and linearity, were rigorously tested to ensure validity.

All statistical modeling and analysis were performed using **SAS 9.4**.

**Results**

By using days of diagnosis as the starting time point, the Kaplan-Meier survival curve (**Appendix B**) for each treatment type highlights a bias favoring sequential therapy (purple curve), caused by immortal time. Patients receiving sequential therapy must survive long enough to begin treatment, resulting in an initial horizontal segment on the sequential survival curve that artificially inflates survival probabilities compared to other treatment groups.

**Kaplan-Meier Survival Curves Corrected for Immortal Time Bias**

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| Product-Limit Survival Curves |
| Figure 1: Kaplan-Meier Survival Curves Adjusted for Immortal Time Bias |

Therefore, the data was adjusted for **immortal time bias** by left-truncating survival times, setting the start of survival time to day 150 instead of the day of diagnosis. This adjustment excluded 6 patients from the chemotherapy-only group, 4 from the concurrent group, and 18 from the no-adjuvant-treatment group. The 150-day adjustment accounts for 90 days of baseline immortal time and 60 days for typical chemotherapy duration, enabling unbiased and clinically meaningful survival comparisons across treatment groups. **All analysis in this report will be based on this adjusted time point.**

The corrected Kaplan-Meier survival curve (**Figure 1**) shows survival probabilities with time zero set to day 150, effectively removing immortal time bias. However, interpreting significant differences in survival times between treatment types remains challenging and may vary depending on further statistical analyses or clinical judgment.

**Log-Rank Test and Wilcoxon Test**

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| Figure 2:Log-Rank Test and Wilcoxon Test |

As shown in **Figure 2**, the Log-Rank Test was used to statistically assess survival differences among the treatment groups. The null hypothesis (H₀), which assumes no differences in survival times across all treatment types (S₁(t) = S₂(t) = S₃(t) = S₄(t) = S₅(t)), was not rejected (p-value = 0.0553). This indicates that there is no statistically significant overall difference in survival times between the treatment groups.

In contrast, the Wilcoxon Test, which gives more weight to early survival trends, identified a statistically significant difference in survival times among the treatment groups (p-value = 0.0288). This result suggests that while overall survival differences are not significant, early survival patterns vary across treatment types.

**Multiple Comparison Test**

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| Figure 3:Tukey multiple comparison test |

Evidence of differences between treatment types enabled the use of Tukey's multiple comparison tests (**Figure 3**), which demonstrated that Sequential treatment is statistically different from Radiation Only (p-value = 0.0389).

In summary:

* Chemotherapy Only, Radiation Only, Concurrent, and No Adjuvant Treatment are statistically equivalent.
* Sequential Treatment is statistically different from this group.

In simpler terms, sequential treatment stands out as distinct, while the other four treatment types show no significant differences among themselves.

**Median Survival Time**

To determine whether Sequential therapy outperforms other treatment types, median survival times were compared using estimates derived from Kaplan-Meier (KM) curves. Median survival time was selected as the metric because it excludes censored data, avoiding potential overestimation of survival time.

* Chemotherapy Only: 870.96 days
* Concurrent Therapy: 694.10 days
* Radiation Only: 565.49 days
* No Adjuvant Treatment: 659.10 days
* Sequential Therapy: 1159.22 days

The results demonstrate that Sequential therapy has the longest median survival time, indicating it is the most effective treatment strategy among the groups analyzed.

**PH Assumption**

The Kaplan-Meier (KM) curves show some crossing between treatment groups, suggesting a potential violation of the proportional hazards (PH) assumption required for the Cox model. This implies that hazard ratios may not remain constant over time across treatment groups.

To investigate this further, diagnostic test, such as the supremum test for goodness of fit, will be conducted to assess the validity of the PH assumption. If the assumption is found to be violated, alternative models or approaches (e.g., stratified Cox models, time-dependent covariates, or flexible parametric models) will be applied to ensure accurate representation and analysis of the data.

**Cox Proportional Hazards (PH) Model**

The Cox Proportional Hazards (Cox PH) model was used to evaluate survival differences among treatment groups by estimating hazard ratios (HR). The model adjusts for potential confounders such as age, gender, and insurance status to improve accuracy and reliability.

**Figure 4** shows the model output, highlighting the effects of treatment type and other covariates on survival outcomes. This approach provides a detailed understanding of the relative risk associated with each treatment type, while accounting for key demographic and clinical factors that may influence survival.

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| **Figure 4**: Cox PH model with covariates treatment type, age, gender, insurance status, and surgery type |

**Interpretation (adjusted for covariates, holding other factors constant):**

* Sequential treatment has:
  + 0.900 times the hazard rate of Chemotherapy Only (1/1.111)
  + 0.708 times the hazard rate of Concurrent (1/1.412)
  + 0.848 times the hazard rate of No Adjuvant Treatment (1/1.178)
  + 0.503 times the hazard rate of Radiation Only (1/1.987)
* Female patients have 0.795 times the hazard rate of Male patients.
* For every 1-year increase in age, the hazard rate increases by 1.035 times.
* Government-insured patients have 0.466 times the hazard rate of uninsured patients (1/2.145).
* Privately insured patients have 0.510 times the hazard rate of uninsured patients (1/1.959).
* Lobar surgery has 0.988 times the hazard rate of Sublobar surgery (1/1.012).
* Pneumonectomy has 0.683 times the hazard rate of Sublobar surgery (1/1.465).

**Functional Form Test**

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| Figure 5: Supremum Test for linearity of covariate age |

**Figure 5** shows the Supremum Test for Functional Form with a p-value of 0.0630 for AGE, which is above the typical significance level of 0.05. This indicates no significant deviation from linearity in the relationship between AGE and the log hazard. Therefore, the assumption of linearity is satisfied for the Cox model.

**Proportional Hazards (PH) Assumption Goodness of Fit Test**

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| Figure 6: Supremum Test for PH assumption of each covariate |

**Figure 6** shows the Supremum Test for Proportional Hazards Assumption, all covariates have p-values greater than 0.05. This indicates that the proportional hazards assumption is not violated for any of the covariates. Therefore, the Cox model in Figure 5 is a good fit for the data under this assumption.

**Conclusion**

Sequential therapy is the most effective treatment for pathological N1 (pN1) small cell lung cancer (SCLC), achieving the longest median survival time compared to other treatments. Early survival benefits were confirmed by the Wilcoxon test (p = 0.0288), and the Cox proportional hazards model showed significantly reduced hazard rates for sequential therapy after adjusting for confounders. Robust methodological adjustments, including correction for immortal time bias and validation of model assumptions, ensured reliability. These findings establish sequential therapy as the optimal adjuvant treatment for improving survival outcomes in pN1 SCLC patients.

**Appendix A –** Frequency Table with descriptive statistics by treatment type

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**Appendix B - Kaplan-Meier Survival Curves and Immortal Time Bias**

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| Product-Limit Survival Curves |
| Figure 1: Kaplan-Meier Survival Curves and Immortal Time Bias |