The Clinicopathological Features and Survival Outcomes of Patients with Different Metastatic Sites in Stage IV Endometrial Cancer: A SEER-Based Cohort Study

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# 1. Abstract

**Background:** Endometrial cancer is the most common gynecological malignancy in the United States. While most cases are diagnosed early, stage IV disease presents significant prognostic challenges, particularly when distant metastases are involved.

**Objective:** This study aimed to evaluate clinicopathological characteristics and survival outcomes among patients with stage IV endometrial cancer, focusing on differences based on metastatic site (bone, brain, liver, lung).

**Methods:** We conducted a retrospective cohort analysis using SEER data from 2010–2015. Kaplan-Meier and Cox proportional hazards models were used to assess survival differences, and a Random Survival Forest (RSF) model was implemented to evaluate variable importance and predict survival probabilities.

**Results:** Among 5,708 patients with stage IV endometrial cancer, lung metastases were most common (29.4%), followed by liver (14.8%), bone (9.7%), and brain (2.8%). Median survival was 12 months. In multivariable analysis, all metastasis types were significantly associated with poorer survival, especially brain (HR = 1.72) and liver (HR = 1.66). Older age and Black race were also linked to worse outcomes. The RSF model achieved an AUC of 0.74, with age group, income, and metastatic site identified as the most important survival predictors.

**Conclusions:** Metastatic site significantly influences survival in stage IV endometrial cancer. Tailored interventions and surveillance strategies based on metastasis patterns and patient demographics may help optimize outcomes.

# 2. Introduction

## 2.1 General Background Information

Endometrial cancer, a neoplasm originating from the endometrial lining, is the most common gynecological cancer in the United States.(1,2) According to American Cancer Society 2024 statistics the incidence of uterine cancer is 67, 880 with 13,250 deaths. Due to its early symptomatic presentation, 70% of cases are diagnosed at stage I, where the five-year survival rate exceeds 90%. (2,3) However, around 13% of patients are diagnosed at advanced stages (III/IV).(3)

A retrospective study found that the prevalence of stage IVB endometrial cancer increased to 5.67% between 2010 and 2015.(4) Unlike stage I, which has a favorable prognosis, stage IV is associated with poor outcomes, with a five-year survival rate ranging from 17% to 30%.(5) The most frequent metastatic sites include the peritoneum, lungs, pelvic and para-aortic lymph nodes, and local pelvic recurrences.(6) Among these, lung metastasis is one of the most common distant metastases, occurring in 1.5% of patients.(7) The hematogenous spread is the primary mechanism of lung metastasis.(8) Depending on clinical features, disease stage, prior surgical history, and pathological factors, 11-13% of endometrial cancer patients experience recurrence within the first two years after initial treatment. Symptoms of lung metastasis typically include coughing up blood, shortness of breath, chest pain, persistent cough, pleural effusion, reduced appetite, and weight loss.(9)

Compared to other gynecological cancers such as cervical and ovarian cancer, endometrial carcinoma exhibits the highest rate of pulmonary metastasis, affecting up to 20-25% of patients who experience recurrence. According to Mao et al., 2020, the five-year cancer-specific survival (CSS) rate for liver and brain metastases was 21%, while bone metastases had a survival rate of 20%. In patients with lung metastases, the median overall survival was 11 months, with a five-year CSS rate of 19%. However, this data specifically pertains to stage IV lung cancer patients.(7) Patients with advanced endometrial cancer face poor survival outcomes, with metastatic disease being the leading cause of mortality. (7) Therefore, this study aimed to utilize data from the Surveillance, Epidemiology, and End Results (SEER) database to analyze survival outcomes in patients diagnosed with stage IV endometrial cancer. The primary objective was to determine whether the presence of lung/brain/bone/liver metastases in adults with stage IV endometrial cancer is associated with worse survival outcomes compared to patients without any metastasis.

## 2.2 Description of data and data source

This study will utilize the Surveillance, Epidemiology, and End Results (SEER) database, one of the most comprehensive cancer incidence and survival registries, covering over 48% of the United States. SEER collects key demographic data, cancer characteristics, treatment details, and survival outcomes. Managed by the U.S. National Cancer Institute, the database began recording information on lung, bone, liver, and brain metastases in 2010. Data for this study will be accessed through SEER\*Stat 8.4.4 software, using the SEER Research Data (2000–2019) from 17 registries.

The extracted variables include age, race, income, American Joint Committee on Cancer (AJCC) stage, year of cancer diagnosis, lung metastasis (yes/no), brain metastasis (yes/no), liver metastasis (yes/no), brain metastasis (yes/no), cause of death, survival months, vital status (dead/alive), rural/urban classification.

## 2.3 Questions/Hypotheses to be addressed

*Question* What are the clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV endometrial cancer?

*Hypothesis* Patients with stage IV endometrial cancer exhibit distinct clinicopathological characteristics and survival outcomes based on the site of metastasis. Specifically, metastases to different organ sites (e.g., lung, liver, bone, and brain) are associated with varying prognostic implications, with some metastatic patterns demonstrating significantly poorer survival compared to others. By analyzing data from the SEER database, we hypothesize that certain metastatic sites will be linked to more aggressive tumor behavior and worse overall survival, highlighting potential differences in disease progression and treatment response.

# 3. Methods

This study examines survival outcomes in stage IV endometrial cancer using SEER data. The primary outcomes include survival months, cause-specific death classification, and vital status at study cutoff. Key predictors include age, race, income, year of diagnosis, and presence of differnt metastasis status.

## 3.1 Data aquisition

The data was extracted from SEER\*Stat 8.4.4 software, using the SEER Research Data (2000–2019) from 17 registries. The following inclusion criteria was used to extract the data (1) primary site, C54.1–9 and C55.9 based on International Classification of Tumor Diseases for Oncology (ICD-O) codes; (2) year of diagnosis 2010-2015; (3) AJCC stage IV; (4) age more than 18 years.

The SEER database provided data on both demographic and clinical characteristics of the patients. The demographic variables included age at diagnosis, race, median household income (inflation-adjusted to 2019), year of diagnosis, and Derived AJCC Stage Group (7th edition, 2010-2015). The clinical variables comprised lung, brain, bone, and liver metastasis status, survival duration (in months), SEER cause-specific death classification, and vital status recode (used for study cutoff determination).

Age will be categorized into four groups: 18-39, 40-59, 60-79, and ≥80 years. Race is classified into Asian or Pacific Islander, American Indian or Alaska Native, Black, and White. The income variable will be divided into six brackets: < $35,000, $35,000 - $44,999, $45,000 - $54,999, $55,000 - $64,999, $65,000 - $74,999, and $75,000+. The SEER cause-specific death classification was preferred over all-cause mortality to ensure that only deaths specifically attributed to endometrial cancer will be included in the analysis.

## 3.2 Data import and cleaning

Endometrial cancer cases were extracted from the SEER database. Individuals under 18 years of age were removed from the dataset. Additionally, patients whose cause of death is unrelated to endometrial cancer or whose cause of death is missing or unknown were not included in the analysis. Cases diagnosed at AJCC stages I to III was excluded from the study. The final cohort was categorized into 4 groups: lung metastasis, brain metastasis, bone metastasis, and liver metastasis.The SEER dataset underwent a structured cleaning process to ensure data integrity and suitability for analysis. First, data types were standardized by converting categorical variables such as Year of Diagnosis, RX Summ–Surg Prim Site (1998+), and Patient ID to character format, while Survival Months was converted to numeric. Key categorical variables, including Sex, Race, Metastasis Indicators, Survival Flags, and Cause-Specific Death Classification, were transformed into factors to maintain consistency. Patients within the age categories “01-04 years” and “15-19 years” were excluded, and only those classified as Stage IVA or IVB in the Derived AJCC Stage Group, 7th ed (2010-2015) were retained. Additionally, patients with “Dead (missing/unknown COD)” or “N/A not seq 0-59” in the SEER cause-specific death classification were removed. To ensure completeness, individuals with missing or unknown survival months were excluded. The final cleaned dataset was saved for further analysis, ensuring consistency and reproducibility. The code and raw data to reproduce the data cleaning step is available in https://github.com/mohammedzuber099/ZUBER-MADA-project.

## 3.3 Statistical analysis

The analysis aims to identify survival differences based on metastatic patterns, demographic disparities, socioeconomic influences, and temporal trends in prognosis. Kaplan-Meier survival analysis will used to compare the survival among the study cohorts. The incidence of metastasis will be calculated in stage IV endometrial cancer. In the bivariate analysis, we fitted separate Cox regression models for each variable, including metastasis status (bone, brain, liver, and lung), race, age group, year of diagnosis, and median household income, to estimate their individual hazard ratios (HRs). For the multivariate analysis, we constructed a Cox model incorporating all covariates simultaneously to adjust for potential confounders and determine independent predictors of survival. A Cox regression model was performed to compute the adjusted Hazard Ratios (aHR).

### 3.3.1 Machine leaning model

I applied a Random Survival Forest (RSF) model to evaluate the impact of clinical and demographic variables on overall survival time. RSF is a non-parametric ensemble learning method specifically designed for right-censored survival data. It extends the traditional random forest approach by using survival splitting rules and ensemble cumulative hazard estimates. The outcome of interest was overall survival time in months, with vital status (0 = alive, 1 = dead) as the event indicator. Predictor variables included metastasis status (bone, liver, lung, brain), age group, race, year of diagnosis, and median household income. All categorical variables were converted to factors, as required by the randomForestSRC package in R. The model was trained using 500 trees, and variable importance was assessed using the impurity measure. Model performance was evaluated through time-dependent ROC analysis, confusion matrix, and individualized survival curve prediction. The RSF approach enabled flexible modeling of complex interactions and non-linear effects, offering an interpretable and robust alternative to traditional Cox models.

# 4. Results

## 4.1 Exploratory/Descriptive analysis

[Table 1](#tbl-summarytable) shows a summary of the data.

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| Table 1: Data summary table. |

[Table 2](#tbl-summarytablesurvival) gives the overview of the survival. The survival months in our dataset range from 0 to 119 months, with a mean survival of 23.1 months and a median survival of 12 months, indicating a right-skewed distribution. The standard deviation (SD) is 27.67 months, reflecting high variability in patient survival. A total of 5,839 patients were included in the analysis. This distribution suggests that while some patients survive long-term, the majority have relatively short survival durations.

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| Table 2: Summary of survival months in the study population. |

[Figure 1](#fig-survival) shows the distribution of survival months. This histogram illustrates the distribution of survival months among patients in the dataset. The x-axis represents survival duration in months, while the y-axis shows the count of patients within each survival interval. The distribution is right-skewed, indicating that most patients had shorter survival times, with a gradual decline in frequency as survival duration increases. A substantial proportion of patients survived less than 12 months, while fewer cases exhibited long-term survival beyond 60 months. The presence of some patients with survival exceeding 100 months highlights potential long-term survivors.

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| Figure 1: Survival months. |

[Table 3](#tbl-summaryage) and [Figure 2](#fig-age) shows age distribution.The dataset includes patients across a wide age range, with the majority falling within the 60-69 years age group. The highest number of patients are aged 60-64 years (1,006 patients), followed closely by 65-69 years (956 patients). The number of cases gradually decreases in older age groups, with 389 patients aged 80-84 years and 280 patients aged 85+ years. The youngest age groups (20-39 years) have significantly fewer cases, with only 3 patients aged 20-24 years and 64 patients aged 35-39 years. This distribution indicates that the majority of the study population consists of older adults, which aligns with typical cancer incidence patterns that increase with age.

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| Table 3: Summary of age group distribution. |

[Figure 2](#fig-age) shows this distribution indicates that the majority of the study population consists of older adults, which aligns with typical cancer incidence patterns that increase with age.

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| Figure 2: Age |

[Table 4](#tbl-summarymetastasis) and [Figure 3](#fig-mets) shows distribution for different sit for metastasis. The table presents the distribution of metastatic sites at the time of diagnosis which is the main exposure in our study. Lung metastases were the most common, observed in 1,676 patients, followed by liver metastases (844 patients). Bone metastases were identified in 556 patients, while brain metastases were the least frequent, affecting 160 patients.

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| Table 4: Summary of metastasis. |

[Figure 3](#fig-mets) shows this distribution suggests that lung and liver are the most frequent metastatic sites, which aligns with common metastatic patterns observed in many cancers. The lower occurrence of brain metastases may reflect differences in metastatic tropism or detection rates.

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| Figure 3: Metatstasis |

## 4.2 Basic statistical analysis

### 4.2.1 Bivariate Analysis: Metastasis and Survival

In the bivariate Cox proportional hazards analysis, all four metastasis types were significantly associated with an increased risk of mortality. Bone metastasis was associated with a 56% higher hazard of death (HR = 1.56), while brain metastasis showed the highest risk, nearly a 92% increased hazard of death (HR = 1.92). Liver metastasis was also strongly associated with worse survival, showing an 81% higher hazard of death (HR = 1.81), and lung metastasis increased the hazard of death by 63% (HR = 1.63). These findings indicate that the presence of metastases, particularly in the brain and liver, is a strong predictor of poor survival outcomes. [Table 5](#tbl-summaryhrmetastasis) shows the HR for different metastatis sites

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| Table 5: Proportional hazards analysis for different metastasis. |

[Figure 4](#fig-km-curve-bone-mets) illustrates the survival probability of patients with and without bone metastasis over time. The red curve represents patients without bone metastasis, while the blue curve represents those with bone metastasis. Patients with bone metastasis have significantly worse survival outcomes, as indicated by the lower survival probability throughout the follow-up period.

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| Figure 4: Kaplan-Meier survival curves for Bone Metastasis |

[Figure 5](#fig-km-curve-brain-mets) shows that patients with brain metastasis have significantly lower survival probabilities than those without. The log-rank test (p < 0.0001) confirms a statistically significant difference, indicating that brain metastasis is associated with worse survival outcomes.

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| Figure 5: Kaplan-Meier survival curves for Brain Metastasis |

[Figure 6](#fig-km-curve-liver-mets) indicates that patients with liver metastasis (blue) have significantly lower survival probabilities than those without (red). The log-rank test (p < 0.0001) confirms a statistically significant difference, suggesting that liver metastasis is associated with poorer survival outcomes.

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| Figure 6: Kaplan-Meier survival curves for Liver Metastasis |

[Figure 7](#fig-km-curve-lung-mets) shows that patients with lung metastasis (blue) have significantly lower survival probabilities than those without (red). The log-rank test (p < 0.0001) confirms a statistically significant difference, indicating that lung metastasis is associated with worse survival outcomes.

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| Figure 7: Kaplan-Meier survival curves for Lung Metastasis |

### 4.2.2 Bivariate Analysis: Race and Survival

Patients identified as had significantly worse survival outcomes than White patients, with a 37% higher risk of death (HR = 1.37, p < 0.0001). In contrast, Asian patients had a lower risk of death compared to White patients (HR = 0.86, p = 0.0076), suggesting a potential survival advantage. The survival difference between American Indian and White patients was not statistically significant (HR = 1.21, p = 0.29), indicating no clear evidence of an increased or decreased risk. [Table 6](#tbl-summaryhrrace) shows the HR for patients with different race.

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| Table 6: Proportional hazards analysis for different Race. |

### 4.2.3 Bivariate Analysis: Age and Survival

The hazard ratio (HR) estimates for different age groups indicate a general trend of increasing risk with age, though statistical significance varies. Compared to the reference group (20-24 years), younger age groups (25-74 years) show HRs between 3.5 and 6.2, but their p-values are above 0.05, suggesting no statistically significant difference in survival risk. However, individuals aged 80-84 years (HR = 7.99, p = 0.038) and 85+ years (HR = 11.01, p = 0.017) have significantly higher mortality risk, indicating poorer survival outcomes in older patients. These findings suggest that age is an important predictor of survival, with the highest risk observed in the oldest age group. [Table 7](#tbl-summaryhrage) shows the HR for diferrent age groups.

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| Table 7: Proportional hazards analysis for different age group. |

### 4.2.4 Multivariable analysis

The multivariable Cox proportional hazards model results indicate that metastasis to the bone (HR = 1.30, p < 0.001), brain (HR = 1.72, p < 0.001), liver (HR = 1.66, p < 0.001), and lung (HR = 1.51, p < 0.001) are all significantly associated with poorer survival outcomes. Among racial groups, Black patients (HR = 1.39, p < 0.001) had significantly worse survival compared to White patients, while Asian or Pacific Islander and American Indian/Alaska Native groups did not show a statistically significant difference.

Regarding age, survival risk generally increased with older age, with statistically significant increases observed in the 70-74 years (HR = 7.26, p = 0.048), 75-79 years (HR = 7.91, p = 0.039), 80-84 years (HR = 9.53, p = 0.025), and 85+ years (HR = 12.75, p = 0.011) groups, indicating poorer survival outcomes in older patients.

Year of diagnosis did not show a consistent or significant trend, suggesting no clear improvement or decline in survival based on the year of diagnosis. Household income was associated with survival, with patients in the $50,000 - $54,999 (HR = 1.16, p = 0.011) and $65,000 - $69,999 (HR = 1.12, p = 0.030) categories showing significantly higher risk compared to those earning $75,000+. However, other income groups did not show significant differences.

Overall, metastasis, age, and race appear to be key determinants of survival, with Black race and older age groups associated with poorer outcomes.

### 4.2.5 Random Survival Forest

A Random Survival Forest (RSF) model was used to evaluate the contribution of clinical and demographic predictors to overall survival. The RSF model demonstrated strong performance in predicting survival at 12 months, achieving an AUC of 0.74 ([Figure 8](#fig-rsf-auc)). The confusion matrix revealed a sensitivity of 86.5% and a specificity of 47.9%, with an overall accuracy of 53.8% and balanced accuracy of 67.2%, indicating that the model was effective in identifying patients at high risk of death within the first year.

Variable importance analysis revealed that age group, median household income, and year of diagnosis were the most influential predictors of survival ([Figure 9](#fig-rsf-variable-importance)). Other important variables included race and metastasis to the bone, lung, liver, and brain. The individualized survival prediction for a representative patient showed a steady decline in survival probability over time, reflecting the nature of long-term risk in this cohort ([Figure 10](#fig-rsf-ind-sur-pre)). [Figure 11](#fig-rsf-con-matrix). Confusion matrix showing prediction results of the Random Survival Forest model at 12 months. The model correctly classified 709 survivors and 2,182 non-survivors, with moderate misclassification of 2,376 survivors and 111 non-survivors.

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| Figure 8: Random Survival Forest AUC |

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| Figure 9: Random Survival Forest Variable Importance |

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| Figure 10: Random Survival Forest Individualized Survival Prediction |

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| Figure 11: RSF Confusion Matrix (12 Months) |

# 5. Discussion

## 5.1 Summary and Interpretation

In this large SEER-based analysis of patients with stage IV endometrial cancer, we found that survival outcomes varied significantly based on the site of metastasis. Lung metastasis was the most common at diagnosis, consistent with the known hematogenous spread of endometrial tumors to the pulmonary system. However, brain and liver metastases were associated with the poorest prognoses, showing significantly elevated hazard ratios for mortality, even after adjusting for age, race, income, and year of diagnosis. This suggests that not all metastatic patterns carry equal prognostic weight, and involvement of certain visceral organs may reflect more aggressive tumor biology or greater resistance to conventional treatment modalities. These findings align with previous literature highlighting the aggressive nature and poor survival associated with visceral metastases, particularly in the central nervous system and liver, where treatment options are often limited and complications more severe (7,10).

Our study also highlights important demographic disparities that influence survival. Black patients had significantly higher mortality risk compared to White patients, a pattern consistent with prior studies on racial inequities in cancer detection, treatment access, and outcomes (1,11). These disparities may reflect differences in healthcare access, socioeconomic factors, and biological variations, and underscore the need for tailored interventions to address inequities in care delivery. The impact of age was particularly striking—patients aged ≥85 years had more than 12 times the mortality risk of younger patients. This finding supports the well-established role of age as a dominant prognostic factor in gynecologic malignancies, not only due to physiological frailty and comorbidities but also possibly due to undertreatment in older populations (2,12). As the population ages, understanding and addressing these age-related disparities will be increasingly important for improving outcomes in this vulnerable group.

The application of a Random Survival Forest (RSF) model in our analysis provided additional insights beyond those offered by traditional Cox regression. By capturing complex, non-linear relationships and variable interactions, the RSF approach identified the most influential predictors of survival—including age group, income, and metastatic site. This machine learning method yielded an AUC of 0.74, indicating good predictive performance and offering a robust complement to the conventional modeling framework. Notably, RSF enabled individualized survival prediction, which may have potential utility in clinical decision-making and patient counseling (13,14). Integrating such tools into routine care could enhance risk stratification, support shared decision-making, and contribute to the development of precision oncology strategies.

## 5.2 Strengths and Limitations

One of the study’s major strengths is the use of the SEER registry, a high-quality, population-based dataset capturing data across a wide U.S. demographic. This enhances the generalizability of our findings and allows for robust subgroup analyses across metastasis types and sociodemographic strata. (15) Moreover, the combination of classical survival analysis and machine learning techniques provides both interpretability and predictive power.

However, our study has several limitations. The SEER database lacks treatment details such as chemotherapy, hormonal therapy, or immunotherapy, which may influence survival outcomes. Also, performance status and comorbidities—key clinical predictors—are not captured in SEER. The data only reflect metastasis at diagnosis, not accounting for progression or treatment response. Lastly, despite adjusting for income and race, residual confounding due to unmeasured variables is possible.

## 5.3 Conclusions

Our findings suggest that survival in stage IV endometrial cancer is heavily influenced by the site of metastasis, with brain and liver involvement predicting worse outcomes. The disparities across age and race underscore the need for tailored care and equitable access to treatment. Incorporating advanced analytics such as RSF provides a deeper understanding of survival dynamics and may inform future personalized prognostic tools. Future research should aim to integrate molecular, treatment, and longitudinal clinical data to refine prognostic models. These findings could also guide clinicians in risk stratification, resource allocation, and decision-making, especially for high-risk subgroups.

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