# Real-world Impact Of Recurrence On Overall Survival (OS) In Patients With Unresectable Locally Advanced (LA) Esophageal/Gastroesophageal Junction Cancer (EC/GEJC) Treated With Definitive Chemoradiotherapy (dCRT) In US Community Oncology Clinics

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## Background

- While surgery is the preferred treatment for patients with early-stage EC/GEJC, dCRT is recommended for patients who are otherwise ineligible for surgery.[1]
- Despite advancements, outcomes for patients with dCRT remain poor; patients with locally advanced EC/GEJC often face relapse or disease progression. Studies have shown a 5-year recurrence rate of up to 45% and a 5-year overall survival (OS) rate of approximately 29%.[2,3]
- Previous studies have shown disease recurrence is associated with worse survival outcomes for EC following surgical intervention, but it is not well understood in a post-CRT setting.[4]
- Additionally, in a meta-analysis of randomized control trials (RCTs), event-free survival (EFS) has been validated as a surrogate endpoint for OS.[5]
- This study aims to describe the impact of recurrence following dCRT on OS among patients with early-stage EC/GEJC in a real-world setting.

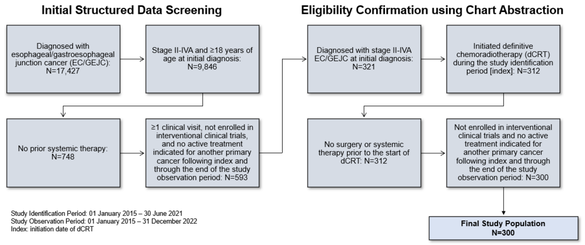
## Objective

**To assess the impact of disease recurrence on overall survival among a cohort of patients with locally advanced unresectable EC/GEJC who received dCRT in the US community oncology setting.**

## Methods

- **Study Design:** Retrospective observational cohort study
- **Data Source:** Structured and chart abstraction data sourced from iKnowMed, an oncology-specific electronic health record (EHR) system which captures outpatient practice encounter histories for patients seen in The US Oncology Network.
- **Study Population:** Adult patients diagnosed with locally advanced, unresectable EC/GEJC who initiated dCRT between January 1, 2015 – June 30, 2021 (see **Figure 1**)
  - The initiation date of dCRT was considered the index date
  - Patients were followed through last patient record or death on or before December 31, 2022
  - Recurrence was defined as the occurrence of distant recurring metastatic event or progression (DRP) during follow-up. Within the overall population, two subgroups were created based on whether recurrence occurred over follow-up to compare outcomes across these two groups.
- **Clinical Outcomes:**
  - Real-world overall survival (rwOS): duration (in months) from index to death
  - Real-world event-free survival (rwEFS): duration (in months) from index to first DRP or death
  - Landmark rwOS was assessed at various timepoints in follow-up (6,12, and 18 months)
- **Statistical Analyses:**
  - Descriptive analyses were performed to summarize baseline demographics and clinical characteristics.
  - Clinical outcomes were assessed using the Kaplan-Meier method.
  - Landmark analyses examined rwOS differences by recurrence status at each landmark.
  - The relationship between rwOS and recurrence was also examined using the Cox proportional hazards model at 6, 12, and 18 months. rwOS served as the dependent variable, with patient recurrence status at the landmark time points was the primary variable of interest, while controlling for other patient characteristics.
  - Correlation between rwEFS and rwOS was estimated using Kendall-Tau's correlation coefficient.

### Figure 1. Study Attrition Diagram




### References

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5.Shah, M, Weiguang X, Ramakrishnan K, et. al. Evaluation of Event-Free Survival (EFS) as a Surrogate for Overall Survival (OS) in Patients with Locally Advanced Esophageal Carcinoma (LA EC) Receiving Definitive Chemoradiotherapy (dCRT). Presented at ASCO GI 2024.

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## Results

### Table 1. Baseline Characteristics

| | Overall (n=300) | Recurrence (n=112) | No Recurrence (n=188) |
|---|---|---|---|
| **Median follow-up time, months (IQR)** | 10.5 (4.0,21.0) | 14.1 (8.8,21.1) | 6.4 (2.7,20.3) |
| **Median age at index, years (IQR)** | 73 (64,80) | 72 (62,80) | 73 (66,80) |
| **Sex (Male) – n (%)** | 223 (74.3%) | 86 (76.8%) | 137 (72.9%) |
| **Race – n (%)** | | | |
| Black/African American | 19 (6.3%) | 5 (4.5%) | 14 (7.4%) |
| White/Caucasian | 221 (73.7%) | 90 (80.4%) | 131 (69.7%) |
| Other | 8 (2.7%) | 3 (2.7%) | 5 (2.7%) |
| Not documented | 52 (17.3%) | 14 (12.5%) | 38 (20.2%) |
| **Stage at initial diagnosis – n (%)[a]** | | | |
| Stage II | 104 (34.7%) | 38 (33.9%) | 66 (35.1%) |
| Stage III | 167 (55.7%) | 65 (58.0%) | 102 (54.3%) |
| Stage IVA | 16 (5.3%) | <10 | 11 (5.9%) |
| Not documented | 13 (4.3%) | <10 | <10 |
| **Baseline ECOG performance status – n (%)** | | | |
| 0/1 | 190 (75.7%) | 71 (76.3%) | 119 (75.3%) |
| ≥ 2 | 61 (24.3%) | 22 (23.7%) | 39 (24.7%) |
| **Histology at diagnosis – n (%)** | | | |
| Adenocarcinoma | 159 (53.0%) | 64 (57.1%) | 95 (50.5%) |
| Squamous Cell | 116 (38.7%) | 37 (33.0%) | 79 (42.0%) |
| Other | 25 (8.3%) | 11 (9.8%) | 14 (7.4%) |
| **Esophageal (vs. GEJ) Tumor – n (%)** | 212 (70.7%) | 75 (67.0%) | 137 (72.9%) |

ECOG = Eastern Cooperative Oncology Group, IQR = interquartile range.
[a]Those without a documented stage had a documented TNM that met the inclusion criteria.

### Table 2. Landmark rwOS at 6-,12-, and 18-Month Intervals by Recurrence Status

| Median rwOS (95% CI) | Recurrence | No Recurrence | Adjusted Hazard Ratio[a] |
|---|---|---|---|
| 6-month (R n=25; RF n=170) | 7.1 (2.9, 13.2) | 21.0 (17.6, 44.8) | 2.9 (95% CI: 1.5, 5.5) |
| 12-month (R n=39; RF n=93) | 8.5 (6.8, 12.0) | 41.5 (38.8, NR) | 4.2 (95% CI: 2.1, 8.2) |
| 18-month (R n=33; RF n=66) | NR (32.8, NR) | 5.6 (3.1, 9.0) | 5.7 (95% CI: 2.3, 14.4) |

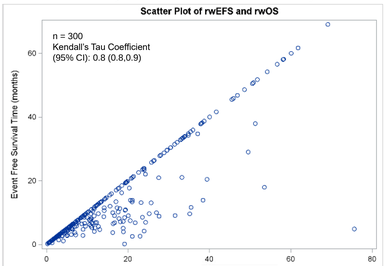
R = Recurrence, RF = No Recurrence, NR = Not reached.
[a]Adjusted for age, sex, ECOG, tumor stage, tumor histology, prior treatment, and tumor location.

### Table 3. Cox Proportional Hazard Model with Recurrence as Time-Dependent Covariate

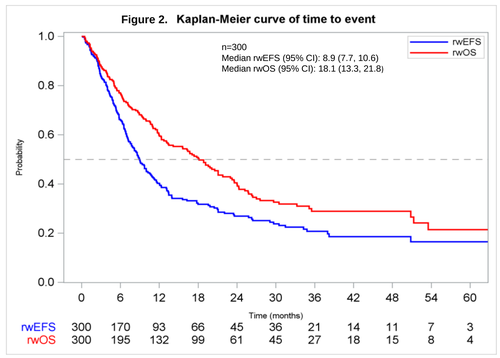
| Model | DF | Parameter Estimate | Standard Error | Chi-Squared | p-value | Hazard Ratio[a] |
|---|---|---|---|---|---|---|
| Unadjusted | 1 | 1.7 | 0.2 | 89.6 | <.0001 | 5.7 (95% CI: 4.0, 8.1) |
| Adjusted | 1 | 1.8 | 0.2 | 92.3 | <.0001 | 5.9 (95% CI: 4.1, 8.4) |

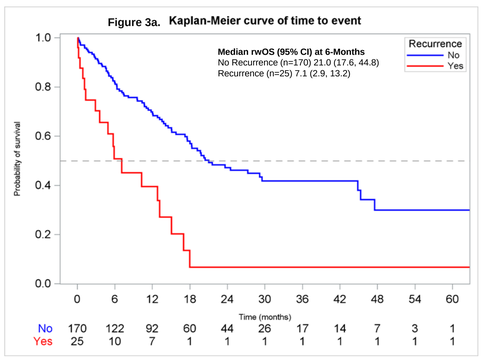
DF = Degrees of freedom
[a]Adjusted for age, sex, ECOG, tumor stage, tumor histology, prior treatment, and tumor location.

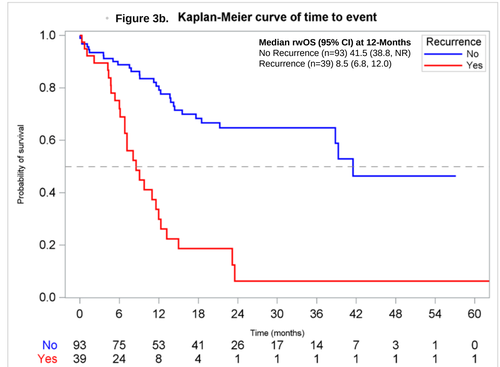
### Figure 4. Endpoint Correlation Analysis (rwEFS and rwOS)

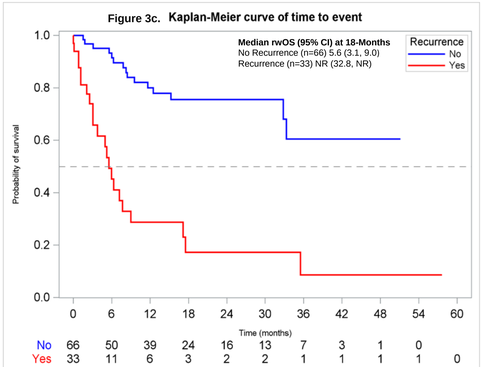



### Figure 2. Kaplan-Meier Curve of Real-world Overall Survival (rwOS) and Event-Free Survival (rwEFS) from Index and Figures 3a-3b: Kaplan-Meier of Landmark rwOS by Recurrence Status at 6-, 12-, and 18-Months from Index date Index by Recurrence Status




### Summary of Results

- Among the 300 patients, 112 (37.3%) patients experienced recurrence over follow-up. Baseline characteristics were similar between the recurrence and no recurrence subgroups (**Table 1**)
- In the overall study population, median rwEFS was 8.9 months (95% CI: 7.7, 10.6), with 66.0% of the study population experiencing an event; median rwOS was 18.1 (95% CI: 13.3, 21.8) months with 53.7% of the study population experiencing an event (**Figure 2**).
- The adjusted hazard ratio (HR) indicated a higher risk of death for patients who experienced disease recurrence compared to those who did not experience disease recurrence (adjusted HR: 5.9, 95% CI: 4.1, 8.4) over time (**Table 3**).
- For those recurring within 6 months (**Figure 3a**), median landmark rwOS was 7.1 months (95% CI: 2.9, 13.2), compared to 21.0 months (95% CI: 17.6, 44.8) for those who had not recurred (adjusted HR: 2.9, 95% CI: 1.5, 5.5;**Table 2**). A similar trend was observed for the 12-month (**Figure 3b**, **Table 2**) and 18-month (**Figure 3c**, **Table 2**) landmark analyses.
- Furthermore, rwEFS and rwOS were estimated to be strongly correlated (r = 0.8; 95% CI: 0.8,0.9; **Figure 4**), indicating more time without recurrence was associated with longer rwOS in this population.

### Limitations

- This study utilized an oncology-specific EHR system that captures outpatient encounters for patients receiving treatment within The US Oncology Network practices. It is not used to collect data for research purposes but for clinical practice reasons.
- Treatment administered in academic hospitals or oncology centers outside of this data source is not reflected in this analysis. There may also be differences in how tumor progression is documented at a practice-level. Additionally, with a small patient sample, results from this study may not be generalizable to all patients.

## Conclusion

- This real-world study demonstrated that patients without recurrence at key landmark points had longer median rwOS than those who had recurred. We observed a 3- to 6-fold increase in adjusted risk of death in patients with recurrence events at key landmark time points.
- Longer time to recurrence was associated with better survival, yet high recurrence rates persisted.
- Extending time to recurrence could improve long-term outcomes, highlighting an unmet need for effective early-stage therapies.

### Disclosures

AV and SB are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). KR was an employee of MSD at the time the study was conducted. LH, JS, HL, GP are employees of Ontada. SN is an employee of The US Oncology Network..

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