Association of a DNA Damage Response (DDRD) Assay with Prognosis in Resected Esophageal and Gastric Adenocarcinoma

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ABSTRACT

Esophageal cancer is the eighth most common cancer worldwide.

- The UK has the highest incidence of the Esophageal Adenocarcinoma (EAC) in the world.
- The five year survival rate is 13% and even in early stage loco-regional confined disease the five year survival only exceeds 40%.
- There is regional variation in neo-adjuvant treatment of resectable EAC and the optimal approach remains unclear.

There is a pressing need to identify biomarkers capable of predicting response to enable clinicians to stratify patients to the most beneficial neo-adjuvant chemotherapy.

The DNA Damage Response Deficiency (DDRD) Assay

- The DDRD assay positively demonstrated a statistically significant association with disease-free survival (HR 0.59; 95% CI 0.40-0.85; p=0.006) (Figure 2).
- Median OS was not reached for RDDR+ve patients vs 32.2 months for RDDR-ve patients.
- RDDR score was significantly higher in RDDR+ve compared to RDDR-ve patients (20.1 months vs 31.6 months; HR 0.63; 95% CI 0.43-0.91; p=0.029) (Figure 2).
- These results indicate that the DDRD assay is a strong prognostic marker in the setting of neo-adjuvant chemotherapy for early stage EAC.

Figure 1: Kaplan Meier and Multivariable Cox regression analysis for a 44 gene signature predictive of response to DNA-damaging chemotherapy.

Figure 2: Boxplot of DDRD scores grouped by response status.

Conclusions

- Matched resection specimens were scored for pathological response according to the Modified Score (23 pathological response).
- 24 cases (8.8%) were pathologically responders with 203 non-responders (74.6%) and resection specimens were evaluable in 46 cases (16.8%).
- RDDR score was a strong predictor of response to neo-adjuvant chemotherapy in setting of surgery.

Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RDDR +ve</th>
<th>RDDR -ve</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Stage</td>
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<td>Pathology</td>
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<td>Chemotherapy</td>
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<td>Survival (OS)</td>
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Table 2: Tumor characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RDDR +ve</th>
<th>RDDR -ve</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Clinical T stage</td>
<td></td>
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<td></td>
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<tr>
<td>Pathological response</td>
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<td></td>
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<tr>
<td>Surgical N stage</td>
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The addition of DDRD to clinical and pathological response to neo-adjuvant chemotherapy in EAC demonstrates a strong association with prognosis.

DORD IN GASTRIC ADENOCARCINOMA:

- 270 resected gastric cancers treated at the Samsung Medical Centre, Seoul, Korea

- Treated with adjuvant platinum-based chemotherapy, chemoradiotherapy or surgery alone

- 132 samples (49%) were DDRD positive with the remaining 138 (51%) DDRD negative.

- DDRD positivity was associated with improved OS (HR 0.48; 95% CI 0.25-0.96; p=0.037)

- Figure 4 demonstrates a strong association with prognosis in gastric cancer.

- DDRD was not associated with DFS in the surgery alone cohort (HR 0.87; 95% CI 0.51-1.58; p=0.56).

Figure 4: Kaplan Meier analysis according to DDRD status in gastric adenocarcinomas treated with (A) surgical resection followed by adjuvant chemotherapy/chemoradiotherapy or (B) surgery alone

ACKNOWLEDGEMENTS

The Northern Ireland Molecular Pathology Laboratory which is responsible for the DDRD assay and the Northern Ireland Cancer Centre, Belfast City Hospital, Belfast has funded the study. The Northern Ireland Cancer Centre, Belfast City Hospital, Belfast was supported by the Health and Social Care Trust, Belfast City Hospital, Belfast, Northern Ireland.

Further funding was received from the Health and Social Care Trust, Belfast City Hospital, Belfast (Northern Ireland Cancer Centre, Belfast City Hospital, Belfast, Northern Ireland).


2. Matched resection specimens were scored for pathological response according to the Modified Score (23 pathological response).

3. 24 cases (8.8%) were pathologically responders with 203 non-responders (74.6%) and resection specimens were evaluable in 46 cases (16.8%).

4. The DDRD assay was significantly higher in RDDR+ve compared to RDDR-ve patients (20.1 months vs 31.6 months; HR 0.63; 95% CI 0.43-0.91; p=0.029) (Figure 2).

5. These results indicate that the DDRD assay is a strong prognostic marker in the setting of neo-adjuvant chemotherapy for early stage EAC.

6. The five year survival rate is 13% and even in early stage loco-regional confined disease the five year survival only exceeds 40%.

7. There is regional variation in neo-adjuvant treatment of resectable EAC and the optimal approach remains unclear.

8. There is a pressing need to identify biomarkers capable of predicting response to enable clinicians to stratify patients to the most beneficial neo-adjuvant chemotherapy.

9. The DDRD assay positively demonstrated a statistically significant association with disease-free survival (HR 0.59; 95% CI 0.40-0.85; p=0.006) (Figure 2).

10. Median OS was not reached for RDDR+ve patients vs 32.2 months for RDDR-ve patients.

11. RDDR score was significantly higher in RDDR+ve compared to RDDR-ve patients (20.1 months vs 31.6 months; HR 0.63; 95% CI 0.43-0.91; p=0.029) (Figure 2).

12. These results indicate that the DDRD assay is a strong prognostic marker in the setting of neo-adjuvant chemotherapy for early stage EAC.

13. Matched resection specimens were scored for pathological response according to the Modified Score (23 pathological response).

14. 24 cases (8.8%) were pathologically responders with 203 non-responders (74.6%) and resection specimens were evaluable in 46 cases (16.8%).

15. The DDRD assay was significantly higher in RDDR+ve compared to RDDR-ve patients (20.1 months vs 31.6 months; HR 0.63; 95% CI 0.43-0.91; p=0.029) (Figure 2).

16. These results indicate that the DDRD assay is a strong prognostic marker in the setting of neo-adjuvant chemotherapy for early stage EAC.

Table 3: Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for overall survival.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Clinical T stage</td>
<td>1.84 (1.29-2.62)</td>
<td>0.004</td>
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<tr>
<td>Pathological response</td>
<td>1.57 (1.20-2.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgical N stage</td>
<td>0.92 (0.78-1.08)</td>
<td>0.251</td>
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Table 4: Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for disease-free survival.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical T stage</td>
<td>2.17 (1.38-3.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pathological response</td>
<td>1.54 (1.15-2.06)</td>
<td>0.005</td>
</tr>
<tr>
<td>Surgical N stage</td>
<td>0.90 (0.71-1.15)</td>
<td>0.428</td>
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