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

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Background
Current strategies to guide the selection of neo-adjuvant or adjuvant therapy in esophageal and gastric adenocarcinomas (EAC/GAC) are inadequate. We assessed a clinically validated 44 gene DNA Damage Response Deficiency (DDRD) assay to predict prognosis following neo-adjuvant DNA damaging chemotherapy (CT) in EAC and adjuvant CT or chemo-radiotherapy (CRT) in GAC.

Methods
Transcriptional profiling of 273 formalin fixed paraffin embedded pre-treatment endoscopic EAC biopsies was performed using the Almac Diagnostics Xcel™ array. All EAC patients were treated with cisplatin-based neo-adjuvant chemotherapy followed by surgical resection between 2003 and 2014 at four UK centers in the OCCAMS consortium. Further validation was performed using a publically available dataset of 270 resected gastric cancers treated with adjuvant platinum-based CT, CRT or surgery alone at the Samsung Medical Centre, Seoul, Korea. The association between the DDRD score and prognosis was assessed by Kaplan-Meier analysis and Cox Proportional Hazards regression.

Results
A total of 66 EAC samples (24%) were characterized as DDRD positive with the remaining 207 samples (76%) being DDRD negative. DDRD assay positivity was associated with improved DFS (HR 0.58; 95% CI 0.36-0.93; p=0.024) and OS (HR 0.56; 95% CI 0.34-0.92; p= 0.023) following multivariate analysis. DDRD positive patients had a higher pathological response rate (p= 0.033) and a higher rate of loco-regional versus distant relapse (30% vs 20%; p= 0.013).

For GAC, 132 samples (49%) were characterized as DDRD positive with the remaining 138 (51%) being DDRD negative. DDRD positivity was associated with improved DFS (HR 0.48; 95% CI 0.25-0.96; p=0.037) following D2 gastrectomy and adjuvant CT or CRT. DDRD status was not associated with DFS in the surgery alone cohort (HR 0.87; 95% CI 0.55-1.38; p=0.562).

Conclusion
The DDRD assay is strongly predictive of benefit from DNA damaging neo-adjuvant CT and esophagectomy in EAC and gastrectomy and CT/CRT in GAC and can be applied to routine diagnostic material.