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

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BACKGROUND

- 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 this figure rarely exceeds 40%.
- There is regional variation in neo-adjuvant treatment of resectable EAC and the optimal approach for individual patients 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 therapy.

DNA DAMAGE RESPONSE DEFICIENCY ASSAY

- The DNA Damage Response Deficiency (DDRD) Assay is a 44 gene signature predictive of response to DNA-damaging chemotherapy.
- The DDRD assay indicates loss of the Fanconi Anaemia (FA)/BRCA pathway essential for the repair of inter-strand crosslinks.
- Approximately 15% of EAC tumours demonstrate sensitivity to DNA-damaging chemotherapy

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ESOPHAGEAL ADENOCARCINOMA- PATIENT COHORT

- 273 formalin fixed paraffin embedded pre-treatment biopsies from resectable EAC patients
- All patients treated with cisplatin-based neo-adjuvant chemotherapy and surgical resection
- All patients treated between 2003 and 2014 at four UK centers in the OCCAMS consortium.
- RNA was extracted and hybridized to the the Xcel™ array (Almac/Affymetrix).
- All samples were scored for DDRD and dichotomized based on a pre-defined threshold.

Patient Characteristics		n=273
Gender:	Male	222
	Female	51
Age	Mean	63.66
	Range	28-83
Clinical T stage	1	4
	2	28
	3	208
	4	8
	Missing	25
Clinical N stage	0	62
	1	160
	2	16
	3	8
	Missing	27

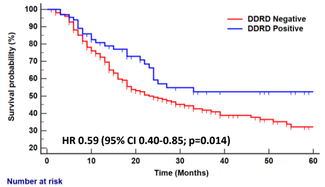
Table 1: Patient characteristics.

Tumor Characteristics		n=273
Surgical T stage	0	12
	1	31
	2	42
	3	175
	4	13
Surgical N stage	0	102
	1	61
	2	58
	3	52
Differentiation	Well	7
	Moderate	90
	Poor	161
	Missing	15
LVI	0	86
	1	178
	Missing	9
Resection Margin status	R0	155
	R1	94
	R2	4
	Missing	20

Table 2: Tumor characteristics.

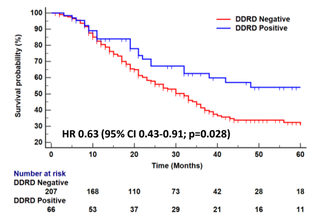
DDRD IN EAC- NEO-ADJUVANT CHEMOTHERAPY

- 66 samples (24%) were characterised as DDRD positive with 207 samples (76%) DDRD negative.
- DDRD assay positivity demonstrated a statistically significant association with disease-free survival (HR 0.59; 95% CI 0.40-0.85; p=0.014) (Figure 1)
- Median DFS was not reached for DDRD+ve patients vs 23.2 months for DDRD-ve patients.
- Median OS was significantly higher in DDRD +ve compared to DDRD –ve patients (61.8 months vs 31.6 months; HR 0.63; 95% CI 0.43-0.91; p=0.028) (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.



Endpoint	RFS	
Covariate	HR [95% CI]	p-value
DDRD +ve	0.58 [0.36-0.93]	0.0243
Clinical N stage	1.57 [1.20-2.06]	0.0012
Clinical T stage	1.18 [0.74-1.88]	0.4753

Figure 1: Kaplan Meier and Multivariable analysis for DDRD predicting disease-free survival (DFS)



Endpoint	OS	
Covariate	HR [95% CI]	p-value
DDRD +ve	0.56 [0.34-0.92]	0.0228
Clinical N stage	1.42 [1.06-1.90]	0.0204
Clinical T stage	1.18 [0.76-1.84]	0.4710

Figure 2: Kaplan Meier and Multivariable analysis for DDRD predicting overall survival (OS)

Endpoint: RFS	DDRD Status	
Covariate	HR [95% CI]	p
DDRD	0.59 [0.40-0.85]	0.0140
Clinical N stage	1.53 [1.19-1.97]	0.0011
DDRD + Clinical N stage	2.29 [1.49-3.53]	0.0002

Endpoint: OS	DDRD Status	
Covariate	HR [95% CI]	p
DDRD	0.63 [0.43-0.91]	0.0280
Clinical N stage	1.40 [1.06-1.83]	0.0171
DDRD + Clinical N stage	2.17 [1.29-3.66]	0.0037

Table 3&4: DDRD status, clinical N stage and both factors combined as predictors of survival outcome

Multivariable analysis results showed that of the clinical factors assessed clinical N stage and DDRD status were the only significant predictors of survival and so DDRD was combined with clinical N stage to see if the performance was improved over the use of DDRD and N stage alone.

The addition of DDRD to clinical N stage significantly improved the ability to predict overall survival compared to clinical N stage alone

DDRD IN EAC- PATHOLOGICAL RESPONSE

- Matched resection specimens were scored for pathological response according to the Mandard Score (≤2 pathological response).
- 24 cases (8.8%) were pathological responders with 203 non-responders (74.3%) and resection specimens were unable to be evaluated in 46 cases (16.8%).
- DDRD score was significantly higher in responders compared to non-responders (Figure 3).
- The DDRD score was predictive of pathological response to neo-adjuvant cisplatin-based chemotherapy in EAC.

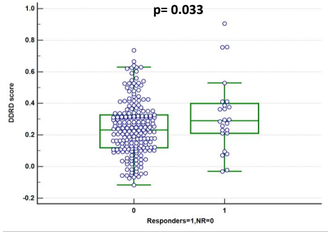


Figure 3: Boxplot of DDRD scores grouped by response status

DDRD IN GASTRIC ADENOCARCINOMA- PATIENT COHORT

Patient and Tumor Characteristics		Adjuvant Chemotherapy/ ChemoXRT (n= 114)	Surgery Alone (n= 156)	p value (Chi squared)
Gender:	Male	83	94	0.038
	Female	31	62	
Age	Median	60	66	<0.0001*
	Range	31-37	24-86	
T stage	2	76	92	0.16
	3	33	48	
	4	5	16	
N stage	0	9	24	0.061
	1	58	58	
	2	32	44	
	3	15	30	
Lauren	Intestinal	62	72	0.56
	Diffuse	46	73	
	Mixed	5	10	
	Indeterminate	1	1	

* Mann-Whitney U test

DDRD IN GASTRIC ADENOCARCINOMA- ADJUVANT CHEMOTHERAPY

- 270 resected gastric cancers treated at the Samsung Medical Centre, Seoul, Korea
- Treated with adjuvant platinum-based chemotherapy, chemo-radiotherapy or surgery alone
- 132 samples (49%) were DDRD positive with the remaining 138 (51%) 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 chemotherapy/chemo-radiotherapy (Figure 4A).
- DDRD was not associated with DFS in the surgery alone cohort (HR 0.87; 95% CI 0.55-1.38; p=0.56) (Figure 4B).

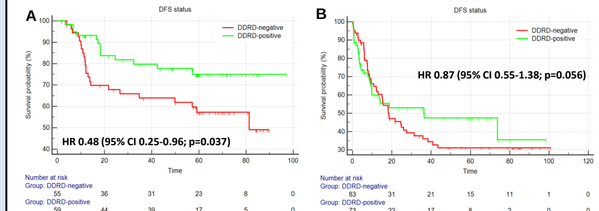


Figure 4: Kaplan Meier analysis according to DDRD status in gastric adenocarcinomas treated with (A) surgical resection followed by adjuvant chemotherapy/chemoradiotherapy or (B) surgery alone

CONCLUSIONS

The DDRD assay:

1. **Is the first gene expression biomarker to utilise FFPE tissue in oesophago-gastric cancer.**
2. **Demonstrates a strong association with prognosis in:**
    1. **EAC patients treated with neo-adjuvant chemotherapy**
    2. **GC patients treated with surgery + adjuvant chemo/chemoXRT**
3. **Predicts Pathological Response to neo-adjuvant chemotherapy**
4. **Could personalise treatment approaches in oesophago-gastric cancer.**

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