

Prognostic significance of nucleotide excision (NER) and base excision (BER) DNA repair gene polymorphisms in esophageal cancer

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Background: DNA repair pathways are involved in cisplatin-induced damage (NER pathway) & radiation damage (BER pathway). Some single nucleotide polymorphisms (SNPs) of DNA repair genes are associated with DNA repair capacity, cancer risk and outcomes. We investigated the prognostic significance of 7 NER/BER SNPs on disease free survival (DFS) & overall survival (OS) in esophageal cancer.

Methods: 150 patients with esophageal cancer treated with cisplatin-based chemoradiation & surgery were genotyped for BER (*XRCC1 Arg399Gln*; *APE1 Asp148Glu*; *hOGG1 Ser326Cys*) & NER (*ERCC1 8092C/A*; *ERCC1 codon 118 C/T*; *XPDAsp312Asn*; *XPD Lys751Gln*) SNPs. Analysis involved Kaplan-Meier curves, log-rank tests and Cox proportional hazards models.

Results: Median age: 63 years (range 28-80); 91% male; 100% ECOG performance status (PS) 0-1; adenocarcinoma 79%; stages IIA 22%, IIB 30%, III 33%, and IVA 15%. No SNPs were associated with stage or PS. Multiple NER SNPs were independently prognostic for OS & DFS (see Table). When compared to individuals who were wildtype in all four studied NER SNPs, individuals with variants in all four NER SNPs were associated with substantial improvement in OS (Adjusted Hazard Ratio (AHR)= 0.40, 95% confidence interval (CI)=0.2-0.7) and DFS (AHR=0.44, 95% CI=0.2-0.8). Furthermore, increasing numbers of variant genotypes were associated with a progressive increase in OS & DFS when all seven NER/BER pathway SNPs were analysed together (Table). There was a 3.8-fold increase in OS (75 vs. 20 months) and five-fold increase in DFS (51 vs. 10 months) when comparing individuals with 6-7 SNPs with variant alleles to individuals with 0-1 SNPs with variant alleles.

Conclusions: The *ERCC1 8092 C/A*, *XPD Asp312Asn* & *XPD Lys751Gln* SNPs in the NER pathway are individually associated with prognosis in esophageal cancer patients treated with cisplatin-based trimodality regimens. In addition, as the number of NER and BER SNPs carrying variant alleles increased, OS & DFS improved dramatically.

Table: Overall and Disease-Free Survival by DNA Repair Gene Polymorphisms

Polymorphism	Genotype	Number	Overall Survival			Disease Free Survival		
			Log-Rank	Median (Months)	Hazard Ratio* (95% CI)	Log-rank	Median (Months)	Hazard Ratio* (95% CI)
<i>ERCC1 8092C/A</i>	A/- vs. C/C	81 vs. 69	P=0.03	53 vs. 30	0.60 (0.4-0.9)	P=0.04	37 vs. 17	0.62 (0.4-0.9)
<i>XPD Asp312Asn</i>	<i>Asn</i> - vs. <i>Asp/Asp</i>	97 vs. 53	P=0.001	52 vs. 24	0.53 (0.3-0.8)	P=0.001	37 vs. 14	0.54 (0.4-0.8)
<i>XPD Lys751Gln</i>	Gln/- vs. Lys/Lys	99 vs. 51	P=0.02	51 vs. 26	0.60 (0.4-1.0)	P=0.11	30 vs. 15	0.70 (0.5-1.1)
Combination of seven DNA repair polymorphisms (# of SNPs with variant alleles)	0-1	10	P=0.01	20	Reference (1.0)	P=0.005	10	Reference (1.0)
	2-3	34		30	0.49 (0.3-1.1)		17	0.47 (0.2-1.0)
	4-5	69		37	0.40 (0.2-0.9)		22	0.40 (0.2-0.8)
	6-7	34		75	0.27 (0.1-0.6)		51	0.27 (0.1-0.6)

* Adjusted for age, gender, performance status and stage