A Six-CpG Panel with DNA Methylation Biomarkers Predicting Treatment Response of Chemoradiation in Esophageal Squamous Cell Carcinoma

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Prognosis of esophageal squamous cell carcinoma (ESCC) patients remains poor, and the chemoradiotherapy (CRT) applied to ESCC patients often failed. Therefore, development of biomarkers to predict CRT response is immensely important for choosing the best treatment strategy of an individual patient. The methylation array and pyrosequencing methylation assay were performed in pre-treatment endoscopic biopsies to identify probes with differential CpG methylation levels between good and poor CRT responders in a cohort of 12 ESCC patients. Receiver operating characteristic curves and multivariate logistic regressions were conducted to build the risk score equation of selected CpG probes in another cohort of 91 ESCC patients to predict CRT response. Kaplan–Meier analysis was used to estimate progression-free survival or time-to-progression of patients predicted with good and poor CRT responses. Nine differentially methylated CpG probes were identified to be associated with CRT response. A risk score equation comprising six CpG probes located in IFNGR2, KCNK4, NOTCH4, NPY, PAX6, and SOX17 genes were built. The risk score was derived from the sum of each probe multiplied by its corresponding coefficient. Such a risk score has a good prediction performance in discriminating poor CRT responders from good responders (AUC: 0.930). Moreover, poor CRT responders predicted by risk score significantly had poorer prognosis in terms of shorter progression-free survival and time-to-progression ($p = 0.004–0.008$). We established a proof-of-concept CRT response prediction panel consisting of six-CpG methylation biomarkers in identifying ESCC patients who are at high risk of CRT failure and need intensive care.

Keywords: CpG methylation biomarker; Chemoradiotherapy; Esophageal squamous cell carcinoma; Endoscopic ultrasonography; Prognosis.