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# Predictive biomarkers for response of esophageal cancer to chemo(radio)therapy: A systematic review and meta-analysis

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ABSTRACT

*Background:* Esophageal cancer remains a major public health issue worldwide. In clinical practice, chemo(radio)therapy is an important approach to patients with esophageal cancer. Only the part of patients who respond to chemo(radio)therapy achieve better long-term outcome. In this case, predictive biomarkers for response of esophageal cancer patients treated with chemo(radio)therapy are of importance. Meta-analysis of P53 for predicting esophageal cancer response has been reported before and is not included in our study. We performed a systematic review and meta-analysis to summarize and evaluate the biomarkers for predicting response to chemo(radio)therapy.

*Method:* PubMed, Web of Science and the Ovid databases were searched to identify eligible studies published in English before March 2017. The risk ratio (or relative risk, RR) was retrieved in articles regarding biomarkers for predicting response of esophageal cancer patients treated with neoadjuvant therapy or chemo(radio)therapy. Fixed and random effects models were used to undertake the meta-analysis as appropriate.

*Result:* Forty-six articles reporting 56 biomarkers correlated with the response were finally included. Meta-analyses were carried out when there was more than one study related to the reported biomarker. Results indicated that low expression of (or IHC-negative) COX2, miR-200c, ERCC1 and TS was individually associated with prediction of response. The RR was 1.64 (n = 202, 95% CI 1.22–2.19, $P < 0.001$), 1.96 (n = 162, 95% CI 1.36–2.83, $P < 0.001$), 2.55 (n = 206, 95% CI 1.80–3.62, $P < 0.001$) and 1.69 (n = 144, 95% CI 1.10–2.61, $P = 0.02$), respectively. High expression of (or IHC-positive) CDC25B and p16 was individually related to prediction of response. The RR was 0.62 (n = 159, 95% CI 0.43–0.89, $P = 0.01$) and 0.62 (n = 142, 95% CI 0.43–0.91, $P = 0.01$), respectively.

*Conclusion:* Low expression of (or IHC-negative) COX2, miR-200c, ERCC1 and TS, or high expression of (or IHC-positive) CDC25B and p16 are potential biomarkers for predicting the response of esophageal cancer patients treated with chemo(radio)therapy.



*Abbreviations:* ESCC, Esophageal squamous cell carcinoma; AC, Adenocarcinoma; TS, Thymidylate synthase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CYFRA21-1, Cytokeratin 19-fragments; CEA, Carcinoembryonic antigen; p53R2, Ribonucleoside-diphosphate reductase subunit M2 B; AFAP1-AS1, AFAP1 Antisense RNA 1; TP, Thymidine phosphorylase; NSE, 2-phospho-D-glycerate hydrolase; PITX2, Paired-like homeodomain transcription factor 2; PFTK1, Serine/threonine-protein kinase PFTAIRE-1; *p*-mTor, Phosphorylated mammalian target of rapamycin; IGFBP-3, Insulin-like growth factor-binding protein-3; SMAC, Second mitochondria-derived activator of caspase; JWA, ADP ribosylation factor like GTPase 6 interacting protein 5; SHH, Sonic hedgehog; MRP-1, multidrug-resistance protein 1; P-gp, P-glycoprotein.

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**Contents**



## 1. Introduction

Esophageal cancer remains a major public health issue worldwide. The overall survival of patients with esophageal cancer is poor, with a 5-year survival incidence of 20.9% [1]. Despite changes in therapeutic management over the past decades, most patients with esophageal cancer will eventually die as a result of their disease [2]. Adenocarcinoma (AC) is a dominant pathological type in the European and the North American countries, while esophageal squamous cell carcinoma (ESCC) is more common in Asian countries. In the USA and parts of Europe, neoadjuvant chemoradiotherapy is recommended as a standard treatment [3,4], whereas neoadjuvant chemotherapy has been recommended in Japan and UK [5]. However, only patients with esophageal cancer who undergo preoperative chemo/radiotherapy and obtain a major pathologic response have improved long term outcome [6,7]. Currently, about 40%–50% of patients, who receive chemo/radio therapy, show a major histopathological response [8]. In addition, those who did not respond well to these treatments, and whose prognosis would be inferior to surgery alone, may lose the option of surgical resection. Therefore, it is essential to identify predictive biomarkers for predicting the response of esophageal cancer patients to help select the appropriate cancer treatment.

Molecular biomarkers for predicting response to esophageal cancer can be classified into seven categories corresponding to tumor suppressors, cell cycle regulators, DNA repair molecules, drug resistance proteins, angiogenic factors, Hedgehog signaling molecules, and cell proliferation, invasion, and metastasis molecules [9]. While prognostic biomarkers are associated with prognosis, death or other clinical outcomes, predictive biomarkers are helpful to determine which patients are suitable for a particular type of therapy. The predictive biomarkers for breast cancer, lung cancer and brain tumors are well established, but reliable predictive biomarkers for esophageal cancer in the clinic is still unestablished. Studies related to predictive biomarkers for the esophageal cancer response to radio/chemotherapy are almost in qualitative measures. There are few studies that use quantitative measurements for analysis. Current clinical parameters are unable to predict responders or non-responders among esophageal cancer patients. P53 has been studied for predicting the response of esophageal cancer in many studies already [10]. Whether another biomarkers relate to esophageal response in quantitative are uncertain. Therefore, we did not include p53 in our meta-analysis. In this systematic review and meta-analysis, we summarize and evaluate potential predictive biomarkers to help find useable predictive biomarkers for clinical application.

## 2. Methods

### 2.1. Search strategy and database

A comprehensive search (using a combined text word and MeSH heading search strategy) was conducted in the PubMed, Web of Science, and OVID databases until April 2017. The following search terms were used: (esophageal neoplasms OR esophageal cancer) AND biomarkers, or (response OR predict) AND esophageal neoplasms, or (chemotherapy sensitivity OR chemoresistance OR radiotherapy sensitivity OR radioresistance) AND (esophageal OR esophagus) AND (cancer OR carcinoma OR adenocarcinoma OR SCC). Searching the reference lists of relevant articles and reviews was also performed manually.

Full papers were obtained and assessed by two independent authors, whose decision was blind to each other. In the process, data was extracted by one author. Any discrepancies were discussed by the authors together until a consensus was reached. Duplicate publications were identified by reviewing the article title, authors, study population and data. For multiple reports on the same study, only the latest publication was included. General information extracted from each study included the title, first author, publication year, number of patients, histology type, the prediction biomarkers, expression assessment methods and the multiple treatment types. The risk ratio (RR) was extracted to evaluate the biomarker's prediction value. A systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) [11].

### 2.2. Article inclusion criteria

All published literature associated with esophageal cancer was searched. Studies meeting the following criteria were included: (1) associated with biomarkers predicting response to esophageal cancer patients treated with chemo(radio)therapy; (2) the patients' biomarker expression and response were assessed; (3) the risk ratio or odds ratio of the response could be retrieved from the article directly or calculated with the provided information.

Article exclusion criteria were as follows: (1) not published in English or the full text was unavailable; (2) reviews, conference