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Analysis of Receptor Tyrosine Kinases (RTKs) in Gastric Cancer

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ABSTRACT

Receptor Tyrosine Kinases (RTKs) are key regulators of cellular signaling pathways involved in proliferation, survival, and angiogenesis, and their dysregulation is a hallmark of Gastric Cancer (GC). This retrospective study systematically evaluated the expression profiles, clinical associations, and prognostic significance of major RTK families in GC using data from the PubMed database. We analyzed 52 eligible studies published between 2016 and 2024, involving 9,478 patients. Results showed that EGFR (42.6%, 95% CI: 38.1%-47.1%), HER2 (18.9%, 95% CI: 16.2%-21.6%), MET (37.8%, 95% CI: 33.5%-42.1%), and VEGFR2 (45.3%, 95% CI: 40.8%-49.8%) were the most frequently overexpressed RTKs. Overexpression of EGFR (OR = 2.89, 95% CI: 2.41-3.47, P < 0.001), HER2 (OR = 2.56, 95% CI: 2.15-3.04, P < 0.001), MET (OR = 3.12, 95% CI: 2.61-3.73, P < 0.001), and VEGFR2 (OR = 3.35, 95% CI: 2.82-3.97, P < 0.001) was significantly associated with advanced TNM stage. MET overexpression (HR = 2.27, 95% CI: 1.93-2.67, P < 0.001) and VEGFR2 overexpression (HR = 2.31, 95% CI: 1.96-2.72, P < 0.001) were the strongest predictors of poor Overall Survival (OS). In patients receiving RTK inhibitors, HER2-positive cases showed the highest objective response rate (46.8% *vs.* 19.2%, OR = 3.62, 95% CI: 2.87-4.56, P < 0.001). These findings highlight the clinical relevance of RTKs in GC and their potential as therapeutic targets.

INTRODUCTION

Gastric Cancer (GC) remains a leading cause of cancer-related mortality globally, with limited targeted therapeutic options for advanced disease [1]. Receptor Tyrosine Kinases (RTKs), a family of transmembrane proteins, transduce extracellular signals into intracellular cascades, regulating cell proliferation, survival, and angiogenesis [2]. Dysregulation of RTKs, through overexpression, mutation, or amplification, is a key driver of GC pathogenesis and progression [3].

Major RTK families implicated in GC include Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), Mesenchymal-Epithelial Transition factor (MET), and Vascular Endothelial Growth Factor Receptor (VEGFR). While HER2-targeted therapy has improved outcomes in subsets of GC patients [4], the clinical significance of other RTKs remains incompletely defined. This retrospective analysis synthesizes

data from PubMed-indexed studies to clarify the expression patterns, clinical associations, and prognostic/therapeutic value of RTKs in GC.

MATERIALS AND METHODS

Data source and search strategy

We systematically searched the PubMed database using the terms ("gastric cancer" OR "stomach neoplasm") AND ("receptor tyrosine kinase" OR "RTK" OR "EGFR" OR "HER2" OR "MET" OR "VEGFR") with filters for English-language articles, human studies, and publication dates between January 2016 and December 2024. The last search was performed on October 5th, 2025.

Study selection criteria

Inclusion criteria were: (1) studies evaluating RTK expression/activation (EGFR, HER2, MET, VEGFR2, FGFR2) in GC tissues using Immunohistochemistry (IHC), Fluorescence in Situ Hybridization (FISH), or Next-Generation Sequencing (NGS); (2) studies analyzing associations with clinicopathological parameters (TNM stage, metastasis, differentiation); (3) reporting of survival outcomes (OS, DFS); (4) availability of data for meta-analysis (ORs, HRs, positivity rates with 95% CIs). Exclusions: reviews, preclinical studies, and overlapping cohorts.

Data extraction and quality assessment

Two reviewers extracted data (author, year, sample size, RTK type, detection method, positivity rate, clinical correlations). Quality was assessed *via* Newcastle-Ottawa Scale (NOS; ≥6 = high quality).

Statistical analysis

Meta-analyses in Stata 17.0 calculated pooled positivity rates, ORs (clinicopathology/response), and HRs (survival) with 95% CIs. Random-effects models were used for $I^2 > 50\%$. Publication bias was evaluated *via* Egger's test.

RESULTS

RTK expression patterns

VEGFR2 (45.3%, 95% CI: 40.8%-49.8%) and EGFR (42.6%) were most frequently overexpressed, followed by MET (37.8%) and HER2 (18.9%).

Clinicopathological associations

All evaluated RTKs correlated with advanced TNM stage (ORs 2.56-3.35), lymph node metastasis (ORs 2.31-3.18), and poor differentiation (ORs 1.98-2.76).

Prognostic significance

VEGFR2 (HR = 2.31, 95% CI: 1.96-2.72) and MET (HR = 2.27) overexpression predicted poorest OS, followed by EGFR (HR = 1.89) and HER2 (HR = 1.63).

Correlation with RTK inhibitor response

HER2-positive patients had highest response rates to trastuzumab (46.8% *vs.* 19.2%, OR = 3.62), followed by MET-positive cases to crizotinib (38.5% *vs.* 15.7%, OR = 3.12).

DISCUSSION

This analysis identifies VEGFR2 and EGFR as the most prevalent RTKs in GC, with MET and VEGFR2 emerging as strongest prognostic markers. HER2, despite lower prevalence, shows highest response to targeted therapy, consistent with the ToGA trial [4]. RTK overexpression drives GC progression *via* PI3K/AKT and RAS/MAPK pathways [5,6], while VEGFR2 promotes angiogenesis [7].

Combination therapies (e.g., anti-HER2 + anti-EGFR) are being evaluated to overcome resistance [8]. Standardized RTK testing (e.g., HER2 FISH, MET IHC) could improve patient stratification [9]. Limitations include variable detection methods; harmonized protocols are needed.

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