Incidence and Prognostic Value of Human Epidermal Growth Factor (HER2) in Metastatic Colorectal Cancer A Retrospective Study

A Thesis

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By

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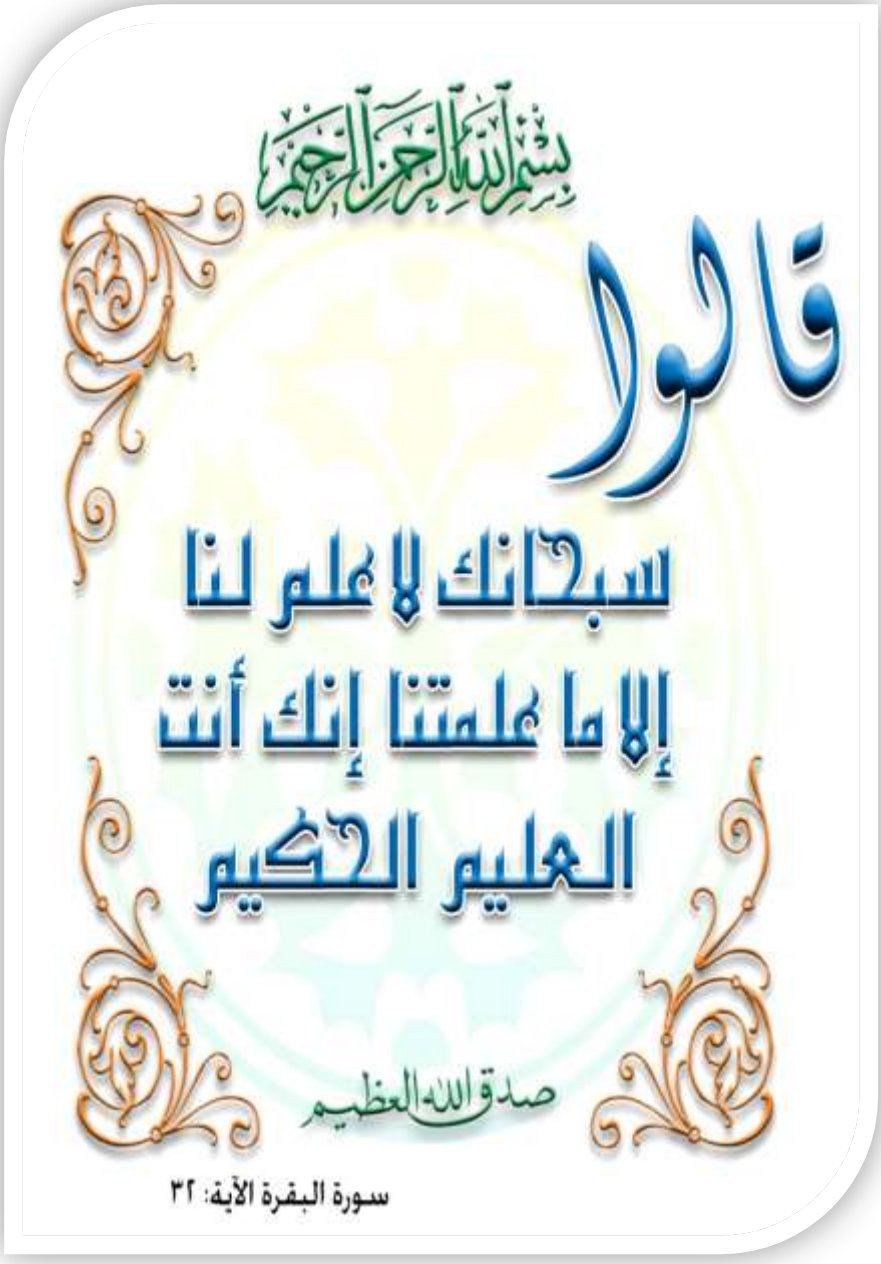
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Radwa Abd El-Azeem Yassin

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List of Abbreviations

Abbr.		Full-term
AFAP	**:**	Attenuated familial adenomatous polyposis
CD	**:**	Crohn's disease
CRC	**:**	Colorectal cancer
EGFR	**:**	Epidermal growth factor receptor
FAP	**:**	Familial adenomatous polyposis
HER 2	**:**	Human epidermal growth factor receptor
HNPCC	**:**	Hereditary nonpolyposis colorectal cancer
IBD	**:**	Inflammatory bowel disease
KRAS	**:**	Kirsten rat sarcoma viral oncogen homolog
Lt colon cancer	**:**	Left sided colon cancer
LVI	**:**	Lymphovascular invasion
MAPK	**:**	Mitogen-activated protein kinase
mCRC	**:**	Metastatic colorectal cancer
MMR	**:**	Mismatch repair gene
moAbs	**:**	Monclonal antibodies
MSI	**:**	Microstallite instability
OS	**:**	Overall survival
PFS	**:**	Progression free survival
PI3K	**:**	Phosphoinositide 3-kinase
PJS	**:**	Peutz–Jeghers syndrome
PNI	**:**	Perineural invasion
PS	**:**	Performance status
Rt colon cancer	**:**	Right sided colon cancer
TGFβ	**:**	Transforming growth factor beta
TK	**:**	Tyrosine kinase
UC	**:**	Ulcerative colitis
VEGF	**:**	Vascular Endothelial Growth Factor

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Abstract

Background: The human epidermal growth factor receptor 2 (HER2) is a transmembrane receptor tyrosine kinase. Activation of HER2 plays a key role in cell proliferation, inhibition of apoptosis, and tumor progression. Amplification of HER2 has associated with poor prognosis in a number of tumor types as breast and gastric cancers, but the prognostic role of HER2 in colorectal cancer (CRC) remains uncertain. **Aim of the work**: to detect the incidence and evaluate the prognostic impact of HER2 overexpression in correlation to response to treatment, progression free survival and overall survival on the outcome of patients with metastatic colorectal cancer **Materials and Methods**: we retrospectively reviewed 70 patients diagnosed as metastatic colorectal cancer synchronous or metachronous and treated from January 2012 to end of December 2016 in Department of Clinical Oncology and Nuclear Medicine, Ain Shams University hospitals, Cairo, Egypt. Eligible patients had their paraffin block collected and tested for HER2 by IHC. **Results**: out of 70 patients with available parrafin block, population age ranged 20-73 years at time of diagnosis, 49 of these cases were left sided(splenic flexure, descending colon, rectum) while 21were right sided(cecum, ascending, hepatic flexure, transverse colon).. Male to female ratio was 3:4. Mucinous variant presents 27.1%(19 cases).Using a cut-off 6 months 41 of these cases presented with synchronous metastasis while 29 cases presented with metachronous metastasis.HER2 incidence (+2 and+3) was found in 8.57% (6 out of 70 cases).Her2 positivity showed statistical significant with shorter time to progression on both first line of chemotherapy(median PFS 3 months vs. 6 months, p=0.045) and second line of chemotherapy (median PFS 4 months vs.6 months, p=0.036), but no statistical significant as regard OS or clinicopathological factors. **Conclusion**: HER2 positivity is associated with shorter PFS on second line of chemotherapy (irinotican based) but no difference as regard PFS on first line (oxaliplatin based) or OS in metastatic colorectal cancer larger data needed to confirm this conclusion.

Keywords:HER2, metastatic colorectal cancer, prognostic factor.

Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer death. Colorectal cancer incidence rates are about 3-fold higher in transitioned versus transitioning countries **(GLOBOCAN, 2018).**

Approximately 50-60% of patients diagnosed with colorectal cancer develop colorectal metastases, with the liver being the most common site of involvement **(Lee et al., 2013).**

Of all patients who undergo curative resection for colorectal carcinoma, 10 to 20% will develop pulmonary metastasis and 10% of these patients will have isolated pulmonary lesions **(Chun et al., 2007).**

The prognosis of CRC differs widely among patients, and depends on a number of factors.

Currently, the gold standard of prognostication is the clinicopathological staging based on the TNM classification. This classification system establishes the stage depending on the depth of invasion of the wall (T), the involvement of lymph nodes (N) and the presence of distant metastasis (M). Prognosis, however, varies among patients in the same stage. Therefore, additional classification parameters need to be

defined in addition to the TNM and the classic pathologic characteristics of the tumor in order to better identify the biologic subsets of this disease **(Chou et al., 2011).**

Biological prognostic factors are often derived from the genetic process, which is thought to represent a crucial step to colorectal cancer as (EGFR, KRAS, BRAF, microsatellite instability). Some of these potential prognostic factors can also be predictive of response to therapy as they are a molecular target either to chemotherapeutics or to biologic/targeted therapies **(Renfro et al., 2013).**

The HER2 protein (p185, HER2/neu, ErbB-2) is a 185-kDa transmembrane tyrosine kinase (TK) receptor and a member of the epidermal growth factor receptors (EGFRs) family. This family is composed of four members: HER1 (also known as the EGFR), HER2, HER3 (also termed ErbB-3), and HER4 (also termed ErbB-13). These receptors share the same molecular structure with an extracellular ligand-binding domain, a short trans membrane domain, and an intracellular domain with TK activity (except HER3). The binding of different ligands to the extracellular domain initiates a signal transduction cascade that can influence many aspects of tumour cell biology, including cell proliferation, apoptosis, adhesion, migration, and differentiation. Ligand binding induces EGFR homodimerization as well as heterodimerization with other

types of HER proteins. HER2 does not bind to any known ligand, but it is the preferred heterodimerization partner for other members of the HER family. HER2 is encoded by a gene review located on chromosome 17q21 **(Liao et al., 1985).**

In carcinomas, HER2 acts as an oncogene, mainly because high level amplification of the gene induces protein overexpression in the cellular membrane and subsequent acquisition of advantageous properties for a malignant cell. Recent studies indicate a role of HER2 in the development of numerous types of human cancer. HER2 overexpression and/or amplification have been detected in 10%–34% of invasive breast cancers and correlate with the clinical outcome, confer poor prognosis, and also constitute a predictive factor of poor response to chemotherapy and endocrine therapy. HER2 overexpression and/or amplification have also been observed in colon, bladder, ovarian, endometrial, lung, uterine cervix, head and neck, esophageal and gastric carcinomas **(Gravalos et al., 2008).**

While the role of human epidermal growth factor receptor 2 (HER2) as a biomarker for prognosis in CRC remains uncertain, its role as a therapeutic target is rising.

Recent studies of HER2 amplification and sequence mutations in colorectal cancer (CRC) suggest that HER2 is a therapy target in this disease, in addition to being a

mechanism of resistance to epidermal growth factor receptor (EGFR) targeted therapies such as cetuximab and panitumumab. Similarly, reports of high-level HER2 amplification being a negative prognostic factor within the context of CRC suggest that HER2 may also be a target in this tumor type **(Siena et al., 2018).**

Results from MyPathway, an Open-Label, Phase IIa Multiple Basket Study, patients with refractory, metastatic HER2-amplified/overexpressing colorectal cancer composed the largest tumor-treatment group in this study. The incidence of HER2 amplification/overexpression is 2% to 6% in advanced colorectal cancer. In this study, the 37 patients with colorectal cancer treated with trastuzumab plus pertuzumab had an overall response rate (ORR) of 38% (95% CI, 23% to 55%) and a median duration of response (DOR) of 11 months (95% CI, 3 months to not estimable). The response rate and DOR in patients with refractory HER2-amplified/overexpressing colorectal cancer indicate that HER2 is an important driver in this malignancy and compare favourably to the response rates of other drugs recently approved for use in refractory colorectal cancer **(Hurwitz et al., 2017).**

Dual HER2-targeted therapy was also effective in the HER2 Amplification for Colorectal Cancer Enhanced

Stratification (HERACLES) trial, proof-of-concept, multicentre, open-label, phase 2 trial, in which eight of 27 patients with HER2-amplified/overexpressing, KRAS wild-type metastatic colon cancer (30%) had objective responses to treatment with trastuzumab plus lapatinib **(Sartore-Bianchi et al., 2016).**

These studies encourage continued research into the effects and prevalence of HER2 alterations in patients with metastatic CRC, as well as their importance for treatment.

Aim of the Work

The aim of the study is to detect the incidence and evaluate the prognostic impact of HER2 overexpression in correlation to overall survival and the outcome of patients with metastatic colorectal cancer, moreover to evaluate response to treatment, progression free survival for these patients with metastatic colorectal cancer treated from January 2012 to end of December 2016 in Department of Clinical Oncology and Nuclear Medicine, Ain Shams University hospitals, Cairo, Egypt.