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Anti-Epithelial Growth Factor Receptors for Prognosis in Management of Metastatic Colorectal Cancer

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ABSTRACT
Background: Up to 60% to 80% of colorectal cancer (CRCs) exhibit epithelial growth factor receptors (EGFR). EGFR promotes cancer in a number of ways, some of which include cell cycle disruption and others that involve signaling through a variety of downstream pathways.
Objective: The aim of the current study is to evaluate the role of Anti-Epithelial Growth Factor Receptors (Anti-EGFR) in management of metastatic colorectal cancer.
Patients and methods: A comparative study was conducted in Medical Oncology Departments in Zagazig University and Maadi Military Hospital including all metastatic colorectal cancer patients from January 2016 to January 2018, with total of 186 patients. All patients were evaluated regarding epidemiological data and response to treatment and survival analysis. **Results:** Median overall survival of whole studied samples (N=186 patients) was 22 months and was higher in patients receiving Anti-EGFR. Among the studied group, patients with wild Kirsten rat sarcoma virus (KRAS) were 73 patients out of which 47 (64.3%) patients received anti–EGFR and chemotherapy and 26 (35.6%) received chemotherapy alone, with overall survival 32 vs. 27 months (P=0.217) and progression free survival 9 vs. 8 months (P=0.824), respectively. Overall survival had significant correlations with receiving previous adjuvant treatment (P=0.001), resection of primary tumor (P=0.001), and site of metastasis with lymph nodes metastasis showing best overall survival up to 39 months (P=0.02). **Conclusion:** Anti-EGFR was beneficial in improving progression-free survival and response rates and overall survival for patients with metastatic colorectal cancer.
Keywords: Anti-Epithelial Growth Factor Receptors, Metastatic Colorectal Cancer, Kirsten rat sarcoma virus.

INTRODUCTION

The prevalence and death from colorectal cancer varies greatly across region ns. According to the World Health Organization, there were 1.8 million new cases of colorectal cancer and roughly 861,000 deaths worldwide in 2018. This makes it the third most commonly diagnosed cancer in males and the second most commonly diagnosed cancer in females. Men have much greater rates than women do. Both the rate of occurrence and the number of fatalities have been declining in the United States [(1)].

On average, there are 145,600 new instances of large bowel cancer each year, with colon cancer accounting for 101,420 and rectal cancer for the remaining cases [(2)].

Up to 60% to 80% of colorectal cancers express EGFR. EGFR promotes cancer through a variety of methods, including disruption of the cell cycle and the upregulation of tumour survival factors [(3)].

Given EGFR's possible essential involvement in cancer, many research groups have successfully developed neutralizing antibodies or kinase inhibitors. Monoclonal antibodies cetuximab and panitumumab have garnered a lot of attention [(4)].

Cetuximab and panitumumab block ligand-dependent activation and receptor dimerization by binding the extracellular domain of EGFR. Antibody-dependent cell-mediated cytotoxicity is another potential mechanism of action for cetuximab in inducing an immunological response [(5)].

Comparison of tumour responses between wild-type and mutant Kirsten rat sarcoma virus (KRAS) cells. Resistance to EGFR inhibitors was shown in tumours with KRAS mutations leading to a constitutively active GTP-binding protein [(6)].

The aim of the current study is to evaluate the role of Anti-Epithelial Growth Factor Receptors (Anti-EGFR) in management of metastatic colorectal cancer.

PATIENTS AND METHODS

This is a retrospective comparative analysis of how Anti-EGFR has been used to treat advanced colorectal cancer. From January 2016 to January 2018, a total of 186 patients with metastatic colorectal cancer were treated in the Medical Oncology Departments at Zagazig University and Maadi Military Hospital.

Primary end point: Progression free survival (PFS).
Secondary end point: Overall survival (OS).
Inclusion criteria:

1) Age more than 18 years old.
2) Pathologically proved colorectal cancer.
3) Metastatic disease.
4) Performance status: 0-2.
5) Available complete data.

Exclusion criteria:

1) Other malignancies.
2) Performance status: >2.

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All patients were evaluated for:

1) History.
2) Physical Examination.
3) Routine Laboratory Workup: CBC, kidney function tests, liver function test, CEA.
4) Radiological Workup: CT Chest, CT abdomen and pelvis.
5) Clinical and demographic data: Age, gender, residence, body mass index , performance status, site of primary tumour, previous adjuvant treatment, resectibility of primary tumour, site of metastasis, type of metastasis (synchronous or metachronous), KRAS status, BRAF status when available, receiving anti-EGFR and response to treatment, progression free survival and overall survival.

The systemic therapy used was either FOLFIRI or FOLFOX-4 with or without anti-EGFR as follow:

FOLFIRI plus (anti-EGFR):

On day one, the standard protocol calls for an infusion of 180 mg/m 2 of irinotecan over 30 minutes to an hour, followed by an infusion of 400 mg/m 2 of leucovorin over the same time period additionally 5FU Total of 2400 mg/m 2 administered over 46-48 hours; 400 mg/m 2 IV bolus on day 1, then 1200 mg/m 2 daily for 2 days.

Consistent infusion; repeat every two weeks. In the event of Cetuximab 500 mg/m 2 IV over 2 hours were given every 2 weeks. Patients received FOLFIRI were 62 patients, 10 patients of them received panitumumab, no patients received cituximab with FOLFIRI.

FOLFOX-4 plus (anti-EGFR):

- **Day 1**: Oxaliplatin (IV) 85 mg/m2 and leucovorin (IV) 200 mg/m2 over 120 minutes, followed by 5-fluorouracil (IV) 400 mg/m2 bolus given over 2–4 minutes, followed by 5-fluorouracil (IV) 600 mg/m2) over 22-hour continuous infusion.
- **Day 2**: Leucovorin 200 mg/m2 IV infusion over 120 minutes, followed by 5-fluorouracil (FU) 400 mg/m2 IV bolus over 2–4 minutes, followed by 5-FU 600 mg/m2 IV infusion over 22 hours of continuous infusion.
- Cetuximab 500mg/ m ^{2} IV over 2 hours or panitumumab dose is 6 mg /KG and adminstered like that of cituximab and received every 2 weeks.

Patients received FOLFOX-4 were 124 patients out of which 37 patients received anti-EGFR, 25 patients received Cituximab and 12 received panitumumab.

Ethical Approval

The Ethical Institutional Review Board at Zagazig University approved the study. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Pearson Chi-Square test and Chi-Square for Linear Trend were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test was used for comparison between groups. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

K-RAS status was done to 117 patients. Out of 117 patients, 73 were wild type and 44 were mutant. 47 patients out of 73 wild profile patients received anti-EGFR with 5FU- based chemotherapy, out of 47 patients 30 patients received panitumumab and 17 patients received cetuximab. Chemotherapy received was either FOLFOX-4 received by 124 patients or FOLFIRI received by 62 patients.

Table 1 shows that **t**he majority of patients were with age mean 59 years, with higher incidence in males than females 109/186 (58.6%) vs. 77/186 (41.4%) respectively. About 82.3% were with performance status 1 vs. 17.7% with performance status 2.

Table (1): Sociodemographic and clinical characteristics of the studied cases.

Variable		No. = 186	
Age	Mean ± SD	58.70 ± 12.99	
	Range	22 – 81	
	≤ 59	78	41.9%
	> 59	108	58.1%
Sex	Male	109	58.6%
	Female	77	41.4%
Residence	Urban	123	66.1%
	Rural	63	33.9%
BMI	Mean ± SD	26.94 ± 4.86	
	Range	18.7 – 40.6	
	Normal	67	36.0%
	Abnormal	119	64%
ECGOG	1	153	82.3%
	2	33	17.7%
CEA initial	Mean ± SD	6.25±1.5	
Site of 1ry tumor	Left colon-Rectal	147	79.0%
	Right colon	39	21.0%
Previous adjuvant treatment	Yes	60	32.3%
	No	126	67.7%
Resected 1ry tumor	Yes	117	62.9%
	No	69	37.1%
Site of metastasis	Liver	52	28.0%
	Lung	7	
	LNS	22	11.8%
	Peritoneal deposits and adnexa	11	5.9%
	Others(brain or bone)	3	1.6%
	Multiple sites	91	48.9%
Type of metastasis	Synchronous	124	66.7%
	Metachronous	62	33.3%
K-RAS	Wild	73	39.2%
	Mutant	44	23.7%
	Not reported	69	37.1%
BRAF status	Wild	14	7.5%
	Mutant	1	0.5%
	Not reported	171	91.9%
Received Anti EGFR+5FU based chemotherapy	Received	47	25.3%
	Not received	139	74.7%
Response to treatment	Progressive course	97	52.2%
	Stationary course	86	46.2%
	Partial response	3	1.6%

Table 2 shows that the two groups did not differ significantly in terms of age, sex, BMI, performance status, or initial CEA value. There was a statistically significant difference between them in terms of where they lived,

Table (2): Association between K-RAS status and sociodemographic and clinical data of the studied patients.

Variable		Wild K-RAS No. = 73		Mutant K-RAS No. = 44		P-value
Age	Mean ± SD Range	56.07 ± 13.40 22 – 79		56.59 ± 13.22 22 – 77		0.838
	<=59 >59	36 37	49.3% 50.7%	20 24	45.5% 54.5%	0.686
Sex	Male Female	41 32	56.2% 43.8%	24 20	54.5% 45.5%	0.864
BMI	Mean ± SD Range	27.00 ± 5.00 19.1 – 39.1		26.96 ± 5.00 19.3 – 40.3		0.970
	Normal Abnormal	28 45	38.4% 61.6%	17 27	38.6% 61.4%	0.950
Residence	Urban Rural	54 19	74.0% 26.0%	22 22	50.0% 50.0%	0.008
ECGOG	1	64	87.7%	38	86.4%	0.838
	2	9	12.3%	6	13.6%	
CEA initial	Mean ± SD	5.70 ±1.35		5.90 ± 1.36		0.948
Site of 1ry tumor	Left colon	64	87.7%	36	81.8%	0.384
	Right colon	9	12.3%	8	18.2%	
Previous adjuvant treatment	Yes	24	32.9%	12	27.3%	0.525
	No	49	67.1%	32	72.7%	
Resected 1ry tumor	Yes	48	65.8%	29	65.9%	0.956
	No	25	34.2%	15	34.1%	
Site of metastasis	Liver	21	28.8%	11	25.0%	0.586
	Lung	3	4.1%	1	2.3%	
	LNS	13	17.8%	4	9.1%	
	Peritoneal deposits and adnexa	3	4.1%	2	4.5%	
	Others (brain or bone)	1	1.4%	0	0.0%	
	Multiple site metastasis	32	43.8%	26	59.1%	
Type of metastasis	Synchronous	49	67.1%	30	68.2%	0.906
	Metachronous	24	32.9%	14	31.8%	
Response to treatment	Progressive course Stationary course Partial response	32 40 1	43.8% 54.8% 1.4%	26 17 1	59.1% 38.6% 2.3%	0.236

P >0.05: Non significant; P ≤0.05: Significant; P ≤0.01: Highly significant. •: Independent t-test; *: Chi-square test.

In wild group of patients median PFS was 9 months with range 2-30 months, while it was 10 months with range 3-20 months in mutant group with no significant association. While median OS was higher in wild group with 20 months with range of 11-32 months versus 18.5 months with range 12-24 months in mutant group, with no significant relation (Table 3).

Table (3): Association of K-RAS status with progression free survival and overall survival.

Variable		Wild K-RAS No. = 73	Mutant K-RAS No. = 44	P-value
PFS (months)	Median (IQR) Range	9 (7 – 12) 2 – 30	10 (8 – 13) 3 – 20	0.544
OS (months)	Median (IQR) Range	20 (11 - 32) 4 – 51	18.50 (12 - 24) 7 – 39	0.426

As shown in Table 4, patients with wild KRAS who received anti-EGFR plus 5FU based chemotherapy had median overall survival 32 months vs. 27 months for those who received 5FU based chemotherapy alone denoting the role of anti-EGFR in improving OS (P=0.217).

Table (4):- Association between anti-EGFR and overall survival in patients with wild KRAS gene.

Wild		Total N	OS (months)		95% CI		P-value
			Median	SD	Lower	Upper	
Received Anti EGFR+5FU based chemotherapy	Received	47	32	8.325	19.096	44.904	0.217
	Not received	26	27	7.74	14.829	45.171	

Table 5 shows that patients with wild KRAS who received anti-EGFR plus 5FU based chemotherapy had median PFS 9 months vs. 8 months for those who received 5FU based chemotherapy alone denoting the role of anti-EGFR in improving PFS (P=0.824).

Table (5): Relation between anti-EGFR and progression free survival in patients with wild KRAS gene.

Wild		Total N	PFS (months)		95% CI		P-value
			Median	SD	Lower	Upper	
Received Anti EGFR + 5FU based chemotherapy	Received	47	9	0.623	7.779	10.221	0.824
	Not received	26	8	1.02	6.001	9.999	

DISCUSSION

Colorectal cancer is the third most common cancer worldwide according to GLOBOCAN 2018 database [(7)]**.** In Egypt, colorectal cancer usually present at an advanced stage and predisposing adenoma are rare [(8)]**.**

As regard age the mean age of the studied group was 58.70 (SD 12.99) years**,** this was consistent with a descriptive cross-sectional hospital-based study in Egypt stated that The mean age was 51 (SD 15) years (age range: 16–80 years) [(9)], but worldwide, the mean age was around 8 years younger than the mean age in our study [(10)]**.**

Our study's gender distribution indicated a comparable male to female split (58.6% to 41.4%, respectively) to that found in a JAMA report from the Austrian Society for Gastroenterology and Hepatology, which found that men across all age categories had greater rates of advanced colorectal cancers than women [(11)]**.**

Our study showed higher number of patients from urban residence 123/186 (66.1%) vs. 63/186 (33.9%) from rural residence, these findings were similar to Gharbiah Cancer Registry findings in Egypt which analysed data of colorectal cancer since 1999 to 2007, 55% of patients diagnosed with colorectal cancer lived in urban regions, compared to 45% of patients diagnosed with the disease in rural areas [(12)]**.**

Our study included 153/186 patients (82.3%) with performance status 1 vs. 33/186 patients (17.7%) with performance status 2, similar to a prospective Finnish nationwide study initiated in 2011, with 1086 mCRC patients enrolled, showed ECOG score 1 in (55%) and 2 in (18%) [(13)]**.**

Initial CEA value in our study showed median CEA 6.25 ng/mL range (0-5659) at time of diagnosis, while using information gathered in the future to inform present decisions. The average baseline CEA level for 395 patients who underwent radical treatment for colorectal carcinoma was 7.51 ng/mL (range 0-157.6 ng/mL) [(14)]. This difference may be due to the higher number of patients than our study.

Similar to a retrospective analysis of two randomized controlled clinical trials carried out by the Dutch Colorectal Cancer Group (CAIRO and CAIRO-2), we found that 117/186 (62.9%) of patients who underwent surgical resection of primary tumour compared to 69/186 (37.1%) of patients who did not undergo resection of 1ry tumour [(15)].

As regards the site of metastases in our study multiple site metastasis 91/186 (48.9%) were most common but if we consider single site metastasis liver

comes in first place with 52/186 (28.0%) and bone metastasis come in last place with 3/186 (1.6%), these results were comparable to what was found by ***Van der Geest*** stating that the most common sites of metastases in metastatic colon cancer were liver (70%) and the least was in bone (12%) [16].

Synchronous metastasis in our study were found in 124/186 (66.7%) of patients while metachronous metastasis occurred in 62/186 (33.3%) of patients, while **Hayashi *et al.*** [17] reported that 34% of patients with MCRC present with synchronous metastases. This may be due to late diagnosis of patients in our study compared to study documented by **Hayashi and his colleagues**[17].

Van Cutsem *et al.* [18] stated that BRAF mutations were 8% to 12% of patients with mCRC, while in our study out of 15 patients tested for BRAF mutation only 1/15 (6.6%) showed mutated type. This may be due to unavailability of BRAF testing for all patients.

Among whole patients in our study 47/186 (25.3%) of patients received 5FU based chemotherapy plus anti-EGFR vs.139/186 (74.7%) of patients received 5FU based chemotherapy alone.

Responses to treatment in our study occurred as follows, 97/186 (52.2%) of patients showed progressive course while86/186 (46.2%) of patients showed stationary course and 3/186 (1.6%) of patients showed partial response**,** Among patients with metastatic colorectal cancer who were treated in a retrospective cohort study approved by the Institutional Review Board at a single outpatient cancer centre, 50.7% had a partial response, 20% had stable illness, and 29.3% showed progressive progression [19]**.** This difference in response may be due to earlier diagnosis, better performance status in studied group and better following of treatment program and guidelines.

Similarly, a retrospective research of 120 patients diagnosed with MCRC between January 2013 and March 2017 at the Medical Oncology Unit of the University of Palermo reported a median PFS of 8.5 months (range 4-23 months) for this patient population [20]**.**

In a Norwegian study, the frequency of K-RAS mutations was significantly related to sex of the patients (P=0.008). K-RAS mutations were much less frequent in colonic tumours in male than female patients at younger ages (<40 years, odds ratio <0.014). In contrast, elder men had more mutations than elder women (e.g. 90 years, odds ratio = 5.8) [21]**.** While in our study, in wild group 41/73 (56.2%) were males vs. 32/73(43.8%) females, while in mutant group 24/44 (54.5%) were males vs. 20/44 (45.5%) females denoting mild increasing incidence percentage of wild profile with males more than in mutant group (P=0.864) but it was not significant.

In our study, regarding KRAS and residence status correlation there is highly significant relation between urban residence and wild KRAS profile as 54/73 (74%) of patients were of urban residence vs. 19/74 (26%) of rural residence (P=0.008), while it shows significant increase in the prevalence of mutant in rural areas (50 %). Eligible cases were identified as New Mexico citizens diagnosed with CRC, and of those with stage IV CRC who were tested for KRAS mutation, 43.3% were positive. When comparing wild-type to mutant prevalence rates across regions, no significant changes were found (P=0.205) [22]**.**

A Study done in China showed that KRAS mutations were more frequently observed in patients with preoperatively elevated serum CEA levels compared to that in normal patients (46.6% vs. 35.0%, P<0.05) [23], while initial CEA median value in our study was 5.7 ng/mL in wild group comparing to 5.9 ng/ml in mutant group with no significant difference (P=0.948).

KRAS status in relation to sidedness of the tumour in our study showed that out of 73 patients with wild KRAS 64/73 (87.7%) were of left-sided colon cancers and 9/73 (12.3%) were of right colon cancers while in mutant group of patients 36 patients out of 44 (81.8%) were of left-sided colon cancer and 8/44 patients (18.2%) were of right colon cancers (P=0.384). While the database of Fujian Provincial Hospital (Fuzhou, China), showed the mutation rate of KRAS was different between primary tumour sites. Compared with that of the left-sided colon, the right colon presented with a significantly greater number of KRAS mutations (47.2% vs. 35.5%, P<0.05) [23]. This difference may be due to racial differences.

In our study, regarding response to treatment in wild group stationary course was achieved in 40/73 (54.8%) of patients vs. 17/44 (38.6%) of patients in mutant group while progressive response occurred in higher percentage of mutant group patients 26/44 patients (59.1%) vs. 32/73 (43%) of wild group and partial response occurred in mutant group in 1/44 (2.3%) patient vs. 1/73 (1.4%) patient of wild group with no statistical difference (P=0.236)

Our study showed that KRAS status in patients who had tested in (117 patients) revealed significant relation with overall survival as patients with wild KRAS status had median overall survival 39 months vs. 21 months for those with mutant KRAS (P=0.015), similar to results of **Dinu *et al.*** [24].

PRIME (phase 3; NCT00364013) compared panitumumab plus FOLFOX versus FOLFOX alone results showed that patients with left-sided wild-type tumours, panitumumab plus 5FU based chemotherapy provided better outcomes than the comparator treatment (5FU based chemotherapy alone), regarding median overall survival (30.3 versus 23.6 months, adjusted hazard ratio = 0.73, P=0.0112) [25]**,** while our study showed that patients with wild KRAS who received

anti-EGFR plus 5FU based chemotherapy had median overall survival 32 months vs. 27 months for those who received 5FU based chemotherapy alone denoting the role of anti-EGFR in improving overall survival but with insignificant (P=0.217).

CONCLUSION

Anti-EGFR was beneficial in improving progression-free survival and response rates and overall survival for patients with metastatic colorectal cancer.

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