Study on Prognostic Implications of HER2/Neu Expression in Colorectal Cancer in Eastern India

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ABSTRACT

BACKGROUND

Colorectal cancer (CRC) is the third most common malignancy with high mortality rate and majority of them are diagnosed with endoscopic biopsy. Further, it requires markers to predict survival and treatment. Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity. Its gene amplification and over expression play an important role in the development and progression of certain cancer types. Targeted therapy against HER2/neu positive cases is well-established in breast and gastric carcinoma but its prevalence and significance in colon cancer is not well documented. We wanted to evaluate the commonest location of colorectal cancer, its prevalence as per age, sex, morphological type, and expression of HER2/neu by immunohistochemistry (IHC).

METHODS

A total of 84 paraffin wax embedded colonoscopy biopsies were studied which comprised of neoplastic lesions, out of which 46 cases of CRC were studied for HER2/neu IHC and scoring was done according to the ASCO/CAP (American Society of Clinical Oncology / College of American Pathologists) for HER2 Test guideline recommendation 2013.

RESULTS

The commonest cancer was adenocarcinoma NOS type; predominantly seen in the left side of colon; in patients over of 50 years of age with male preponderance. Out of 46 cases included for IHC, expression of HER2/neu with positive score 3+ (6.52%), having cytoplasmic and membranous staining was seen in moderately and poorly differentiated adenocarcinoma. Equivocal score 2+ (26.09%) with membranous staining was found in moderately differentiated adenocarcinoma.

CONCLUSIONS

Due to prominent membranous staining in higher stages and grades of colorectal cancer, Herceptin therapy could be helpful in patients with distant metastasis.

KEYWORDS

Colorectal Carcinoma (CRC), Colonoscopy Biopsy, Adenocarcinoma, Immunohistochemistry HER2/neu

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DOI: 10.18410/jebmh/2020/299

How to Cite This Article:
Mohanty M, Mohapatra D. Study on prognostic implications of HER2/Neu expression in colorectal cancer in Eastern India. J. Evid. Based Med. Healthc. 2020; 7(29), 1414-1419. DOI: 10.18410/jebmh/2020/299

Submission 04-05-2020,
Peer Review 09-05-2020,
Acceptance 07-06-2020,
Published 20-07-2020.

BACKGROUND

Worldwide digestive diseases are common in population and can range from mild to severe, acute to chronic, and can be benign or malignant. Colorectal cancer (CRC) is the third most common cancer in men worldwide and second most common in women.[1,2] The incidence rates of CRC is highest in Europeans countries and lowest in Africa.[3] The developed Asian countries show high incidence rates than the South Asian countries.[1,3] In the Indian scenario the incidence is the lowest.

Colorectal cancer usually occurs at a higher age, the risk increasing after the age of 50 years. However, in India the rectal cancer is more common than colon and the incidence is common in the urban sector.[4] The cause of CRC is related to environmental and genetic factors.[5,6] the former are dietary in origin, particularly animal protein. Evidence for decreased risk was found for physical exercise, dietary fiber, calcium, garlic, non-starchy vegetables and pulses. Evidence for increased risk was uncovered for obesity, red meat, processed meat; animal fat, alcohol, sugar and long-term smoking.[7] Patient in older age group have a poorer survival rate than younger ones. The site of the tumor has been investigated as a possible prognostic factor. Patients with colon cancer are considered to have a better survival than those with rectal cancer.[8,9] The proto-oncogene HER2/neu is localized to chromosome 17 q and encodes a transmembrane tyrosine kinase growth factor receptor; a component of four-member family receptors including epidermal growth factor (EGFR), HER-3 and HER-4.[10] In normal cells, activation of this receptor controls normal cell growth, differentiation and motility.[11] Dysregulation of the EGFR pathway by mutation, over expression, or EGFR stimulation by an excess in growth factors promotes growth and progression of many tumors, including CRC.[12] It is reported that 50% to 70% of colorectal cancers exhibit EGFR expression, but as yet there is no conclusive evidence with regard to the role of EGFR as a prognostic marker. The expression of HER2/neu has been studied in prostate, ovarian and lung cancers as well as in several forms of gastrointestinal malignancies including colorectal cancer.[13,14] The latter has reported HER2/neu over expression rate ranging from 4% to 83%[15] is significantly associated with tumor grade. The most promising monoclonal antibody targeting EGFR is cetuximab causing direct inhibition of tyrosine kinase activity and blockade of the EGFR signaling pathways, which results in pro apoptotic and anti-invasive effects.[16]

METHODS

The present study is a prospective study undertaken from July-2013 to Oct-2015, in the Department of Pathology, Institute of Medical Sciences & Sum Hospital, Bhubaneswar, which is a tertiary care Hospital and a referral center for cancer for Easter India.

After obtaining a well-informed consent, all patients were subjected for a thorough clinical examination with detailed clinical history. Endoscopy was done by using a flexible forward viewing video endoscope. Four to six biopsies were taken and fixed in 10% buffered formalin and processed routinely. Cases with histopathological diagnosis of colonic adenocarcinoma were prepared for IHC (HER2/neu) examination using automated Benchmark ultra-system Ventana 4B5 antibody. A total number of 84 colonoscopy biopsy lesions with diagnosis of colon carcinoma was received which was confirmed by histopathology and 46 of them were subjected to immunohistochemistry HER2/neu. Different spectrum of cancer as per site and types (table 1), HER2/neu score according to site (table 2) and HER2/neu score according to histological type (table 3) were taken into the study. The cases which had received prior chemotherapy were excluded.

Scoring

Evaluations of the results were done according:
American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) FOR HER2 Test Guideline Recommendations 2013[17]

Score	Staining	
0	Negative	No staining is observed or any membranous reactivity that is incomplete and is barely perceptible and within in ≤ 10% of the of the tumor cells
1 +	Negative	Incomplete membrane staining that is faint/ barely perceptible and within>10% of tumor cells
2+	Equivocal	Circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of tumor cells OR complete and circumferential membrane staining that is intense and within ≤ 10% of tumor cells
3+	Positive	Circumferential membrane staining that is complete, intense and within > 10% of tumor cells

RESULTS

From the 84 cases of colonoscopy biopsy studied the incidence of cancer in left side of colon was found to be more than the right side and predominance was seen in male population (59.52%). The median age was found to be 50-60 years in both sexes.

Site	Adenocarcinoma	Mucinous	Signet Ring Type	Basaloid	Adenosquamous
Colon	28 (32.09%)	7 (8.3%)	1 (1.19%)	0	0
Rectum/ Anorectum	30 (35.71%)	13 (15.47%)	2 (2.38%)	3 (3.57%)	2 (2.46%)
Total	57 (67.8%)	19 (22.6%)	3 (3.57%)	3 (3.57%)	2 (2.46%)

Table 1. Morphology of Carcinoma as per Site and Type (n=84)

The commonest type of cancer was found to be of a morphology is adenocarcinoma, NOS (67.8%) followed by mucinous adenocarcinoma (22.6%), signet ring type (3.57%) and basaloid type (3.57%) and is adenosquamous

was least common occurring in 2.46%. The commonest location was rectum (59.52%) followed by right side colonic

HER2/neu Expression at Site	HER2/neu Positive & Equivocal		HER2/neu Negative		Total	
	n	%	n	%	n	%
COLON	6	13.04	13	28.26	19	41.30
RECTUM / ANORECTUM	9	19.57	18	39.13	27	58.70
Total	15	32.61	31	67.39	46	100.00

Table 2. Distributions of HER2/neu Scores According to Site of Lesion (n=46)

Positive score of HER2/neu (2+& 3+) were found in 32.61% of CRC whereas HER2 negative expression (Score 1+ & 0) were found in 67.39% and invariably both positive & negative scores were found in carcinoma rectum, than right sided colonic carcinoma, showing 19.57% and 39.13% respectively.

Scoring	Adenocarcinoma		Mucinous		Signet Ring Type		Basaloid		Adenosquamous		Total	%
	n	%	n	%	n	%	n	%	n	%	n	
HER2/neu Positive score 3+	3	6.52	0	-	0	-	0	-	0	-	3	6.52
HER2/neu equivocal score 2+	11	23.91	1	2.17	0	-	0	-	0	-	12	26.09
HER2/neu Negative score 1+	2	4.35	0	-	0	-	1	2.17	0	-	3	6.52
HER2/neu Negative score 0	20	43.48	4	8.70	2	4.35	1	2.17	1	2.17	28	60.87
Total	36	78.26	5	10.87	2	4.35	2	4.35	1	2.17	46	100.00
HER2/neu Positive%	6.52%											

Table 3. Immunohistochemistry: HER2/neu Score According to Histological Type (n=46)

Out of 46 cases included in the IHC HER2/neu, 3 cases of adenocarcinoma was positive with score 3 +, (figure 1) 11 cases of adenocarcinoma showing equivocal score 2+, 01 case of mucinous type had equivocal score 2+, whereas 02 cases of adenocarcinoma, 01 case basaloid type was negative with score 1+. 20 cases of adenocarcinoma, 04 cases of mucinous, 02 case of signet type and 01 case each of basaloid and adenosquamous were negative with score 0. Overall HER2/neu positivity is 6.52%. The well differentiated adenocarcinoma (figure 1) showed HER2/neu negativity score 1+ (figure 10), moderately differentiated adenocarcinoma rectum (figure 2) showed HER2/neu positivity score 2+ (figure 9), poorly diff adenocarcinoma showing diffuse infiltrating type morphology (figure 3) with strong HER2/neu positivity score 3+ (figure 8). The basaloid squamous cell carcinoma (figure 6) of rectum showed HER2/neu negative score 0 (figure 11). The other subtypes of poorly diff adenocarcinoma included were mucinous carcinoma colon (figure 4) and signet ring carcinoma (figure 5), both showing showed HER2/neu negativity score 0.

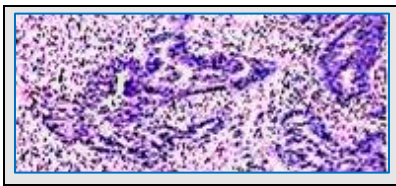

Figure 1. Photomicrograph of Adenocarcinoma (Well Differentiated) Colon (H&E, x 400)

Figure 2. Photomicrograph of Adenocarcinoma Rectum, Moderately Differentiated (H&E, x 400)

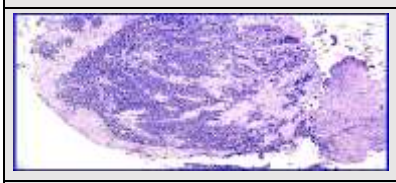

Figure 3. Photomicrograph Adenocarcinoma Colon, Poorly Differentiated (H&E, x 400)

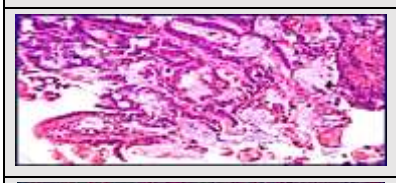

Figure 4. Photomicrograph Showing Mucinous Carcinoma Colon (H&E, x 400)

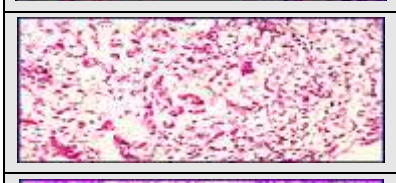

Figure 5. Photomicrograph Showing Signet Ring Type Carcinoma Colon (H&E, x400)

Figure 6. Photomicrograph Showing Basaloid Carcinoma of Colon (H&E,x400)

Figure 7. Photomicrograph IHC HER2/neu Positive Control (H&E, x 400)

Figure 8. Photomicrograph IHC HER2/neu Score 3+ (H&E, x400)

Figure 9. Photomicrograph Showing IHC HER2/neu Over Expression Score 2+ in Adenocarcinoma Colon (H&E, x 400)

Figure 10. Photomicrograph IHC HER2/neu Score 1+ (H&E, x 100)

Figure 11. Photomicrograph IHC HER2/neu Score 0 (H&E, x400)

DISCUSSION

Colorectal carcinoma comprised 35% of total cases and commonly adenocarcinoma, NOS type (67.8%). The carcinomas were commonly located in the rectum i.e 59.52% (Table 1) with male predominance and seen in patients over 50 years of age. This correlated with the study of Boyle et al., (2002),[18] where they indicated colorectal cancers to be 2 times more common in men than in women. Likewise, the study, by Köseoğlu et al., (2012),[19] also reflected male incidence (58.1%) to be more and median age of presentation above 50 years. The colorectal carcinomas in this study were mostly of the adenocarcinoma type (67.8%). A similar finding was reported by Ochs AM et al., (2003),[20] who reported 98% of colon cancer was adenocarcinoma type. Likewise, a study done by Sure et al. (2011)[21] where about 60% of patients were male and 66% was located in the rectum and of which adenocarcinoma comprised the bulk.

Serdar et al., (2014),[22] observed that (65.92%) male in the age group of 45 years were commonly affected with colon cancer, of which adenocarcinoma (6.67%) histology was majority. A study by Azadeh S. et al.,(2008)[23] done in West Iran showed that the mean age and incidence of males affected with CRC was 54.3±14.5 in comparison to females and the commonest histology type being adenocarcinoma. In a similar study by Pahlavan PS et al., (2006)[24] conducted on 200 patients of colorectal cancer of which 57% were males and 43% were females and mostly the lesions were located in rectum, the commonest histology being adenocarcinoma. Likewise, Nathanson DR et al., (2003)[25] studied 169 patients with colorectal cancer of which 86 were men and 83 women and median age of 66 years.

Shabbir A et al., (2016)[26] conducted a study during August 2014 - February 2016 on 95 patients of colorectal biopsies. He found the mean age was about 46 yrs., males (53.7%) and females (46.3%). 75 cases were HER2/neu positive out of which 26.6% showed membranous staining and 25.3% were cytoplasmic and membranous. The high-grade tumours were having maximum HER2/neu staining and mostly found in non-mucinous adenocarcinoma.

The correlation of clinical diagnosis of colonoscopy biopsies were well correlated with histopathology final diagnosis. 09 cases diagnosed negative for malignancy, which were found to be malignant and 05 cases of suspicious of malignancy were frank malignant in histopathology study. Thus, the percent accuracy was high i.e. 92.5%.

In view of defining a predictive marker for colorectal cancer IHC staining for HER2/neu was done. The findings have been illustrated (Table 3). Out of 46 cases included in the IHC HER2/neu, 3 cases of adenocarcinoma NOS was positive with score 3 +, 11 cases of adenocarcinoma showing equivocal score 2+, 01 case of mucinous type had equivocal score 2+, whereas 02 cases of adenocarcinoma, 01 case basaloid type was negative with score 1+(figure 10). 20 cases of adenocarcinoma, 04 cases of mucinous, 02 case of signet type and 01 case each of basaloid and adenosquamous were negative with score 0 (figure 11).

HER2/neu expression was most common in the cancers located in the rectum (Table-2). The adenocarcinoma, NOS type show HER2/neu of score 3+ in (6.52%.), showing both cytoplasmic and membranous staining in moderate to poorly differentiated carcinomas (figure 8, 9), score 2+ in 23.91% cases of adenocarcinoma, which were found mostly in moderately differentiated (figure 9) cancer colon showing predominant membranous positivity.

Ingold Heppner et al., (2014)[27] concluded in his study that 1.6% of cases were HER2/neu positive in higher stages. The positivity had no impact on survival of patient and often displays a tendency to poorer courses.

The studies by Conrad et al., (2014),[28] who screened for HER2/neu positivity found most cases to be positive in rectum, was also seen in the studies of Sclafani F et al.,(2014)[29], who also reported positive percent of HER2/neu as 4.3% and AnaNaSeo et al (2014),[30] in her study showed score 3+ (2.2%), score 2+ (2.9%) and score 1+(14.4%). Ochs AM et al., (2004)[20] conducted IHC HER2/neu on 134 cases and found that 98% were histological adenocarcinoma of which only 12% exhibited HER2/neu expression. Over expression of HER2/neu were located more commonly in the rectum and inversely proportional to grade of the tumour. Tavangar SM et al., (2005)[31] in his study reported 21.8% showed positive HER2/neu staining of 55 cases done. The more advanced stage of the disease and the tumour grade correlated with HER2/neu over expression which was also observed in our study. In a study similar to our observation was done by Manmeet Kaur Gill et al., (2011)[32] done on 40 colorectal carcinoma cases of which 60% were males and 40% were females. In 17 cases lesions were present in right colon and 23 cases were found in left colon and rectum. Histopathology mostly was adenocarcinoma type. Immunostaining with HER2/neu was done and 65% showed positive staining and 35% were HER2/neu negative. 30% were 3+ staining, 12.5% were 2+ staining and 22.5% were 1+. In this study the majority was cytoplasmic with only three cases showing both membranous and cytoplasmic staining, of which two were conventional adenocarcinoma and one was mucinous adenocarcinoma.

A similar study by Richman SD et al., (2016)[33] showed HER2 amplification occurring in stage II-III CRC. In a study, by Essapen S. et.al, (2004)[34] 170 specimens of colorectal cancer were analysed, using an anti-HER2 monoclonal antibody. Overall, 87% of cases showed cytoplasmic HER2 staining of which 54% had cytoplasmic and 41% strong membranous positivity. Half E et al., (2004)[35] analysed immunostaining of HER2/neu in 96 colorectal cancer HER-2 membranous staining was detected in only 5 of 96 (5.2%) and majority of the malignant cells showed strong 3+ staining in all cases. Colorectal cancers with well or moderate differentiation more frequently expressed cytoplasmic HER-2 proteins than did poorly differentiated tumours. Similarly, in a study by Suma S et al., (2018)[36] 50 cases of colorectal carcinoma were taken. The median age was 60.04 years and mostly men. HER2/neu staining was done for all the patients and 44% were HER2/neu positive

of which majority of cases were both membranous and cytoplasmic staining.

CONCLUSIONS

Colorectal cancer is most commonly located in the rectum (57.14%) and has male preponderance (59.52%). The commonest morphology was adenocarcinoma NOS type (67.8%), followed by mucinous type (22.6%), adenosquamous (4.1%), signet ring type and basaloid type (3.37%). Clinical correlation with histopathologic diagnosis was found to have a sensitivity of 89.29% and specificity of 94.23% with an accuracy of 92.5%. Positive expression of IHC HER2/neu was found in adenocarcinoma NOS type. They were positive with a score of 3+, showing both cytoplasmic and membranous staining in moderately and poorly differentiated cancer. The positive percentage was (6.52%). Equivocal score 2+ (26.09%) with membranous staining was found in moderately differentiated adenocarcinoma type (23.17%) and mucinous type (2.17%). Negative staining with score 1+ (6.52%) and scores 0 (60.87%) comprised other variants of colorectal cancer. Though HER2/neu staining is positive (both cytoplasmic and membranous) in moderately differentiated cancer, in higher grades there was decrease in positive staining with predominant membranous staining. Because of more prominent membranous staining in higher stages and grades, Herceptin therapy could be helpful in patients with lymph nodes or distant metastasis. However, there was no correlation between HER2/neu expression with age and sex.

REFERENCES

[1] Curado MP, Edwards B, Shin HR, et al. Cancer incidence in five continents. Vol. 9. International Agency for Research on Cancer: IARC Press 2007.

[2] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer 2015;136(5):E359-E386.

[3] Nandakumar A. National cancer registry programme. Indian Council of Medical Research, Consolidated report of the population based cancer registries, New Delhi, India, 1990: p. 96.

[4] Mohandas KM, Desai DC. Epidemiology of digestive tract cancers in India. V. Large and small bowel. Indian Journal of Gastroenterology 1999;18(3):118-121.

[5] Mendeloff AI. Dietary fiber and the gastrointestinal tract. Critical assessment. In: Beek JE, edr. Developments in digestive diseases. Philadelphia: Lea & Febiger 1979.

[6] Weisburger JH. Causes, relevant mechanisms and prevention of large bowel cancer. Seminars in Oncology 1991;18(4):316-336.

[7] World Cancer Research Fund / American Institute for Cancer Research. Food, nutrition, physical activity and the prevention of Cancer: a global perspective. Washington, DC. AICR 2007.

[8] Laohavinij SM, Maneechavakajorn J, Techatenol P. Prognostic factors for survival in colorectal cancer patients. J Med Assoc Thai 2010;93(10):1156-1166.

[9] Al-Shamsi SR, Bener A, Al-Sharhan M, et al. Clinicopathological pattern of colorectal cancer in the United Arab Emirates. Saudi Medical Journal 2003;24(5):518-522.

[10] Lupu R, Cardillo M, Harris L, et al. Interaction between erbB-receptors and heregulin in breast cancer tumor progression and drug resistance. Seminars in Cancer Biology 1995;6(3):135-145.

[11] Lee KF, Simon H, Chen H, et al. Requirement for Neuregulin receptor erbB2 in neural and cardiac development. Nature 1995;378(6555):394-398.

[12] Pierce JH, Arnstein P, DiMarco E, et al. Oncogenic potential of erbB-2 in human mammary epithelial cells. Oncogene 1991;6(7):1189-1194.

[13] Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. Journal of Clinical Oncology 2002;20(3):719-726.

[14] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. New England Journal of Medicine 2001;344(11):783-792.

[15] Ross JS, McKenna BJ. The HER2/neu oncogene in tumors of the gastrointestinal tract. Cancer Investigation 2001;19(5):554-568.

[16] Lee JC, Chow NH, Wang ST, et al. Prognostic value of vascular endothelial growth factor expression in colorectal cancer patients. European Journal of Cancer 2000;36(6):748-753.

[17] Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Archives of Pathology and Laboratory Medicine 2014;138(2):241-256.

[18] Boyle P, Leon ME. Epidemiology of colorectal cancer. British Medical Bulletin 2002;64(1):1-25.

[19] Köseoğlu Z, Kara B, Bildedoğan Ü, et al. Etiologic factors, risk factors, diagnoses and importance of colonoscopy in patients hospitalized due to lower gastrointestinal bleeding from emergency services. Journal of Academic Emergency Medicine/Akademik Acil Tip Olgu Sunumlari Dergisi 2012;11(1):6-10.

[20] Ochs AM, Wong L, Kakani V, et al. Expression of vascular endothelial growth factor and HER2/neu in stage II colon cancer and correlation with survival. Clinical Colorectal Cancer 2004;4(4):262-267.

[21] Ahmet TE, Mustafa S, Kader I. Colonoscopic polypectomy results of gastroenterology unit. GastroenterolojiKlinigi 2011.
[22] Yanık S, Akkoca AN, Özdemir ZT, et al. Evaluation of results of lower gastrointestinal endoscopic biopsi. International Journal of Clinical and Experimental Medicine 2014;7(12):5820-5825.
[23] Azadeh S, Moghimi-Dehkordi B, Fatem SR, et al. Colorectal cancer in Iran: an epidemiological study. Asian Pacific Journal of Cancer Prevention 2008;9(1):123-126.
[24] Pahlavan PS, Kanthan R. The epidemiology and clinical findings of colorectal cancer in Iran. Journal of Gastrointestinal and Liver Diseases 2006;15(1):15-19.
[25] Nathanson DR, Culliford 4th AT, Shia J, et al. HER 2/neu expression and gene amplification in colon cancer. International Journal of Cancer 2003;105(6):796-802.
[26] Shabbir A, Mirza T, Khalid AB, et al. Frequency of HER2/neu expression in colorectal adenocarcinoma: a study from developing South Asian Country. BMC Cancer 2016;16(1):855.
[27] Heppner BI, Behrens HM, Balschun K, et al. HER2/neu testing in primary colorectal carcinoma. British Journal of Cancer 2014;111(10):1977-1984.
[28] Marx AH, Burandt EC, Choschzick M, et al. Heterogenous high-level HER2 amplification in a small subset of colorectal cancers. Human Pathology 2010;41(11):1577-1585.
[29] Sclafani F, Roy A, Cunningham D, et al. HER2 in high-risk rectal cancer patients treated in EXPERT-C, a randomized phase II trial of neoadjuvantcapecitabine and oxaliplatin (CAPOX) and chemoradiotherapy (CRT) with or without cetuximab. Annals of Oncology 2013;24(12):3123-3128.
[30] Seo AN, Kwak Y, Kim DW, et al. HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression. PLoS One 2014;9(5):e98528.
[31] Tavangar SM, Shariftabrizi A, Soroush AR. Her–2/neu over-expression correlates with more advanced disease in Iranian colorectal cancer patients. Medical Science Monitor 2005;11(3):CR123-CR126.
[32] Gill MK, Jain K, Manjari M, et al. Expression of HER2/neu in colon carcinoma and its correlation with the histological grades and the lymph nodes status. JCDR 2011;5(8):1564-1568.
[33] Richman SD, Southward K, Chambers P, et al. HER2 overexpression and amplification as a potential therapeutic target in colorectal cancer: analysis of 3256 patients enrolled in the QUASAR, FOCUS and PICCOLO colorectal cancer trials. The Journal of Pathology 2016;238(4):562-570.
[34] Essapen S, Thomas H, Green M, et al. The expression and prognostic significance of HER2 in colorectal cancer and its relationship with clinicopathological parameters. International Journal of Oncology 2004;24(2):241-248.
[35] Half E, Broaddus R, Danenberg KD, et al. HER-2 receptor expression, localization and activation in colorectal cancer cell lines and human tumors. International Journal of Cancer 2004;108(4):540-548.
[36] Suma S, Ummerali SK. HER2/neu expression in colorectal cancers. International Journal of Contemporary Medical Research 2017;4(6):1240-1243.