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Comparision Of BRAF V600E, COX–2 and p53 As Biomarkers For The Early Detection Of Colorectal Cancer

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ABSTRACT:

Colorectal cancer (CRC) is one of the most common types of gastrointestinal cancer. Almost two million new cases of CRC are diagnosed every year, making CRC the third most common cancer and the fourth most common cancer-associated cause of mortality in the world. The onset and development of CRC is induced by a combination of genetic and environmental factors including social, cultural and lifestyle factors. Age is considered as main risk factor for the colorectal cancer, there is remarkable increase past the fifth decade of life. Because of its high incidence and mortality rate worldwide, colorectal cancer (CRC) has become a global public health problem. Patients with CRC are typically asymptomatic and therefore it is difficult to diagnose disease until advanced stages, where the disease becomes incurable. Early diagnosis and therapy is able to decrease the risk of CRC in this asymptomatic population; however, early diagnosis of CRC remains a challenge in clinical practice. This review article was a comparative study and aims to explore the ability of the selected markers for early diagnosis of colorectal cancers for long term survival. Hence, identification of novel non-invasive diagnostic methods for early tumor detection in CRC is required. Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early curable stage. There is need for the implementation of new speci?c and more sensitive biomarkers in upcoming future which will improve diagnostic strategies and allowing clinicians to detect CRC cases in the earliest stages of the disease, to improve the prognosis of thousands of patients.

Keywords: BRAF V600E, COX-2, p53, Colorectal carcinoma, Early detection.

INTRODUCTION:

Colorectal cancer is the most prevalent cancer of gastrointestinal tract globally and is the leading cause of cancer-related death. Every year around two million new cases are diagnosed all over the world. The risk of colorectal cancer increases gradually and it is related with some demographic features like age, gender, disease history and lifestyle. There is diversity in genetic predisposition for colorectal carcinoma cases. There is transition of normal mucosa into a premalignant polyp and ultimately develops in to a cancer due to certain genetic and epigenetic changes.[1,2]

Recent evidence suggests that one third of sporadic colorectal cancers are thought to arise from the progression of premalignant serrated lesion.[3,4] There are various mutations involving the tumour suppressor genes,proto oncogenes and the genes responsible for DNA repair mechanisms.The mechanisms accountable for the pathogenesis of colorectal cancer are chromosomal instability (CIN), CpG islandmethylator phenotype (CIMP) and microsatellite instability (MSI). Mutations in APC, MYC, KRAS, BRAF, TP53, COX-2and TGF signaling genes are detected frequently in CRCs. [5] The reported 5-year survival rate of colorectal cancer is about 90% and it can decreases up to 14% for the early stage of this lesion. [6] CRC may develops from a benign adenoma, and the estimated time for the development of adenoma into adenocarcinoma is approximated 5–10 years.[7,8]At present colonoscopy is the gold- standard early diagnostic test to determine the colonic pathology.[9,10]Screening colonoscopy is estimated to reduce colorectal cancer incidence by 69% and mortality by 68%.[11]As colorectal cancer is a heterogeneous disease for which chemotherapy is considered to be the backbone of treatment, specific biomarkers now have been established for detection of tumors at an early stage of disease and also to predict the treatment adequacy to improve the survival time.[12,13] Some of such biomarkers include BRAF V600E, COX-2 and, P53.

BRAF (v-Raf murine sarcoma viral oncogene homolog B1) is a member of the RAS/RAF family, an which has coding an enzyme, and suggested as integral component of the cascade. BRAF oncogene has presented as direct effector of RAS and promotes the phosphorylation of MEK, which further causes tumour growth and survival. For colorectal cancer,BRAF mutations have accounts for about 8 % of cases. [14] At present >95% of BRAF point mutations have been observed to at BRAF V600 in which GTG>GAG substitution results in V600E amino acid change i-e the substitution of glutamate by the valine at residue 600. [15,16]

COX-2 has been recognized as important member of Cyclooxygenases (COXs) family which appears as an important regulator of cell proliferation. COX-2 is an inducible enzyme which accounts for the development of epithelial cell dysplasia, carcinoma, invasion and metastasis thus contributing to the development or progression of malignancy.[17]

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In various studies p53 has been recognized as a cellular SV40 large T antigen-binding protein. [18] The p53 signaling has been frequently impaired in CRC. p53 is a well-known tumor suppressor which promotes the transcription of various targeted genes namely p21 and p27. It also has a significant central role in cell cycle control, senescence, and apoptosis and in the prevention of cellular stress by mediating up-regulation of p21 and PTEN, inhibition of AKT, and decrease of cyclin E/CDK2.[19] Early detection of CRC improves the 5 years survival rate from 12-13% in stage IV metastatic disease to 90% in stage I-II early stage disease.[20] This review article was a comparative study and aimed to explore the ability of the selected markers for early diagnosis of colorectal cancers for long term survival.

METHODOLOGY:

A Literature search was done by using Pubmed and Google scholar from 2009 – 2018.Key words and phrases used were ,colorectal cancer, early diagnosis, biomarkers, BRAF-V600E, P53, COX-2. Multiple studies were scrutinized for the use of immunohistochemistry in early detection of colorectal cancer. 47 relevant articles are included for write up of this review article. The articles were analyzed and then composed the review article to assess the comparative analysis of these biomarkers for the early detection of colorectal cancer.

LITERATURE REVIEW:

BRAFV600E:

The BRAF oncogene is an integral component of the MAP kinase signaling pathway (RAS-RAF-MEK-ERK).Oncogenic activation of BRAF leads to constitutive kinase activity and phosphorylation of downstream targets of the RAS/RAF/MAPK signaling pathway.BRAF mutation constitues an alternative molecular pathway in the early carcinogenesis and accounts for 15% cases of sporadic colorectal cancer.V600E mutation is assumed an early event in serrated pathway of tumourigenesis and is greatly associated with proximal location, female gender, CpG island methylator phenotype and microsatellite instability (MSI). [21,22]

KRAS and BRAF are prime oncogenic drivers for colorectal cancer. Mutational analyses of these two important proto-oncogens have been a centre of research interest in recent years. [23] The *BRAF*V600E are generally mutually exclusive with another proto-oncogene such as KRAS, both of them have been implicated in the equivalent downstream effects in tumorigenesis . Mutations of these genes might play distinct roles in tumor initiation and/or maintenance. The activating *BRAFV600E* mutations have been revealed to play a role in tumor invasion and evasion of apoptosis.

BRAF mutations are found in 7% of cancers, with *BRAF* V600E accounting for >90% of mutations in *BRAF*-mutated cancers. Between 8% and 12% of metastatic CRC (mCRC) cases harbor a *BRAF* mutation. [24]*BRAFV600E* significantly increases the DNA methylation of CIMP-associated markers in primary colorectal tumors. Moreover these *BRAF* mutations and have been observed in early precursor lesions of colorectal cancer. [25] This mutation has been observed as an important predictive factor for adjuvant therapy for colorectal cancer thereby the mutation status of the tumor should be screened right before starting the treatment. The mutation status of BRAF has shown great diversity among different populations and regions.[26] BRAF mutations could be considered as a stratification factor for the adjuvant therapy.For patients having MMR-deficient (dMMR) CRC, BRAFV600E mutation revealed a sporadic origin.[27] Therfore both BRAF mutation and mismatch repair (MMR) statuses should be determined in all CRC to differentiate sporadic tumors from Lynch syndrome-related tumors.[28]

The early screening of *BRAF V600E* might improve the evaluation of the risks for colorectal cancer and give the effective management of the patients and also important in predicting the prognosis of early CRCs.[29] A study revealed BRAF mutations in 4.0% of colorectal cancers.[30] Previous studies have suggested *BRAF V600E* mutation as an independent prognostic factor which is significantly linked with prolonged DFS (disease free survival).The association of *BRAFV600E* and MSI phenotype showed a better survival for earlier tumor stage. [31]Various studies have proved that for (HNPCC) diagnostics, (a hereditary condition) *BRAF V600E* mutation within BRAF has been proposed as a convenient, reliable, fast, and low cost strategy which simplifies genetic testing for HNPCC and therefore should be recommended for early diagnosis as it can improve the efficiency of genetictesting for HNPCC. [32]

At present BRAF VE1 immunohistochemistry has been identified as a useful screening tool for the detection of *BRAF V600E* mutation in CRCs. The BRAF VE1 IHC is more cost-effective and less time-consuming than *BRAF* sequencing studies. [33] It reveals good diagnostic performance and excellent sensitivity on IHC (sensitivity, specificity, and positive predictive values are 96.1%, 94%, and 89.15 respectively).Moreover the BRAF *V600E* mutation has been appraised as an early event in colorectal cancer with multifaceted roles for progression, diagnosis and the prognosis of colorectal cancer. [34,35]

P53:

A well- known tumor suppressor gene p53 has been recognized as important components of our body's defense system which has been working for cancer progression control. Multiple studies have been proposed that the CRC carcinogenesis has significantly involves the mutations in various recognized proto-oncogenes namely the *K-Ras*, *APC* and *p53*. Among them the p53 mutation is playing an important role in colorectal carcinogenesis. It also helps in determining the biologic basis of the disease which is implicated in the early stages of ulcerative colitis and tumorogenesis of the colorectum.[39]

This marker has been considered as a good competitor for early detection marker panel of colorectal cancer. Along with it the antibodies to p53 tumor suppressor protein have been identified as early biomarker for colorectal cancer.[40]

The protein expression of p53 in dysplastic crypts may serve as an important biomarker for colorectal cancer.0–85% of colitis-associated cancers have defective *p53* gene which can be recognized via immunohistochemistry. Now a days screening method like Immunohistochemistry for the p53 biomarker in tissue samples has been considered as a useful tool for estimating the risk of morphological changes, distinction of intraepithelial neoplasms, and the progression in to malignant neoplasm involving the colonic epithelium. Also Immunohistochemistry (IHC) has been identified as a fast, most convenient and reliable method in detecting the level of p53 mutations in early precursor lesions for colorectal carcinogensis.[41]

The Overexpression of p53 in colonic epithelia has been identified as a most valuable tissue biomarker in surveillance of colorectal carcinogenesis. Also p53 has been recommended for a better quantification of the risk for colon cancer. The reactivation and remodeling of p53 function has an unconventional role in colorectal carcinoma. Proper understanding of screening of this marker may allow a better stratification of early dysplastic changes and invasive carcinoma, in order to personalize treatment and surveillance.[42]

COX -2:

The levels of cyclo oxegenase-2 in early stages of colorectal cancer have been proposed for the early detection of CRC. [43]It has been recognized as a useful diagnostic marker for the CRC patients with Stage I or II disease. Cox-2 has been found as potential blood markers and may be useful in identifying early stage CRC.[44] Targeting the inhibition of COX-2 expression may help to control the progression of carcinoma, including colonic carcinoma.[45]

Review of numerous studies reveales that expression of COX-2 is related with some important clinicopathological parameters namely the lymphovascular invasion, serosal involvement, metastasis of multiple lymph nodes, Duke's stage, and poorly differentiated cancer. It has synergistic effects in colorectal cancer carcinogenesis. COX-2 influences different steps in cancer progression. It increases the production of prostaglandin, inhibits tumor cell apoptosis and promotes cell proliferation and tumor angiogenesis, and activates the prototype of carcinogenic substances. Significantly higher levels of COX2 in precancerous lesions and carcinoma in situ point towards an early event in tumorigenesis.[45]COX-2 has also been recognized as a useful prognostic marker for colorectal cancer and its highest levels of expression may correspond with tumor recurrences. Routine screening of COX-2 may provide an effective index for prognosis of those at higher risk of disease metastases.

Further *BRAF V600E* is currently under focus as a potential prognostic and predictive biomarker which may improve assessment of colorectal cancer risk and guiding tool for patient management.

CONCLUSION:

BRAF V600E, p53 and COX-2 have been recognized as markers for early detection for colorectal cancer. Amongst these markers mutated *BRAFV600E* is now considered as the most promising tool especially those associated with MSI.

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