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Review Article

An Insight in Biomarkers for Colorectal Cancer

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Abstract

Colorectal cancer is a leading cause of death worldwide which affects the parts of digestive system. It is considered as third most common cancer in the world. The incidence of colorectal cancer is strongly linked to so call western lifestyle. Incidence is increases with age and is higher in men than women. Most of the colorectal cases are sporadic and develop in individual patients slowly. However, its hereditary aetiology is also well established. There are several methodologies for treatments are employed although none of them provide complete prevention from colorectal cancer. By advances in medical imaging technology early and accurate diagnosis of metastatic lesions is now possible. The treatment roadmaps followed are surgery, neoadjuvant radiotherapy and adjuvant chemotherapy. The resection of lung, liver and other organ metastases is required for patient survival when and is followed by other treatment and rigorous follow up regimen. In patients with advance stage of cancer (stage III/IV) adjuvant chemotherapy is followed to increase the life expectancy of patients. It's a dreadful full disease with high mortality rate. 5 year survival rate is 90% in stage I and approximately 10% in stage IV patients. The regular screening of a person can reduce incidence as well as mortality from colorectal cancer. However, due to economic concern and lack of awareness regular screening programmes are not implemented in most of the countries.

Keywords: Neoadjuvant; Colorectal cancer; Survival; Radiotherapy; Neoplasm

Abbreviations

CRC: Colorectal Cancer; HNPCC: Hereditary Nonpolyposis Colorectal Cancer; FAP: Familial Adenomatous Polyposis; MACC1: Metastasis Associated in Colon Cancer 1; MMR: Mismatch Repair; MSI: Microsatellite Instability; APC: Adenomatous Polyposis Coli; FOBT: Faecal Occult Blood Testing; MCRC: Metastatic Colorectal Cancer

Introduction

The cancer is defined as the cells abnormal growth with capability to spread in to different or other organs of the body [1]. Colorectal Cancer (CRC), develops from the rectum/colon (i.e., a parts of large intestine) [2]. Signs and symptoms of CRC include change in bowel movements, blood in the stool, loss of appetite, weight loss and feeling tired all the time [1,2]. CRCs mostly arise due to lifestyle and old age associated factors. However, small number of CRC cases might be due to underlying genetic diseases [3]. CRCs are associated with some of the risk factor such as obesity, diet, smoking and absence of physical activity. Some of the dietary reasons that might enhance the risk of CRC include processed and red meat along with alcohol. Other risk factor is inflammatory bowel disorders such as ulcerative colitis and Crohn's disease. Inherited genetic diseases that can cause CRC include familial adenomatous polyposis along-with hereditary non-poly colon cancer. Therefore, these diseases show less than 5% cases [4-6]. In starting, it typically acts as a benign tumor, generally in polyp form, which in later stages it becomes cancerous. Globally, colorectal cancer is reported as third most general type of cancer, which accounts for about 10% of whole cases [7]. In developed countries, CRC is more common and it constitutes more than 65% of cases. In CRC, is less common in women as compared than men. [8].

Signs and Symptoms

Colorectal cancer, signs and symptoms depends on the position of tumour in the bowel and its metastasis to other organs of body. The classic warning signs includes, worsening constipation, decrease in stool caliber (thickness), blood in the stool, nausea or vomiting, loss of appetite and loss of weight [9]. However, rectal bleeding or anaemia is high-risk features in patients over 50 year of age [10]. Other symptoms such as weight loss as well as bowel habit change are taken in consideration if included with bleeding [10,11].

Cause of Colorectal Cancer

CRC occurs in more than 75-95% persons having little or no prior genetic defects [12,13]. Risk factors consisting male gender, older age and heavy intake of fat diet, red meat, alcohol, processed meats, smoking, obesity and absence of physical exercise [13]. Estimated 10% of CRC cases are associated with insufficient physical activity [14]. The alcohol consumption risk appears to increase after more than one drink in a day [15]. While drinking 5 glasses of water per day decrease the risk associated with colorectal cancer as well as adenomatous polyps [16]. Streptococcus gallolyticus infection is also associated with colorectal cancer [17]. However, some strains of Streptococcus bovis and Streptococcus equinus complex are considered as safe and consumed by millions of people daily [18]. People nearly 25 to 80% with Streptococcus bovis/gallolyticus bacteremia have concomitant colorectal tumors [19]. Therefore, Streptococcus bovis/gallolyticus seroprevelance is considered as a candidate marker for the early recognition of CRC in an unrevealed bowel laceration in highly exposed population [19]. It has been identified that the presence

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Table 1: Various risk factors associated with colorectal cancer.

Sr. No.	Risk Factor	Description	Reference
	Environmental		
1	Age	Majority cases are reported in older than 50 years of age. High prevalence after 60 years age.	[28] [29] [30]
2	Sex	In the literature the incidence of CRC is the same in males and females. Females are shown to be older and to have right-sided tumors and less advanced diseases	[31]
3	Lifestyle	Long term smoking Association betweendiets consisting of red meat is between presences of heme-iron in meat. Alcohol consumption interferes with folate synthesis by production of acetaldehyde. This causes chromosome damage and finally leading to carcinogenesis.	[32,33] [34] [35] [36] [37] [38] [39]
	Genetic		
4	APC	The Adenomatous Polyposis Coli (APC) gene, located on chromosome 5, is a tumor suppressor, which is mutated in most of sporadic cases of colon adenocarcinomas.APC mutation leads to an increased amount of β-catenin and to the activation of theWnt signaling pathway that is involved in cellular activation	[40] [41] [42]
5	Chromosomal instability	Chromosomal instability is a common factor that intervenes in the adenoma-carcinoma sequence. It causes the inactivation of wild-type allele of tumor suppressor genes, such as SMAD4, APC, and p53, the loss of heterozygosity, and the alteration in chromosome number, like aneuploidy.	[43] [44]
6	BRAF	RAS and RAF are two oncogenes which activate the Mitogen-Activated Protein Kinase (MAPK) pathway.KRAS has a GTPase activity that activates RAF proteins; BRAF's serine-threonine kinase activity initiates the MAPK signaling cascade, with the activation of several transcription factors.	[45] [46]
7	RAS	Small polyps present BRAF mutation, whereas in serrated adenomas, hyperplastic polyps and proximal colon cancer RAS is more often mutated	[47]
8	DCC	Deleted in Colorectal Cancer (DCC) is a tumor suppressor gene sited on the long arm of chromosome 18 (18q21.3). It is a transmembrane protein that stops cell growth in absence of Netrin and its ligand. Its mutation prevents the bond with Netrin-1 and results in abnormal cell survival. Loss of Heterozygosity (LOH) of chromosome 18q is seen in more than 70% of advanced CRC	[48] [49]
9	Family history	Patients affected by FAP develop thousands of polyps in gastrointestinal system, especially in the colon, starting from the second decade of life; if not treated they will develop a CRC in early adulthood. Hereditary Nonpolyposis Colorectal Cancer (HNPCC) or Lynch Syndrome is the most common hereditary form of CRC (2–4% of all CRC). A characteristic trait of NHPCC is Microsatellite Instability (MIS) due to the inherited mutation of the Mismatch Repair Genes (MMR) that control the length of microsatellites, short nucleotides' sequences repeated in DNA.	[50] [51] [52]

of antibodies specific to Streptococcus bovis gallolyticus antigens in the bloodstream may be act as markers for identification of the carcinogenesis in colon [19].

Inflammatory Bowel Disease

People having inflammatory bowel disease (Crohn's disease and ulcerative colitis) are considered as higher risk of colon cancer [20, 21]. As longer a person has the disease, risk for CRC increases [22,23]. In high risk group people prevention with regular aspirin use followed by colonoscopies are suggested [21]. Annually, less than 2% of colon cancer cases are detected in people having inflammatory bowel disease. It is reported that 2% patients having Crohn's disorder acquire colorectal cancer following 10 years, 20 years (8%) and 30 years (18%) [23]. However, 16% people having ulcerative colitis develop either a cancer antecedent for the colon cancer more than 30 years [23].

Genetics

Persons commence a family record in two/more first-degree associations (e.g. parent/sibling) having same fold of higher chance of disease (Table 1). Such cluster accounts about 20% of the entire cases of CRC. A variety of genetic syndromes are also linked with greater rates of colorectal cancer. Hereditary Nonpolyposis Colorectal Cancer is the most general form of these diseases (HNPCC/Lynch syndrome) [12]. In addition to these, other syndromes such as Familial Adenomatous Polyposis (FAP) and Gardner syndrome are sturdily linked with colorectal cancer [24]. People having these syndromes are at risk for CRC and makes up around 1% of the cancer cases [25]. In CRC most deaths occur due to metastatic colon cancer. Stein al has reported a potential gene associated with metastatic disease i.e., Metastasis Associated in Colon Cancer 1 (MACC1) [26]. MACC1, transcriptional factor that affects the hepatocyte growth factor expression and linked with the production, incursion and spreading of colon cancer in animal cell culture and tumour growth as well as metastasis in mice. However, still more clinical studies are required on MACC1 to use as a potential target for cancer intervention [27].

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

About 3% of all CRC called as Lynch syndrome, an autosomal dominant genetic condition caused by mutations in DNA Mismatch Repair Genes (MMR) MLH1, MSH2, MSH6 and PMS2 [12,53]. Such mutations affect the coding and non-coding microsatellites called as Microsatellite Instability (MSI). This in turn increases the risk of

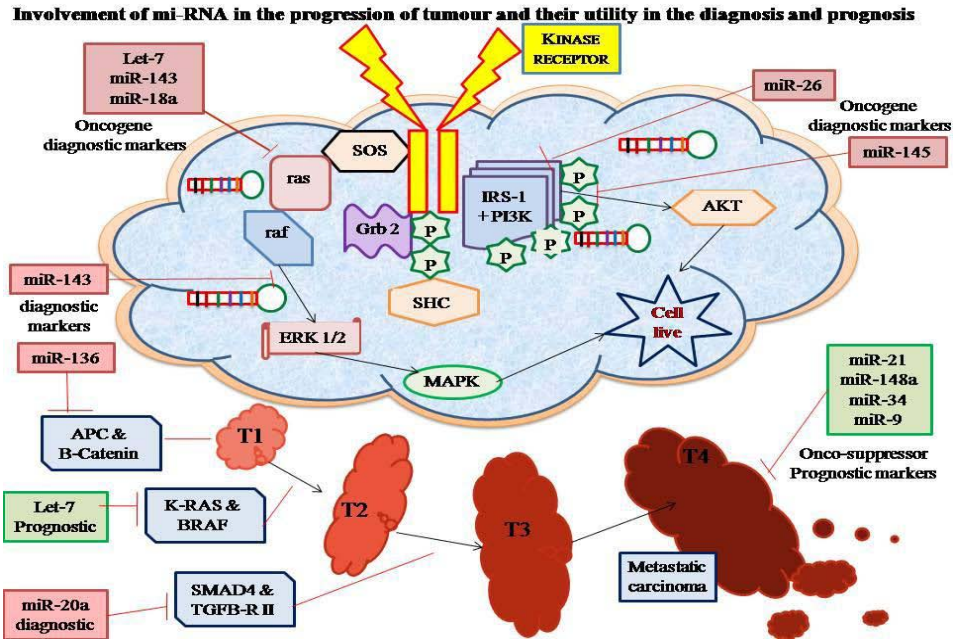

Figure 1: Role of mi-RNA in the progression of tumour and their utility in the diagnosis and prognosis and markers important for staging of colorectal cancer.

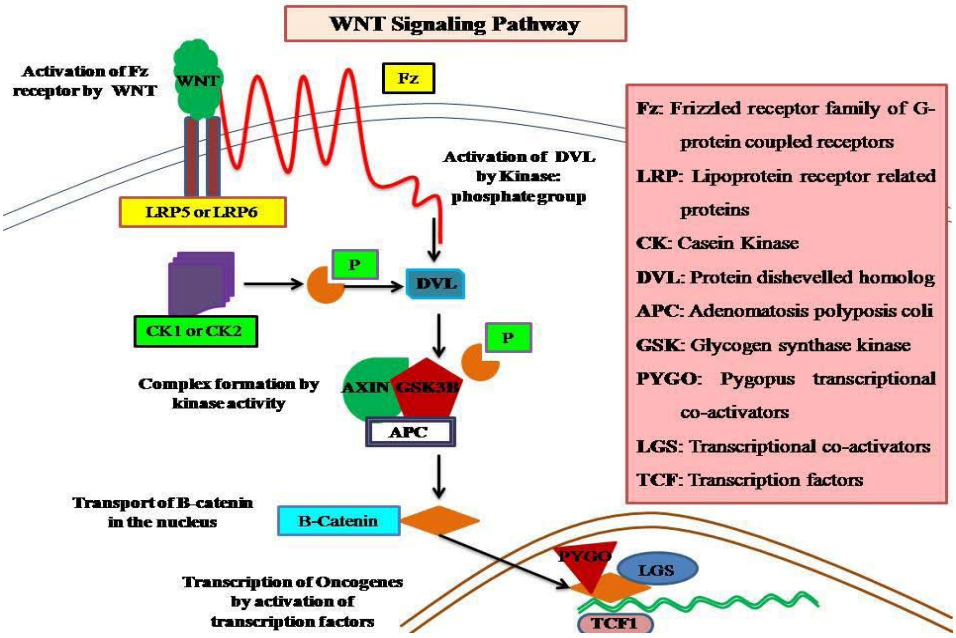

Figure 2: Canonical WNT pathway showing a cascade of kinase activity triggered by WNT in combination with frizzled receptor ultimately leading to the transcription of genes responsible for induction of cancer.

extra colonic cancers such as cancers of small intestine, stomach, hepatobiliary tract, urinary tract, brain and ovary [54]. Lynch syndrome can also be classified into Lynch syndrome I (familial colon cancer) and Lynch syndrome II (other cancers of the gastrointestinal or reproductive system). People suffering with HNPCC usually develop colon cancer before 50 year of age. When chromosomal damage occurs in inner lining cells of colon, these polyps start developing with uncontrolled growth and cells spread as cancerous growth. In Asian countries (i.e., Korea and Japan) HNPCC cancer spectrum includes higher number of stomach cancer [55]. Characteristics for Lynch syndrome tumours include proximal colonic location, mucinous or signet ring cell type, poor differentiation with presence of infiltrating lymphocytes [56].

Familial Adenomatous Polyposis (FAP)

It is a rare disorder which contributes around 1% of all CRC occurrences. FAP is second most common genetic syndrome predisposing to CRC. It is caused by mutation of the Adenomatous

Polyposis Coli (APC) gene on chromosome 5 [57]. Patients in their 30s hundreds to thousands of polyps develop in colon and rectum lining. These polyps usually develop to cancer if surgically not removed at early stage. Patients with FAP usually show polyps in the upper gastrointestinal tract in nearly 90% of cases which predisposes the patients with risk of developing other type of cancers such as cancers of thyroid gland, stomach as well as benign tumours called desmoid tumours [58]. For people with FAP, a total proctocolectomy may be recommended as a preventative measure. Removal of colectomy from colon may not be enough as precautionary measure because great chance of rectal cancer if the rectal leftover [59].

KRAS

KRAS mutations are more commonly seen in MSI-L and MSS tumours, early events in CRC tumorigenesis and which occurs in 30-50% of all CRC cases [60,61].

Epigenetic

Epigenetic changes are more general in colon cancer as compared to genetic changes. Epigenetic factors like irregular DNA methylation of tumour suppressor enhancer also take part in expansion of CRC [62]. Vogelstein et al. 2013 reported that an average colon cancer has only ½ oncogene mutation oncogene mutations 1 to 5 tumour suppressor mutations, along with about 60 "passenger" alterations [63].

Studies showed that, epigenetic changes in colon cancers can affect hundreds of genes. Some of the micro RNAs expression has also been reported in tumor tissues which can mark protein coding genes and reduce their expression. Expression of such micro RNAs is possible epigenetically. The epigenetic alteration in colorectal carcinogenesis in CpG island by methylation of the DNA sequence encoding miR-137 gene reduces its expression. The changed adjoining tissues linked among these cancers are depicted as field defects. Inhibition/silencing of miR-137 gene reduce its expression [64].

Alterations in the miR-137 expression level outcome of changed mRNA expression of the targeted genes by 2 -20-fold and matching though often slight, changes in expression of the genes protein products. Additional micro RNAs, with liable equivalent numbers of target genes are still more often epigenetically altered in colonic defects. Such micro RNAs comprise miR-124a, miR-34b/c along with miR-342, that are silenced through CpG island methylation of their associated encoding DNA sequences in prime tumors at rate of 99%, 93% and 86% correspondingly, and in the neighbouring regular looking mucosa at chances of 59%, 26% and 56%, correspondingly [65,66].

In addition to epigenetic alteration in miRNAs expression, further epigenetic changes in cancers comprise straight hypermethylation/hypomethylation of CpG islands present in protein encoding genes and changes in histones and chromosomal structural design [67,68]. For example, 147 hypermethylations along with 27 hypomethylations of protein encoding genes were commonly linked through colorectal cancers. Along with hypermethylated genes, Addition 10 were hypermethylated in cases of 100% of colon cancers along with a lot of others were hypermethylated in more than 50% of cases of colon cancers. Additionally, 96 hypomethylations and 11 hypermethylations of miRNAs were also linked by colorectal cancers [69]. Modern studies indicate that premature epigenetic reductions in DNA repair enzyme expression possible direct to the epigenomic and genomic instability, which is feature of cancer tissues [70-73] (Figure 1).

Pathogenesis

Colorectal cancer originates from the epithelial cells lining of colon or rectum of the gastrointestinal tract mostly due to mutations in the Wnt signaling pathway that increase signaling activity (Figure 2). The mutations are most probably occurring in the APC gene in intestinal crypt stem cell [74-76]. The APC gene produces APC protein which inhibits the gathering of B-catenin protein. In absence of APC protein, β-catenin accumulates and translocates to nucleus, and triggers the proto-oncogenes transcription. Although these genes are significant for stem cell replenishment and segregation, but after inappropriate expression at elevated levels, they can induce cancer. APC gene is mutated in the majority of colon cancers. Due to mutations in β-catenin (CTNNB1), some cancers have increased β-catenin level and block its own breakdown. Moreover, some additional genes having function alike to APC (AXINI, AXIN2, NKDI, TCF7L2) may also get mutated which explains the increase in level of B-catenin in CRC [77]. Along with Wnt signaling pathway defects, additional mutations such as mutations in p53 gene must also happen for the cell to turn into cancerous. The p53 protein checks the cell division and kills cells if they posses Wnt faulty pathway. Ultimately, a cell line attains a mutation in TP53 gene (which produces p53 protein) and changes the cell from a normal epithelial tumor to a persistent epithelial cell cancer. It was also reported that in some cases another protective protein named BAX get mutated while TP53 gene remain normal [77].

In some cases of colorectal cancer, programmed cell deaths are deactivated by TGF-B and DCC proteins. At least in half of colorectal cancers, TGF-B with deactivated mutation [78]. In other mechanism, TGF-B remains normal, but a protein, SMAD in downstream position is deactivated. DCC normally posses a deleted fragment of chromosome during colorectal cancer [78].

In case of colorectal cancer, human genes just about 70% are expressed, including 1% of having enhanced expression in case of colorectal cancer when compared with different types of cancer [79]. Some genes are over expressed defined as oncogenes found in colorectal cancer. These genes coding the different proteins such as KRAS, RAF, and P13K, which usually encourage the cell to divide in response of growth factors, can attain alterations that result in over-stimulation of cell propagation. The sequential command of mutations is from time to time significant. If a preceding APC change occurred, a main KRAS mutation frequently becomes to cancer relatively than a self-limiting intermediate lesion [80]. PTEN, a tumour inhibitor, usually inhibits P13K, but can be on occasion developing into mutated and non-functional [78].

The genome-scale investigation has discovered that colorectal carcinomas can be divided into non-hypermutated and hypermutated tumors. Additionally to the numerous changes defined for the genes on top of, non-hypermutated samples also include mutated genes (CTNNBI, SOX9, FAM123B, ARIDIA and ATM). Succeeding during a different set of genetic steps, hypermutated tumors show

Table 2: Various tests specified for colorectal cancer diagnosis.

Test name	Description	Reference
Faecal screening test	Occult blood in stool, which is nonspecific but can be detected especially in larger polyps and CRC. It is important to collect samples from consecutive bowel movements	[90] [91]
a) Guaiac faecal occult blood test (gFOBT)	Detects qualitatively heme in the stool, using a guaiac material to which hydroperoxidase is added. Heme promotes a process that leads to the guaiac's oxygenation and to a blue discoloration	[92] [93]
b) Fecal immunochemical tests (FITs)	Utilization of monoclonal or polyclonal antibodies to detect human haemoglobin. They can give qualitative or quantitative results. FIT is more accurate than gFOBT.	[94]
Endoscopic screening test		
a) Flexible Sigmoidoscopy	Flexible Sigmoidoscopy is a screening option that allows examining the rectum and the lower part of the colon. It is an invasive technique that requires simple bowel preparation but cannot detect lesion in the whole colon	[92,94]
b) Colonoscopy	Colonoscopy is esteemed as the gold standard for CRC screening; it allows exploring the whole colon and removing the suspicious lesions. It is an invasive and expensive exam that must be performed if any other test has a positive result.	[95,96]
CT-Colonography CTC	CTC is a noninvasive test that has become a common method for CRC screening. It requires a bowel preparation, but sedation is not needed. The estimated sensitivity and sensibility in detecting polyps > 1 cm are high, above 90%.	[97] [98]

Table 3: Predictive markers for diagnosis of colorectal tumours.

Sl. No.	Marker	Mechanism of Expression	References
1	KRAS	activation of EGFR pathway	[101][102]
2	BRAF	causing the constitutional activation of MAPK pathway	[103, 104] [105]
3	Phosphoinositide-3-kinase	an activation of the pathway and cell proliferation	[106] [101]
4	PTEN (Phosphatase and Tensin Homolog Protein)	Its inactivation causes deregulation of the PI3K pathway. The loss of PTEN has been associated with aggressive CRCs	[107] [108] [109]
5	ERCC-1. Excision repair cross-complementing-1	prevent DNA damage by nucleotide excision and repair.	[110]
6	Ezrin	An increased cytoplasmatic expression of Ezrin correlates with a greater aggressiveness of CRC	[111] [112]
7	Cyclooxygenase-2 (Cox-2)	Its level is increased in the majority of CRCs, especially in advanced stages.	[113]

Table 4: Expression markers for diagnosis of colorectal tumours.

Sr. No.	Marker	Expression	Reference
1.	Microsatellite Instability (MSI)	MSI has a higher prevalence in stage II CRC	[50] [114]
2.	Insulin-Like Growth Factor Binding Protein 2 (IGFBP2)	levels are increased for an overexpression of its mRNA	[115] [116]
3.	Telomerase.	increased Telomerase Activity (TA)	[117] [118]
4.	Pyruvate Kinase M2 (PKM2)	level is higher in CRC (stool marker)	[119] [120]

mutated types of ACVR2A, MSH3, TGFBR2, SLC9A9, MSH6, BRAF and TCF7L2. All such changes are concerned in TGF-B and WNT signaling processes, resulting in improved activity of MYC, play a central role during colorectal cancer [81].

Field Defects

The field cancerization term describes an area of epithelium that has been preconditioned to predispose for development of cancer (Slaughter et.al., 1953). Later on, the terms "field cancerization", "field defect", "field carcinogenesis" and "field effect" have used during new cancers which are likely to arise from pre-malignant or pre-neoplastic tissue [82]. Field defects are important in progression to colon cancer [70-71, 82-83].

The greater part of cancer research studies in have been completed on well established tumors *in vivo*, or as well as *in vitro* on discrete neoplastic foci. However, it is established that higher than 80% of the somatic changes occur in human colorectal tumours, before the beginning of fatal clonal expansion [84]. Vogelstein et al. 2013 reported that greater than 50% of somatic changes in tumors happened in a pre-neoplastic stage, of actually ordinary cells [63]. The expanded view of field effect is termed as etiologic field effect, which explains not only pathologic and molecular changes in pre-neoplastic cells but also explains influences of exogenous environmental factors and molecular changes in local microenvironment which may lead to neoplastic evolution [85].

Diagnosis

Diagnosis of bowel cancer can be done by obtaining a colon tissue sample during colonoscopy followed by medical imaging to know if the disease infection has been spread or not [13,86] (Table 2). Early screening is effective in preventing the disease and reduction of mortality from CRC [86]. Screening of CRC is suggested during the ages 50 to 75 year [87]. During colonoscopy, sometimes small polyps and sometimes a large poly or tumour is removed if found,

Table 5: Protein markers for diagnosis of colorectal tumours.

Sr. No.	Name of the marker	Sensitivity		Specificity	References
	Protein markers	Carcinoma	Adenoma		
	CA 242	55% 36%	15%	90% 96%	[121] [122]
	CA 19-9	34% 26%	4%	98% 98%	[123] [122]
	CA195	71%	ND	100%	[124]
	CA M26	22%	ND	99%	[125]
	CA 50	67% 51%	ND	99% 51%	[126] [127]
	CA 72-4	43%	ND	98%	[128] [122]
	CA M43	42%	ND	99%	[129]
	CEA	57% 56%	10%	85% 95%	[130] [131]
	CO 29.11	41%	ND	95%	[132]
	SLEX	25%	ND	96%	[133]
	PA 8-15	45%	ND	95%	[134]
	SIMA	36% 27%	ND	95% 89%	[135] [136]
	u-PA	76%	ND	80%	[137]
	NCA-50/90	35%	ND	95%	[138]
	TPA-M	70%	ND	96%	[131]
	NCC-ST 439	27%	ND	94%	[139]
	p53	26%	ND	100%	[140,141,142]
	DDX-48	10%	ND	100%	[143]
	sFasL	33%	8%	100%	[144]
	VEGF (plasma)	35%	8%	100%	[145]
	IGF-II + IGFBP-2		94%	31%	[115]
	SCF	89%	ND	17%	[146]
	Villin	51%	ND	97%	[147]
	Tenascin	25%	ND	95%	[148]
	TATI	74%	ND	34%	[127]
	a-L-fucosidase	69%	ND	85%	[149]
	CD26+	64%	ND	100%	[150]
	sCD26	90%	ND	90%	[151]
	BSP	100%	ND	88-96%	[152]
	Progesterone	M 64% F 57%	ND	37% 40%	[153]
	sP-selectin	21%	ND	99%	[154]
	Fibrin degradation	80%	ND	93%	[155]
	Laminin	89%	ND	88%	[156]

a biopsy may be done to check it nature if it is cancerous. Condition of the body and metastatic nature of tumor is usually monitoried by a CT scan of the pelvis, chest and abdomen region. Other useful imaging tests including MRI and PET may also be helped depending on the disease condition [13]. Colon cancer staging is usually based on radiology and pathology of tumor. TNM scheme which includes how much the preliminary tumor has extend, lymph node metastasis and distant metastases in more visceral organs, usually in liver [13].

Tumour cells are microscopically characterized by investigation of sample taken from biopsy. A pathology report describes the microscopic features of the tumor cells/tissue that includes both tumor cells as well tumor cells attack into healthy tissues. The commonest type of colon cancer is adenocarcinoma followed by sporadic cases of lymphoma and squamous cell carcinoma [88,89].

Immunohistochemistry

The suspected case of metastasis from colorectal cancer is properly diagnosed by immunohistochemistry. Usually proteins that are commonly expressed in colorectal cancers such as cytokeratin 20, CDX2, SATB2 & CDH17 are used as diagnostic markers. Nucleic acid and expressed surface or circulatory protein based several markers have been identified for CRC diagnostic and prognostic application (Table 3,4,5,6). Most of the colorectal adenomas (50%) and other colorectal cancers (80–90%) are contemplation to over express the cyclooxy genase-2 enzyme. This enzyme is usually not present in healthy colon, but is thought to fuel irregular cell growth [99,100].

Staging

Staging is chiefly made according to TNM staging process from the WHO, AJCC and UICC. The Astler-Coller categorization (1954) (Figures 3a, 3b) and the Dukes categorization (Figures 3c, 3d) (1932) are currently less used in staging classification [177, 178]. The commonest metastasis loci for colorectal cancer are lung, liver and peritoneum [179, 180].

Tumour Budding

Colorectal cancer tumour budding is loosely termed by the occurrence of individual cells as well as small tumour cells clusters. It acts as a well established independent marker for colorectal carcinoma. Tumour budding may allow differentiate the different people with various risk categories than those explained by TNM staging and may direct management decisions, particularly in T1 as well as T3 NO colorectal carcinoma. Unluckily, its widespread acceptance as a reportable factor has been occur with reverence to both quantitative and qualitative tumour budding aspects [181].

Prevention

It is anticipated that 50% of CRC cases are linked with faulty

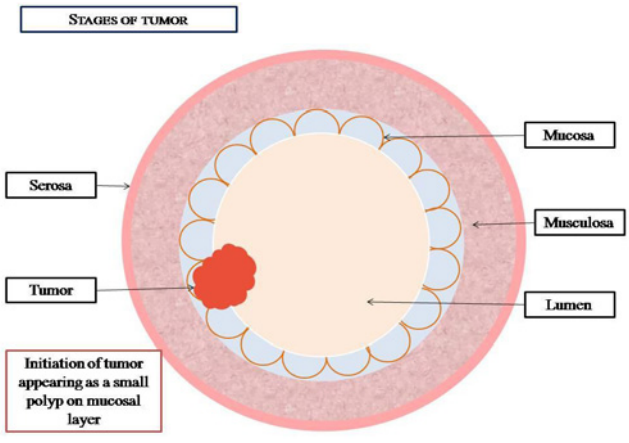

Figure 3a: Dukes stage A of colorectal cancer, showing characteristic polypoid growth of tumor in the in nermucosal layer and small protrusion in the luminal cavity of intestine.

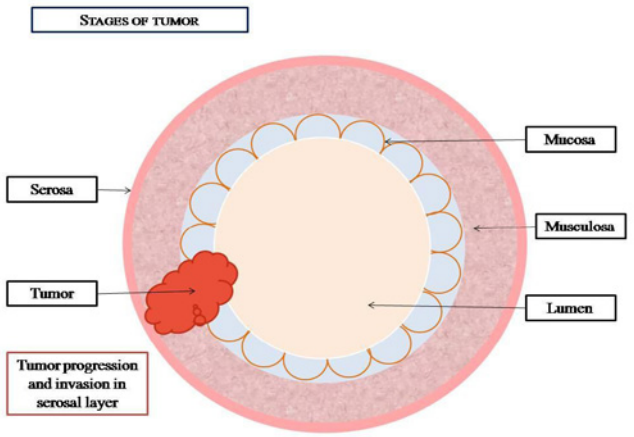

Figure 3b: Dukes stage B of colorectal cancer, showing characteristic progression of tumor into muscular layers of intestinal lining.

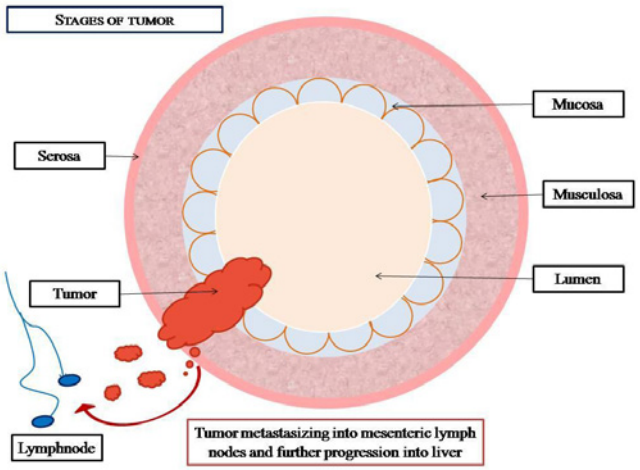

Figure 3c: Dukes stage C of colorectal cancer, showing characteristic progression of tumor and metastasis in the lymph nodes.

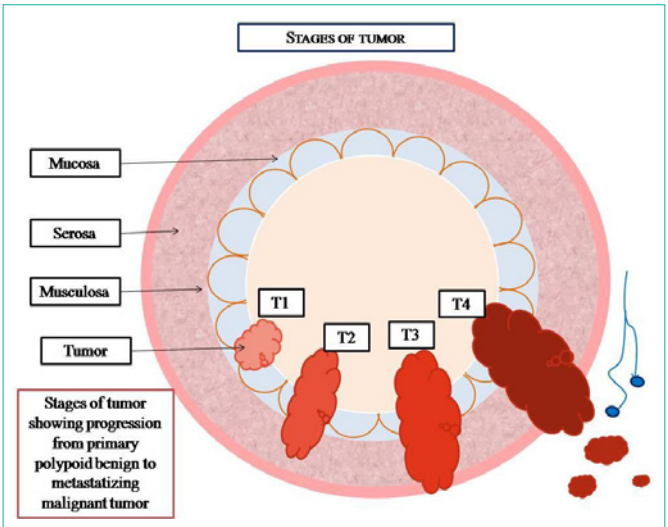

Figure 3d: The 'T' stages of Colorectal cancer starting from T1 and progressing upto T4 stage of metastasis.

lifestyle and about a quarter of cases are curable [182]. Growing surveillance, sufficient physical activity, fibre rich diet and alcohol Consumption Reduce the Chances of CRC [183].

Lifestyle

To prevent CRC, recent dietary recommendations include the consumption of whole grains, fruits and vegetables, and reducing the intake of red and processed meats [184]. Higher physical activity is also recommended to prevent CRC [185]. Physical exercise is linked with a modest decline in colon but not the rectal cancer chance [186,187]. Heavy Physical activity decline the chance of colon cancer by about 21% [188]. Regular sitting for lengthened period is linked with higher transience from colon cancer. The risk of CRC is not completely removed by regular exercise, though it is lowered [189]. The evidence for any defensive effect provided by fiber, fruits and vegetables is not well documented [190]. The chance of colon can also be decreased by maintained a usual weight of the body [191].

Medication

In persons with high risk group, aspirin and celecoxib seems to decline the chance of colorectal cancer [192-194]. The general use of NSAID is not suggested for this reason due to adverse effects. Aspirin is recommended in 50 to 60 years old persons, with risk for cardiovascular disease and colorectal cancer [87]. However, Aspirin is not suggested in those at typical risk of CRC [195]. Vitamin D intake and blood level of Vitamin-D is associated with reduced colon cancer chance [196,197].

Screening

Colorectal cancers arise in more than 80% from adenomatous polyps. Therefore, selection is effective for both early detection and prevention of CRC [13]. Screening of cases of colorectal cancer may indicate the CRC before 2-3 year of actual onset of clinical symptoms [13]. Any polyps that are found can be detached by surgical treatment which may prevent them from turning into cancerous growth. Selection has the potential to decrease colorectal cancer mortalities by 60% [198]. Selection has the potential to decrease colorectal cancer mortalities by 60%. The selection tests are done by colonscopy, fecal occult blood testing and flexible sigmoidoscopy [199]. Flexible sigmoidoscopy, is the best test for declining the chances of death due to CRC [200]. Other test such as stool DNA screening and virtual colonoscopy testing is also done [199]. Virtual colonoscopy *via* a CT scan appears as good as standard colonoscopy for detecting cancers and large adenomas. However, it has certain drawbacks such as expensive in nature, radiation exposure and detected abnormal growths cannot be removed by this test. For removal of abnormal growth standard colonoscopy is required [13]. Faecal Occult Blood Testing (FOBT) of the stool sample is suggested every two years [13]. In abnormal FOBT results, participants should undergo colonoscopy examination for further confirmation. FOBT selection from yearly to every two year may reduce colorectal cancer deaths by 16% Persons participating in regular screening for colorectal cancer mortality can be declined up to 23%, although it has not been verified to decline all -reason mortality [201]. Immunochemical tests are very precise and do not necessitate dietary changes before testing [202]. The stool DNA test uses biomarkers linked with precancerous lesions and colorectal cancer including blood haemoglobin and altered DNA.

Table 6: Nucleic acid Markers for diagnosis of colorectal tumours.

Sr. No	Name of the marker	Sensitivity for Carcinoma	Specificity	References
		DNA marker		
	K-ras	63%	73%	[157]
	APC	14%	100%	[158]
	P^{53}	13%	86%	[158]
	hMLH1Methylations	39%	98%	[159]
	HLTF Methylations	31%	93%	[159]
		mRNA marker		
	CEA	41%	100%	[160]
	CEA CK19	61%	100%	[161]
	CK20	22%	100%	[162,163,164]
	CK19	44%	97%	[162,163,164,165]
	hTERT	98%	64%	[166]
	CK8/CK19/CK20	56%	96%	[162]
	ProtM/CEA/CK20	13%	100%	[167]
	GCC	74%	95%	[168]
	CGM2	59%	100%	[169]
	uMAGE-A	32%	100%	[170]
	L6	`79%	100%	[171]
	Thymidylate synthase	47%	77%	[172]
		mi-RNA Markers		
	Diagnostics miR-21	71.6%	73.3%	[173]
	miR-92a	55%	73.3%	[173]
	miR-31- 3p and miR-31-5p (therapeutic)	Strongly associated with time to progression in patients treated with cetuximab but not in those treated with penitumumab		[174]
	miR-200b, miR-200c, miR-141 and miR-429 (Prognostic Markers)	After comparing all these markers, miR-200C was found to be over expressed in the patients having metastasis in Liver tissue, giving clear-cut idea about prognosis of patient.		[175]
	miR-200c, miR-224, miR-182 , miR-124, miR-30b and miR-155. (Prognostic Markers)	After comparing all these markers, miR-200C was found to be over expressed in the patients having metastasis in Liver tissue, giving clear-cut idea about prognosis of patient.		[175]
	miR-532-3p, miR-331, miR-195, miR-17, miR-142-3p, miR-15b, miR-532, and miR-652	These markers are able to identify polyps from controls and also able to differentiate stage IV colorectal cancers from controls.		[176]

Positive results should be further tested by colonoscopy.

Recommendations

CRC screening in the United States is recommended for people range between age of 50 to 75 years [87]. Person lies in range of age 76 and 85 years the judgment to screen should be individualized [87]. Different screening methods used for CRC are employed viz., stool based test taken place in every 3 years and sigmoidoscopy in every 5 years and colonoscopy can be made through in every 10 years. Conversely, it is not obvious that which of these two methods is enhanced [203]. For those persons who are at elevated risk, screening methods often begin at approximate age of 40 years [13]. Colonoscopy may find out more cancers in the first part of colon. Though, it is very costly and has many more complication. For those people who are with average risk who have had high-quality colonoscopy with usual results, screening in next 10 years is not required [204]. For people who are over the age of 75 year or those who are with life expectation less than 10 years, transmission is often not required [205]. Furthermore, it takes about 10 years after the screening for only one out of 1000 people to assistance [206]. In the people Canada, those who are at the age of 50 to 75 year are at usual risk and faecal immunochemical test of FOBT is required in every two years or sigmoidoscopy in every 10 years. Colonoscopy is often less chosen [131]. Some countries have national colorectal transmission programs which recommend FOBT screening for adults within a particular age group range between age 50 to 60 years. Examples of such type of countries with organized transmission program of CRC comprise United Kingdom [207], Netherlands [208] and Australia [209].

Treatment

The cure of colorectal cancer is generally targeted for palliation or cure. Treatments of CRCs comprise amalgamation of surgery, chemotherapy, targeted therapy and radiation therapy. The verdict of treatment option to take on depends on so numerous factors, counting the person's preferences and health, as well as stage of tumor [210]. When colorectal cancer is diagnose at an early stage (limited within wall of the colon), surgery might be curative. Conversely, when it is diagnosed at later on stage (remote metastases are present),

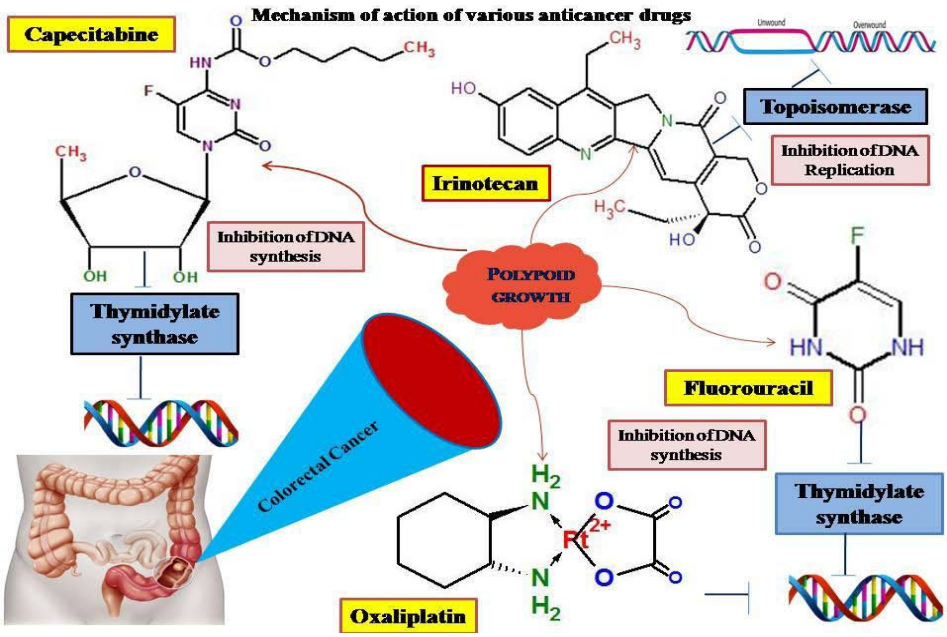

Figure 4: Schematic representation of mechanism of action of various anti cancer drugs frequently used in the treatment of colorectal cancer. Thymidylate syntheses and topoisomerase are the targeted enzymes used for inhibiting the growth of cancerous cells.

this is fewer like to treat and cure is often aimed at palliation, to mitigate symptoms that mainly caused due to tumor and keep the person as relaxed as possible [13]. Five year endurance rates are reported approximately 65% in the USA [211]. Conversely, survival rate depends on how complex the cancer is, whether or not all of the cancer can be cured with surgery, and the patient complete health situation.

Surgery

If the cancer is diagnosis takes place at incredibly very early stage, it can be cured during colonoscopy. Cure with complete surgical removal is a better choice of treatment for people who are suffering from localized cancer. Surgical removal can either be performed through an open laparotomy or few times laparoscopically [13]. The colon may after that may be reconnected or person might have colostomy. If there are barely some metastases in the lungs or liver they can perhaps also be cured. Occasionally chemotherapy is also useful before the surgery and shrink the cancer before attempting to cure it. The two most frequent sites of recurrence in colorectal cancer are lungs and liver [13].

Chemotherapy

In the CRC, chemotherapy perhaps is used in addition with surgery in some certain cases. The decision of adding chemotherapy in the executive of CRC depends on disease stage. In the stage 1 colon cancer, there is no chemotherapy offered and surgery is only the ultimate treatment. The main function of chemotherapy in the Stage II colon cancer is controversial, and is frequently not presented except risk factors such as T4 tumor or insufficient lymph node samples are recognized. It is very well recognized that the people who carry abnormality of mismatch to repair genes that do not benefit from the chemotherapy. In the stage III and for IV colon cancer, chemotherapy is an essential part of the treatment [13]. If cancer has spread to the lymph nodes or in distant organs, is the case with stage III and stage IV colon cancer correspondingly, chemotherapy agents such as fluorouracil, capecitabine or oxaliplatin can augment life expectancy. If the lymph node does not contain cancer cells, the settlement of chemotherapy are notorious. If the cancer is commonly metastatic or unrespectable, treatment is then analgesic. Usually in this situation, number of different chemotherapy medication can be applied [13]. Chemotherapy drugs are used in this type of conditions which can comprise oxaliplatin, irinotecan, fluorouracil, UFT and capecitabine (Figure 4). The drugs fluorouracil and capecitabine are transposable, associated with capecitabine being a verbal medication whereas fluorouracil being a spatial intravenous medicine. Some definite regimens used in FOLFOXIRI and CRC, FOLFIRI, and FOLFOX [212]. Antiangiogenic drugs such as bevacizumab are usually added in the first line therapy. A different type of the drugs is used in the second line of treatment are growth of epidemal factor receptro inhibitors, which the two FDA accepted ones are cetuximab and panitumumab [213]. The main difference in the approach to low stage rectal cancer is the amalgamation of the radiation therapy. Frequently, it is used in combination with the chemotherapy in the neoadjuvant fashion to allow surgical resection, so that eventually as colostomy is not compulsory. Conversely, this may not be probable in low deceitful tumors, in this case, a enduring colostomy might be required. In stage IV rectal cancer is cured alike to the colon cancer of stage IV [138].

Radiation Therapy

When the radiation and chemotherapy are combined, these may be helpful to rectal cancer [13]. Though, its exercise in colon cancer is not in practice due to the compassion of the entrails to radiation [214]. Just for chemotherapy, we can also use radiotherapy in neo-

adjuvant and adjuvant surroundings for few stages in rectal cancer.

Immunotherapy

Immunotherapy is associated with some immune checkpoint inhibitors has found to be useful for the type of colorectal cancer associated with divergence fewer repair deficiency and instability in microsatellite [215, 216]. Nearly all of the patients recover earlier, still condition get worse after few months or it may take years.

Palliative Care

The medical care's which focuses on the treatment of symptoms vary from serious illness is called Palliative care, like cancer and improving the survival quality of life in patients by the improving symptoms, nervousness and prevent the admissions to hospitals [217]. Recommendation of Palliative care is for any kind of person who has suffering from advanced colon cancer or has considerable symptoms. In the people who are associated with inoperable colorectal cancer, palliative care be capable of consisting of procedures that alleviate symptoms and complications from the cancer but don't stab to treat underlying cancer. Surgical options may include non-curative surgical removal of some of the cancer tissue, bypassing part of the intestines, or stent placement. These procedures can be considered to improve symptoms and reduce complications such as bleeding from the tumor, abdominal pain and intestinal obstruction [218]. Non-operative methods of symptomatic treatment include radiation therapy to decrease tumor size as well as pain medications [219].

Prognosis

In Europe, five-year survival rate for colorectal cancer is less than 60%. In the developed world about a third of people who get the disease die from it [13]. Survival straight related to the revealing and the kind of cancer implicated. Survival rates of premature stage revealing are nearly five times larger than that of last stage cancer. Many people with tumor, has not breach the muscular is mucosa (TNM stage Tis, N0, M0) have five-year and have 100% rate of survival. Patients with persistent cancer with TI (inside the submucosal layer) or T2 (inside the muscular layer) have an average of five-year persistent rate is just about 90%. Those with more persistent tumor yet lacking node participation (T3-4, N0, M0) have an average rate of survival five-year survival is about 70%. Patients of metastasis to regional lymph nodes (any T, N1-3, M0) with an average of five-year survival rate is about 40% whereas persons with far-away metastases (any T, any N, M1) with an average five-year survival with approximately 5% rate [220].

According to the American Cancer Society, around 20% of the people with colorectal cancer approach to medical analysis when the disease is previously advanced (stage IV) with equal to 25% of this grouped in isolated liver metastasis and is potentially resectable. In this kind of discriminatory group, those person who undergoes remedial resection experience of five-year survival outcome in a third of the cases [221]. Fewer than 600 genes are associated with outcomes incolorectal cancer [4]. These comprise both adverse genes, wherever high appearance is related to the poor outcome, for illustration heat shock 70 kDa protein 1 (HSPA1A), and favorable genes with high expression is allied with improved survival for example alleged RNA-binding protein 3 (RBM3) [222].

Conclusion

Colorectal cancer is one of the common metastatic neoplasms in human. Its spread to other organs is a complex process which involves several mechanisms and molecular pathways. However, advances in modern medical techniques allow early and accurate diagnosis of metastatic cancers irrespective of their location. The advancement in basic research in colorectal cancers lead to easy understanding of molecular basis of origin and spread which can be further translated into its control and therapy. However, the monitoring of colorectal metastases has undergone little improvement in the last decades. With advances in liver-directed therapy, systemic therapy and understanding of how to treat primary tumor, overall patient survival continued to increase. The combination therapies using classic and recent chemotherapies along with other biological agents increased over all patient survival rates. Patients suffering with metastatic Colorectal Cancer (mCRC) should be treated by a multidisciplinary team consisting of onco-surgeon, radiologist and gastroenterologist to provide the most appropriate therapy. With the advancement in targeted therapy potential paradigm shifts in treatment of rectal cancer can be expected in coming future.

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