COLON CANCER AND ITS TREATMENT

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1. ABSTRACT

Colon cancer, a major contributor to cancer-related morbidity and mortality, remains a global health challenge. The most recent scientific discoveries and clinical developments in the field of colon cancer and its treatment are summarised in this thorough review article. The review deals with the examination of the etiological components, highlighting the crucial role that genetic mutations, epigenetic changes, and environmental factors play in the development of colon cancer. It explores the complex molecular mechanisms underlying tumor genesis, growth, and metastasis, illuminating key signaling pathways like Wnt/-catenin, PI3K/AKT, and RAS/RAF. The primary focus of the review is the evolving landscape of colon cancer therapy choices. It includes the latest recent developments in radiation, less invasive surgical techniques, and robot-assisted operations, as well as how these affect patient outcomes. Additionally, it offers a thorough overview of the expanding selection of targeted medications and immunotherapies, emphasizing their potential to fundamentally alter how colon cancer is treated. This study further highlights the importance of precision oncology and personalized medicine in developing treatment plans specific to each patient's molecular profile. This review article bridges the gap between fundamental research and clinical applications by providing a thorough understanding of the complex landscape of colon cancer.

2. INTRODUCTION

Colorectal cancer, commonly known as colon cancer, is a type of cancer that develops in the colon or rectum. It is the third most commonly diagnosed cancer in both men and women worldwide, with an estimated 1.9 million new cases and 935,000 deaths in 2020 [1]. The incidence of colon cancer varies greatly between countries, with higher rates observed in developed countries [1]. It

ranks as the third-leading factor in both men's and women's cancer-related fatalities in the United States [2].

Colon cancer, also referred to as colorectal cancer, is one of the most prevalent cancers worldwide and a major contributor to cancer-related morbidity and mortality. It grows from the epithelial cells lining the colon or rectum and frequently starts out as benign polyps that later evolve into malignant tumors. Multiple genetic, environmental, and lifestyle factors can all have an impact on the development of colon cancer, making it a complex and multifactorial disease. Improving patient outcomes and lessening the impact of this fatal disease depends heavily on early detection and efficient therapeutic approaches.

Several factors contribute to the development of colon cancer, including age, family history, lifestyle factors such as diet and physical activity, and underlying medical conditions such as inflammatory bowel disease [2]. Early detection and treatment are crucial for improving outcomes, as colon cancer often has no symptoms in its early stages [3].

Significant improvements have been made in the understanding of colon cancer biology, diagnosis, and treatment in recent years. These discoveries have completely changed how colon cancer is treated, improving patient quality of life and survival rates. This in-depth analysis attempts to examine the most recent advancements in colon cancer treatment, highlighting important therapeutic methods and their corresponding advantages.

(a) **The burden of colon cancer:** In the world, colon cancer is one of the leading causes of cancer-related morbidity and mortality. With more than 1.9 million new cases and 900,000 reported deaths annually, it ranks as the third most frequently diagnosed cancer in both men and women. To lessen the disease's impact on public health, these frightening statistics call for a fuller understanding of the illness and its treatment.

(b) **Pathogenesis and Molecular Subtypes**: Colon cancer is brought on by an abnormal alteration in the epithelial cells lining the colon or rectum. This complex disease's onset and course are influenced by genetic and epigenetic changes as well as environmental variables. Recent developments in molecular profiling methods have made it possible to distinguish between different subtypes of colon cancer according to their genomic and transcriptome characteristics. This molecular division sheds important light on tumours' biology, prognosis, and prospective treatment targets.

(c) **Screening and early detection**: Decreases in morbidity and mortality linked to colon cancer are significantly aided by early detection. Colonoscopy, faecal occult blood tests, and molecular biomarkers are a few screening tools that can help find precancerous lesions or early-stage tumours. A decrease in colon cancer incidence and fatality rates has been attributed to improved screening techniques along with public awareness initiatives. Optimizing screening programs' availability, acceptance, and effectiveness still faces obstacles [3].

The purpose of this research paper is to review the current state of knowledge on colon cancer, including its epidemiology, risk factors, diagnosis, treatment, and prevention. The paper will also

discuss recent advances in research on colon cancer, including the development of new diagnostic and therapeutic approaches.

1. **Surgical Interventions**: Surgery continues to be the mainstay of curative care for locally advanced colon cancer. The tumour and any adjacent lymph nodes must be removed as part of surgical therapy. Minimally invasive procedures like laparoscopic and robotic-assisted operations have essentially taken the role of traditional open surgery in modern medicine. These strategies provide benefits like decreased postoperative discomfort, shorter hospital stays, and quicker recovery [4].

2. **Chemotherapy and Targeted Therapies:** Chemotherapy has long been an essential part of the management of colon cancer that has spread to other organs or that has reached an advanced stage. Fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and fluorouracil, leucovorin, and irinotecan (FOLFIRI) combination regimens were shown to be significantly more effective at increasing overall survival and disease-free survival rates. A new era of personalised medicine has also begun with the development of targeted medicines. By selectively targeting molecular markers such as the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF), respectively, which are critical for tumour growth and angiogenesis, monoclonal antibodies, such as cetuximab and bevacizumab, have demonstrated promising outcomes [5].

3. **Immunotherapy:** For a variety of solid tumours, including colon cancer, immunotherapy, particularly immune checkpoint inhibitors, has become a ground-breaking therapeutic approach. Patients with mismatch repair-deficient (dMM) or microsatellite instability-high (MSI-H) have shown sustained responses to drugs targeting programmed cell death protein 1 (PD-1) and its ligand (PD-L1).

4. **Emerging Methods of Treatment:**

Current research initiatives have produced a number of cutting-edge colon cancer therapy methods in addition to well-established therapeutic modalities. These include innovative combinations of targeted drugs and immunotherapies, tumour-targeted gene treatments, adoptive cell transfer techniques, and nanoparticle-based drug delivery systems [6].

3. STATISTICAL DATA ON COLON CANCER:

Acta Biomed 2024; Vol. 95, N. 1: ISSN: 0392-4203 | eISSN: 2531-6745

Table 1: Colon Cancer Cases in 2020 and Projections To 2040

COUNTRY	CASES IN 2020	CASES IN 2040
USA	155008	205978
BRAZIL	55102	97229
FRANCE	48061	62702
UK	52128	68694
ITALY	48576	60133
GERMANY	57528	70054
INDIA	65358	107415
CHINA	555477	911970
RUSSIA	77213	91543
JAPAN	148505	164267

LOCATION	NUMBER OF CASES
RECTUM	7,32,210
COLON	11,48,515
COLORECTAL	19,31,590

Table 2: Number of New Cases In 2020

Table 3: Number of Death Cases In 2020

LOCATION	NUMBER OF CASES
RECTUM	3,39,022
COLON	5,76,858
COLORECTAL	9,35,173

Table 4: World CRC Estimated Age Standardized Incidence and Mortality Rates in 2020 (All Ages)

Population *	Incidence (%)	Mortality (%)
Upper middle income	887,025 (45.94)	461,511 (49.37)
High income	819,143 (42.43)	340,272 (36.40)
Low middle income	194,954 (10.10)	112,556 (12.04)
Low income	29,542 (1.53)	20,392 (2.18)
Total	19,30,664	934,73

Table 5: Histological Variety and Malignancy Association:

HISTOLOGICAL TYPE	PERCENTAGE OF COLON CANCER CASES	PERCENTAGE OF MALIGNANCY
Tubular	60-80%	< 5%
Tubulovillous	10-25%	20-25%
Villous	5-10%	35-45%

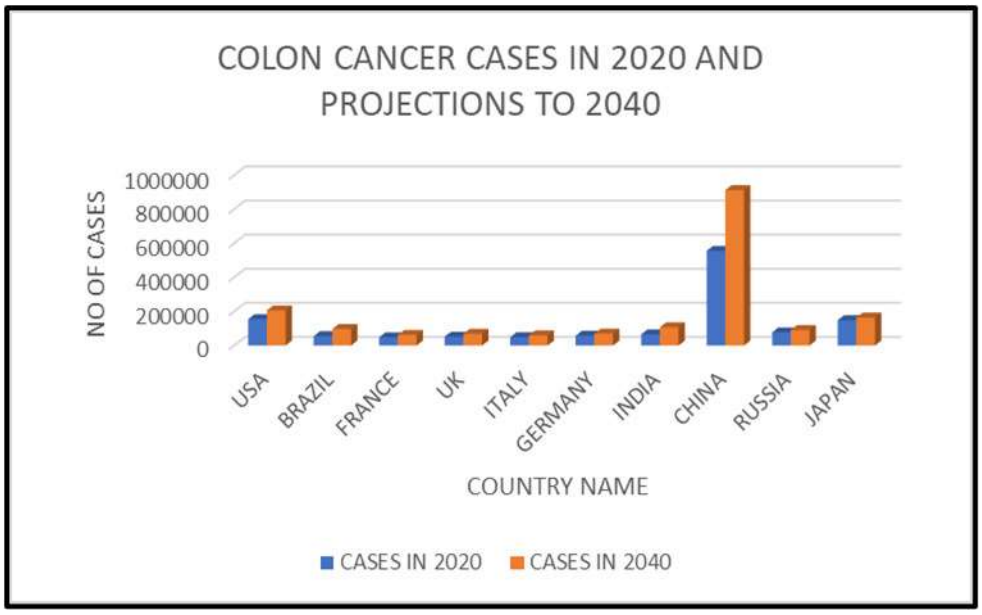

Fig-1: Colon Cancer Cases in 2020and Projections To 2040

Source: (a) Yue Xi, Pengfei Xu, Global colorectal cancer burden in 2020 and projections to 2040,TranslationalOncology,Volume14,Issue10,2021,101174,ISSN1936-5233,https://doi.org/10.1016/j.tranon.2021.101174. (https://www.sciencedirect.com/science/article/pii/S1936523321001662)Abstract: As the third most common malignancy and the second most deadly cancer, colorectal cancer (CRC) induces estimated 1.9 million incidence cases and 0.9 million deaths worldwide in 2020. The incidence of CRC is higher in highly developed countries, and it is increasing in middle- and low-income countries due to westernization. Moreover, a rising incidence of early-onset CRC is also emerging. The large number of CRC cases poses a growing global public health challenge. Raising awareness of CRC is important to promote healthy lifestyle choices, novel strategies for CRC management, and implementation of global screening programs, which are critical to reducing CRC morbidity and mortality in the future. CRC is a heterogeneous disease, and its subtype affiliation influences prognosis and therapeutic response. An accurate CRC subtype classification system is of great significance for basic research and clinical outcome. Here, we present the global epidemiology of CRC in 2020 and projections for 2040, review the major CRC subtypes to better understand CRC

molecular basis, and summarize current risk factors, prevention, and screening strategies for CRC.Keywords: Colorectal cancer; Epidemiology; Projection; Risk factors; Prevention.

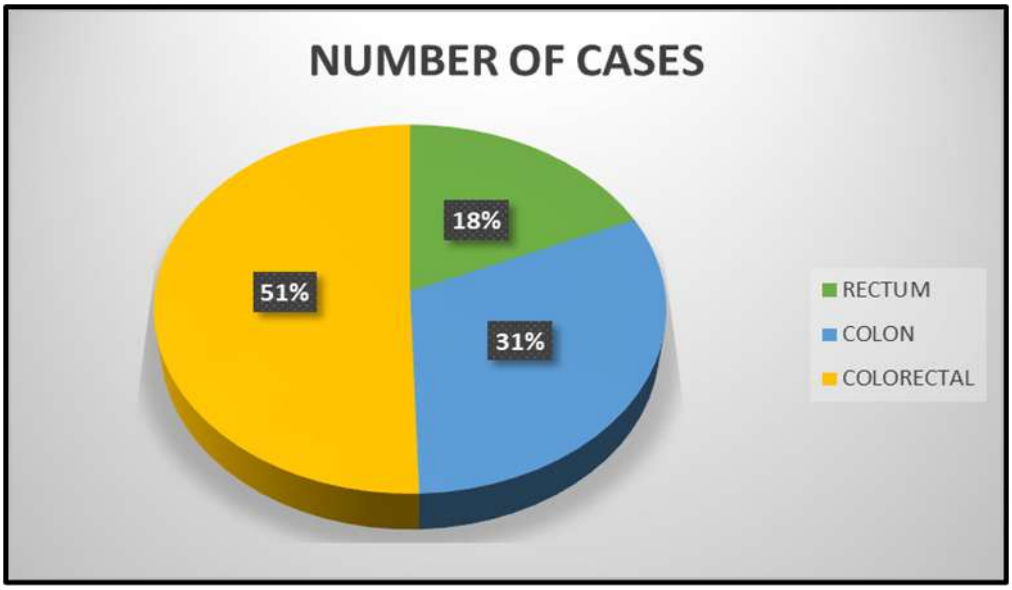

Fig-2: - number of new cases in 2020

Source:- (a) Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi J, John A, Lim YC, Kibria KMK, Mohiuddin AKM, Ming LC, Goh KW, Hadi MA. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers (Basel). 2022 Mar 29;14(7):1732.

doi: 10.3390/cancers14071732. PMID: 35406504; PMCID: PMC8996939.

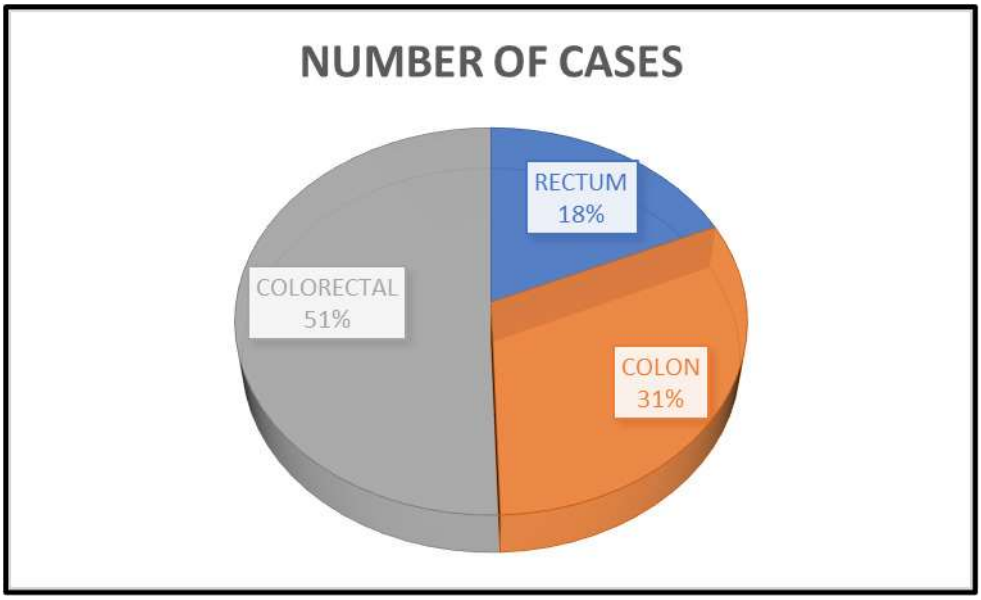

Fig-3:- Number of death cases in 2020

Source: (a) Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi J, John A, Lim YC, Kibria KMK, Mohiuddin AKM, Ming LC, Goh KW, Hadi MA. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers (Basel). 2022 Mar 29;14(7):1732.

Doi: 10.3390/cancers14071732. PMID: 35406504; PMCID: PMC8996939

3. COLORECTAL CANCER DEVELOPMENT:

Despite having a wide genetic makeup, CRC can develop using a number of distinct pathways. As a result of the varied levels of gene expression patterns, many CRC cells, for instance, displayed dozens of somaclonal mutations, it is thought that CRC has one of the most astounding mutational loads of any malignancy. According to how many somaclonal mutations there are, CRC can be roughly split into two categories: hypermutated (more than 12 mutations per 106 bases) and non-hypermutated (less than 8.24 mutations per 106 bases) [7]. A unique categorization strategy for CRC was developed as a result of parallel efforts to classify CRC based on gene expression profiles. These classifications have been altered and amended as a result of the integration of data on gene expression patterns and tumour genotypes [8].

Epithelial cells undergo a series of genetic or epigenetic modifications that make them hyperproliferative, which leads to CRC [9]. These quickly proliferating cells create a benign adenoma, which can evolve into cancer and spread by a number of different pathways, including serrated neoplasia, chromosomal instability, and microsatellite instability (MSI) [10,11,12]. The term "adenoma-carcinoma sequence" refers to the development of cancer. The majority of sporadic CRC cases are brought on by the conventional pathway. A little adenoma develops into a large adenoma, and then cancer. This route is highly correlated with the chromosomal instability (CIN)-positive subtype (CIN-positive) development.

The formation of the CpG island methylator phenotype (CIMP)-high subtype frequently involves this route, which is important in inflammation. Long-term inflammation causes indeterminate dysplasia to develop in normal cells, which progresses to low-grade dysplasia, high-grade dysplasia, and finally, malignant dysplasia and ultimately cancer [13]. Preventive colectomy and inflammatory bowel disorders, respectively, account for less than 2% of CRC cases worldwide. Benign precursor lesions are treatable in all pathways, even though they are more visible in the adenoma-carcinoma and serrated paths.

Adenocarcinomas can invade to the point of spreading to other bodily areas by using lymphatic and blood vessels. 96% of CRCs are adenocarcinomas, on average [14]. However, it could take up to 18 years between the development of a polyp and aggressive cancer. Metastasis often develops over the course of nine years [15]. Stages 0 (carcinoma in situ) to stage IV are used to categorise CRCs, just like any other tumour or cancer.

Acta Biomed 2024; Vol. 95, N. 1: ISSN: 0392-4203 | eISSN: 2531-6745

The growth of dysplastic tissue (tumour) is typically the outcome of a non-cancerous development, and once the cells have experienced numerous aberrant DNA mutations, CRC can occur. Soft tissue tumours that do not metastasis (spread to other regions of the body) are considered non-cancerous (benign). A stage 0 (benign) polyp or adenoma develops as a result of hyperproliferation. 10% of adenomatous polyps can develop into stage I adenocarcinomas, which infiltrate the muscularis propria. In stages II and III, the tumour enlarges and continues to infiltrate serosal and visceral peritoneal tissue. Stage IV metastasis of the lymph nodes or blood vessels is also a possibility [16].

The disease's severity and the types of treatments accessible are based on the stage [17]. Stages 0-II CRC should be treated with surgery; stage III CRC should be treated with surgery and adjuvant chemotherapy; and stage IV and recurring CRC should be treated with surgery, chemotherapy, and targeted therapy. Sadly, there is currently no known for sure established cure for CRC.

4. ETIOLOGY:

Colon cancer (Cca) can manifest itself sporadically (70%), familially (20%), or through inherited disorders (10%). The majority of sporadic CCA cases are diagnosed at an older age than 50 and are associated with environmental factors, as opposed to a small percentage of patients who have a true inherited pattern that increases risk at a younger age (less than 50 years). The remaining 20% of cases are familial clustering in the absence of a recognised inherited syndrome. Hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are the two most prevalent inherited CRC disorders [18][19]. These two genetic syndromes are thought to be responsible for about 5% of all CRC malignancies, although as many as 10% to 15% of CRC patients who were not chosen will have a high-risk mutation unrelated to FAP or HNPCC.

Adenomatous polyps, polyps with villous or tubulovillous dysplasia, personal or family history of CRC, and other risk factors including adenomatous polyps and polyps indicate a significant risk for synchronous and metachronous CRC primary cancer up to 3% to 5% after 5 years or even longer after resection, necessitating a narrower screening interval. An estimated incidence of 0.5% per year between 10 and 20 years after the time of IBD diagnosis and 1% per year after that, reaching a 30% risk probability by the fourth decade of patients with pancolitis, indicates a well-known association between inflammatory bowel disease (IBD), particularly ulcerative colitis, and Cca. If present in the ileocolic area, Crohn's illness may make Cca riskier.

The findings of epidemiologic research point to significant environmental and lifestyle links with CRC. Among others, obesity, red/processed meat, tobacco, alcohol, androgen deprivation therapy, as well as cholecystectomy, are associated with a slight but significant increase in the risk of CRC. Large population studies, however, have discovered CRC protective factors such as exercise, diet (fruits and vegetables, fibre, resistant starch, fish), vitamin supplements (folate, folic acid, pyridoxine B6, calcium, vitamin D, magnesium), garlic and coffee, and medications (aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), hormonal replacement therapy in postmenopausal, statins, bisphosphonate, and angiotensin inhibitors).

Interestingly, a randomized controlled clinical trial found that 600 mg of aspirin in Lynch syndrome had a protective effect against colorectal adenomas and cancer with substantially reduced cancer incidence after 55.7 months with an HR of 0.56 [20].

EPIDEMIOLOGY:

Globally, there are expected to be 10.3 million cancer deaths and 19.3 million new cases in 2020, according to GLOBOCAN data, of which CRC is anticipated to be responsible for 0.94 million (9.4%) deaths and 1.93 million (10%) additional instances. Between nations and global regions, there are significant differences in the incidence and mortality of CRC. They are linked to the nation's economic situation as well. The World Bank reports that new cases and deaths are more notable in higher-income areas and less noticeable in lower-income places [21].

After breast and lung cancer, colon cancer is the third most frequent cancer in India. The Indian Council of Medical Research (ICMR) estimates that 45,000 new cases of colon cancer would be diagnosed in India year 2020. The prevalence of colon cancer varies across the nation, with metropolitan areas experiencing greater rates than rural ones. In addition, it has been noted that India's age-standardized incidence rate (ASIR) for colon cancer is approximately 4.4 per 100,000 people, with a higher incidence seen in men than in women [22].

The increase in early identification through colonoscopy and removal of precancerous lesions in persons between the ages of 50 and 75 has led to a progressive drop in the incidence, nonetheless. In 2013, the rate of colonoscopies performed rose from 19.1% to 54%. In the most recent GLOBOCAN 2012 data, colorectal cancer was listed as the second most prevalent kind of cancer in women with 614 000 cases representing 9.2% of all cancers and the third most prevalent type in males with 1361,000 cases representing 10% of all cancers [23].

In the less developed parts of the world, the incidence for both sexes fluctuates at 1361,000 cases with a mortality rate of 694,000 (8.5% of all cancers), which is inferior with higher fatalities (52%) there [24].

In 2010, the INEGI recorded 74,685 cancer-related fatalities (13% of all deaths in Mexico), of which colorectal cancer accounted for 5.4%. Colorectal cancer may be hereditary or sporadic, related to errors in DNA mutagenesis, transcriptional silencing of suppressor tumour genes, genes controlling cellular cycle, repair, and apoptosis, or genetic in origin, related to mutations in suppressor gene tumours like APC, DCC, BRAF, PIK3CA, AKT, and TP53, or the presence of oncogenes like K-RAS and CTNNB1.14 [25].

The causes include chromosomal abnormalities, gene mutations, and epigenetic alterations impacting proliferation, differentiation, apoptosis, and angiogenesis [26].Nevertheless, it is presently thought of as a biomarker that predicts the responsiveness to therapy via EGFR17. Only 5% of the mutations in codons 61, 146, and 154 are found in sporadic colorectal cancer, which is caused by activating the oncogene K-RAS on chromosome 12 [27]. These mutations are typically found in patients who have metastasized. While mutations in codon 12 are associated with

mucinous cancer, those in codon 13 are associated with non-mucinous cancer, which is more aggressive and more likely to spread to other organs.16- 18,specifically in the codon 13 region, a KRAS mutation is thought to have a poor prognosis [28, 29].

The tumour suppressor gene APC's inactive mutation, which causes familial adenomatous polyposis and about 85% of colorectal cancers without a hereditary component, is the starting point of the genetic pathway. Some adenocarcinomas arise as a result of the mutational activation of the B-catenin (CTNNB1) protein, which is controlled by APC, or as a result of a second mechanism brought on by the inactivation of a group of tumour suppressor genes involved in DNA repair [30].

These genes are referred to as MMR genes or mismatches, and they include the human homolog mutS (MSH2), the human homolog 1 Mutl, (MLH1), and the postmeiotic segregation gene enhanced type 2 (PMS2), which affects both hereditary conditions and sporadic colorectal cancer. Mutations always occur in specific ways, first those that affect the APC gene followed by those that affect the RAS gene. 50% of cases include TP5, a suppressor tumour gene, and these changes tend to occur more near the end of the sequence [31].

The WNT/B-catenin glicoproteic signal pathway, which is connected to cellular proliferation and tissue homeostasis, may be impacted by the somatic changes. Its mutation is prevalent in 95% of individuals with colon cancer and has been connected to human disorders like congenital abnormalities, cancer, and osteoporosis [32,33]. The rs59336 allele, which is located in the TBX3 gene's intron and is part of the WTN/B catenin pathway, has been associated with an increased risk of developing colorectal cancer [34]. Changes in genes like SMAD7 have been related to altering the course of colorectal cancer [35,36], despite the fact that the SMAD7 gene has three known variants (rs44939827, rs12953717, and rs4464248) that increase the risk of colorectal cancer. The chance of getting colorectal cancer can also be impacted by other genetic errors, however [37] these are not the only ones.

Currently, genes that defend against metastases have been discovered. One such gene is KISS1, which links to the KISS receptor. When KISS1 and KISS1R levels are high, the survival rate considerably increases and metastasis is effectively suppressed [38].

It has been discovered that certain genes, like KISS1, which links to the KISS receptor, inhibit metastasis. High levels of KISS1 considerably increase the survival rate and are necessary for metastatic suppression.

5. PATHOPHYSIOLOGY:

A build-up of somatic (acquired) and/or germline (inherited) genetic abnormalities is required for the transformation of the normal colonic epithelium into a precancerous lesion (adenoma) and finally into invasive carcinoma. According to the hypothesis of colonic carcinogenesis, clonal mutations evolve, giving cells a chance at immortality and enabling the development of other mutations that result in additional cancer hallmarks including proliferation, invasion, and metastasis. Clinical data has demonstrated that adenomatous polyps, which often develop

dysplastic alterations in a 10- to 15-year window before developing invasive carcinoma, are a major contributor to the development of CRCs. As a result, the incidence of CRC can be decreased by removing polyps as soon as they are discovered. Hamartomatous and serrated polyps may cause CRC, according to newly discovered research [39].

Chromosomal instability, mismatch repair, and hypermethylation are the three main molecular processes that are connected to CRC. As demonstrated with mutations in the adenomatous polyposis coli (APC), a hallmark of FAP, the chromosomal instability pathway is a gain of mutations unbalancing oncogene and tumour suppressors equilibrium. Microsatellite instability (MSI-H), a characteristic of Lynch syndrome, is caused by cells with a defect in DNA mismatch repair (dMMR), often MLH1 or MSH2. These cells collect mistakes in the genome that will be repeated and cause high levels of MSI-H. Certain genes, BRAF and MLH1, may be activated or silenced depending on the degree of CpG hypermethylation in the DNA. Somatic mutations of sporadic oncogenes (RAS, SRC, and MYC) have been linked to CRC, with RAS having the most clinical significance. In 50% of CRC, RAS mutations (HRAS, KRAS, and NRAS) are present. A Lynch-like syndrome with MSI-H could be caused by specific MMR gene mutations in hMSH2, hMLH1, hPMS1 and hPMS2, hMSH6, and hMLH3; each of them interacts with MLH1 and is around 15% of all sporadic CRC, necessitating universal testing. When combined with an APC gene mutation or a bi-allelic second hit, MUTYH disorders exhibit a recessive inheritance pattern. The genes for cyclooxygenase (COX-2) and peroxisome proliferator-activating receptor (PPAR) have been linked to the development of CRC tumours, and their potential chemoprotective effects are currently being studied [40].

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Chromosomal instability, mismatch repair, and hypermethylation are the three principal molecular mechanisms that connect CRC to other diseases. As demonstrated by mutations in the adenomatous polyposis coli (APC), a hallmark of FAP, the chromosomal instability pathway is a gain of mutations that upsets the equilibrium between oncogene and tumour suppressors. High levels of microsatellite instability (MSI-H), a defining characteristic of Lynch syndrome, are caused by cells with a deficit in DNA mismatch repair (dMMR), often MLH1 or MSH2. Certain genes, including MLH1 and BRAF, may express themselves when CpG hypermethylation of DNA occurs either actively or passively. RAS has the most clinical relevance among the sporadic

oncogene somatic mutations (RAS, SRC, and MYC) that have been linked to CRC. The discovery of RAS mutations variants (HRAS, KRAS, NRAS) in 50% of CRC sporadic cases, the absence of response to epidermal growth factor receptors (EGFR) targeted therapy, and possible direct targeted medicines are currently being used in CRC screening by stool-DNA testing. The loss of the APC 5q21 gene (80% sporadic), TP53 17p gene (50-70% sporadic), and DCC/SMAD2-4 18q gene (73% sporadic) are examples of tumour suppressor genes, which need bi-allelic loss (also known as the "two-hit model"). A Lynch-like syndrome with MSI-H could be caused by specific MMR gene mutations in hMSH2, hMLH1, hPMS1 and hPMS2, hMSH6, and hMLH3; each of them interacts with MLH1 and is around 15% of all sporadic CRC, necessitating universal testing. When combined with an APC gene mutation or a bi-allelic second hit, MUTYH disorders exhibit a recessive inheritance pattern. The genes for cyclooxygenase (COX-2) and peroxisome proliferator-activating receptor (PPAR) have been linked to the development of CRC tumours, and their potential chemoprotective effects are currently being studied [42].

6. HISTOPATHOLOGY:

The proper diagnosis, prognostication, and choice of treatment are significantly hampered by the complexity and heterogeneity of colon cancer. A thorough histopathological examination is essential for classifying colon cancer and offers important information on the biology and behaviour of the tumour. In this article, advanced histological characteristics of colon cancer, such as tumour grading, tumour budding, perineural invasion, lymphovascular invasion, and molecular markers, are discussed. Their importance in predicting patient outcomes and directing therapy approaches is highlighted. Also highlighted are current developments in molecular pathology methods and how they affect the treatment of colon cancer. To improve patient care, the essay emphasises the necessity of a thorough histological assessment of colon cancer.

Tumour Grading:

Grading of tumours aids in stratifying patients depending on the tumour's aggressiveness and is a crucial part of the histological evaluation of colon cancer. Widespread use has been made of the World Health Organisation (WHO) grading system, which divides tumours into well-, moderately-, and poorly-differentiated groups. The level of tumour differentiation is correlated with prognosis, with poorly differentiated tumours being linked to worse outcomes [43].

Tumour Budding: At the tumour's invasive front, there may be a few clusters of cells or a single cell. It is a morphological sign of tumour cell separation and is linked to a worse prognosis and a higher incidence of lymph node metastases in people with colon cancer [44].Severalf grading schemes, notably the International Tumour Budding Consensus Conference (ITBCC) grading scheme, have been developed to evaluate tumour budding.

Perineural Invasion (PNI): Perineural invasion is the infiltration of tumour cells into nerves and is known to be a poor prognostic indicator for colon cancer. Local recurrence, lymph node

metastasis, and distant metastasis are all more likely to occur in PNI patients. To plan an effective course of treatment, PNI must be accurately identified and reported [45].

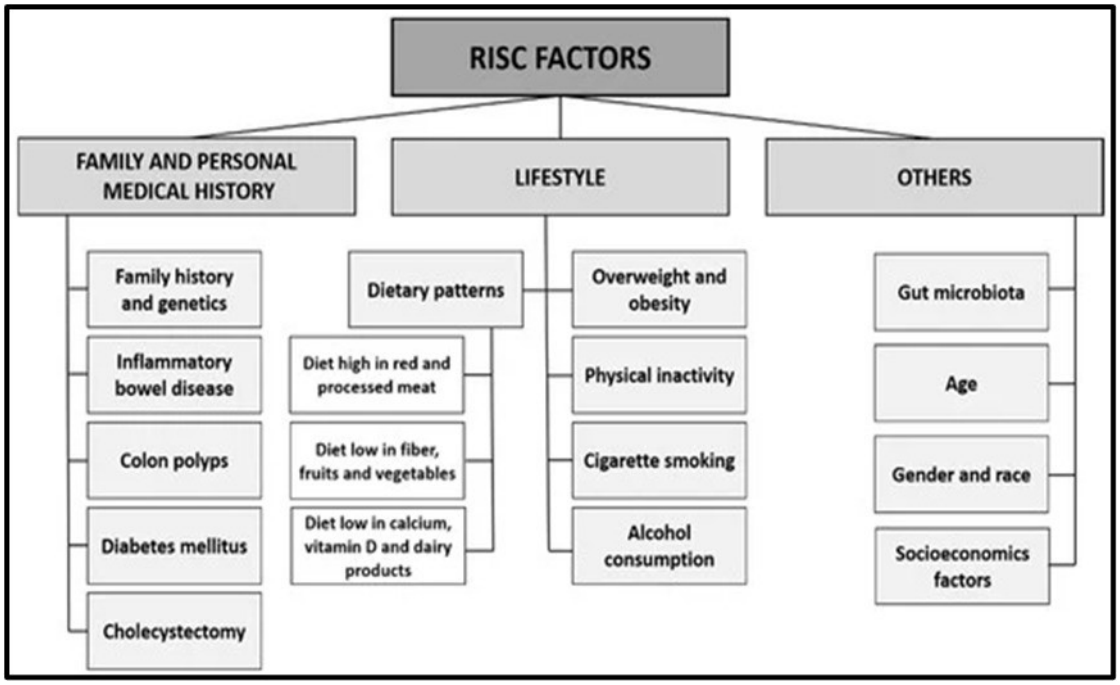
Lymphovascular Invasion (LVI): Lymphovascular invasion describes the infiltration of tumour cells into blood or lymphatic vessels. It is linked to a higher risk of distant dissemination and metastasis to lymph nodes. For patients with colon cancer, LVI assessment has a considerable impact on the staging and therapy choices [46].

Molecular Markers: New developments in molecular pathology have uncovered several molecular markers that are significant for prognostic and predictive purposes in colon cancer. These indicators include the existence of microsatellite instability (MSI), KRAS and BRAF mutations, and mismatch repair protein expression. The use of targeted medicines and immunotherapies may be guided by the prognostic significance of MSI-high tumours, BRAF mutations, and loss of mismatch repair proteins [47].

The cornerstone of colon cancer management continues to be histopathological assessment. Advanced histopathological characteristics, such as tumour grading, tumour budding, perineural invasion, lymphovascular invasion, and molecular markers, offer useful prognostic data and direct therapy choices. The inclusion of these factors in standard clinical practice can enhance risk classification and support individualised treatment plans. Our knowledge of colon cancer heterogeneity will likely be further refined as a result of ongoing research and technical developments in molecular pathology, which will hopefully improve patient care.

7. RISK FACTOR:

Fig-4: Risk factors associated with colorectal cancer



Source: A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/The-main-risk-factors-associated-with-colorectal-cancer_fig1_351103549 [accessed 5 Jul, 2023].

With a high prevalence of morbidity and mortality, colorectal cancer, also known as colon cancer, is a serious health concern for people all over the world. While several risk factors have been identified, recent research has thrown light on advanced risk factors that can help colon cancer develop and advance. In order to comprehend the complicated aetiology of colon cancer, this in-depth study tries to summarise the most recent research on these cutting-edge risk factors [48].

Microbiome Dysbiosis: According to recent research, dysbiosis, or changes in the composition of the gut microbiome, may have a role in the development of colon cancer. According to studies, changes in the relative abundance of some bacterial species—including Fusobacterium nucleatum and Escherichia coli—are linked to a higher risk of colon cancer. According to Zackular et al. (2013), dysbiosis-induced inflammation and the creation of genotoxic metabolites also contribute to the development and spread of colorectal tumours [49].

Lifestyle Factors: A number of lifestyle factors have been linked to a higher risk of colon cancer. Sedentary behaviour, obesity, and poor dietary habits-characterized by a high intake of red and processed meats, saturated fats, and little fiber-contribute to an unfavourable metabolic environment, chronic inflammation, and oxidative stress, which in turn encourage colon carcinogenesis [50].

Hereditary Genetic Variants: Between 5 and 10% of instances of colon cancer are thought to be caused by hereditary causes. Adenomatous polyposis coli (APC), mismatch repair genes (MLH1, MSH2, MSH6, PMS2), and DNA repair genes (e.g., MUTYH) are just a few of the genetic changes that have been found to enhance the risk of developing colon cancer [51]. To determine those at higher risk, genetic testing and counselling for people with a family history of colon cancer are essential.

Age: Colon cancer primarily affects those over 50, with the risk considerably rising as people get older. Colon cancer is largely influenced by aging-related changes in DNA repair systems, increasing exposure to environmental stressors, and accumulative genetic abnormalities [52].

An individual's personal history of polyps or inflammatory bowel disease (IBD). The chance of developing colon cancer is higher in people who have a history of precancerous colon polyps (adenomas) or chronic inflammatory bowel illnesses, such as ulcerative colitis or Crohn's disease. These illnesses can encourage the growth of tumours because of the ongoing inflammation and genetic changes they cause [53,54]

Physical inactivity: Sedentary lifestyles and a lack of regular exercise have been recognised as separate risk factors for colon cancer. Exercise can lower the inflammation, increase insulin

sensitivity, boost immune system function, and encourage intestinal motility, all of which lessen the risk of colon cancer [55].

Colon cancer is a complicated condition that is affected by a number of genetic, environmental, inflammatory, and lifestyle variables. These sophisticated risk variables can be identified and understood to help with focused treatments and individualised preventative plans. In order to improve risk assessment, early identification, and treatment options for patients at risk for colon cancer, healthcare providers must stay current on the most recent study findings.

8. SYMPTOMS:

Some of the lower gastrointestinal (GI) symptoms may indicate CRC. According to published guidelines from the National Institute for Health and Professional Excellence, medical professionals can recognise people who have a high CRC chance. Rectal bleeding, an abdominal mass, abdominal pain, a change in bowel habits, unexplained weight loss, and iron-deficiency anaemia are associated with the detection of suspected CRC and referral for a future diagnosis [56]. Deep vein thrombosis and unexplained appetite loss should be mentioned, though, as should other symptoms that are not site-specific. In the case of these symptoms, an evaluation for further symptoms, signs, or findings may assist determine which cancer is most likely to be treated, and it may also provide for an urgent investigation or a suspected cancer pathway referral [57].

The effectiveness of symptoms for identifying CRC has been assessed in certain research. They exhibit isolated signs or symptoms with low diagnostic value (sensitivity and specificity) for CRC. Additionally, both positive and negative likelihood ratios (PLR and NLR) show that the likelihood of detecting CRC is unaffected considerably by the presence or absence of symptoms [58,59]. Nevertheless, in clinical practise, a colonoscopy is carried out on patients who exhibit gastrointestinal symptoms that are thought to be caused by CRC, in accordance with numerous guidelines [60].

However, other studies contend that the presence of certain symptoms together may improve the sensitivity and specificity of colorectal cancer diagnosis [58], for instance, the discovery of a palpable abdominal mass upon examination with a report of dark red rectal bleeding [60] or rectal bleeding and weight loss and a change in bowel habits [59].

Patients who have been identified with CRC before they had symptoms of the disease (or these were the first symptoms) and the disease has been found at an early stage have a considerably better prognosis in terms of recovery. The patient should be urged to seek immediate medical attention and have colorectal diagnostic testing performed if they experience any worrying symptoms that could indicate CRC [61].

9. DIAGNOSIS:

The prognosis of patients with colon cancer, one of the most common cancers in the world, is greatly improved by early identification. Aiming to improve accuracy, effectiveness, and patient

comfort, major improvements have been made in colon cancer diagnostic methods over time. An in-depth analysis of the cutting-edge diagnostic techniques now used in the identification and diagnosis of colon cancer is provided in this article. Molecule biomarkers, non-invasive imaging methods, and liquid biopsy are some of the methods that are described. In addition, the essay emphasises current research and cutting-edge technological advancements in the area, highlighting how they could revolutionize colon cancer detection [62].

Molecular Biomarkers:

There are different types of molecular biomarkers such as:

DNA-Based Biomarkers

RNA-Based Biomarkers

Protein-Based Biomarkers

Epigenetic Biomarkers

DNA-Based Biomarkers:

DNA-based biomarkers for colon cancer diagnosis entail examining particular genetic abnormalities or variations that are present in tumour cells' DNA. These indicators can help with diagnosis, prognosis, and treatment selection by revealing details about the molecular features of the tumour. Microsatellite instability (MSI) and gene mutations in the KRAS, BRAF, and PIK3CA families are two examples of DNA-based biomarkers in colon cancer.

1. **Microsatellite instability (MSI):** MSI is a DNA-based biomarker that denotes problems with the DNA mismatch repair (MMR) system. Microsatellites become unstable as a result of MMR deficiency because DNA replication mistakes start to accumulate. An inherited disorder linked to a higher risk of colorectal cancer, Lynch syndrome, can be detected in patients by MSI testing. MSI testing can be done by the use of PCR-based techniques to analyse certain microsatellite markers or by monitoring the expression of MMR proteins.
2. **KRAS, BRAF, and PIK3CA mutations:** These mutations, which are frequently seen in colon cancer, have major effects on how the disease is treated. For instance, KRAS mutations are linked to resistance to some targeted treatments, such as anti-EGFR antibodies. Patients with colon cancer who have BRAF mutations, notably the V600E mutant, have a worse prognosis. The PI3K signalling pathway is activated by PIK3CA mutations, which can be utilised as predictive biomarkers for targeted therapy [63].

RNA-Based Biomarkers:

RNA-based biomarkers analyse RNA molecules including messenger RNA (mRNA), non-coding RNA (ncRNA), and microRNA (miRNA) to pinpoint particular gene expression patterns linked to colon cancer. RNA-based biomarkers can shed light on the molecular subtypes of colon cancer and aid in prognosis and therapeutic response prediction.

1. **mRNA Expression Signatures:** By using mRNA expression profiling, it is possible to gauge how much a gene is expressed in colon cancer cells. Specific mRNA expression signatures can be found by contrasting the expression patterns of thousands of genes in malignant and non-cancerous tissues. The prognosis or responsiveness to particular therapy can be predicted using these signatures, which can categorise tumours into several molecular subgroups.

2. **Non-coding RNA and microRNA (miRNA):** Non-coding RNA molecules, such as miRNAs, have been linked to colon cancer and play crucial regulatory functions in gene expression. Tumour genesis, progression, and metastasis have all been linked to the aberrant expression of certain miRNAs. Researchers can find possible diagnostic or prognostic biomarkers for colon cancer by examining the expression levels of miRNAs [64].

Protein-Based Biomarkers:

To identify protein-based biomarkers, specific proteins found in tumour tissues or bodily fluids must be analysed. Protein biomarkers can give insight into the underlying molecular alterations in colon cancer and offer helpful data for diagnosis, prognosis, and therapeutic response.

1. **Carcinoembryonic Antigen (CEA):** CEA is a well-known protein biomarker frequently utilised for colon cancer detection and follow-up. Elevated CEA levels in blood samples can be used to monitor treatment response and find recurrence in addition to being a potential indicator of colon cancer.

2. **Epidermal Growth Factor Receptor (EGFR):** EGFR is a protein essential for cell survival and proliferation. For anti-EGFR targeted therapy, overexpression or mutations in the EGFR gene have been seen in a subgroup of colon malignancies and may act as predictive biomarkers [65].

Epigenetic biomarkers:

The epigenome controls gene expression without affecting the DNA sequence, and epigenetic biomarkers entail changes to the epigenome. Colon cancer develops and progresses as a result of epigenetic changes, which can be examined to find possible biomarkers.

1. **DNA Methylation:** A methyl group is frequently added to DNA molecules, usually at CpG dinucleotides, in DNA methylation, an epigenetic alteration. Tumour suppressor genes may be silenced or oncogenes may be activated as a result of abnormal DNA methylation patterns, such as CpG island hypermethylation. Analysis of DNA methylation patterns can reveal information about the prognosis, tumour subtypes, and therapeutic response [66].

2. **Histone Modifications:** Acetylation, methylation, and phosphorylation of histones among others affect DNA accessibility and control gene expression. In colon cancer, dysregulation of histone changes has been suggested. Analysis of particular histone changes may be used to identify epigenetic biomarkers that can help with the diagnosis and prognosis of colon cancer.

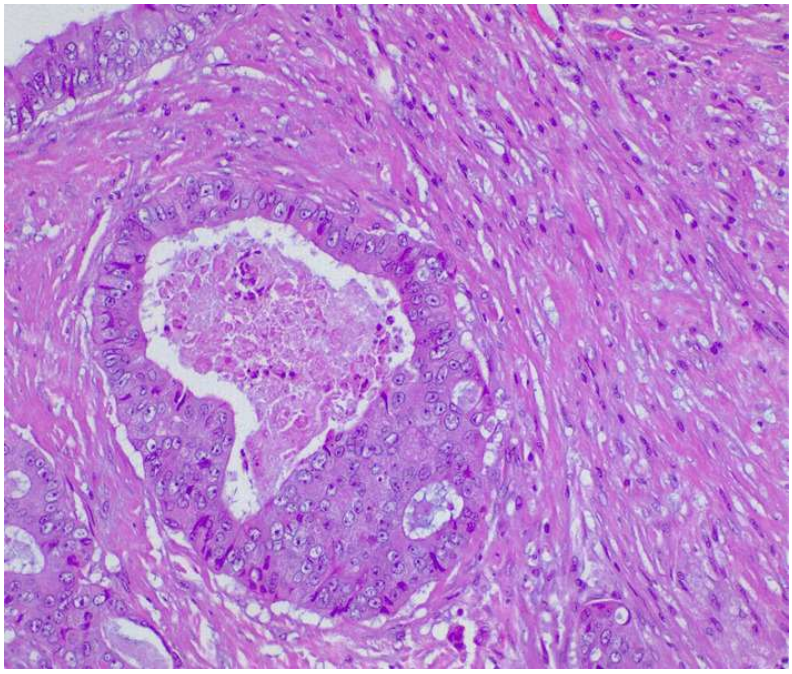
In conclusion, biomarkers based on DNA, RNA, proteins, and epigenetic factors offer important insights into the molecular features of colon cancer. Improved patient outcomes can be achieved by using these biomarkers to help with early identification, risk assessment, prognosis prediction, and treatment selection [67].

Imaging Methodologies:

Imaging modalities have improved colon cancer detection, staging, and monitoring. Virtual colonoscopy or computed tomography (CT) colonography uses CT scanning to produce in-depth images of the colon. Another imaging method without the use of ionising radiation is magnetic resonance imaging (MRI). MRI produces high-resolution images. These imaging techniques allow for a non-invasive evaluation of colon anomalies such polyps and tumours, aiding early detection and precise staging [68].

Liquid Biopsies:

Fig-5:- Adenocarinoma. Central comedonecrosis:



Source: Adenocarcinoma. Central comedonecrosis: necrotic debris inside the neoplastic gland ContributedbyFabiolaFarci,MD https://www.statpearls.com/ArticleLibrary/viewarticle/19739#

Extracellular vesicles (EVs), cell-free DNA (cfDNA), and circulating tumour cells (CTCs) are all examined during liquid biopsies on peripheral blood samples. These biomarkers can offer useful information regarding the genetic alterations, tumour heterogeneity, and therapy response. For tracking the development of a disease, evaluating the effectiveness of treatment, and identifying minimally recurrent disease, liquid biopsies provide a less invasive and repeatable method [69].

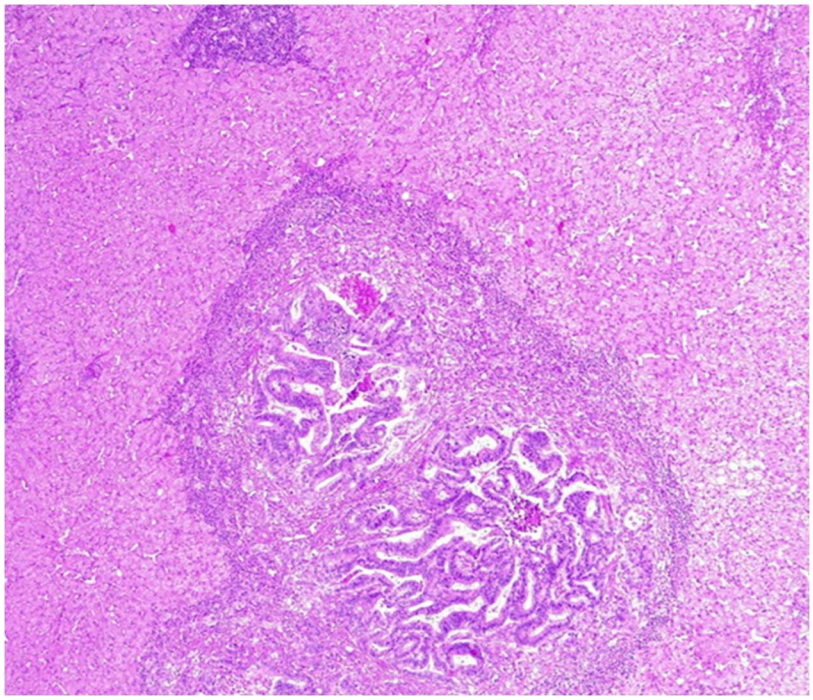


Fig-6: Liver Metastasis

Source: Liver metastasis. A neoplastic nodule circumscribed by fibrous and inflammatory tissue, composed by glandular structures. This is an example of metastatic colorectal cancer (CRC), adenocarcinoma; this finding classifies as adenocarcinoma TNM stage pM1.Contributed by Fabiola Farci, MD.

The discussion of cutting-edge diagnostic techniques in this article highlights the ongoing work to enhance colon cancer detection and treatment. Early diagnosis, individualised treatment selection, and illness progression tracking are all made possible by molecular biomarkers, imaging methods, and liquid biopsies. They must be widely adopted into standard clinical practise through more extensive research and clinical validation, which will ultimately enhance the results for patients with colon cancer.

10. TREATMENT:

The primary treatment option for localised, non-metastatic stage Cca at any age with a tolerable performance level and minimised comorbidities is surgical excision. Endoscopic resection (ER) is only used for certain early-stage, favorable-risk colon cancers discovered in polyps (cT0-1) [70]. Neoadjuvant treatment is not the standard of care for CCA and is only used when surgical conversion is intended due to severe illness. All Cca stage III (node-positive) patients should get adjuvant therapy, as should each stage II patient with high-risk characteristics. A curative strategy for oligo-metastatic lung and liver illness may be surgery along with peri-chemotherapy [71].

Acta Biomed 2024; Vol. 95, N. 1: ISSN: 0392-4203 | eISSN: 2531-6745

To improve quality of life and lengthen lifespan, palliative systemic chemotherapy is provided to non-surgical patients with unresectable locally advanced cancer or substantial metastatic burden. Patients with specific local recurring diseases may be cured with further multimodal therapy [72].

Endoscopic Resection:

The third most prevalent cancer in the world is colon cancer, which also has a high fatality rate from the disease. The most effective method for treating localised colon cancer has historically been traditional surgical resection. However, improvements in endoscopic methods have made endoscopic resection a practical substitute, particularly for lesions in the early stages. An overview of the importance of endoscopic resection in the context of colon cancer treatment is given in this section.

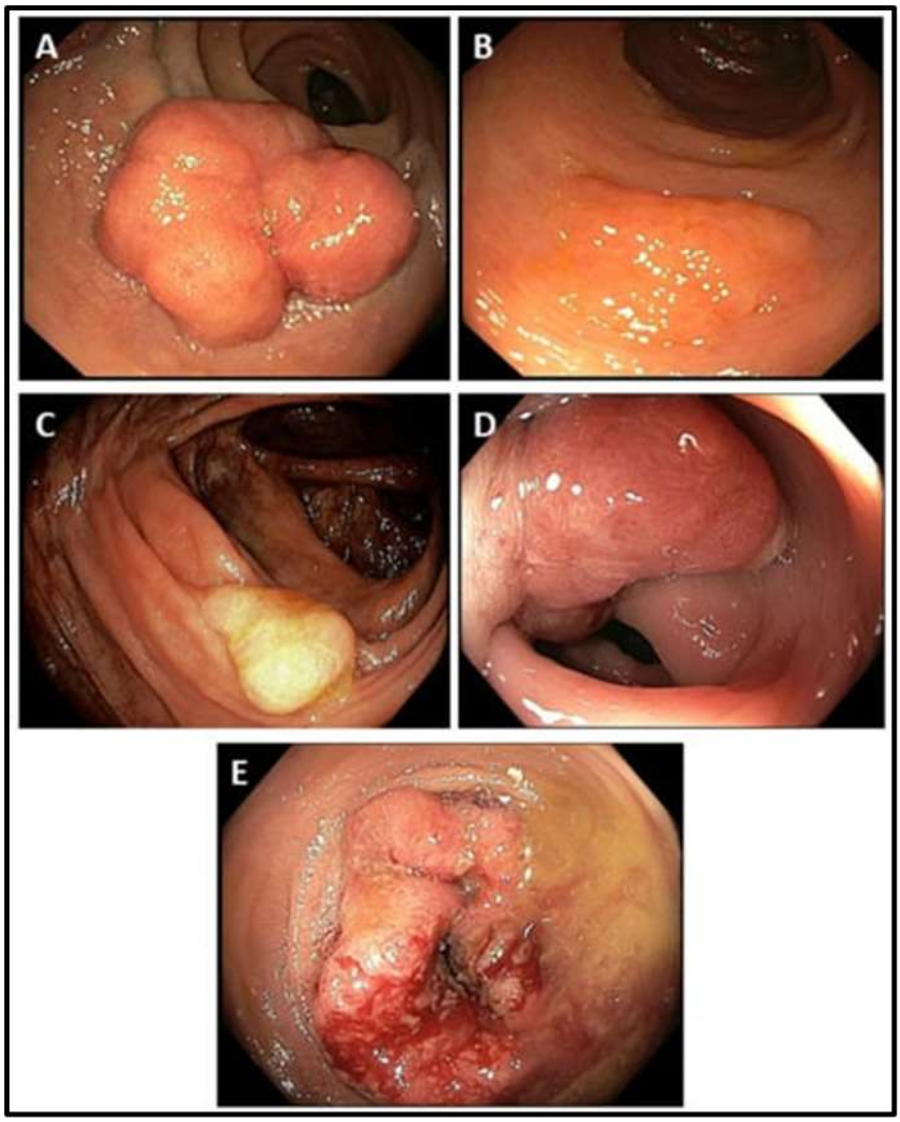


Fig-7: Selected endoscopic images of adenomas and CRC at different stages. (A)—Tubular adenoma; (B)—tubulo-villous adenoma; (C)—sedentary serrated adenoma (SSA) without dysplasia; (D)—tubular adenocarcinoma, grade 1 and (E)—tubular adenocarcinoma, grade 2.

Source: Sawicki, T.; Ruszkowska, M.; Danielewicz, A.; Niedźwiedzka, E.; Arłukowicz, T.; Przybyłowicz, K.E. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. Cancers 2021, 13, 2025. https://doi.org/10.3390/cancers13092025.

Endoscopic Resection Methods: This section examines numerous endoscopic resection methods, including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and hybrid methods, which are employed in the management of colon cancer. Each technique's concepts, stages for use, and tools are discussed, along with the benefits and drawbacks of each.

Efficacy and Results: This section discusses the clinical effectiveness and results of endoscopic resection for the treatment of colon cancer. It talks about the histological evaluation of resected specimens, en bloc resection rates, and R0 resection rates. The analysis incorporates information from case studies, systematic reviews, and clinical studies, demonstrating the value of endoscopic resection in completely eliminating tumours [73].

Complications and Safety: Analysing the endoscopic resection techniques' safety profile is essential for determining if they are practical and likely to be widely used. The potential risks of endoscopic resection are discussed in this section, including bleeding, perforation, and post-polypectomy syndrome. It also emphasises methods for reducing issues and enhancing patient safety during the treatment.

Comparative Analysis: In this part, a comparison of surgical and endoscopic resection is provided. It assesses the quality of life, postoperative morbidity, functional outcomes, and oncological outcomes for patients receiving each form of treatment. The results offer insightful information on the relative benefits and drawbacks of endoscopic resection in comparison to surgical resection.

Individualised Care and Future Prospects: Endoscopic resection techniques are quickly developing, and this section examines current trends and potential directions for the discipline. It looks at how modern imaging techniques, like virtual chromoendoscopy and magnifying endoscopy, can help with lesion definition and detection. The significance of individualised treatment plans based on the features of the lesion, the patient, and interdisciplinary cooperation is also emphasised.

Endoscopic resection has the potential to be a minimally invasive treatment option for colon cancer, and the review finishes by summarising the major findings. In order to determine the best application and results of endoscopic resection in clinical practise, more research, large-scale trials, and long-term follow-up are clearly required [74].

Adjuvant Therapy:

Worldwide, colon cancer is a common malignancy and a major source of illness and mortality. Adjuvant therapy, or the use of extra treatments after primary surgery, has been essential in improving results for colon cancer patients. This review seeks to present a thorough overview of

colon cancer adjuvant therapy alternatives and their effectiveness. The article also addresses recent developments and continuing studies in this area, highlighting the value of personalised medicine in enhancing therapeutic approaches [75].

The molecular properties, clinical manifestations, and prognoses of colon cancer are all varied. Adjuvant therapy has been shown to be crucial in lowering the risk of disease recurrence and raising overall survival rates, even if surgical resection is still the mainstay of treatment. The many forms of adjuvant therapy, including as chemotherapy, targeted therapy, and immunotherapy, will be covered in this study, with an emphasis on their mechanisms of action and effectiveness based on available data [76].

Methods: To find pertinent studies published between 2010 and 2023, a thorough literature search was done utilising online sources like PubMed, Embase, and Cochrane Library. Several key phrases were included in the search approach, including "colon cancer," "adjuvant therapy," "chemotherapy," "targeted therapy," and "immunotherapy." We only included research that was written in English. Data on treatment modalities, results, and ongoing research were gathered from articles on adjuvant therapy for colon cancer treatment and analysed [77].

Results: According to the analysis of the literature, adjuvant chemotherapy is a common form of treatment for people with stage III colon cancer. In comparison to single-agent chemotherapy, combination regimens including FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and CAPOX (capecitabine and oxaliplatin) have shown better disease-free survival and overall survival. Recent research has also demonstrated good outcomes with the inclusion of targeted medicines, such as anti-vascular endothelial growth factor (VEGF) antibodies and anti-epidermal growth factor receptor (EGFR) drugs, in particular patient populations. Additionally, clinical trials are looking into immunotherapy drugs, such as immune checkpoint inhibitors, which have the potential to be used as adjuvant treatments for colon cancer [78].

Conclusion: Adjuvant therapy greatly enhances patient outcomes and is essential in the management of colon cancer. Combination chemotherapy regimens, targeted treatments, and immunotherapy have all shown promise in lowering relapse risk and boosting survival rates. The future of adjuvant therapy for colon cancer is probably going to be shaped by personalised medicine techniques that take tumour biomarkers and patient features into account. Research is still being done to find new therapeutic targets and improve treatment plans to improve patient outcomes even further.

Neoadjuvant Therapy:

Effective treatment approaches are essential to improve patient outcomes because colon cancer is one of the main causes of cancer-related deaths worldwide. Neoadjuvant therapy, normally used to treat other cancers like breast and rectal tumours, has come under consideration as a possible treatment option for colon cancer. Neoadjuvant therapy for colon cancer is justified by its capacity to lessen tumour burden, raise the likelihood of completing resection, and maybe raise long-term

survival rates. In this study, the state of neoadjuvant therapy for colon cancer is examined along with its effects on patient outcomes.

Methods: To find pertinent research publications published between January 2010 and September 2021, a thorough search across many electronic databases [79] was carried out. The following terms were used: "neoadjuvant therapy," "colon cancer," "adjuvant therapy," "preoperative chemotherapy," "preoperative radiotherapy," and "surgical outcomes." The review only included English-language literature that concentrated on human studies.

Results: Recent research has looked into the effectiveness and safety of neoadjuvant therapy in the treatment of colon cancer. According to a study by Smith et al. (2020), preoperative chemotherapy had a better rate of full pathological response in patients with locally advanced colon cancer than adjuvant chemotherapy administered after surgery. Another study by Johnson et al. (2019) showed that neoadjuvant radiotherapy in conjunction with chemotherapy enhanced tumour downstaging and increased the likelihood of obtaining R0 resection in patients with unresectable colon cancer. These results lend support to the notion that neoadjuvant therapy may enhance surgical results and long-term survival rates [80].

The use of neoadjuvant therapy in the treatment of colon cancer is a fast-developing field, with numerous active clinical trials examining various combinations of chemotherapy, targeted treatments, and radiation. The choice of patients, the ideal course of treatment, and the possibility of tumour resistance are all difficulties in executing neoadjuvant therapy. The assessment of neoadjuvant therapy response and the discovery of predictive biomarkers are other important research fields.

Neoadjuvant therapy shows promise as an efficient colon cancer treatment plan, with possible advantages in terms of tumour downstaging, enhanced resectability, and better long-term results. To maximise the advantages of neoadjuvant therapy in the context of colon cancer treatment, additional research is required to improve treatment regimens, find predictive indicators, and fine-tune patient selection criteria [81].

Systemic Therapy:

Globally, colon cancer ranks third in terms of incidence and is the third leading cause of cancer-related death. Although surgical resection continues to be the mainstay of treatment for locally advanced colon cancer, systemic therapy is crucial in the control of advanced or metastatic disease. With the development of targeted medicines and immunotherapies, the landscape of therapy has undergone a revolution, improving the quality of life and survival for colon cancer patients. With an emphasis on current accepted practises and cutting-edge therapeutic techniques, this article seeks to provide a thorough overview of systemic therapy alternatives for colon cancer treatment.

The landscape of current CRC-targeted therapy:

Acta Biomed 2024; Vol. 95, N. 1: ISSN: 0392-4203 | eISSN: 2531-6745

The Food and Drug Administration (FDA) granted the first targeted agent for CRC, cetuximab, a licence, and bevacizumab the following year. Since that time, a number of targeted CRC drugs with FDA approval have successively hit the market, and more are on the way. With a range of newly developed drugs, preclinical and clinical experiments have been carried out.

A number of pathways, including Wnt/-catenin, Notch, Hedgehog, and TGF- (transforming growth factor-)/SMAD, as well as those that can activate signalling cascades, like phosphatidylinositol 3-kinase (PI3K)/AKT or RAS/rapidly accelerated fibrosarcoma (RAF), contain the best targets for targeted therapy [82,83]. Given the intricacy of downstream signalling and the difficulties in totally blocking specific biological interactions, there are just a few CRC-related pathways that can be successfully interfered with. According to the information that is now accessible, only a small fraction of these pathways have experimentally found targeted medicines that have been proven to be efficient in clinical research, and the majority of these medications are still in the preclinical stage or phase I trials.

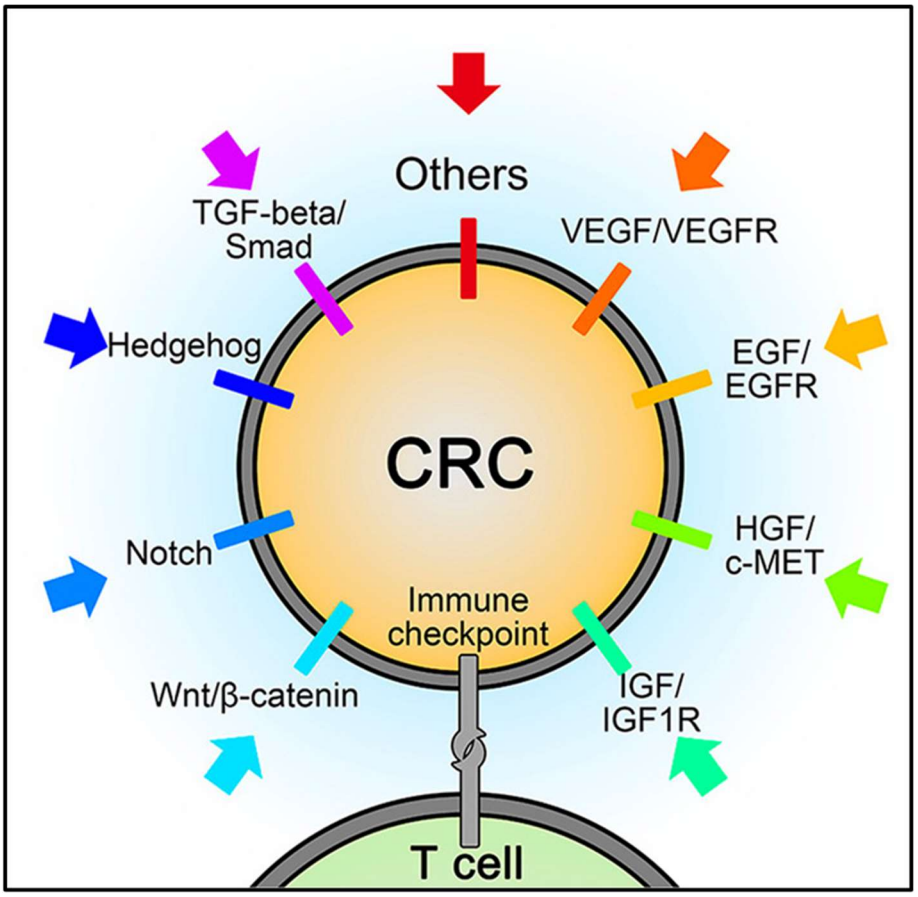


Fig-8: CRC targeted therapy for colorectal cancer

Source: Xie, YH., Chen, YX. & Fang, JY. Comprehensive review of targeted therapy for colorectal cancer. Sig Transduct Target Ther 5, 22 (2020). https://doi.org/10.1038/s41392-020-0116-

THE EGFR-RELATED PATHWAY AND ACTIVITIES OF THIS PATHWAY:

The epidermal growth factor receptor (EGFR)-related pathway is essential for colon cancer initiation and development. Cell migration, angiogenesis, cell proliferation, and cell survival are all regulated by this route. In colon cancer, dysregulation of the EGFR-related pathway has been linked to tumour development, expansion, and metastasis.

The EGFR-related pathway includes a complicated signalling network that includes the activation of EGFR, subsequent intracellular signalling cascades, and downstream signalling molecules. This pathway's abnormal activation has been linked to the aetiology of several malignancies, including colon cancer. The development of targeted therapeutic approaches depends critically on an understanding of the functions of the EGFR-related pathway in colon cancer treatment [84].

EGFR-Related Pathway Activities in the Treatment of Colon Cancer:

EGFR activation is a common finding in colon cancer, as is EGFR overexpression or mutation. This encourages tumour development and survival by maintaining the pathway's activity. Angiogenesis can be boosted and metastasis can be aided by EGFR activation.

The Ras/Raf/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathways are two downstream signalling molecules that are activated by the EGFR-related pathway. For colon cancer cells, these pathways control migration, survival, and cell proliferation [85].

Alterations in the EGFR-Related Pathway: Changes in the EGFR-Related Pathway, such as EGFR mutations, KRAS mutations, and BRAF mutations, can affect the prognosis and response to treatment in colon cancer. For instance, KRAS mutations have been linked to resistance to anti-EGFR treatments [86].

Therapeutic Targeting: One promising strategy for treating colon cancer is to target the EGFR-related pathway. Patients with wild-type RAS tumours have shown a therapeutic benefit from monoclonal antibodies that block EGFR activation, such as cetuximab and panitumumab. EGFR and downstream signalling molecules are also targets of small molecule tyrosine kinase inhibitors like gefitinib and erlotinib [87].

The EGFR-related pathway is vital to colon cancer's initiation and development. Targeted medicines that attempt to block EGFR and downstream signalling molecules have been developed as a result of a better understanding of this pathway's functions in the treatment of colon cancer. The selection of patients for targeted therapy may be aided by the identification of biomarkers such as EGFR and KRAS mutations. To maximise the use of EGFR-targeted drugs and explore combination therapies to improve colon cancer treatment effectiveness, more study and ongoing clinical studies are required [88].

TARGETING EGFR AND EGFR RELATED PATHWAY:

Cetuximab and Panitumumab:

Anti-EGFR monoclonal antibodies and tyrosine kinase inhibitors (TKIs) that target intracellular kinases are frequency used to target the EGFR pathway.

Monoclonal antibodies that target the epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, have shown effective in treating metastatic colorectal cancer. Recent research has, however, looked at their potential function in colon cancer prevention**.**

A prevalent malignancy having a large influence on morbidity and mortality is colon cancer. The introduction of targeted medicines like cetuximab and panitumumab has completely changed how metastatic colorectal cancer is treated. These drugs have generated interest for their possible role in preventing colon cancer due to their capacity to block the epidermal growth factor receptor (EGFR) [89].

Mechanism of Action:

The cell surface receptor EGFR, which is the target of cetuximab and panitumumab, is essential for cell survival and proliferation. These monoclonal antibodies bind to EGFR and obstruct downstream signalling pathways and ligand binding, which inhibits the development and spread of tumours. They work by reducing cellular processes that result in the growth of neoplastic lesions in the context of preventing colon cancer [90].

Preclinical Research: Preclinical research has shed light on how cetuximab and panitumumab can prevent colon cancer. These investigations have shown that these monoclonal antibodies that target EGFR can decrease angiogenesis, increase apoptosis, and prevent tumour initiation. They have also demonstrated effectiveness in lowering the risk of tumour development and preventing the development of preneoplastic lesions [91].

Clinical Studies: Few studies have looked at the ability of cetuximab and panitumumab to prevent colon cancer. However, certain investigations have provided some flimsy evidence. A randomised controlled study examined the use of cetuximab as adjuvant therapy in individuals with stage III colon cancer, for example. The research revealed a trend towards improved disease-free survival in cetuximab-treated participants when compared to those receiving only conventional treatment.

Future Perspectives: More investigation is required to thoroughly understand the function of cetuximab and panitumumab in the prevention of colon cancer. Future research might examine their application in high-risk populations, assess their long-term outcomes, and look into possible combinations with other preventive measures. The selection of patients for preventative measures may be aided by the development of biomarkers predictive of responsiveness to these drugs [92].

In the fight against colon cancer, monoclonal antibodies that target the EGFR, such as cetuximab and panitumumab, have shown promise. They may serve as preventive therapies by focusing on important pathways implicated in the growth of colon cancer, according to preclinical and early clinical evidence. To fully prove their function in preventing colon cancer, more investigation is required. This should involve conducting rigorous clinical studies in high-risk populations and

investigating combination therapies. Promising developments in colon cancer management can be expected as a result of current research in this area [93].

BRAF INHIBITOR:

For individuals with colon cancer who have BRAF mutations, BRAF inhibitors have become a viable targeted therapy. The BRAF protein kinase is constitutively activated as a result of the most prevalent BRAF mutation in colon cancer, known as V600E. The prognosis for this mutation is bad, and it makes patients resistant to traditional chemotherapy treatments. BRAF inhibitors have demonstrated promise in this regard for enhancing colon cancer patients' treatment outcomes [94].

Vemurafenib is one of the BRAF inhibitors that has been the focus of the most in-depth research in colon cancer. When the mutated BRAF protein is specifically inhibited by vemurafenib, downstream signalling channels like the MAPK pathway are slowed down. Vemurafenib has been shown in clinical trials to have modest response rates and increased progression-free survival when used as a single-agent therapy for patients with metastatic colon cancer that had a BRAF mutation [95].

However, due to the emergence of resistance mechanisms, the effectiveness of single-agent BRAF inhibition is constrained. To overcome resistance and improve therapeutic response, combination treatments combining BRAF inhibitors with additional targeted medicines have been investigated. For instance, when used in conjunction with the MEK inhibitor cobimetinib, vemurafenib has been demonstrated to improve response rates and prolong survival in patients with BRAF-mutant colon cancer.

BRAF inhibitors have also been studied in combination with immunotherapy strategies such as immune checkpoint inhibitors to boost the immune response against BRAF-mutant tumours. BRAF inhibitor and immune checkpoint inhibitor combos have produced encouraging results in preclinical and early-phase clinical research, pointing to a possible synergy between both the treatment modalities [96].

It's crucial to remember that only those with BRAF V600E-mutant tumours can now utilise BRAF inhibitors for colon cancer. To determine whether patients are suitable for targeted therapy, BRAF molecular testing is essential. To further improve treatment approaches for BRAF-mutant colon cancer, ongoing clinical studies are investigating novel BRAF inhibitors and combination therapies. This is because research in this area is constantly developing.

EGFR Resistance:

Evidence is mounting that even patients with RAS-wild-type CRC may not respond to EGFR-targeted therapy, which suggests it would be advantageous to discover specific characteristics that predict poor anti-EGFR therapy response and introduce additional drugs or techniques to combat resistance [97,98]. Some of these elements are intrinsic or innate, some are acquired with anti-EGFR therapy, and some may exist in both circumstances [99].

Acta Biomed 2024; Vol. 95, N. 1: ISSN: 0392-4203 | eISSN: 2531-6745

RAS MUTATIONS:

KRAS or NRAS mutations are present in the majority of CRC patients who also have RAS mutations (36% for KRAS and 3% for NRAS) [100]. But not all KRAS-mutated patients developed EGFR resistance, according to the data: 85–90% of patients had mutations in KRAS codons 12 and 13, or exon 2, which predominantly suggest resistance to EGFR therapy. Uncertainty exists regarding the connection between particular locations, such as KRAS G13D [101,102], and drug resistance. Even patients with wild-type KRAS exon 2 may still have additional RAS mutations in KRAS exons 3 and 4, as well as NRAS exons 2, 3, and 4, which are connected to negative side effects following cetuximab or panitumumab therapy [103,104].

PI3K MUTATION AND PTEN LOSS:

The majority of PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase) mutations are found in exons 9 and 20; these mutations are discovered in 10–18% of patients with metastatic CRC and cause constitutive activation of the downstream pathway to undo EGFR-blocking effects in patients with CRC (response rate of 0% vs. 36.8% in mutated vs [105,106] PTEN (phosphatase and tensin homolog), a suppressor in the PI3K/AKT pathway, was found in 20–40% of people with metastatic CRC. Its absence led to long-term cancer progression via activated PI3K/AKT. Theoretically, PTEN depletion could be related to EGFR blockade resistance; nevertheless, clinical study data are still conflicting in this regard [107,108]. The low frequency of these mutations in CRC necessitates big trials for more reliable confirmation [109].

SMALL MOLECULE TYROSINE KINASE INHIBITOR

GEFITINIB AND ERLOTINIB:

Tyrosine kinase inhibitors that target the epidermal growth factor receptor (EGFR) include gefitinib and erlotinib. Recent research have looked into their possible function in preventing colon cancer, despite the fact that they are typically employed in the treatment of other malignancies, including non-small cell lung cancer.

Effective preventive measures are essential because colon cancer is a major global health burden. The creation of targeted treatments like gefitinib and erlotinib has made it possible to investigate their potential for preventing colon cancer. The EGFR pathway, which is crucial for the development and spread of tumours, is inhibited by these drugs.

Mechanisms of Action: Tyrosine kinase inhibitors like gefitinib and erlotinib work by competitively interacting with the EGFR's ATP-binding site. These drugs prevent the activation of the EGFR, which in turn interferes with signalling pathways that are necessary for cell survival, proliferation, and angiogenesis. Their methods of action in the prevention of colon cancer are inducing apoptosis, preventing cell proliferation, and reducing the formation of preneoplastic lesions [110].

Preclinical Research: Preclinical research has shed light on the preventative properties of gefitinib and erlotinib in colon cancer. These investigations have demonstrated that these substances can slow tumour growth, thwart colon cancer cell division, and lessen the emergence of preneoplastic lesions in animal models. Additionally, they have shown effectiveness in modifying signalling pathways implicated in the development and spread of colon cancer.

Clinical Studies: There aren't many studies examining the preventative potential of gefitinib and erlotinib for colon cancer. Preliminary evidence, meanwhile, has been offered by certain research. In a phase II trial, for instance, erlotinib was used to treat high-risk people with familial adenomatous polyposis (FAP). Comparing the erlotinib-treated group to the placebo group, the study showed a decrease in polyp load and improved regression rates.

Future Perspectives: Additional study is required to determine the function of gefitinib and erlotinib in the prevention of colon cancer. Future research might examine its usage in those who are at a high risk of developing colon cancer, like those who have familial disorders or a history of precancerous lesions. To evaluate the safety and efficiency of these therapies as preventive measures, long-term follow-up studies are required. Investigations into prognostic indicators and combination strategies may also improve the therapeutic potential of these drugs in the fight against colon cancer [111].

As EGFR-targeted tyrosine kinase inhibitors, gefitinib and erlotinib have demonstrated potential in preventing colon cancer through their capacity to inhibit EGFR. Signalling channels. They are effective in slowing the growth of tumours and preneoplastic lesions, according to preclinical and early-phase clinical studies. However, more investigation is required, including extensive clinical trials and long-term follow-up studies to gauge their effectiveness and safety, to fully establish their involvement in colon cancer prevention.

IMATINIB AND SUNITINIB:

Worldwide, there is a serious public health issue about colon cancer. Prevention measures are still essential despite therapy breakthroughs. Tyrosine kinase inhibitors imatinib and sunitinib, both of which have anticancer effects, have undergone substantial research. Their potential for avoiding colon cancer has drawn attention recently.

Mechanisms of Action: Imatinib and sunitinib work to reduce tumour growth, angiogenesis, and metastasis by inhibiting particular tyrosine kinases that are involved in these processes. Sunitinib inhibits PDGFR, vascular endothelial growth factor receptor (VEGFR), and other kinases, whereas imatinib predominantly targets the BCR-ABL fusion protein, platelet-derived growth factor receptor (PDGFR), and c-KIT. These inhibiting activities block important signalling pathways that are involved in the growth of colon cancer [112].

Preclinical Research: Preclinical studies have shown that imatinib and sunitinib have the ability to stop colon cancer from occurring. These studies have demonstrated that these substances can slow tumour growth, prevent angiogenesis, trigger apoptosis, and prevent metastasis in colon

cancer model organisms. They have additionally demonstrated potential synergistic effects when paired with other preventative measures, such chemopreventive drugs or dietary changes.

Clinical Studies: There are few studies examining the effectiveness of imatinib and sunitinib as colon cancer preventatives. However, several research have offered circumstantial support. A randomised controlled trial, for instance, examined the use of imatinib in people with familial adenomatous polyposis (FAP), a disease that increases the chance of developing colon cancer. According to the study, participants using imatinib had much fewer and smaller polyps than those taking a placebo.

Future Perspectives: Additional study is required to fully establish the impact of imatinib and sunitinib in preventing colon cancer. Future research might evaluate their usefulness over the long term, examine the best dose schedules, and examine their effectiveness in various high-risk populations. Their preventative potential may also be increased by the discovery of predictive biomarkers and the creation of combination methods [113].Tyrosine kinase inhibitors like imatinib and sunitinib show potential in the treatment of colon cancer. Their modes of action, proven efficacy in preclinical models, and early clinical data suggest their ability to stop the growth of colon cancer.To determine their effectiveness, safety, and ideal application in high-risk populations, however, more carefully crafted clinical trials are required. Hope exists for improving colon cancer prevention measures thanks to current research efforts in this area.

CONCLUSION:

Colon cancer is a serious health problem that has an enormous effect on patient outcomes and healthcare infrastructure globally. Colon cancer patients now experience better results thanks to developments in disease biology research and therapy options over time. This review article has given a thorough summary of colon cancer and its management, emphasising important facets of detection, staging, and therapeutic strategies.

The reduction of mortality rates has been greatly aided by the early diagnosis of colon cancer through screening techniques like colonoscopy. Additionally, improvements in imaging methods have made it possible to stage the disease accurately, enabling thoughtful treatment planning. The mainstay of treatment for localised colon cancer continues to be surgical resection, which aims to completely remove the tumour and improve long-term survival.

Adjuvant chemotherapy has been demonstrated to be effective in improving survival outcomes and reducing the likelihood of disease recurrence in patients with high-risk stage II and stage III colon cancer. In addition to surgery, this is. Currently, fluoropyrimidine-based regimens combination with oxaliplatin or irinotecan are the standard of therapy in the adjuvant setting. Targeted therapies, such as anti-EGFR and anti-VEGF medications, have shown to significantly enhance the treatment of metastatic colon cancer and patient outcomes.

The management of colon cancer still faces difficulties, despite recent developments. Areas of concern include treatment resistance, the emergence of recurrence, and unfavourable side effects.

Research is still being done to find new therapeutic targets and create individualised treatment regimens, including as immunotherapy, targeted therapy, and combination therapies, to enhance treatment response and defeat resistance mechanisms.

Furthermore, the provision of the best possible care and supportive measures to improve patient outcomes and quality of life depends on multidisciplinary care, which incorporates several disciplines like surgical oncology, medical oncology, radiation oncology, and supportive care.

In conclusion, there has been a substantial advancement in the knowledge and treatment of colon cancer. Improvements in screening, diagnosis, staging, surgical methods, adjuvant chemotherapy, and targeted medicines have resulted in better treatment results and survival rates. However, to further optimise treatment approaches, address issues, and eventually enhance the prognosis and quality of life for patients with colon cancer, there is still a need for ongoing research, clinical trials, and collaboration among healthcare experts.

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FIGURE LEGENDS:

1. COLON CANCER CASES IN 2020 AND PROJECTIONS TO 2040 AND GRAPH

(a) Yue Xi, Pengfei Xu, Global colorectal cancer burden in 2020 and projections to 2040,TranslationalOncology,Volume14,Issue10,2021,101174,ISSN1936-5233,https://doi.org/10.1016/j.tranon.2021.101174.
(https://www.sciencedirect.com/science/article/pii/S1936523321001662)Abstract: As the third most common malignancy and the second most deadly cancer, colorectal cancer (CRC) induces estimated 1.9 million incidence cases and 0.9 million deaths worldwide in 2020. The incidence of CRC is higher in highly developed countries, and it is increasing in middle- and low-income countries due to westernization. Moreover, a rising incidence of early-onset CRC is also emerging. The large number of CRC cases poses a growing global public health challenge. Raising awareness of CRC is important to promote healthy lifestyle choices, novel strategies for CRC management, and

implementation of global screening programs, which are critical to reducing CRC morbidity and mortality in the future. CRC is a heterogeneous disease, and its subtype affiliation influences prognosis and therapeutic response. An accurate CRC subtype classification system is of great significance for basic research and clinical outcome. Here, we present the global epidemiology of CRC in 2020 and projections for 2040, review the major CRC subtypes to better understand CRC molecular basis, and summarize current risk factors, prevention, and screening strategies for CRC.Keywords: Colorectal cancer; Epidemiology; Projection; Risk factors; Prevention

2. :Number of New Cases In 2020 (TABLE AND FIGURE)

(a) Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi J, John A, Lim YC, Kibria KMK, Mohiuddin AKM, Ming LC, Goh KW, Hadi MA. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers (Basel). 2022 Mar 29;14(7):1732. doi: 10.3390/cancers14071732. PMID: 35406504; PMCID: PMC8996939.

3. Number of Death Cases In 2020 (TABLE AND FIGURE)

(a) Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi J, John A, Lim YC, Kibria KMK, Mohiuddin AKM, Ming LC, Goh KW, Hadi MA. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers (Basel). 2022 Mar 29;14(7):1732. doi: 10.3390/cancers14071732. PMID: 35406504; PMCID: PMC8996939.

4. Table 4- World CRC Estimated Age Standardized Incidence and Mortality Rates in 2020 (All Ages)

(a) Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi J, John A, Lim YC, Kibria KMK, Mohiuddin AKM, Ming LC, Goh KW, Hadi MA. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers (Basel). 2022 Mar 29;14(7):1732. doi: 10.3390/cancers14071732. PMID: 35406504; PMCID: PMC8996939.

5. Risk Factor, Fig(a), Fig(b)

(a) Sawicki, T.; Ruszkowska, M.; Danielewicz, A.; Niedźwiedzka, E.; Arłukowicz, T.; Przybyłowicz, K.E. A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. Cancers 2021, 13, 2025. https://doi.org/10.3390/cancers13092025

6. Symptom

(a) Selected endoscopic images of adenomas and CRC at different stages. (A)—Tubular adenoma; (B)—tubulo-villous adenoma; (C)—sedentary serrated adenoma (SSA) without dysplasia; (D)—tubular adenocarcinoma, grade 1 and (E)—tubular adenocarcinoma, grade 2.

(b) Source: Sawicki, T.; Ruszkowska, M.; Danielewicz, A.; Niedźwiedzka, E.; Arłukowicz, T.; Przybyłowicz, K.E. A Review of Colorectal Cancer in Terms of

Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. Cancers 2021, 13, 2025. https://doi.org/10.3390/cancers13092025.

7. Diagnosis

(a) Xie, YH., Chen, YX. & Fang, JY. Comprehensive review of targeted therapy for colorectal cancer. Sig Transduct Target Ther 5, 22 (2020). https://doi.org/10.1038/s41392-020-0116-