Colorectal Cancer: Insight into Incidence, Risk Factors, Diagnosis, and Prognostic Markers

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Abstract

Background: Colorectal cancer is one of the most common malignancies and a leading cause of cancer death worldwide.

Objectives: The current review aimed to highlight colon cancer incidence, risk factors, diagnosis, and prognostic markers. Colorectal cancer is the second most common type of cancer, it was responsible for 18.7% and 15.1%, of all cancer in Portugal. The mean age of incidence is about 60 years. The aetiological and pathogenesis of colorectal cancer are usually related to both environmental and genetic factors. Patients with inflammatory bowel disease have a definite predisposition to colorectal carcinoma. Some genetic syndromes transmitted in the family from generation to generation can increase the risk of colon cancer. The most well-defined environmental risk is exposure to ionizing radiation. If the patient has benign glandular tumors before, he is more likely to have colon or rectal cancer. Also, medical history, alcohol consumption, age, diet, physical activity, diabetes, smoking, and geographic differences are from risk factors for colorectal cancer. One of the best methods for detection of colon cancer is a screening program with blood in stool, routine physical and endoscopic examination. The person who is on risks such as personal history of adenomas or CRC, family history of CRC or adenomas in first degree relatives before age 60 years, inflammatory bowel disease, and family history of hereditary syndromes. The usual clinical picture of an early colorectal cancer is a change of bowel habit and painless mild bleeding particularly in the left side tumors. Abdominal lymph nodes (38%) are the second most frequent site of metastasis (38%), just after liver, which is, the organ that most frequently involved (38–60% of cases) and followed by the lung (38%) and the peritoneum (28%). Colon cancers can be graded according the degree of differentiation to well differentiated (grade I). Grading Adenocarcinomas are graded predominantly on the basis of the extent of glandular appearances, and should be divided into well, moderately and poorly differentiated, or into low-grade (encompassing well and moderately differentiated adenocarcinomas) and high-grade (including poorly differentiated adenocarcinomas and undifferentiated carcinomas). the mitotic activity index (MAI) is an independent prognostic factor for recurrence free survival. SMI is a bit more efficient than MAI as a prognosticator. Classical prognostic markers in histopathology are histological grade, mitotic activity, histological type, angiogenesis, and tumor necrosis. Multivariate clinicopathological prognostic indices, molecular prognostic markers in colon cancer, the younger is the patient, the greater is the cellular proliferation and the lower is the degree of differentiation. With increasing malignancy an increased frequency of invasion and metastasis are observed and hence poor prognosis of the tumor Cell proliferation markers. Rational mutations in one allele of the p53 gene associated with congenital or acquired congenital loss of the other leads to continuous cell growth the later can promote carcinogenesis in many organs, including colon, lung, and breast. Ki-67 is a cell proliferation marker. Tumors associated with microsatellite instability tend to be mucinous or poorly differentiated with a prominent host response a circumscribed growth pattern and right-sided location in one study presence of tumor-infiltrating lymphocytes was found to be the best histological predictor of microsatellite instability.

Conclusion: It can be concluded that the colorectal cancer is one of the most common malignancies. The aetiological and pathogenesis of colorectal cancer are usually related to both environmental and genetic factors. The colorectal cancer risk factors are medical history, alcohol consumption, age, diet, physical activity, diabetes, smoking, and geographic differences. the best methods for detection of colon cancer are a screening program with blood in stool, routine physical and endoscopic examination. Classical prognostic markers in histopathology are histological grade, mitotic activity, histological type, angiogenesis, and tumor necrosis. With increasing malignancy an increased frequency of invasion and metastasis are observed. Rational mutations in one allele of the p53 gene associated with congenital leads to continuous cell growth the later can promote carcinogenesis in the colon. Tumor-infiltrating lymphocytes were found to be the best histological predictor of microsatellite instability. Further studies about colorectal cancer are needed to prove strategies for controlling the prevalence of the disease and the more accurate method for diagnosis.

Key Words: colorectal cancer; incidence; risk factors; diagnosis; prognostic markers

1.Introduction

Colorectal cancer (CRC) is one of the most common malignancies and a leading cause of cancer death worldwide [1, 2]. European countries rank the highest in the global statistics in terms of both CRC incidence and mortality [3 , 4], although in recent years, a decline in CRC mortality rates has been observed, mostly due to improvement in earlier diagnosis and treatment [3 , 5]. Among the key risk factors associated with the presence of adenomas is a factor closely linked to the development of malignant neoplasm. The chances of cure and survival of such cancer are high when detected at an early stage. The management of adenomas has an important role in the prevention of colorectal cancer, making it necessary to conduct studies to determine new prognostic factors related to its development and progression. The cell cycle is controlled by several genes, the main function of these genes is the synthesis of proteins that promote perfectly organized cell proliferation, and the other genes that suppress the proliferation.

2. Incidence of colon cancer

Carcinoma of the large intestine is common in Northwest Europe, North America, and other Anglo-Saxon areas and low in Africa, Asia, and some parts of South America [6, 7].

In Portugal for example, CRC is the second most common type of cancer, in both men and women. In 2008, it was responsible for 18.7% and 15.1%, respectively, of all cancer in Portugal [8]. Regarding mortality, unlike European data [9], there was an average increase of 3% from 2000 to 2005 [10], in 2012, incidence and mortality rates are higher than European rates [11].

In the United States, it is by far the most common and most curable carcinoma of the gastrointestinal tract. There is some evidence of a further increase in its occurrence, particularly in young blacks [12]. Males and females are affected equally. The mean age of incidence is about 60 years [13, 14].

3. Risk factors

One specific cause for colon cancer has not been identified. However, the aetiological and pathogenesis of colorectal cancer is usually related to both environmental and genetic factors [15, 16]. The former is largely dietary, particularly in terms of fast animal protein and fatty food they are related to their influence on the intestinal microflora and ultimately on the chemical composition of the intraluminal content [17, 18].

The relationship between epithelial polyps and colorectal carcinoma and the sequence of molecular alterations that have been detected in these lesions have already been recognized. Patients with inflammatory bowel disease (such as ulcerative colitis) have a definite predisposition to colorectal carcinoma, [19, 20] however they consist only a small fraction of the colonic cancer patients in the general population. Polyps of juvenile and/or adenomatous type can also occur at this juncture [21, 22]. Interestingly, these changes are preceded by abnormal colonic mucin secretion [23].

3.1. Family history and genetics:

Although the aetiology of colon cancer is not fully understood, many studies have been done on the effects of family history and inherited mutation. Up to 10% of colon cancers have been found to have genetic predisposition, some genetic syndromes transmitted in the family from generation to generation can increase the risk of colon cancer. They are also responsible for 5% of case. One of these syndromes is called adenomatous polyposis coli, which is rare and characterized by presence of thousands adenomatous polyps within the rectum and on the intestinal walls [24].

3.2. Environmental factors:

The most well-defined environmental risk is exposure to ionizing radiation. Some cases of colorectal carcinomas have been seen as a late complication of pelvic irradiation of cervical carcinoma [19].

3.3. Medical history:

If the patient has colon cancer or benign glandular tumors before, he is more likely to have colon or rectal cancer.

3.4. Alcohol consumption:

The excessive use of alcohol is an important factor in the increased risk of colon cancer

3.5. Age:

The majority of people with colon cancer are 60 years old. Young people can also develop colorectal cancer, but their incidence is very low in these cases.

3.6. Inflammatory bowel diseases:

Ulcerative colitis and Crohn's disease; are example of inflammatory bowel diseases their presence increases the risk of colon cancer.

3.7. Diet:

High-fat diets, calories, or low fibres foods may be a cause of colon or rectal cancer.

3.8. Physical Activity:

Physical activity plays an important role in maintaining the body's organs. It also helps maintain muscle activity and bone health. It helps the body to get rid of harmful substances and stimulates it to resist diseases such as cancer or internal infections. It also protects the body from obesity, which is another cause of colon cancer.

3.9. Growth hormone disorders:

an imbalance in the growth hormone produced by the pituitary gland. This imbalance may be due to a defect in the work of the gland, which adversely affects the growth of the body organs properly, and thus increase the risk of various diseases, including colon cancer.

3.10. Diabetes:

People with diabetes are more likely to develop colon cancer.

3.11. Smoking:

People who smoke in large quantities are more likely to develop colon cancer, because the accumulation of nicotine in the body turns over days to cancers, including to colon cancer.

3.12. Geographic differences:

There is a big variation in age adjusted incidence rate for colon cancer seen among countries. Carcinoma of the large intestine is common in Northwest Europe, North America, and other Anglo-Saxon areas and low in Africa,

Asia, and some parts of South America [6, 7]. In the United States, it is by far the most common and most curable carcinoma of the gastrointestinal trac

4. Diagnosis of colon cancer

One of the best methods for detection of colon cancer is a screening program with blood in stool, routine physical and endoscopic examination [25].

4.1. Screening for colon cancer by endoscopy

Screening means the use of investigations on asymptomatic persons, to detect the disease at an early stage in order to lower the risk of death, or complications of therapy [26].
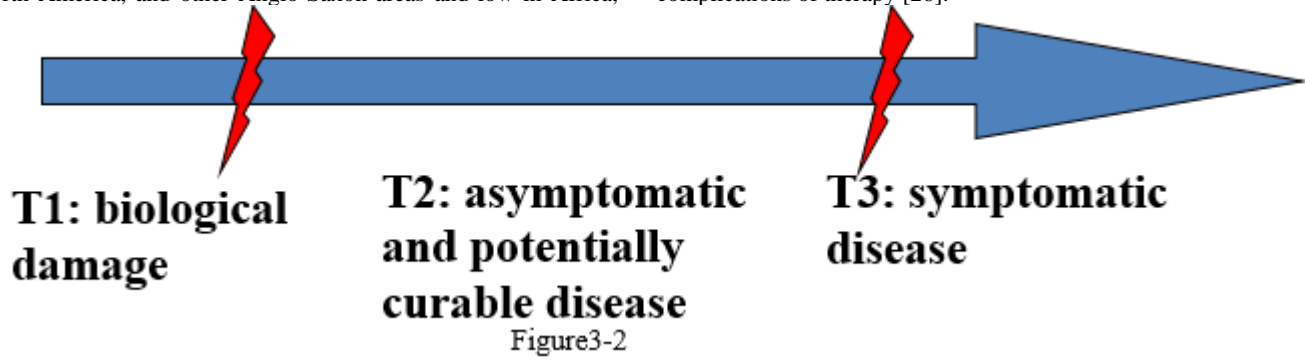

Figure 1: Hutchinson Diagram

Screening program should begin by classifying the individual patient level of risk based on personal, family, and medical history, which will determine the appropriate approach to screening in that person [27]. For example the person who is on risks such as following:

Personal history of adenomas or CRC, family history of CRC or adenomas in first degree relative (s) before age 60 years, inflammatory bowel disease (IBD), and family history of hereditary syndromes [24].

In addition to average risky person such as: healthy people with no known risk factors other than age, In general, practical guidelines recommend starting screening at age 50 years [28,29]. Because only 38% of patients are diagnosed when the cancers are localized to the bowel wall, it is likely that widespread implementation of screening could significantly improve the outcome. Colorectal cancer screening is cost effective, irrespective of the methods used. In addition to currently available methods (fecal occult blood, flexible sigmoidoscopy, colonoscopy, and double contrast barium enema). There are further experimental methods for screening are Fecal DNA test and computed topographic colonography (virtual colonoscopy) [30,31].

4.2. Clinical examination

The usual clinical picture of an early colorectal cancer is a change of bowel habit and painless mild bleeding particularly in the left side tumors. Other less common clinical features of colorectal cancer are; constipation with penciled like stool and signs of intestinal obstruction, ulceration with signs of intestinal perforation [32].

Systemic complaints like fatigue, cough, anemia, ascites, or musculoskeletal discomfort, may also present During palpation, oddly shaped, hard lump that can be felt might also be sings for cancer [33].

4.3. Colon biopsies (endoscopic biopsy and open biopsy)

A positive biopsy should always be obtained from colorectal carcinoma before performing radical surgery. In large lesions, it is advisable to perform several biopsies from different regions. Those biopsies which are taken from the center may show only granulation tissue, and those which are taken from the very periphery may contain only hyperplastic (so-called-transitional) colonic epithelium. Lesions below the peritoneal reflection should be removed in to wherever possible to facilitate their orientation for section by the pathologist. Although most adenocarcinomas are easily diagnosed, the

main problems being presented by the well differentiated tumors and- the highly malignant signet ring carcinomas in which only a few tumor cells may by present [30].

43.1. Endoscopy biopsy

The endoscopic tissue biopsies are usually with size about of 3x1 mm, and the biopsy can be performed under local anesthesia. The endoscopic biopsy allows the diagnosis as well as the distinction between invasive and in situ cancer. However, both false positives and negatives can occur. It is also very helpful in the differential diagnosis of adenomatous polyp, and hyperplastic polyp or from cancer, but examiner experience is highly required to properly performing this task. Increased utilization of endoscopic biopsy for obtaining tissue samples has led to major advances in both detection and diagnosis [30].

4.3.2. Open biopsy

The proper diagnostic procedure for patients with suspected colon cancer is the open excisional biopsy of the mass. Generally, this often applied to benign lesions that the patient wants be removed, and also to removal of doubtful lesions, if a malignancy has not been demonstrated by endoscopic biopsy. When the lesion is still suspected to be cancer, or if a mass is likely to be malignant, and the biological makeup of the tumor seems to be abnormal, the biopsy can be examined as a frozen section by the pathologist for a quick, but preliminary diagnosis. More commonly, the biopsy is processed routinely, and a diagnosis is made. If a malignancy is found within the cancer cases [30].

5. Classical clinicopathological prognostic markers

For CRC, the pathologic clinical stage is currently the single most important prognostic factor [1, 3, 34, 35], correlating with long-term survival [3, 36 ,37], although it does not fully predict individual clinical outcome [3, 37 , 38]. This is particularly true for those tumours with intermediate stage disease (T3-T4N0M0) [38], where one-third of patients with tumor-free lymph nodes have recurrences, and therefore adjuvant chemotherapy may be beneficial [39]. In this group, carcinoma cells are not detected in lymph nodes by conventional staging methods in 24% of patients. Therefore, the

lymphatic staging is essential to improve treatment of these patients. Indeed one-third of the patients submitted to curative intent surgery die of local and/or distant tumor recurrence [49 , 3]. Abdominal lymph nodes (38%) are the second most frequent site of metastasis (38%), just after liver, which is, the organ that most frequently involved (38–60% of cases) and followed by the lung (38%) and the peritoneum (28%) [49, 35].

5.1. Tumor size

Although a correlation between size of the tumour and prognosis exists, there are too many exceptions for this to be a reliable prognostic indicator . Along the same lines, there is little relation between the size of the tumor and the incidence of nodal metastases [2].

5.2. Lymph node status

Lymph node involvement is inversely correlated with tumor survival rate. Once the tumor has spread to the lymph nodes, the 5-year survival rate drops sharply. The location and extent of lymph node involvement are also significant" Cures are very rare when nodes other than those in the immediate vicinity of the tumor are involved [42, 43] Involvement of tie apical node is a particularly ominous feature [44, 45]. The greater the number of lymph nodes involved the worse the prognosis in one study [46]. if more than 6 lymph nodes contained metastatic carcinoma" Less than 10% of the patients

survival more than 5 years If more than 16 mesenteric lymph nodes contained carcinoma all patients died within the 5-year period. The former extent of involvement was not observed in carcinomas less than 2cm in greatest diameter and the latter extent of involvement was not observed in carcinomas less than 3cm in diameter, With in these parameters there was correlation between degree of lymph node involvement and size of tumor. it has been claimed that nodal micrometaslases detected only immunohistochemically or molecularly (with a RT – PCR technique for CEA) are also associated with a decreased survival [47,48].

5.3. Clinical staging

The practical clinical decision is dependent on summing the above basic features of a tumor by means of a staging system. American Joint Committee (AJC) on cancer staging has modified the TNM staging system that was proposed by the International Union Against Control of Cancer (IUAC) and based upon the size of tumor (T), degree of spread to lymph nodes (N) and systemic metastasis (M) at the time of diagnosis. The staging system goes from stage I to stage IV. Staging is regarded as the most important prognostic factor. As stage increases the prognosis deteriorates. For example; the 5 years survival in stage I colon cancer is more than 90% while patients with stage IV disease have very poor prognosis and a 5 years survival are less than 30% [49]
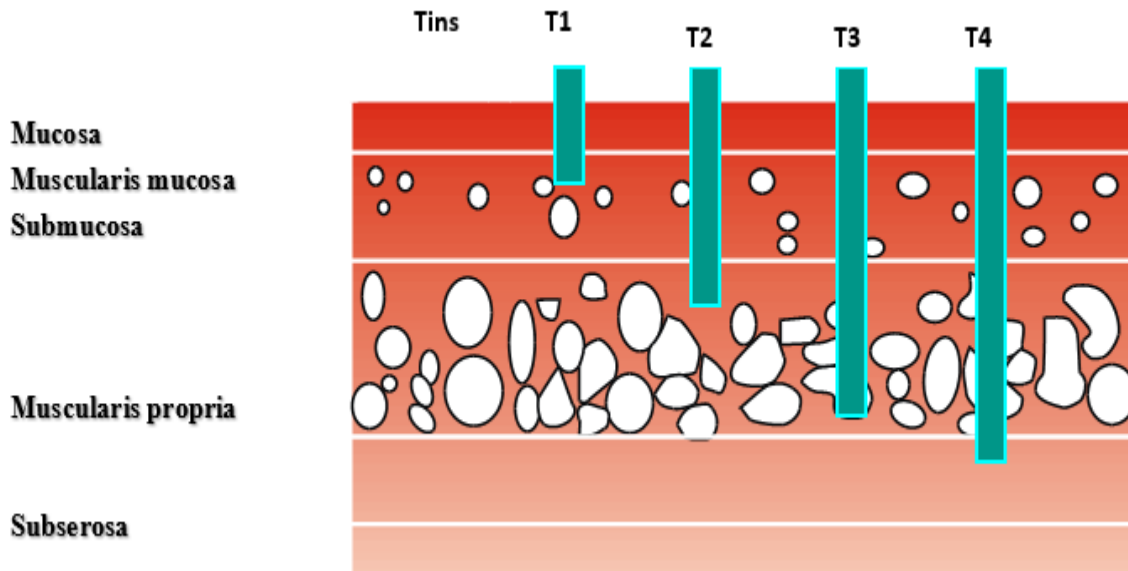

Figure 2: Layers of colon (Taylor, 2012)

6. Classical prognostic markers in histopathology

6.1 Histological grade

Colon cancers can be graded according the degree of differentiation to well differentiated (grade I), Grading Adenocarcinomas are graded predominantly on the basis of the extent of glandular appearances, and should be divided into well, moderately and poorly differentiated, or into low-grade (encompassing well and moderately differentiated adenocarcinomas) and high-grade (including poorly differentiated adenocarcinomas and undifferentiated carcinomas). Poorly differentiated adenocarcinomas should show at least some gland formation or mucus production; tubules are typically irregularly folded and distorted. When a carcinoma has heterogeneity in differentiation, grading should be based on the least differentiated component, not including the leading front of invasion. Small foci of apparent poor differentiation are common at the advancing edge of tumours, but this feature is insufficient to classify the

tumour as poorly differentiated [51]. The percentage of the tumour showing formation of gland-like structures can be used to define the grade. Well differentiated (grade 1) lesions exhibit glandular structures in > 95% of the tumour; moderately differentiated (grade 2) adenocarcinoma has50-95% glands; poorly differentiated (grade 3) adenocarcinoma has 5-50%; and undifferentiated (grade 4) carcinoma has < 5%. Mucinous adenocarcinoma and signet-ring cell carcinoma by convention are considered poorly differentiated (grade 3). Medullary carcinoma with MSI-H appears undifferentiated. Additional studies of the biological behavior of MSI-H cancers are needed to relate the morphological grade and molecular subtypes of mucinous, signet- ring cell and medullary carcinoma to outcome since MSI-H carcinomas have an improved stage-specific survival [52,53, 54]

6.2 Mitotic activity

Several authors suggested that evaluation of mitotic activity alone can be as prognostic as the grading system or even more powerful [55,56]. There are

many available ways to measure cell proliferative activity e.g. by counting the number of mitoses from ten high power fields from the most cellular area of the sample, using a standard light microscope (objective, x40; numeric aperture, 0.75; field diameter, 420µm), or by expressing the count by square millimeter, which produces the standardized mitotic index (SMI), also called volume fraction corrected mitotic index (M/Vv index) [56,57 ,55]. Many studies on different organs demonstrated that the mitotic activity index (MAI) is an independent prognostic factor for recurrence free survival. SMI is a bit more efficient than MAI as a prognosticator [57].

6.3 Histological type

Cancer at the site (CIS) consists of sever dysplasia. They are classified as pre-invasive cancers. In theory, it can be curable without any threat to life when surgically removed. Colorectal cancer and invasive adenocarcinomas have a slightly better prognosis than mucinous carcinoma [58].

6.4 Angiogenesis (Microvessel density)

Neo-vascularisation is the formation of new micro vessels in stroma. There is general agreement that angiogenesis has an important role in growth and metastasis of malignant tumors [14,25].

6.5 Tumor necrosis

Tumor necrosis is morphologically characterized by nuclear karyorrhexis, pyknosis and karyolysis, often accompanied by granular eosinophilic cytoplasm. When tumor necrosis has been present for a prolonged time it may be associated with fibrosis. Necrosis is usually related to adenocarcinoma of non-specific type, especially when has high grade [60]. A few studies suggested that tumor necrosis is accompanied with lowered survival and early treatment failure [58]. However, low reproducibility in evaluating necrosis may limit its use as a prognostic factor.

6.6 Multivariate clinicopathological prognostic indices

In last few years many authors combined different independent prognostic factors in multivariate indices in many organs including breast cancer and colon cancer. They found that these models are better prognostic indicators than the traditional grading system alone and can be expected to be more reproducible [61,58].

Typically, mitotic count has an important position in these models. It is important to notice that most multivariate models include lymph node status as a contributing feature and for that reason multivariate models or indices are applicable to both LN+ and LN- patients. One of the most common prognostic indices is Nottingham prognostic index which combines tumor size, lymph node status, and Nottingham histological grade [11].

6.7 Molecular prognostic markers in colon cancer.

A common feature of all cancers is the imbalance that exists between the proliferative activity and cell death; therefore, the evaluation of cell proliferation rate may be interesting in the study and characterization of tumors [63]. Some molecules, such as the Ki-67 protein, permit this assessment and are used as markers of proliferation because Ki67 expression is dependent of cell division rate; thus, over expression of these markers may suggest a disruption in the proliferation mechanism leading to the appearance of tumors [63].

Ki-67 protein, when used to evaluate the percentage of dividing cells, allows us to determine neoplastic growth [63] and has been documented to correlate with neoplastic progression [64] showing different levels of expression between normal mucosa, adenoma, and adenocarcinoma [65], verifying a progressive increasing of positive Ki-67 expression from the first (normal mucosa) to the last part of the tissue (adenocarcinoma) [64, 66 , 67].

Other studies correlate Ki-67 with the degree of malignancy, tumour invasiveness [67, 68], metastatic potential [63], patient survival, and the risk of relapse [69 ,70]. Thus, a high Ki-67 expression in tumour cells is assumed to correlate with a poor tumour differentiation and an increased tumor size

[66, 68]. Micev *et al.* [71] demonstrated that there is an association between Ki-67 expression and a less effective response in patients undergoing chemotherapy.

Other correlations with clinical and pathological data were also investigated and a correlation was detected between a high expression of this protein and the following variables; Patient's age [67], tumor size [72], tumor localization [70], dysplasia degree [72], the presence of lymph node metastasis [63, 67 ,70], and TNM [67] and Dukes [70] classification.

Accordingly, the younger is the patient, the greater is the cellular proliferation and the lower is the degree of differentiation. With increasing malignancy a increased frequency of invasion and metastasis are observed and hence poor prognosis of the tumor [67].

6.7.1 p53.

The p53 gene is located on chromosome 17p13.1, and is encoded for p53 protein. p53 is thought to be the gate keeper in the cell cycle, also called the guardian of the genome. When active, the main function of p53 is to suppress cell proliferation and activate apoptosis. When DNA is damaged, p53 inhibits the evolution of the cell cycle from G1 to stage S and activates DNA repair genes. The cell is directed with irreversible DNA to apoptosis by activating the estrogenic genes [73,74 ,75]. Rational mutations in one allele of the p53 gene associated with congenital or acquired congenital loss of the other leads to continuous cell growth the later can promote carcinogenesis in many organs, including colon, lung, and breast [75]. A p53 mutation increases the half-life of the non-functional p53 protein, accumulated in the cancer cell nucleus.

The accumulated p53 protein can be identified with IHC [76]. p53 hyperplasia has been detected in many human cancers including breast cancer [76], [75].and is often associated with poor prognosis[77]. p53 mutations, which can be detected by DNA sequence, appear to be independent indicators [78] Allred and his group reported in 1993 that p53 predicted a disease-free survival in patients with colon cancer. However, it has been shown that the expression of mutated p53 protein is also associated with more aggressive tumors, including the early recurrence of disease and early death in colon cancer [79].

6.7.2 *Bcl-2*

Family of membrane proteins that control apoptosis. It has been stated that immunohistochemical expression of bc1-2 is associated with an improved prognosis [80].

6.7.3 Cell proliferation markers

A. MIB-1 (Ki-67)

Ki-67 is a cell proliferation marker. It is a non- histone DNA binding protein that can be detected by immunohistochemistry [81, 82]. It is expressed in all phases of cell cycle except the resting phase [81]. The Ki-67 positive cells are in preparing for the S phase. Ki-67 labeling index (fraction of Ki-67 positive nuclei of all cells nuclei) indicates the fraction of cells in proliferation or near S-phase in the cell cycle. Several authors detected that high Ki-67 labeling index correlate with high histological grade [83], and large tumor size of colon cancer [73]. Therefore, Ki67 when used to evaluate the percentage of dividing cells, allows us to determine neoplastic growth [63] and has been documented to correlate with neoplastic progression [64] showing different levels of expression between normal mucosa, adenoma, and adenocarcinoma [65], verifying a progressive increasing of positive Ki-67 expression from the first (normal mucosa) to the last part of the tissue (adenocarcinoma) [64, 66, 67].

Ki-67 labeling index (determined e.g. by the MIB1; IgG monoclonal antibody used for detection Ki-67 in paraffin embedded material) showed a significant adverse correlation with survival in colon cancer, particularly among patients without LN involvement [58]. However, the independent prognostic significance of MIB-1 is much less than that of mitotic count (as

determined with either MAI or SMI [57,84]. The molecular classification of colon cancer based on gene expression profiling, The identification of several types of carcinoma of the large intestine has led to the discovery of some of the genetic alteration associated with (and presumably path-genetically responsible for) these tumors [85,186]. It was subsequently shown that somatic mutations of these genes also occur in sporadic colorectal cancer [87,88 89]. the most important of these genes are APC mismatch repair genes p53, k-ras and DCC [90].

In CRC, the analysis of colon adeno4mas has shown a different pattern for Ki-67 expression between normal tissue, adenomas, and adenocarcinomas. This was limited to the crypts in normal tissue and expressed both in the crypts and in the surface epithelium in adenomatous polyps e.g. (tubular, villous) [67], and distributed homogeneously in adenocarcinoma [92]. Nussrat et al. [72] also observed an increase in Ki-67 rates which was associated with the growth and rise of dysplasia in adenomas.

Studies on CRC indicated that Ki-67 is a prognostic marker since the survival rate for patients with high expression of Ki-67 is significantly lower compared to those with low expression [67, 93 94] and a predictor of CRC recurrence [95]. Also, significant associations were found between higher index of Ki-67 and increased tumour penetration [94, 96], the presence of lymph node [64, 94] and distant [94], metastasis, advanced TNM stage [92, 94], highest degree of differentiation, and subtypes of adenocarcinoma other than mucinous [97].However, not all studies were in agreement, and no correlations were found between patient age, gender, tumor location [64, 72, 93 98], and the type of adenoma [72] in some cases. Although, Jansson and Sun [98], did not find any associations between index Ki-67 and clinicopathological data or prognosis, Allegra and his group [99], described opposite associations, between a low rate of Ki-67 and high recurrence rate and poor overall survival. Regarding the use of Ki-67 in CRC metastasis, no full information is available, and the only similar study found compares Ki-67 index in primary tumour with peritoneal metastasis and had observed a lower proliferative index in metastasis compared with the primary tumor [100]. However, in other types of cancer, in particular breast cancer, a higher Ki-67 index was found in systemic and lymph node metastasis than in primary tumors [101 ,102], suggesting greater aggressiveness of these [102], it might be using of Ki-67 in lymph node metastasis in selecting the appropriate treatment for certain subgroups of patients [103].

6.7.4 Other molecular prognostic markers.

DNA mismatch repair deficiencies with resulting microsatellite instability MSI has been found to be an important alternate pathway present in approximately 15% of cases it operates in hereditary nonpolypsis colorectal carcinomas [104,105 ,106]. and is possibly a marker for the cancers arising from hyperplastic polyps and serrated adenomas [107].

Tumors associated with microsatellite instability tend to be mucinous or poorly differentiated with a prominent host response a circumscribed growth pattern and right-sided location in one study presence of tumor-infiltrating lymphocytes was found to be the best histological predictor of microsatellite instability [108,109]. it has been further pointed out that differences may exist depending on the specific type of mismatch repair gene involved [110].

Another group of molecules thought to play an important role in the pathogenesis of colorectal carcinomas is that of E-cadherin and catenins [110,111, 112] β-catenin is associated with APC protein and is dysregulated at all stages of the adenoma-carcinoma sequence [113,114] the expression of E-cadherin and α-catenin in colorectal carcinoma correlates with local invasion and metastases [115], mutations of p53 have been detected by molecular techniques in the majority of colorectal carcinomas [116]. E-cadherin and α-catenin have been correlated with an overexpression of the p53 protein that coded by the abnormal gene as detected immunohistochemically [109]. Approximately, half of the tumors showed positive staining of these proteins but do not seem to differ from others in terms of site of differentiation or DNA ploidy [117, 118]. As expected the

(transitional) mucosa present between the edge of the carcinoma and the normal mucosa is uniformly negative for this marker [119].

Mutations of the *rats* oncogene have been found in a minority of colorectal carcinoma particularly those in the metastatic group. [120, 121] expression of this gene which is said to influence the morphogenesis of early cancers [105] can be detected immunohistochemically in histologic and cytogenetic preparations[123, 124] Deletion of the von Hippei-Lindau gene has been detected in a high proportion of colorectal adenocarcinoma cases [125]. An enhanced expression of the *c-myc* oncogene occurs in approximately 90% of colorectal carcinomas [126] The increased proliferative activity of colorectal carcinoma has been measured by S-phase determination staining for Ki-67 or PCNA.

7. Conclusion

It can be concluded that the colorectal cancer is one of the most common malignancies**.** The aetiological and pathogenesis of colorectal cancer are usually related to both environmental and genetic factors. The colorectal cancer risk factors are medical history, alcohol consumption, age, diet, physical activity, diabetes, smoking, and geographic differences. the best methods for detection of colon cancer is a screening program with blood in stool, routine physical and endoscopic examination. Classical prognostic markers in histopathology are histological grade, mitotic activity, histological type, angiogenesis, and tumor necrosis. With increasing malignancy an increased frequency of invasion and metastasis are observed. Rational mutations in one allele of the p53 gene associated with congenital leads to continuous cell growth the later can promote carcinogenesis in the colon. Tumor-infiltrating lymphocytes were found to be the best histological predictor of microsatellite instability. Further studies about colorectal cancer are needed to prove strategies for controlling the prevalence of the disease and the more accurate method for diagnosis.

References

1. Svagzdys S., Lesauskaite V., Pavalkis D., Nedzelskiene I., Pranys D., Tamelis A. (2009) Microvessel density as new prognostic marker after radiotherapy in rectal cancer. BMC Cancer. 9, article 95
2. Martins S. F., Garcia E. A., Luz M. A. M., Pardal F., Rodrigues M., Filho A. L. (2013) Clinicopathological correlation and prognostic significance of VEGF-A, VEGF-C, VEGFR-2 and VEGFR-3 expression in colorectal cancer. Cancer Genomics & Proteomics. 10(2):55–67.
3. Martins S. F., Reis R. M., Rodrigues A. M., Baltazar F., Filho A. (2011) Role of endoglin and VEGF family expression in colorectal cancer prognosis and anti-angiogenic therapies. World Journal of Clinical Oncology. 2(6):272–280.
4. Zavoral M., Suchanek S., Zavada F., et al. (2009) Colorectal cancer screening in Europe. World Journal of Gastroenterology. 15(47):5907–5915.
5. Bosetti C., Levi F., Rosato V., et al. (2011) Recent trends in colorectal cancer mortality in Europe. International Journal of Cancer. 129(1):180–191.
6. Boyle P, Zaridze DG, and Smans M. (1985) Descriptive epidemiology of colorectal cancer.. International Journal of Cancer, 36(1), 9-18.
7. Berg jW, Howell MA. (1974) The geographic pathology of bowel cancer. Cancer 34: 807-814.
8. Roreno. Corpo Humano—Roreno—Registo Oncológico Regional do Norte,
9. Malvezzi M., Bertuccio P., Levi F., La Vecchia C., Negri E. (2013) European cancer mortality predictions for the year 2013. Annals of Oncology. 24(3):792–800.
10. Pinto C. G., Paquete A. T., Pissarra I. (2010) Colorectal cancer in Portugal. European Journal of Health Economics. 10(1):S65–S73.

11. Ferlay J., Steliarova-Foucher E., Lortet-Tieulent J., et al. (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European Journal of Cancer. 49(6):1374–1403

12. Mills SE, Allen MS Jr. (1979) Colorectal carcinoma in the first decades of life. Am J Surg Patho13: 443-448.

13. Farquhar CM, Marjoribanks J, Lethaby A, Lamberts Q, Suckling JA. (2005) Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev:CD004143.

14. Nelson RL, Dollear T, Freels S, Persky V. (1997) The relation of age, race, and gender to the subsite location of colorectal carcinoma. Cancer 80: 193–197

15. Mendeloff AI. (1979) Lea & Febiger Dietary fiber and the gastrointestinal tract. Critical assessment. In Seek JE (ed.): Developments in digestive diseases. Philadelphia,

16. Wcisburger JH. Causes, relevant mcchanisms, and prevention of large bowel cancer. Semin OncoI 199·1, 18: 316-336.

17. Hill MJ. (1974) Bacteria and the etiology of colonic cancer. Cancer 34: 815-818.

18. Lynch HT, de la Chapelle A. (2003) Hereditary colorectal cancer. N Engl j Med 348: 919-932.

19. Black WC, Ackerman LV. (1965) Carcinoma of the large intestine as a late complication of pelvic radiotherapy. C1in Radio1 16: 278-281

20. Qizilbash AH. (1974) Radiation-induced cilrcinoma of the rectum. A late complication of pelvic irradiation. Arch Patho1 98: 118-12l.

21. Cipolla R, Garcia RL. (1984) Colonic polyps and adenocarcinoma complicating ureterosigmoidostomy. Report of a case. Am J Gastroenterol : 453-457.

22. Lasser A, Acosta AE. (1992) Colonic neoplasms complicating ureterosigmoidostomy. Cancer 1975, 35: 1218-1222. 770 Levin B. Nutrition and colorectal cancer. Cancer 70: 1723-1726

23. Marcheggiano A, lannoni C, Pallone F, Frieri G, Gallucci M, Caprilli R. (1984) Abnormal patterns of colonic mucin secretion after ureterosigmoidostomy. Hum Patho1 15: 647-650.

24. Henrikson, N. B., Webber, E. M., Goddard, K. A., Scrol, A., Piper, M., Williams, M. S., and Whitlock, E. P. (2015) Family history and the natural history of colorectal cancer: systematic review. Genetics in medicine, 17(9), 702-712.

25. Rex, D. K., Boland, C. R., Dominitz, J. A., Giardiello, F. M., Johnson, D. A., Kaltenbach, T., and Robertson, D. J. (2017) Colorectal cancer screening: recommendations for physicians and patients from the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology, 153(1), 307-323.

26. Boncheva, V., Bonney, S. A., Brooks, S. E., Tangney, M., O'sullivan, G., Mirnezami, A., & Guinn, B. A. (2013) New targets for the immunotherapy of colon cancer—does reactive disease hold the answer?. Cancer gene therapy, 20(3), 157-168.

27. Chyke Doubeni, MD, FRCS, (2018) MPHScreening for colorectal cancer: Strategies in patients at average risk Literature review current through: Aug 2018. | This topic last updated:

28. National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2017 -- October 10, 2017.

29. Juwid E. Abdallah, Mussa Al Ragig, Eshtiwii Ali, Boder M. Jamela and Abdalla B. (2015) Fathi. Different Colonos-copy Presentation Patterns with ClinicopathologicalFea-tures of Colonic Cancer Patients Admitted in Misurata Cancer Center (MCC), Libya Int. J. Curr. Res. Biosci. Plant Biol. 2(7): 117-123

30. Winawer S et al, (2003) Colorectal Cancer Screening and Surveillance: Clinical Guidelines and Rationale Update Based on New Evidence. American Gastroenterological Association. Gastroenterology 124:544-560

31. Petkovic Marija. (2015) Clinical presentation and the early detection of colorectal cancer GLOBAL Journal of Medicine and Public Health Gjmedph 4(4)

32. American Cancer Society: colon cancer American Can-cer Society, (2014). Also

33. Gurzu S., Jung J., Azamfirei L., Mezei T., Cîmpean A. M., Szentirmay Z. (2008) The angiogenesis in colorectal carcinomas with and without lymph node metastases. Romanian Journal of Morphology and Embryology. 49(2):149–152.

34. Cascinu S., Georgoulias V., Kerr D., Maughan T., Labianca R., Ychou M. (2003) Colorectal cancer in the adjuvant setting: perspectives on treatment and the role of prognostic factors. Annals of Oncology. 14(2):25–29.

35. Alexander D. D., Waterbor J., Hughes T., Funkhouser E., Grizzle W., Manne U. (2007) African-American and Caucasian disparities in colorectal cancer mortality and survival by data source: an epidemiologic review. Cancer Biomarkers. 3(6):301–313.

36. Ries L. A. G., Wingo P. A., Miller D. S., et al. The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer. 2000;88(10):2398–2424.

37. Barozzi C., Ravaioli M., D'Errico A., et al. (2002) Relevance of biologic markers in colorectal carcinoma: a comparative study of a broad panel. Cancer. 94(3):647–657.

38. Bilchik A. J., DiNome M., Saha S., et al. (2006) Prospective multicenter trial of staging adequacy in colon cancer: preliminary results. Archives of Surgery. 141(6):527–533.

39. Calvo H. J., Ortega G. D., Pardo R. J. M., López M. A. J., Cubo T. (2000) Biologia molecular del proceso metastásico del cancer colorectal. Cirugia Española. 68:577–587.

40. Wolmark N, Cruz I, Redmond CK, Fisher B, (1983) Fisher ER and contributing N5ABP investigators. Tumor size and regional lymph node metastasis in colorectal cancer. A preliminary analysis from the NSABP clinical trials. Cancer 51: 1315-1322

41. Hermanek P, Altendorf A. (1981) Classification of colorectalcarcinomas with regional lymphatic metastases. Pathol Res Pract 173:1-11.

42. Newland RC,Chapuis PH, Smyth EJ. (1987) The prognostic value of substaging colorectal carcinoma. A prospective study of 1117 cases with standardized pathology. Cancer 60: 852-857.

43. Menon AG, Morreau H, Tollenaar RAEM, Alphenaar E, van Puijenbroek M, Putter H, Janssen-Van Rijn CM, van de Velde CjH, F1euren G), Kuppen PjK. (2002) Down-regulation of HLA-A expression correlates with a better prognosis in colorectal cancer patients. Lab Invest 82: 1725-1733

44. Newland RC, Dent OF, Lyttle MN, Chapuis PH, Bokey EL. (1994) Pathologic determinants of survival associated with colorectal cancer with lymph node metastases. A multivariate analysis of 579 patients. Cancer 73: 2076-2082.

45. Spratt JS Jr. Spjut HJ. (1967) Prevalence and prognosis of individual clinical and pathologic variables associated with colorectal carcinoma. Cancer, 20: 1976-1985.

46. Greenson JK, Isenhart CE, Rice R, Mojzisik C, Houchens 0, Martin EW Jr. (1994) Identification of occult micrometastases in pericolic lymph nodes of Duke's B colorectal cancer patients using monoclonal antibodies against cytokeratin and CC49. Correlation \-\'ith long-term survival. Cancer 73: 563-569.

47. Liefers GJ, Cleton-Jansen AM, van de Velde CJ, Hermans J, van Krieken JH, Cornelisse CJ, Tollenaar RA. (1998) Micrometastases and survival in stage IIcolorectal cancer. N Engl J Med 339: 223-228.

48. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 6th ed. Springer, New York 2006.

49. Taylor C. Best practice in colorectal cancer care. Nursing Times, 2012; 108:12, 22-25

50. Compton CC. (2003) Colorectal carcinoma: diagnostic, prognostic and molecular features. Mod Pathol 16:376-388.

51. American Society of Clinical Oncology. (1996) Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. Adopted on May 17, 1966 by the American Society of Clinical Oncology. J Clin Onco1 14: 2843-2877.

52. Hara A, Saegusa M, Mitomi H, Kurihara M, Ishihara K, Hotta K, Okayasu 1. (2000) Colonic mucin-carbohydrate components in colorectal tumors and their possible relationship to MUC2, p53 and DCC immunoreactivities. Pathol Res Pract 196: 159-166.

53. Patt OJ, Brynes RK, Vardiman JW, Coppleson LW. (1975) Mesocolic lymph node histology is an important prognostic indicator for patients with carcinoma of the sigmoid colon. An immunomorphologic study. Cancer 35: 1388-1397.

54. FerasAbdelmalik, Mohamed Elfageih, MosaElrgig and FathiAbdalla: (2018) Apoptotic and anti-apoptotic activity in Libyan colon cancer. La TunisieMedicale 96: 181-182

55. Collan Y, Kuopio T, Auranen A, Linna M. Prognostication of breast cancer by multivariate methods. AdvClin Path 1997; 1:269-273.

56. Collan Y, Kuopio T, Baak J, Becker R, BogomoletzW,DeverellM,Diest P, Galen C,Gilchrist K, Javed A, Kosma VM, Kujari H, Luzi P, Mariuzzi G, Matze E, Montironi R, Scarpelli M, Sierra D, Sisti S, Toikkanen S, Tosi P, Whimster W, Wisse E. (1996) Standardized mitotic counts in breast cancer evaluation of the method. Path Res Pract 192:931-941.

57. Kumar V, Abbas AK, Fausto N. Robbins and Cotran (2007) Pathologic Basis of Disease. 8th ed. Elsevier Inc

58. Folkman J. (1990) What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 82: 4-6.

59. AlragigMussa, Awaid Rabia, ElsaghayerWesam, Boder M Jamela, AbdelmalekFiras, Abdalla B. Fathi: (2015) Clinicopathological Characteristics of Colon Cancer In Libya. MMSJ 2.

60. Ikpatt OF. (2002) Nigerian breast cancer: Prognostic value of histomorphometry, AnnalesUniversitatisTurkuensis 487, 128 pages, Turku

61. Elston CW, Ellis IO. (1991) Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathol 19: 403-410.

62. Scholzen T., Gerdes J. (2000) The Ki-67 protein: from the known and the unknown. Journal of Cellular Physiology. 182(3):311–322.

63. Guzinska-Ustymowicz K., Stepien E., Kemona A. (2008) MCM-2, Ki-67 and PCNA protein expressions in pT3G2 colorectal cancer indicated lymph node involvement. Anticancer Research. 28(1):451–457.

64. Freitas D., Goulão M. H., Camacho E., et al. (2002) Clinical relevance of proliferation biomarkers and p53 expression in rectal mucosa and sporadic colonic adenomas: a prospective study. Hepato-Gastroenterology. 49(47):1269–1274.

65. Saleh H. A., Jackson H., Khatib G., Banerjee M. (1999) Correlation of bcl-2 oncoprotein immunohistochemical expression with proliferation index and histopathologic parameters in colorectal neoplasia. Pathology & Oncology Research. 5(4):273–279.

66. Lin M. X., Wen Z.-F., Feng Z.-Y., He D. (2008) Expression and significance of Bmi-1 and Ki67 in colorectal carcinoma tissues. Ai Zheng. 27(12):1321–1326.

67. Dziegiel P., Forgacz J., Suder E., Surowiak P., Kornafel J., Zabel M. (2003) Prognostic significance of metallothionein expression in correlation with Ki-67 expression in adenocarcinomas of large intestine. Histology and Histopathology. 18(2):401–407.

68. Bai X. Z., Masters J. R. W., O'Donoghue N., et al. (1999) Prognostic markers in clinically localised prostate cancer. International Journal of Oncology. 14(4):785–791.

69. Gao W. X., Feng J. G., Yang Y. F., et al. PCNA in colorectal carcinoma and the prognosis. Xian Dai Yu Fang Yi Xue. 2007;2(34):225–229.

70. Micev M., Micev-Cosić M., Todorović V., et al. (2004) Histopathology of residual rectal carcinoma following preoperative radiochemotherapy. Acta Chirurgica Iugoslavica. 51(2):99–108.

71. Nussrat F. L., Ali H. H., Hussein H. G., Al-Ukashi R. J. (2011) Immunohistochemical expression of ki-67 and p53 in colorectal adenomas: a clinicopathological study. Oman Medical Journal. 26(4):229–234.

72. Han JS, Cao D, Molberg KH, Sarode VR, Rao R, Sutton LM, Peng Y: Hormone receptor status rather than HER2 status is significantly associated with increased Ki-67 and p53 expression in triple-negative breast carcinomas, and high expression of Ki-67 but not p53 is significantly

73. Kastan MB, Onyekwere O, Sidransky D, Vogelstein B, Craig RW. (1991) Participation of p53 protein in the cellular response to DNA damage. Cancer Res 51:6304-6311.

74. Levine AJ. p53 the cellular gate keeper for growth and division. Cell 1997; 88: 323-331.

75. Kim K, Chie EK, Han W, Noh DY, Park IA, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW. (2010) Prognostic Value of p53 and bcl-2 Expression in Patients Treated with Breast Conservative Therapy. Korean Med Sci 25: 235-239.

76. Temmim L , Baker H , Sinowatz F (2001) Immunohistochemical detection of p53 protein expression in breast cancer in young Kuwaiti women.Anticancer Research , 21(1B):743-748

77. Shinichi Tsutsui Shinji Ohno Shigeru Murakami Yoichi Hachitanda Shinya Oda (2001) Prognostic value of p53 protein expression in breast cancer; An immunohistochemical analysis of frozen sections in 514 Japanese women August Volume 8, Issue 3, pp 194–201

78. Thanos D. Halazonetis1. Vassilis G. Gorgoulis2, Jiri Bartek3 (2008) An Oncogene-Induced DNA Damage Model for Cancer Development Science Vol. 319, Issue 5868, pp. 1352-1355

79. Leahy DT, Mulcahy HE, O'Donoghue DP, Parfrey NA. (1999) bcl-2 protein expression is associated with better prognosis in colorectal cancer. Histopathology 35: 360-367.

80. Kikuchi M, Mikami1 T, Sato T, Tokuyama1 W, Araki1 K, Watanabe M, Saigenji K, (2009) Okayasul I: High Ki-67, Bax, and thymidylate synthase expression well correlates with response to chemoradiation therapy in locally advanced rectal cancers: Proposal of a logistic model for prediction. Br J Cancer, 101: 116-123.

81. Romero Q, Bendahl P, Klintman M, Loman N, Ingvar C, Rydén L, Rose C, Grabau D Borgquist S. (2011) Ki67 proliferation in core biopsies versus surgical samples; a model for neo-adjuvant breast cancer studies BMC Cancer 11:341.

82. Petit T, Wilt M, Velten M, Millon R, Rodier JF, Borel C, Mors R, Haegelé P, Eber M, Ghnassia JP: (2004) Comparative value of tumour grade, hormonal receptors, Ki-67, HER-2 and topoisomerase II alpha status as predictive markers in breast cancer patients treated with neoadjuvant anthracycline-based chemotherapy. Eur J Cancer, 40: 205-211.

83. Jalava P, Kuopio T, Juntti-Patinen L, Kotkansalo T, Kronqvist P, Collan Y. Ki-67 (2006) immunohistochemistry: A valuable

marker in prognostication but with a risk of misclassification: Proliferation subgroups formed based on Ki-67 immunoreactivity and standardized mitotic index. Clin Can Res 48:674-682.

84. Kinzler KW, Vogelstein B. (1996) Lessons from hereditary colorectal cancer. Cell 87: 159-170.

85. Parsons R. (1997) Molecular genetics and hereditary cancer: hereditmy nonpolyposis colorectal carcinoma as a model. Cancer 80: 533-536.

86. Ilyas M, Tomlinson IP. (1996) Genetic pathways in colorectal cancer. Histopathology, 28: 389-399.

87. Jothy 5, Flanders TY, Nowacki PM. (1996) New developments in the molecular pathology of human colon cancer relevance to pathogenesis and diagnosis. Adv Anat PathoI , 3: 343-350.

88. Mueller E, Vieth M, Stolte M, Mueller J. (1999) The differentiation of true adenomas from colitis-associated dysplasia in ulcerative colitis: a comparative immunohistochemical study. Hum Pathol 30:898-905

89. Bosman FT. (1999) Molecular pathology of colorectal cancer. Cytogenet Cell Genet 86: 112-117.

90. Toru S., Bilezikçi B. (2012) Early changes in carcinogenesis of colorectal adenomas. West Indian Medical Journal. 61(1):10–16.

91. Hashimoto Y., Skacel M., Lavery I. C., Mukherjee A. L., Casey G., Adams J. C. (2006) Prognostic significance of fascin expression in advanced colorectal cancer: an immunohistochemical study of colorectal adenomas and adenocarcinomas. BMC Cancer. 6, article 241

92. Oshima C. T. F., Iriya K., Forones N. (2005) M. Ki-67 as a prognostic marker in colorectal cancer but not in gastric cancer. Neoplasma. 52(5):420–424..

93. Valera V., Yokoyama N., Walter B., Okamoto H., Suda T., Hatakeyama K. (2005) Clinical significance of Ki-67 proliferation index in disease progression and prognosis of patients with resected colorectal carcinoma. British Journal of Surgery. 92(8):1002–1007.

94. De Menezes H. L., Jucá M. J., Gomes E. G. D. A., Nunes B. L. B. B. P., Costa H. O., Matos D. (2010) Analysis of the immunohistochemical expressions of p53, bcl-2 and Ki-67 in colorectal adenocarcinoma and their correlations with the prognostic factors. Arquivos de Gastroenterologia. 47(2):141–147.

95. Ghiţă C., Vîlcea I. D., Dumitrescu M., et al. (2012) The prognostic value of the immunohistochemical aspects of tumor suppressor genes p53, bcl-2, PTEN and nuclear proliferative antigen Ki-67 in resected colorectal carcinoma. Romanian Journal of Morphology and Embryology. 53(3):549–556.

96. Nabi U., Nagi A. H., Sami W. (2008) Ki-67 proliferating index and histological grade, type and stage of colorectal carcinoma. Journal of Ayub Medical College, Abbottabad. 20(4):44–48.

97. Jansson A., Sun X.-F. (1997) Ki-67 expression in relation to clinicopathological variables and prognosis in colorectal adenocarcinomas. APMIS. 105(9):730–734.

98. Allegra C. J., Paik S., Colangelo L. H., et al. (2003) Prognostic value of thymidylate synthase, Ki-67, and p53 in patients with Dukes' B and C colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project collaborative study. Journal of Clinical Oncology. 21(2):241–250.

99. Yamauchi H., Suto T., Kigure W., et al. (2011) The progression potential of peritoneal dissemination nodules from gastrointestinal tumors. International Surgery. 96(4):352–357.

100. Buxant F., Anaf V., Simon P., Fayt I., Noël J. C. . (2002) Ki-67 immunostaining activity is higher in positive axillary lymph nodes than in the primary breast tumor. Breast Cancer Research and Treatment75(1):1–3.

101. Cabibi D., Mustacchio V., Martorana A., et al. . (2006) Lymph node metastases displaying lower Ki-67 immunostaining activity than the primary breast cancer. Anticancer Research26(6B):4357–4360.

102. Tawfik K., Kimler B. F., Davis M. K., Fan F., Tawfik O.(2013) Ki-67 expression in axillary lymph node metastases in breast cancer is prognostically significant. Human Pathology. 44(1):39–46.

103. Edmonston TB, Cuesta KH, Burkholder S, Barusevicius V, Rose D, Kovalich AJ, Boman B, Fry R, Fishel R, Palazzo JP. (2000) Colorectal carcinomas with high rnicrosatellite instability: defining a distinct immunologic and molecular entity with respect to prognostic markers. Hum Patho1., 31: 1506-1514.

104. Gafa R, Maestri I, Matteuzzi M, Santini A, Ferretti S, Cavazzini L, Lanza G. (2000) Sporadic colorectal adenocarcinomas with high- frequency microsalellite instability. Cancer 89: 2025-2037.

105. Loukola A, Salovaara R, Kristo P, Moisio A-L, Kaariainen H, Ahtola H, Eskelinen M, Harkonen N, Julkunen R, Kangas E, Ojala S, Tulikollra J, Valkamo E, Jarvinen H, Mecklin JP, de la Chapelle A, Aaltonen LA. (1999) Microsatellite instability in adenomas as a marker for hereditary non polyposis colorectal cancer. Am J Pathol]55: 1849-1853.

106. Hawkins NJ, Ward RL. (2001) Sporadic colorectal cancer with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. J Natl Cancer Inst 93: 1307-1313.

107. Greenson, J. K., Bonner, J. D., Ben-Yzhak, O., Cohen, H. I., Miselevich, I., Resnick, M. B., and Gruber, S. B. (2003) Phenotype of microsatellite unstable colorectal carcinomas: well-differentiated and focally mucinous tumors and the absence of dirty necrosis correlate with microsatellite instability. The American journal of surgical pathology, 27(5), 563-570.

108. Shia J, Ellis NA, Paty PB, Nash GM, Qin J, Offit K, Zhang X-M,Markowitz AJ, Nafa K, Guillem JG, Wong D, Gerald WL, Klimstra DS. Am J Slirg PathoI2003, 27: 1407-1417.

109. Wright CL, Stewart ID. (2003) Histopathology and mismatch repair status of 458 consecutive colorectal carcinomas. Am J Surg Pathol 27: 1393-1406.

110. Dorudi S, Sheffield jP, Poulson R, Northover JM, Hart IR. Patho1 (1993) E-cadherin expression in colorectal cancer. An immuno cytochemical and in situ hybridization study. Am J 142: 981-986.

111. EI-Baharawy MA, Poulsom R, Jeffery R, Talbot I, Alison MR. (2001) The expression of E-cadherin and catenins in sporadic colorectal carcinoma. Hum Patho1, 32: 1216-1224.

112. Brabletz T, Jung A, Reu S, Prozner M, Hlubek F, Kunz-Schughart LA, Knuechel R, Kirchner T. (2001) Variable beta-catenin expression in colorectal cancers indicates tumors progression driven by the tumor environment. Proc Natl Acad Sci USA 98: 10356-1 0361.

113. Brabletz T, Jung A, Kirchner T. (2002) Beta-catenin and the morphogenesis of colorectal cancer. Virchows Arch 441: 1-11.

114. Greenson JK, Bonner JD, Ben-Yzhak 0, Cohen HI, Miselevich I, Resnick MB, Trougouboff P, Tomsho LD, Kim E, Low M, Almog R, Rennert G, Gruber S8. (2003) Phenotype of microsatellite unstable coloreca! carcinomas. Am J Surg Palhol 27: 563-570

115. Rodrigues NR, Rowan A, Smith MEF, Kerr IB, Bodmer WF, Gannon JV, (1990) Lane Dr. p53 mutations in colorectal cancer. Proc Nail Acad 50i USA 87: 7555-7559.

116. Hanski C, Bornhoeft G, Shimoda T, I-Ianski ML, Lane OP, Stein H, Riecken EO. '(1992) Expression of p53 protein in invasive colorectal carcinomas of different histologic types. Cancer 70: 2772-2777.

117. Purdie CA, O'Grady J, Piris J, Wylie AH, Bird Cc. (1991) p53 expression in colorectal tumors. Am J Pathol 138: 807-813.

118. Connelly JH, Bruner JM, Robey-Cafferty SS, Sahin A. (1992) p53 protein expression in transitional mucosa and adenocarcinomas of the coloreclum. Mod 5: 537-539

119. Finkelstein SD, Sayegh R, Christensen S, Swalsky PA. (1993) Genotypic classification of colorectal adenocarcinoma. Biologic behavior correlates with K-ms-2 mutation type. Cancer 71: 3827-3838.

120. Meyers FJ, Gumerlock PH, Kokeris SP, deVere White RW, McCormick F. (1989) Human bladder and colon carcinomas contain activated faS p21. Cancer 63: 2177-2181.

121. Kobayashi M, Watanabe H, Ajioka Y, Honma T, Asakura H. (1996), Effect of K-ras mutation on morphogenesis of colorectal adenomCls Clnd eClrly CClncers: reiCltionship to distribution of proliferating cells. Hum 27: 1042-1049.

122. Czerniak B, Herz F, Koss LG, Schlom J. (1987) ras oncogene p21 as a tumor marker in the cytodiagnosis of gastric and colonic carcinomas. Cancer 60: 2432-2436.

123. Jansson DS, Radosevich JA, Carney WP, Rosen ST, Schlom J, StaTen ED, (1990)Hyser MJ, Gould VE. An immunohistochemical analysis of ras oncogene expression in epithelial neoplasms of the colon. Cancer, 65: 1329-1337

124. Zhuang Z, Emmert-Buck MR, Roth MJ, Gnarra J, Linehan WM, Liotta LA, Lubensky IA. (1996) Von-Hippel Lindau disease gene deletion detected in microdissected sporadic human colon carcinoma specimens. Hum 27: 152-156.

125. Matsumura T, Dohi K, Takanashi A, Ito H, Tahara E. (1990) Alteration and enhanced expression of the c-11IYc oncogene in human colorectal carcinomas. Pathol Res Pract]86: 205-211.

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