

**Pathology 2016: Microsatellite instability, BRAF and KRAS mutations in colorectal cancer - Boudida-Berkane Kenza - P&M Curie Center, Algeria.**

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**Aims:** This retrospective study aims to analyze the frequency of tumor hot spot mutations in KRAS, BRAF and Micro Satellite Instability (MSI) status of tumors in Algerian patients with advanced colorectal cancer (CRC), which can predict prognosis and contribute to decisions on treatment strategies.

Colorectal cancer (CRC), also acknowledged as bowel cancer, colon cancer, or rectal cancer, is the development of cancer of the colon or rectum (parts of the large intestine). Cancer is the abnormal evolution of cells that have the capacity to invade or spread to other parts of the body. Signs and symptoms may include blood in the stool, changes in stools, weight loss, and feeling permanently tired. Most colorectal cancers are due to aging and lifestyle factors, with only a small number of cases due to underlying genetic disorders. Other risk factors comprise diet, obesity, smoking, and lack of physical activity. Dietary factors that upsurge the risk contain red meat, processed meat, and alcohol. Another risk factor is inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. Some of the inherited genetic disorders that can cause colorectal cancer include familial adenomatous polyposis and hereditary nonpolyposis colon cancer; however, these represent less than 5% of cases. It usually begins with a benign tumor, often in the form of a polyp, which over time becomes cancerous.

Bowel cancer can be diagnosed by obtaining a sample of the colon during a sigmoidoscopy or colonoscopy. This is then trailed by medical imaging to regulate if the disease has spread. Screening is effective in preventing and reducing deaths from colorectal cancer. Screening, by one of the many methods, is recommended from ages 50 to 75. During colonoscopy, small polyps may be removed if they are found. If a large polyp or tumor is found, a biopsy may be done to check if it is cancerous. Aspirin and other nonsteroidal anti-inflammatory drugs lower the risk. Their general use, however, is not recommended for this purpose due to side effects.

Treatments used for colorectal cancer may include a combination of surgery, radiation therapy, chemotherapy, and targeted therapy. Cancers confined to the colon wall can be cured with surgery, while

cancer that has spread widely is generally not curable, with management geared towards improving quality of life and improving symptoms. . The five-year survival rate in the United States is about 65%. The likelihood of individual survival depends on how advanced the cancer is, whether or not all of the cancer can be removed by surgery, and on the general health of the person. Globally, colorectal cancer is the third most common type of cancer, accounting for about 10% of all cases. In 2018, here remained 1.09 million new cases and 551,000 deaths from the disease. It is more common in developed countries, where more than 65% of cases are detected. It is less common in women than in men.

**Inflammatory bowel disease**

People with inflammatory bowel disease (ulcerative colitis and Crohn's disease) are at increased risk for colon cancer. The risk increases with the duration of the disease and the severity of the inflammation. In these high risk groups, prevention with aspirin and regular colonoscopies are recommended. Endoscopic surveillance in this high-risk population may reduce the development of colorectal cancer through early diagnosis and may also reduce the risk of dying from colon cancer. People with inflammatory bowel disease account for less than 2% of colon cancer cases each year. [29] In people with Crohn's disease, 2% get colorectal cancer after 10 years, 8% after 20 years and 18% after 30 years. In people with ulcerative colitis, about 16% develop either a precursor to cancer or colon cancer over 30 years.

**Genetics**

Those with a family history of two or more first-degree relatives (such as a parent or sibling) have two to three times the risk of disease, and this group accounts for about 20% of all cases. A sum of genetic syndromes are also associated with higher rates of colorectal cancer. The most mutual of these is hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) which is present in about 3% of people with colorectal cancer. Other syndromes that are strongly allied with colorectal cancer include Gardner syndrome and familial adenomatous polyposis (FAP). For people with these syndromes, cancer almost always occurs and accounts for 1% of cancer cases. Total proctocolectomy may be endorsed for people with FAP as a preventative measure

due to the high risk of malignancy. Colectomy, the removal of the colon, may not be enough as a preventative measure because of the high risk of rectal cancer if the rectum remains. The most common polyposis syndrome affecting the colon is serrated polyposis syndrome, which is associated with a 25-40% risk of CRC. Mutations in the gene pair (POLE and POLD1) have been associated with familial colon cancer. Most colon cancer deaths are associated with metastatic disease. A gene that appears to contribute to the potential for metastatic disease, colon cancer-associated metastasis 1 (MACC1), has been isolated. It is a transcriptional factor that influences the expression of hepatocyte growth factor. This gene is associated with the proliferation, invasion and spread of colon cancer cells in cell culture, as well as tumor growth and metastasis in mice. MACC1 may be a potential target for cancer intervention, but this possibility needs to be confirmed by clinical studies.

**Methods:** KRAS exon 2, BRAF exon 15 were analyzed by direct sequencing of PCR products amplified in 102 tumor patients with advanced CRC cancer. MSI was determined using a panel of five single nucleotide markers (BAT25, BAT26, NR21, NR22 and NR24).

**Results:**

BRAF and KRAS mutations were detected in 4.9% and 31.3% of tumor patients, respectively. Activation of mutations in codons 12 and 13 in KRAS was localized in the right colon at 40.6% versus 25% in the left colon. (62.5%) with KRAS mutations are well or abstemiously differentiated. Amino acid changes are more frequently seen in codon 12 (29/32) than in codon 13 (3/32) and G12D (43.8%) is the most common mutation. The BRAF v600E mutation is observed in the proximal colon in 3 of 5 tumors (60%) in patients older > 50 years (53.1%). BRAF wild-type tumors (79%) were associated with MSI-H.

**Conclusion:** The results of the analysis of KRAS and BRAF mutations could be used in the selection of Algerian patients with CRC for anti-epidermal growth factor receptor (anti-EGFR) treatment and MSI-H status associated with the type wild BRAF (W t) may be suggesting the possible presence of hereditary nonpolyposis colorectal cancer syndrome (HNPCC).