Table 1: Stage systems AJCC, Dukes, and Astler-Coller. AJCC system is the most used and precise staging system for CRC and combines three letters (T: for the primary tumour, N: for spread to lymph nodes, and M: for metastasis) and numbers from 0 to 4 (indicating more severity for a higher number).

AJCC/TNM		Dukes	Astler-Coller
Stage 0	Tis, N0, M0	—	—
Stage I	T1-T2, N0 , M0	A	A, B1
Stage IIA	T3, N0, M0	B	B2
Stage IIB	T4a, N0, M0	B	B2
Stage IIC	T4b, N0, M0	B	B3
Stage IIIA	T1-T2, N1, M0 T1, N2a, M0	C	C1
Stage IIIB	T3-T4a, N1, M0 T2-T3, N2a, M0 T1-T2, N2b, M0	C	C1, C2
Stage IIIC	T4a, N2a, M0 T3-T4, N2b, M0 T4b, N1-N2, M0	C	C2, C3
Stage IV	Any T, Any N, M1a Any T, Any N, M1b	—	D

Tis: The cancer is in the earliest stage (*in situ*). It involves only the mucosa. It has not grown beyond the muscularis mucosa (inner muscle layer).

T1: The cancer has grown through the muscularis mucosa and extends into the submucosa.

T2: The cancer has grown through the submucosa and extends into the muscularis propria (thick outer muscle layer).

T3: The cancer has grown through the muscularis propria and into the outermost layers of the colon or rectum but not through them. It has not reached any nearby organs or tissues.

T4a: The cancer has grown through the serosa (also known as the visceral peritoneum), the outermost lining of the intestines.

T4b: The cancer has grown through the wall of the colon or rectum and is attached to or invades into nearby tissues or organs.

Nx: No description of lymph node involvement is possible because of incomplete information.

N0: No cancer in nearby lymph nodes.

N1: Cancer cells are found in or near 1 to 3 nearby lymph nodes.

- N1a: Cancer cells are found in 1 nearby lymph node.
- N1b: Cancer cells are found in 2 to 3 nearby lymph nodes.
- N1c: Small deposits of cancer cells are found in areas of fat near lymph nodes, but not in the lymph nodes themselves.

N2: Cancer cells are found in 4 or more nearby lymph nodes.

- N2a: Cancer cells are found in 4 to 6 nearby lymph nodes.
- N2b: Cancer cells are found in 7 or more nearby lymph nodes.

M0: No distant spread is seen.

- M1a: The cancer has spread to 1 distant organ or set of distant lymph nodes.
- M1b: The cancer has spread to more than 1 distant organ or set of distant lymph nodes, or it has spread to distant parts of the peritoneum (the lining of the abdominal cavity).

Combining the information of each letter, in a process called stage grouping, the stage is expressed in Roman numerals from stage I (the least advanced) to stage IV (the most advanced). Some stages are subdivided in letters (Table 1).

Another factor used to analyze the survival is the grade of the cancer [7]. Grade is a description of how closely the cancer looks like normal colorectal tissue when seen under a microscope. The scale used for grading a CRC goes from G1 (where the cancer looks like normal colorectal tissue) to G4 (where the cancer looks very abnormal). The grades G2 and G3 fall somewhere in between. The grade is often simplified as "low grade" (G1 or G2) or "high grade" (G3 or G4) [2]. Low-grade cancers tend to grow and spread more slowly than high-grade cancers.

1.1. Classical Model of Carcinogenesis: Multihit Hypothesis. Cancer is classically generated by a three step process, consisting of initiation, promotion, and progression (Figure 1). A simple mutation is not enough to develop a cancer, and thus the multiple-hit hypothesis indicates that cancer is the result of accumulated mutations to a cell's DNA. This hypothesis was first proposed by Nordling [8] and later by Knudson [9].

Initiation includes the formation of a malignant cell after a carcinogenic initiator damages DNA. Carcinogenic initiators include UV light, ionization radiation, thermal disruption, or chemical sources [10]. Genotoxic initiators mutate cellular DNA by five main types of DNA damage including

(i) oxidation of bases (e.g., 8-oxo-7,8-dihydroguanine (8-oxoG)) and generation of DNA strand interruptions (usually produced by reactive oxygen species),

(ii) alkylation of bases (specially methylation, e.g., in 1-methyladenine, or 7-methylguanine),

(iii) hydrolysis of bases (e.g., deamination, depurination, and depyrimidination),

(iv) bulky adduct formation (e.g., aristolactam I-dA adduct, or benzo[a]pyrene diol epoxy-dG adduct),

(v) mismatch of bases, due to errors in DNA replication.