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Original Research Paper

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# IMMUNOSCORE VS CLASSICAL STAGING OF COLON CANCER

**Dr. Rand M. Anwer**

Ibn Sina University of Medical and Pharmaceutical Sciences, Iraq, Baghdad.

**ABSTRACT**

Cancer is a vibrant, active, and a very complex disease that can be characterized using a certain systems and the stage of the tumor can be determined and evaluated based on a certain tumor hallmarks using special techniques. This review is article is planned and carried out to determine and evaluate the stage of the colorectal cancer (CRC) using classical systems vs. immunoscore technique; each classification system was defined and explained and the CRC tumor data that was collected from each system was evaluated and compared with the other technique. The article reached a certain conclusions such as; there two main systems that can be used to evaluate the CRC stage NM, and immunoscore systems, each system has its own mistakes, and the best method that can be used to calssify the CRC stage is by combining both systems (TNM vs. immunoscore).

**KEYWORDS :** TNM, CRC, immunoscore, tumor, staging

## INTRODUCTION

Cancer is a dynamic, and a very complex and difficult disease that can be characterized by main and a certain properties and hallmarks, that can preserve the reproductive signals, evade from the growth prohibitory factors, make the immortality (eternity) possible, defy and resist the death of the cells, redistribute the metabolism energy, metastasis and invasion activity, suggest angiogenesis, and avoid the destruction of the immune system [1].

Recently, the most regular and familiar system for classification of cancer is carried out according to Weitz et al., in 2005 [2], and Locker et al., 2006 [3], the authors of both articles recommend "AJCC/UICC" (American Joint Cancer Committee / Union Internationale Contre le Cancer), applying this system on tumors can easily classify and characterize cancer tumors. In addition to that other factors must take in the consideration (TNM), which was explained in 2002 by Sobin and Wittekind [4] as the staging of TNM that can be described as following:

- Primary tumor extent (T).
- Lymph nodes involvement (N).
- Metastases distant (M).

Further parameters that can used in a sign or indication and essential in the biological characterization of the presence of the tumors which can also predict and estimate the progression of the tumor, these biological signs are needed before the resection surgery. Both, the outcome of clinical tests and the AJCC/UICC-TNM can be considered to determine and verify the stage of the tumor histologically, because the staging of TNM system cannot afford complete information to predict and decide the tumor stage as well as the status of the tumor immune, thus it is not possible to predict the response toward different therapeutic methods [5,6].

In 2011, Nagtegaal and his coworkers [5] mentioned that in 2009, the UICC a new guideline for classification of tumors based on TNM, and the reports and the data that comes from pathologists, these data can help to integrate the stage and the grade of the tumor that are associated with different dynamic processes like; death, and when the tumor occur, and more. The accurate statistics, information, and the data can participate in the progression of the disease globally, because this information is very essential to provide a snapshot about the progression of the tumor and may help to decide the strategy of the treatment plan by linking both staging system of the TNM with the pathologist's information.

In 2011, Mlecnik et al. [6], mentioned that in some rare cancer cases, the advance stage can stay and remain without any changes for many years (stable), and the metastatic regression of the tumors can be full or partial and spontaneously. However, rapid progression in tumor that ends with death of the patient can be related to about 25% of TNM stage I/II of CRC patients (Colorectal Cancer), even if the resection surgery was done and completed with no tumor residue. The progression of the disease and the predication of the stages are assumed by what is called the process of cell-autonomous. This classification is focused on the cells of the tumor, and disregards the response of the immune system of the host as depicted by Bindea and his coworkers [7].

### Factors associated with tumor

The tumor genotype is controlled by environment of the tumor as well as the component of epithelial, meaning the other 3 factors can be associated with the tumor, and these factors are:

- Infiltrate of the inflammation.
- The mesenchyme.
- The status of the other cells near the tumor (in contact).

As it was explained by Hanahan and Weinberg in 2011 [8], the above three hallmarks can determine all the cell inputs such as; metabolites, the molecules of cell-cell adhesion, soluble factors, ligands, and oxygen. The information that are collected regarding the spatial organization of the cell and the key proteins, however, the new imaging techniques can offer a high resolution and potential data to the dynamics of the spatio-temporal to a huge records of the proteins [9].

The classification of cancer according to TNM was not overridden in the multivariate analysis by alternative techniques such as; genetic features and there molecular signature, DNA cytometry, tumor biomarkers and there immuno histochemistry. The analysis of a specific type of immune response within a tumor was already superior comparing to that of multivariate analysis used by TNM system. Therefore, the progression of tumor can be considered now as consequences of anequilibrium between defense system (which is affected by the response of the host immunity), and the invasive tumor [10].

Figure 1 represents the Pie Chart of the possible approaches that can used to classify cancer. The left side of the figure is the characteristic of only the cell such as; the morphology of the tumor (such as budding of the tumor, location, invasion of lymph), the origin of tumor cells, the pathway of the molecule, status of mutation. In spite of the presence a satisfactory evidences that indicating the immuno-score, while the current classification of the cancer doesn't contains any parameters that are related to the immune (the right side of the figure) [11].

### The classification of colorectal cancer according to the Immunoscore

Immunoscore is a test to diagnose that carried out to the patients in vitro to predict the relapse risk of colon cancer in the early stage, by measuring the immune response of the host at the location (site) of the tumor; this tool can provide assessment risk that gives advanced and independent prognostic rate than regular risk parameters to the tumor which proposed to be used to help in classification of TNM to determine the management guide to the patients.

The response of host immune into prognostic accuracy improvement and into the classification of cancer is incorporated with the effect of the immunoscore. It confirm the measurement of the populations of two T lymphocytes (CD8/CD45RO, or CD3/CD8, CD3/CD45RO) in the center and at the tumor periphery [9].

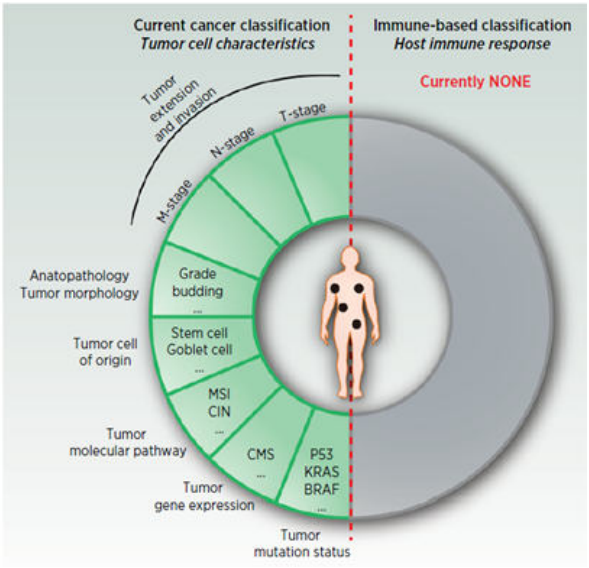


**Figure 1: Classification of cancer based on i) left: characteristics of the tumor; ii) right: No parameters of immune [11]**

The increasing and the rising in the evidence numbers will display the progression and the development of the cancer tumor and reflect its dependence on TEM (Tumor Micro Environment). The TME includes a variety of entities of the cells that includes; the endothelial cells, fibroblasts, lymph vessels, blood vessels, and the immune system cells. It has been shown the predictive value to the adaptive immune cell infiltration that can goes beyond the traditional criteria for tumor invasion such as; metastatic status, stage, and grade [12, 13].

The key immunological information associated with survival is known as "immune context" [14, 15], specified as a type, the location of immuno corrective adaptive cells within specific tumor regions, location of density, and the functional orientation [15,16].

Additionally, the tumor physical status, components, and properties within a tumor, TME may comprise many soluble agents for instance; metabolism products of the cells, chemokines, and cytokines, therefore the progression of the tumor and the survival of the patients can be a sign of the molecular interaction, and the complex cellular between the host immunity and the tumor [14].

Usually the Immunoscore can be evaluated upon at the center of the tumor (CT), in particular the invasive margin (IM), to investigate the T cells of cluster of differentiation CD8+, and CD3. The Immunoscore can afford a certain system called "Scoring System" that raged between high density (the Immunoscore =4), while the Immunoscore of the low density is zero (0) which can be found at IM and CT [17], the increasing of the Immunoscore value is correlated to the survival of the patient and vis versa as shown in figure 2, and figure 3.

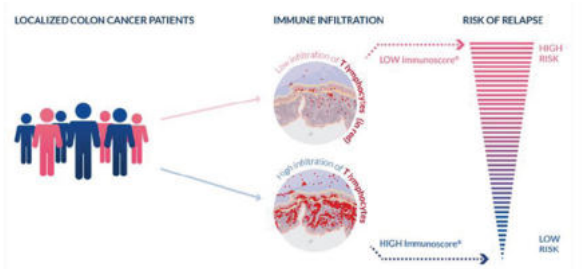


**Figure 2: the correlation between Immunoscore and the patient survival [19]**

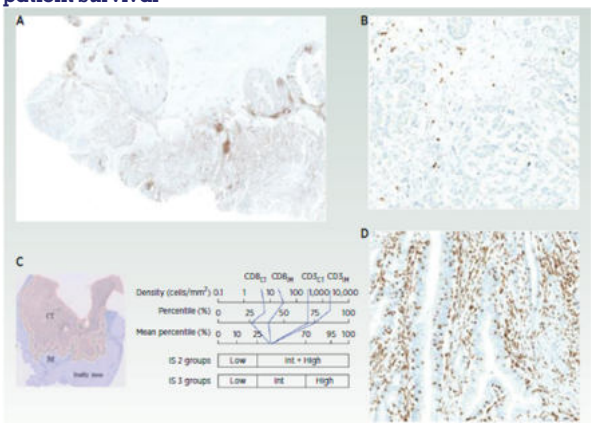


**Figure 3: A: CD3 staining; B: staining in low Immunoscore; C: area of tissue including healthy tissue, IM, and CT; D: staining in high Immunoscore [11]**

The C part in figure 3 includes the cutoffs in the density of the cells which indicates also the CD8, and CD3. (CD8IM, CD8CT, CD3IM, and CD3CT).

### Staging of colon cancer

In general, the staging of colorectal cancer represents the spreading of tumor, and how far the tumor affects the surrounding tissues and cell, as well as the effect of the tumor on the immunity of the patient [20,21].

The most common system used to determine the stage of the CRC tumor is TNM. Figure 4 shows the classification of the CRC stages according to TNM system

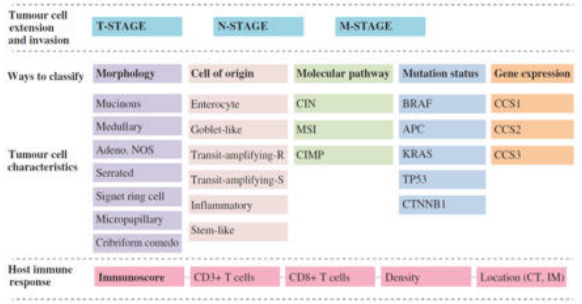


**Figure 4: Evaluating the CRC stage according to the classification system [9].**

In the bottom of figure 4, shows the determination of the CRC stage according to Immunoscore system, while the middle part of the figure represent the determination of the CRC stage based on the characteristic of the cell of the tumor cell, and the top part of the figure is based on invasion and extension of the cell [22,23].

Ultimately, each stage of CRC tumor has its own symptoms, and as the tumor develops, and spread, the stage will be changed (raised) i.e. from stage I to stage II, and the symptoms will be changed as well (more sever), also the survival of the patient will be less, as well as the rate of the Immunoscore will be low [24, 25]. Thus the treatments that can be used for colorectal cancer may include some combination of radiation therapy, surgery, targeted therapy, and chemotherapy [26].

Figures 5 and 6 indicate the summery of the interferences between the CRC stages with the Immunoscore.

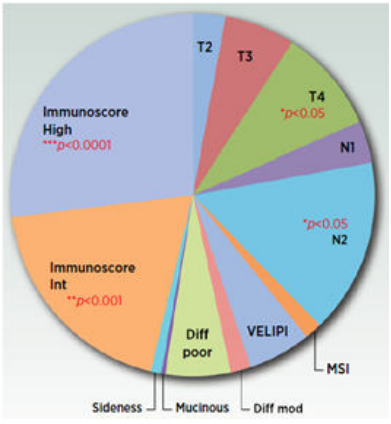


**Figure 5: the multivariate investigation and analysis to overall survival (OS) vs. Immunoscore (P < 0.0001, P < 0.001, P < 0.05)** [9]

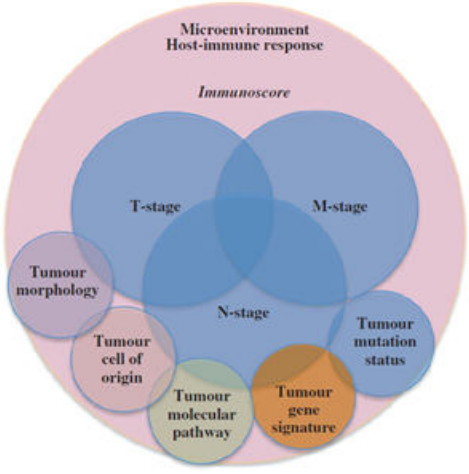


**Figure 6: Classification of the tumor stage based on the parameters that are related to the TNM, and immunoscore** [9]

## CONCLUSIONS

- Colorectal cancer has different stages.
- Each stage indicates the development of the tumor.
- There many systems to determine and classify the stage of the CRC.
- Most common systems to evaluate the CRC stage are TNM, and Immunoscore.
- The best technique to analyze the CRC stage is by combining TNM system and Immunoscore to reach an accurate evaluation.

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