



# TNMI may improve current cancer staging

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Even though there are several cancer staging systems, the American Joint Committee on Cancer (AJCC) TNM staging system is the most used by clinical oncologists worldwide and is the standard in cancer staging. During the 20<sup>th</sup> century, the Union for the International Control of Cancer, created a clinical system for cancer staging, known as TNM, based on the local tumor extension (T), lymph node invasion (N), and presence or absence of metastasis (M) distant from the local origin. The TNM system allowed clinicians to use similar treatments on cancer patients around the world and has proven to be the most successful guide in clinical oncology. The TNM staging system has been modified regularly by the AJCC over the past years, to improve uniform clinical practices in cancer treatments; multidisciplinary teamwork including managing physician, pathologist, and radiologist, created the basis for clinical trials and for evaluating outcomes. The oncologist treating physician is responsible for assigning the TNM stage of patients. The current TNM staging system

in the 2018 recent publication is better than its original form because it has incorporated new information that improved treatment results<sup>1</sup>; however, discrepancies still exist, for example, biomarkers as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor that have shown to be important prognostic factors have not been included in the actual TNM staging system for breast cancer<sup>2</sup>.

It is clear that patients with similar cancer extension, lymph node invasion, and metastasis respond differently to same anti-cancer therapies including surgery, radiotherapy, and chemotherapy; differences are attributed mainly to genetic cancer biology diversity.

Advances in molecular biology sequencing techniques and multiple gene expression applied to human cancer study, help us to understand the presence of mutations in cancer cells; this information advanced our knowledge in cancer biology

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and raised great expectations that the generated information will produce an important impact in clinical oncology. To date, it is known that the number of mutations in cancer cells may vary from small to great numbers, and some studies demonstrated that the presence of great number of mutations correlated positively with better outcome<sup>3,4</sup>. In some cancer therapies based on checkpoint inhibitors, other authors found better responses in low mutation burden<sup>5,6</sup>. Controversial results are coming to the idea that these genetic studies are complex, expensive and have little impact in today's clinical oncology daily work<sup>7</sup>.

Immunotherapy using checkpoint inhibitors with anti-PD-1 and PD-L1 monoclonal antibodies in the past 10 years has revolutionized cancer therapy; this treatment in addition to surgery, radiotherapy, and chemotherapy showed in the past few years its great benefit in some cancer patients. The number of patients that benefit from immunotherapy is not homogenous and not high in all cancer patients. The explanation for this different effect is not clear. Several works addressed this point trying to define a biomarker that helps to predict and select patients that will benefit from the immunotherapy using checkpoint inhibitors. The percentage of tumor cells expressing the PD-1L in more than 1% responded better in one clinical trial of non-small-cell lung<sup>8</sup>.

There are other immune-based therapies in cancer, i.e., dendritic cells vaccines that are good immunogens and capable of inducing a strong active and long-lasting antitumor response<sup>9</sup>. The vaccine for prostate cancer approved by the Food and Drug Administration is safe and highly immunogenic to induce a robust active immunity<sup>10</sup>. Chimeric antigen receptor (CAR) T-cell is another good example of immune therapies that have shown success; however, cytokine-release syndrome and severe toxicities are present and limit extensive use. As new technologies appear such as the third-generation CAR T-cell and other immunotherapies<sup>11</sup>, the severity of toxicity should

decrease. Tumor neoantigens, peptide vaccine, and other forms of active and passive immunity are currently under investigation. Immune oncology revolution in cancer treatment is complex and expensive; results from molecular biologists, immunologists, and oncology clinicians together will speed the development of new treatments. For sake of its use in clinical oncology today, it is necessary to create simple and solid concepts to assimilate new information and get familiar with it.

Recently, success has been demonstrated in cancer immunotherapy in elderly people, so the term "immunosenescence" does not mean an impairment of their immune system to respond to cancer<sup>12</sup>.

Here, we propose that immune status (Is) identification will be of help to classify patients that benefit most from immunotherapy, therefore, by adding and I for Is information to current TNM staging system, it will provide a better definition and selection of patients groups for clinical trials (TNMI).

Is, here, is considered not only the presence or absence of immune competence but also mainly the identification of actual systemic and local immune interaction between host and cancer cells at the time of diagnosis. For example, primary or secondary immune-deficient patient's status is known to have poor prognosis in cancer treatment. Our proposal is to include a classification of Is in a 0, 1, and 2, where 0 represents an immune-competent patient with abundant T lymphocytes cells infiltrating (TIL) the cancer tissue as found in a biopsy tissue, with high expression of PD-1 and/or high PD-L1 in tumor cells. TNMI 1 includes immune-competent patients but with little number of TIL and poor PD-1 or PD-L1 expression. TNMI 2 refers to cancer patients with a primary or secondary immune deficiency. It is clear that this classification will be modified as soon as new information is generated. Undoubtedly, the research in the immune-cancer interaction status in human patients will provide better results in cancer therapy.

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## CONFLICTS OF INTEREST

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Authors declare that they have no conflicts of interest.

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