The Philosophy of Staging in Lung Cancer: Prognosis or Treatment Planning?

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ABSTRACT

Tumor staging is one of the cornerstones of oncology. The purpose of staging is to provide a universal terminology regarding the anatomical extent of cancer without causing incomprehensibility. This allows for reliable communication between clinicians without room for doubt, a common language in clinical studies, and the evaluation of the results of planned treatment strategies. Although it is critical to represent staging with a terminology that is used consistently and coherently, periodic revisions are also necessary. The terminology is also improved in parallel with the obtainment of new data regarding the definition of the anatomical extent of tumors with developments in technology. Although the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) are institutions that define and periodically review the classification systems and work together in order to ensure the universal consistency of staging, staging in thorax malignancies has been regulated under the lead of the International Association for the Study of Lung Cancer (IASLC) for the last two decades. The aim of this review is to summarize and discuss the philosophy of staging in lung cancer.

Keywords: Lung cancer, staging, philosophy.

INTRODUCTION

Survival rate in cancer patients is higher in cases with localized disease in comparison to cases when the disease has spread outside the organ. In the light of this fact, cancer cases have been divided into groups called stages. Selection of the treatment to be administered in accordance with objective data obtained from patient groups that are at a stage similar to the cancer stage at the time of diagnosis is the key factor that determines the prognosis. There are many staging systems used throughout the world. The difference between these systems stems from the differences in the purpose and needs of clinicians, as well as in population screening. The most commonly used staging system throughout the world is the tumor-node-metastasis (TNM) staging system developed by the AJCC and UICC jointly due to its clinical practicality (1). With the TNM staging system, cancers are classified with the help of anatomical variables, such as the size and extent of the primary tumor (T), regional lymph node involvement (N), and presence or otherwise of distant metastases (M), as well as some non-anatomical variables for some cancer types in recent years. Numbers next to these three components indicate the grading of cancer extent and are expressed as T0, T1 (mi, a-c), T2 (a, b), T3, T4, N0, N1, N2, N3, M0, M1 (a-c). The AJCC and UICC meticulously revise the TNM classification based on evidence periodically due to the changes in clinical data, developments in cancer biology, and better understanding of the prognostic factors. TNM staging

is revised every 6-8 years. The most up-to-date version of the TNM staging for lung cancer is the 8th edition that has been in use since January 1, 2017. Unlike previous stagings, the last two revisions of lung cancer staging were made by the IASLC using multinational data. The IASLC database was created by analyzing more than 100,000 cases from four continents and nearly twenty countries. Despite this data diversity, it was shown that staging could be performed successfully. Data from cases that received non-surgical treatment were also included, as well as cases that received surgical treatment. The success of clinical staging was investigated by analyzing data from cases that were administered non-surgical treatment (cases that received only chemotherapy or only radiotherapy or chemoradiotherapy) (2).

The TNM System's Philosophy of Classification and Staging

A simple classification scheme that can be applied universally is the main goal of the TNM system proposed by the AJCC and UICC. A useful staging system should include the characteristics that define the biological behavior of the tumor. AJCC classification is based on the premise that cancers in the same anatomical region with the same histology share similar patterns of growth and have similar outcomes. In other words, criteria that define the anatomical extent of the disease will differ for tumors of different histological type and for tumors in different anatomical regions. There are two defined classifications for each region; a) Clinical classification denoted as cTNM is the basis of treatment choice

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and evaluation. It is an evidence-based classification obtained from physical examination, biopsy, bronchoscopy, endoscopy, and such examinations. b) Pathological classification denoted as pTNM. This is the classification based on the examination of a surgically resected case that has sufficient tissue for evaluating T, N or M classification. It provides the most accurate data for reaching a final outcome and predicting the prognosis. Most of the time, cancer spreads to regional lymph nodes and/or has distant metastases before it is noticed in the clinical examination. Therefore, the examination during surgical procedure and the histological examination of surgically resected tissues may result in a difference between surgical stage and clinical stage. The post-treatment stage (yTNM) documents the spread of the disease in cases that have received chemotherapy or radiotherapy before surgery, or in cases that will not have surgery and continue the primary treatment with chemotherapy or radiotherapy. Post-treatment recurrent cancers are assessed according to a similar criteria to those used in clinical staging before treatment. "Restage" classification (rTNM) for recurrent cancer provides therapeutic guidance and helps predict the prognosis under the recently emerging conditions (3).

It is important to evaluate the anatomical extent of cancer clinically and develop a treatment strategy in accordance with this evaluation before starting treatment. The anatomical extent of cancer is determined by the presence of local tumor growth, spreading to regional lymph nodes, and distant organ metastasis. This anatomical extent (TNM) is the shortest and simplest way of expressing the cancer grade or disease severity within a certain time period. As the extent of untreated cancer increases, the possibility of regional lymph node involvement and/or developing distant metastases will increase, leading to a worse prognosis. A different staging system that employs descriptive criteria other than T, N and M is used in order to determine the prognosis in some tumor types such as Hodgkin's disease and lymphomas as an exception. Although staging recommendations for most cancer types relate to disease extent from an anatomical aspect, non-anatomical factors that significantly affect prognosis such as histological "grade" (soft tissue sarcoma) and age (thyroid carcinoma) have also been included in staging as necessary (1). Lung cancer has not been included in the staging for non-anatomical prognostic factors in the 8th edition of TNM staging (4).

Prognostic factors include many heterogenous variables to help understand the natural course of cancer. Although, it is exciting to predict the course of cancer and other diseases, it is not possible to make an exact prediction for each patient and only possibilities can be mentioned. This is because studies in this field are conducted on patient groups, rather than individuals. Therefore, only a connection can be made between data obtained from patient groups and a single patient. Hence, it is not possible to make a critical prediction for cancer patients on an individual basis. TNM classification is a universal system that records the anatomical extent of the disease. However, there is no optimal system similar to TNM for the classification of prognostic factors. On the other hand, prognostic factors are frequently used in cancer practice. These factors are included in all phases of decision making about the disease and in treatment planning, i.e. briefly

in the broadest management scheme of the cancer patient. For example, the efficacy of targeted therapy administered to a case with Stage 4 lung adenocarcinoma in the presence of the epidermal growth factor receptor gene (EGFR) mutation would be higher in comparison to standard chemotherapy. Knowing the EGFR mutation status increases the capacity for prognosis, as well as for treatment selection. However, when these molecular prognostic parameters will be included in staging is a question that is frequently asked. TNM staging is an anatomical staging. Therefore, the answer actually lies within. Nonetheless, multidisciplinary prognostic grouping studies that include a reasonable number of prognostic factors based on TNM and molecular classification are ongoing today. This is one of the most important duties of the IASLC Staging and Prognostic Factors Committee during the third phase of the IASLC staging study being conducted between 2017-2024 (4).

In the future, it may be possible to make additions to anatomical indicators in cancer classification when the importance of tumor-associated (tumor histology, invasion pattern, histological grade, tumor markers, genetic mutations), patient-associated (age, gender, comorbidity, performance status) and environmental (socioeconomic status) prognostic factors are proven (5).

DISCUSSION

In medicine, the prediction of prognosis has always been necessary and important. In the early 20th century, Halsted et al. (6) believed that solid tumors could gradually spread from the primary tumor zone to distant organs via the lymphatic system and that the patient would have a gradually worsening prognosis at each stage. As a result of this opinion and other following studies that were supported, it was thought that clinical and pathological T, N, and M factors could provide information regarding the spread of the disease and prognosis. In 1953, French surgeon Pierre Denoix proposed to the UICC that these three factors should be standardized and integrated into a prognostic system that could be used in all solid tumors. This suggestion of having a common language of prognosis in solid tumors is considered as the beginning of the TNM staging system that is now used throughout the world (7). The TNM system has been revised eight times so far under the guidance of the AJCC founded in 1959 in the United States.

The TNM staging system is a "box model". Patients are separated according to T-N-M prognostic factors and each patient is placed in a box. These boxes are grouped in order to create a more extensive, larger box called a stage. The average survival of the patients in a box is used in order to predict the prognosis of a new patient placed in a box. For instance, when a new patient is placed in a box, it is predicted that the disease-specific 5-year survival of that patient will be the same as the average survival of all patients placed in that box 5 years ago (8). It is possible to select suitable patients for optimal treatment and provide prognosis predictions for patients with this system. However, staging is comprised of data from patients who have received specific treatment. Therefore, it is important to remember that staging is not a treatment guide but a tool that can provide suggestions for treatment.

It is important to understand the relationship between stage classification and prognosis. In the 8th edition of TNM staging for lung cancer, it is primarily seen that for a tumor up to 5 cm in size, every cm is redefined (T1a-c and T2a,b) and in this way, the emphasis is put on the importance of tumor size in terms of prognosis. It is observed that minimally invasive adenocarcinoma was included as T1mi, partial or total atelectasis were included in the same group (T2) without differentiating, and diaphragm invasion was moved to a higher category (T4) as it exhibits poor prognosis. Proximal tumors were moved to a lower category (T2), as it was determined that the distance of tumor from the carina did not affect the prognosis. No changes for N descriptors were proposed. For metastases, redefinition of the number of organs and metastases (M1a-c) can be summarized as the new TNM changes. In the new version, differences in prognosis between corrected multi-variable regression analyses and multiple subgroups were calculated in order to divide tumors into sufficiently well and homogenous groups. Five-year survival probabilities for Stage IA, IA2, IA3, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, and IVB were calculated as 92%, 83%, 77%, 60%, 53%, 36% in clinical staging and 90%, 85%, 80%, 65%, 56%, 41% in pathological staging, respectively (9-11). However, lung cancer belongs to a heterogenous disease group that involves genomic differences. Therefore, it is possible to state that the new version is also insufficient, despite anatomical variables being more detailed.

CONCLUSION

Although staging is a well-defined universal terminology, which is comprised of the anatomical aspects of cancer with clear boundaries, the stage of the disease at the time of diagnosis might not only be a reflection of tumor growth and spread rate, but also of tumor type and tumor-patient relation. Therefore, it would be wrong to separate prognostic factors from purely anatomical tumor staging. It should be noted that tumor stage, which is the most important indicator of cancer, is only one of the broad prognostic factor pools that contain multiple heterogenous variables. Hence, considering these factors in the selection of a specific treatment method will affect the success of treatment.

The TNM staging system will continue to be useful in the future as long as it makes improvements as a result of the increase in cancer population screenings for finding new targeted therapies and for the use of new molecular biological indicators.

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