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REVIEW ARTICLE

A Paradigm Shift in Cancer Staging - Seeing the Unseen with Circulating Tumor Cell Measurement

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ABSTRACT

The U.S. National Cancer Institute (NCI) defines the stage of cancer as the extent of cancer, with categories that reflect tumor size and tumor spread. Staging is meant to assist physicians to understand the seriousness of the cancer (for example chance of survival), and to select the best treatment plan to achieve optimal outcomes. By way of clinical experience, physicians understand that there are significant limitations of the current staging system. It is not unusual, for example, to see patients deemed to have a favorable prognosis or limited disease (by standard accepted staging), who develop early disease recurrence and distant spread. By examining the staging model more closely, it becomes clear that there is a serious omission: modern staging systems only factor in local invasion, micro and macroscopic lymphatic spread and macroscopic spread, while failing entirely to measure hematogenous spread. In recent years, new techniques have been developed that measure and quantify microscopic hematogenous spread, namely circulating tumor cell (CTC) identification and quantification. Hematogenous spread is a well-recognized phenomenon, and extensive data already exists which correlates CTC counts with disease recurrence and patient survival for many solid tumor types. Therefore a revision to the cancer staging system to include hematogenous spread is proposed. It is suggested that the new classification category "Hematogenous" (H) be adopted and measured through the routine use of CTC testing. This addition could result in a significant impact on patient survival for a wide range of cancer types.

Keywords:
cancer; staging; TNM; carcinoma; circulating tumor cells; CTC; liquid biopsy; EpCAM; hematogenous; metastases; invasion.

Introduction:

Cancer staging systems are used to categorize the extent of cancer, including tumor size and tumor spread. Staging has traditionally been used to estimate prognosis and to select the most appropriate therapy to achieve the best outcomes. Cancer is staged by macroscopic measurements and microscopic measurements based on tissue pathologies. Modern staging systems consider lymphatic spread (both macroscopic and microscopic) but measurement of hematogenous spread of cancer is absent, even though it is highly relevant. This limitation must be addressed to improve the success of the staging process.

Conventional Staging of Solid Tumors

There are two staging systems in common use which apply to most solid tumors (leukemia, lymphoma and central nervous system tumors are staged differently): the TNM (Tumor / Node / Metastasis) classification, and the numerical system (Stage 0 / I / II / III / IV). With both systems, a patient's cancer stage is defined by the degree of spread of cancer cells[1]. The TNM system also adds assessment of tumor size and more precisely defines the degree of spread, compared to the numerical system. A brief summary of both staging systems follows:

The TNM system uses a scale from T0 to T4 to describe the size of the primary tumor, N0 to N3 to specify the number of regional lymph nodes involved with cancer, and M0 or M1 to describe the absence or presence of distant metastases. Further subcategories of each stage may be defined in order to provide more details, for example M1a, M1b or M1c for lung cancer[2].

With the numerical staging system, Stage 0 refers to *in situ* cancer (malignant cells present which have not begun to invade or metastasize), Stage I refers to localized cancer, Stage II refers to a larger localized cancer, Stage III refers to a cancer that has spread to the nearby region, and Stage IV refers to the presence of distant spread[3].

Both TNM and numerical staging systems rely primarily on macroscopic tumor measurement by visual observation of the patient or at the time of surgery, and by evaluation based on imaging studies like computerized tomography (CT) scan or magnetic resonance imaging (MRI). Microscopic measurement is typically limited to tissue evaluation in the form of surgical pathology showing tissue invasion, presence of cancer cells in lymph nodes or the presence of cancer cells in distant organs, as well as genetic analysis of the tumor cells.

Conventional Staging is Outdated

Both staging systems were created based on a presumption that solid tumor cancers will normally progress from less serious (potentially curable) to more serious disease (potentially incurable) in a fixed sequential manner beginning with local invasion, progressing to regional tissue invasion / regional node invasion, and finally to distant metastases[4]. Using such staging methodology to estimate prognosis is based on this presumed sequence of progression.

It is now widely recognized that metastases do not only occur through the lymphatic system but also through the hematogenous

route. Since metastases account for about 90% of cancer deaths (not the primary tumor itself)[5], correct and complete evaluation of both metastases and metastatic potential is paramount. A major shortcoming of TNM and numerical staging systems is that neither provide any evaluation of the hematogenous route of cancer cell dissemination, despite this being the key pathway leading to distant metastases[6].

Frequent Failure of Staging

In many instances, cancer may metastasize through the hematogenous route in the absence of lymph node involvement and regional metastasis, although the reasons for this are not well understood[7]. The clinician may observe this phenomenon as a failure of traditional staging. For example: a young breast cancer patient with $T_2N_0M_0$ disease who presents with small lung and bone metastases 6 months after curative partial mastectomy with sentinel axillary node dissection and adjuvant loco-regional radiotherapy. Patients similar to this sample case are suddenly transferred from a "curative" to "palliative" category which can be emotionally devastating. Catastrophic outcomes such as this example are theoretically preventable if cancer staging methods were more accurate and highly sensitive re-staging (i.e. recurrence monitoring) was used more often.

Based on decades of combined clinical experience of the authors, this type of unfortunate occurrence is not a rare phenomenon. The observation that hematogenous spread (via CTCs) can precede nodal spread is confirmed by existing research. For example, in a study of 140 colon cancer patients, CTCs measured by the CellSearch® method were detected in 5.3% of patients with negative lymph nodes. In the same study, the presence of CTCs correlated with impaired overall survival ($p=0.05$)[8] highlighting the clinical significance of this finding.

Circulating Tumor Cell (CTC) Counts

TNM staging was developed by French surgical oncologist Pierre Denoix in the 1940s[9]. TMN did not include evaluation of hematogenous spread since there were no methods available for its measurement at the time. Since then, advanced technologies have been developed which allow the reliable measurement of live cancer cells circulating in the blood.

CTC detection methods may rely on the identification of specific cell surface markers that distinguish normal blood cells from foreign cells in the circulation. Use of the epithelial cellular adhesion molecule (EpCAM), also known as human epithelial antigen (HEA), is a reliable method of separating cells which are potentially cancerous from normal erythrocytes, leukocytes and platelets. Most epithelial cancers express EpCAM[10]. Since healthy cells that express EpCAM are not normally found in the circulation, EpCAM detection can be an elegant method of identifying live cancer cells in the blood. Maintrac®[11] and CellSearch®[12] are extensively researched CTC tests that rely on EpCAM identification. Another well-studied CTC counting method is the Rarecells ISET® technology (Isolation by SizE of Tumor cells)[13] which relies on the larger size of CTCs compared to blood cells, without measurement of cell surface markers.

Methods of CTC Evaluation

Early CTC measurement suffered from low sensitivity and low specificity[14]. Newer CTC measurement systems such as Maintrac®[15], ISET®[16] and CellSearch®[17] have reported good correlation between high CTC levels and poor outcomes[18,19,20], or correlation of rising CTC levels with therapy failure / impending recurrence[21,22,23].

It is important for the CTC counting method to not only distinguish cancer cells from blood cells, but to also distinguish between live whole cancer cells and cancer cell fragments[24]. The reason is that natural anti-cancer immunity results in the destruction of a percentage of circulating cancer cells[25]. Counting necrotic cancer cell fragments will result in significant errors in the enumeration of CTCs.

Limitations of CTC Evaluation

For EpCAM-based CTC tests, measurement around the time of an infection, recent surgery, recent injury, or other event that may release non-cancerous epithelial cells into the circulation can result in false positives. Improper blood collection technique may also cause false positive results due to contamination of the blood sample with skin cells released during venipuncture[26]. Transport of live blood to the CTC testing facility must be prompt to avoid sample degradation and false negative results. Generally, this will involve overnight shipment by air from the point-of-care facility to the lab, or even same-day shipment if the lab is near the point-of-care facility. False negative results may also occur in some cases due to a downregulation of EpCAM in CTCs that have undergone epithelial-mesenchymal transition[27].

Potential Application of CTC Measurement to Staging

CTC testing at the time of initial staging to determine course of therapy (e.g. before surgery) can help determine the need for adjuvant therapy[28]. Re-staging with CTC during systemic therapy can help determine therapy efficacy and allow early therapy changes before the patient is harmed by dangerous and ineffective medications[29]. Baseline pre-treatment CTC measurement with regular ongoing CTC re-staging after systemic therapy can anticipate recurrent disease well before new tumors form[30]. Re-staging CTC testing is also significantly advantageous compared to pre-treatment genetic testing for recurrence risk stratification (e.g. Oncotype DX ®). The reason is that genetic testing only provides a prediction of future cancer behavior based on a tumor gene profile collected at a single point in time. Tumors can mutate and gene expression can change due to numerous factors[31], with associated changes in cancer behavior, rendering a single genetic profile meaningless. On the other hand, CTC testing offers ongoing real-time re-assessment of metastatic behavior.

Due to the increase in use of powerful immunotherapies (for example the checkpoint inhibitor family of drugs), a new problem involving early assessment of treatment success has come to light. Immunotherapy can be associated with pseudo-progression - a phenomenon in which standard imaging tests such as CT and MRI scans present a false picture of cancer growth resulting from immune cell infiltration into tumors. Imaging misinterpretation clearly can have disastrous

consequences for the patient. CTC counts are theoretically independent of pseudo-progression because they are independent of tumor imaging. This makes CTC measurement a potentially valuable tool for re-staging after immunotherapy, when used alone or preferably to complement existing tools such as positron emission tomography (PET)[32], perfusion MRI[33] or power Doppler tumor vascularity measurement[34].

Evidence for CTC Use in Staging

Much research has been published about CTC testing over the last two decades. A large body of evidence is available for the EpCAM CTC detection methods. Studies have shown that CTC testing can accurately predict:

1. the presence of microscopic amounts of cancer in healthy individuals[35]
2. whether cancer is undergoing hematogenous spread in newly diagnosed patients[36]
3. systemic therapy / chemotherapy success or failure[37]
4. recurrence of cancer for patients in remission, months before CT scans[38]
5. overall survival in cancer patients[39,40,41,42].

Proposed Inclusion of CTC in Staging

Based on the strong new evidence favoring the use of CTC counts, the authors propose the addition of a new category to the TNM classification: **"H" or hematogenous stage**. One potential method of defining the "H" stage could be:

H0 = no detectable live CTCs
H1 = "low" CTC count
H2 = "moderate" CTC count
H3 = "high" CTC count
H4 = "very high" CTC count
Hx = unknown CTC count

Definitions of "low" to "very high" would be precisely outlined based on the individual characteristics of each CTC test method. An "H" number would be assigned for initial staging (before therapy). During or after therapy, the "H" stage would be re-evaluated. Both initial "H" stage and a change in "H" stage (stable / rising / falling) would establish novel and useful indicators that help guide therapy decisions beyond the T, N and M data.

Conclusions

Now that over 2 decades of extensive CTC research has been published, the authors conclude that adequate evidence exists to justify adding CTC measurement to the current TNM staging system. Reliable CTC detection methods with ample published supporting literature are clearly preferred (for example the Maintrac® system). CTC staging and re-staging by minimally invasive blood sampling has the potential to assist with surgical decision-making, improve therapy monitoring and strengthen recurrence prevention, all of which can improve quality of life and survival in cancer patients.

Future Directions

Future directions could include measurement of novel mechanisms of metastases such as tumor cell migration along the outside of blood vessels (extravascular migratory metastases or EVMM)[43] and measurement of circulating cancer stem cells (tumorspheres)[44]. Further research is required to elucidate the potential roles of these novel metastatic mechanisms in cancer staging.

Conflict of Interest:

The authors have a financial interest in providing circulating tumor cell (CTC) testing to cancer patients in a clinical setting.

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