

Collaborative Stage Data Collection System, Version 2: An Introduction to Site-Specific Factors: A New Focus of Abstracting

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It is important to note that the changes in the American Joint Committee on Cancer (AJCC) seventh edition *Cancer Staging Manual* were evidence-based, which means that revisions were the result of analysis of hundreds or thousands of cases, not just a whim on the part of the chapter authors. Despite the literally thousands of emerging predictive and prognostic factors, the T, N, and M in the form of the stage group remain an important prognostic factor and an important component of personalized medicine for treatment decisions. And because the *Collaborative Stage Data Collection System* is based on TNM, the information determined by the authors of the seventh edition *Cancer Staging Manual* to be required for staging or clinically significant for a particular primary site was included in Collaborative Stage version 2 (CSv2).

Further information about the site-specific instructions can be found in part I of the CSv2 Coding Instructions, which is divided into two sections. Section 1 is the coding rules themselves, both the general rules of CS and the rules that apply to individual data fields. Section 2 is a greatly expanded section that includes information about site-specific issues, such as the lymph node data items for head and neck and breast, clarification of other problem areas, and detailed information on lab values, tumor markers, and other site-specific factors (SSFs). Researchers anticipate that molecular biomarkers will considerably improve the clinical decision-making process and clinical outcomes, and with the help of informatics technology, the opportunity exists for integrating this data into clinical practice. Therefore, it is extremely important that we familiarize ourselves with these new terms and tests in order to provide statistically significant information to the clinicians and researchers who value the data we strive to perfect.

As we are all updating our registry software to enable us to begin coding the seventh edition *Cancer Staging Manual* and, therefore, CSv2, we would like to take a moment to further explain a very useful addition to the *Collaborative Stage Data Collection System Manual, Version 2*.

The expansion of the number of SSFs from 6 to 25 between CS versions 1 and 2 was the result of efforts by the authors and editors of the seventh edition *Cancer Staging Manual* to make TNM more clinically relevant by capturing non-anatomic information about some cancers while maintaining the anatomic base (tumor-regional lymph nodes—distant metastases).

A number of articles had been published in medical journals indicating that TNM was not meeting the needs of clinicians and patients for a variety of reasons. Among these reasons was a desire for more personalized medicine; in

other words, tailoring medical treatment to the individual characteristics of each patient. For some types of cancer, anatomic staging by itself was not sufficient to predict individual outcomes. For other cancers, additional information was needed to plan treatments customized to individual patients. In the past decade, additional diagnostic methods and alternative ways of estimating the patient's prognosis have been developed that are more useful than anatomic staging for some primary cancers. A simple example is the Gleason score for prostate, which by itself is an indicator of the aggressiveness of the cancer independent of how far the cancer has spread at the time of diagnosis. The Gleason score has been incorporated into a nomogram or computer algorithm together with the prostate-specific antigen (PSA) value and the clinical stage of the patient to predict the specific risk that the patient has extracapsular disease. In this nomogram, anatomic staging (clinical stage) is only one third of the equation.

Prognostic and Predictive Factors

In response to the challenges to anatomic staging, the authors of the seventh edition *Cancer Staging Manual* were charged with including data items that were clinically significant to planning an individual patient's treatment and/or predicting the patient's outcome. These included biologic, genetic, and molecular profiling, lab tests, tumor markers, and other types of information that can predict whether the patient will respond to a particular drug, whether the patient will have a better or worse than average survival, and other aspects of the patient's cancer.

Prognostic and predictive items comprise a large proportion of the CSv2 SSFs. They provide additional non-anatomic information about the patient's cancer and enhance the clinical relevance of both TNM staging and the cancer registry data base. If the registry records this type of information, even though the data field is not required by a standards-setting organization, the value of the registry will be increased. A prognostic factor is one that helps estimate the patient's outcome, whether that is recurrence or overall survival. A predictive factor is one that, as the name implies, predicts whether the patient will respond to a particular drug or type of treatment. Other types of SSFs can be predictive or prognostic, such as lab tests, tumor markers, molecular profiling, and pathologic findings from biopsies or the resected specimen. Most are not required for staging but are clinically relevant, to use the terminology of the seventh edition *Cancer Staging Manual*. Some prognostic and predictive factors have been in place since before CS began in 2004. Since the mid-1980s, estrogen

and progesterone receptors in breast cancer have been an important predictor of whether the patient will respond to hormone therapy. A patient whose resected tumor is estrogen- and/or progesterone-receptor positive will likely be offered a post-operative course of anti-estrogen therapy, such as Tamoxifen, or another aromatase inhibitor, such as Arimidex, to suppress the growth of any breast cancer cells remaining in the patient's body. If the patient is estrogen/progesterone-receptor negative, the patient will probably be offered chemotherapy instead of hormone therapy should the tumor recur. Human Epidermal growth factor Receptor 2 (HER2) is a protein on the surface of cancer cells that accepts growth signals. The presence of too many HER2 receptors ("overexpression") indicates that the tumor may grow more aggressively and recur sooner. About 20% of breast cancers overexpress HER2. Overexpression is both a prognostic and predictive factor for breast cancer. The information obtained from these tests plays a critical role in treatment planning, because HER2-positive patients tend to respond favorably to the expensive drugs Herceptin (trastuzumab) or Tykerb (lapatinib), which work by blocking these receptors and preventing growth signals from getting through to the cancer cell. A lack of overexpression indicates the patient may not respond to Herceptin or Tykerb.

Here are a few new prognostic or predictive factors that you may not be familiar with:

The **circumferential resection margin (CRM)** is also called the radial margin or the mesenteric resection margin for colon and rectum cancers. The CRM is defined as the distance from the most advanced growth edge of the tumor to the closest soft tissue margin of the specimen. In other words, the CRM is the width of the surgical margin at the deepest part of the tumor in an area of the large intestine or rectum without serosa (*non-peritonealized* rectum below the peritoneal reflection) or only partly covered by serosa (upper rectum, posterior aspects of ascending and descending colon). In areas where there is serosa completely surrounding the bowel, such as the transverse colon, the CRM may be called the mesenteric margin. The CRM is not the same as the distance to the proximal and distal margins of the colon specimen. For rectal cancers, the circumferential resection margin is the most important predictor of local recurrence.

KRAS is an oncogene (a gene that, when mutated or overexpressed, helps turn a normal cell into a cancer cell). This is a predictive SSF: mutations of KRAS indicate that a patient may not respond to the expensive targeted anti-EGFR drugs cetuximab (Erbix) or panitumumab (Vectibix). The American Society of Clinical Oncology (ASCO) recommends that Stage IV colorectal patients be tested for KRAS if anti-EGFR therapy is being considered.

Another colorectal predictive factor is **18q Loss of Heterozygosity**. Loss of heterozygosity (LOH) in a chromosome means that genetic material normally found in a specific area of a chromosome is missing. In other words, this is damage to the chromosome that results in failure of tumor suppression, which in turn may cause the development or progression of a malignancy. A special molecular diagnostic test looks for the specific chromosomal defect on the long arm (q) of chromosome 18. Normal cells have two

complete copies of each chromosome, a state called heterozygosity, and when the chromosome is damaged, one of the pairs is missing. The presence of 18q LOH is an adverse prognostic factor and may predict resistance to fluorouracil-based chemotherapy. Special molecular diagnostic tests look for missing genetic material.

Tumor Markers or Lab Values

Some SSFs are tumor markers or lab values—measurements based on blood tests or examination of tissue. Estrogen and progesterone receptors (previously discussed as a predictive factor) are among the most common tumor markers used in oncology. The field may record either the actual value of the test or the clinician's interpretation of the test. Some markers and lab tests have 2 fields: 1 for the value and 1 for the interpretation. Most tumor markers and lab values are not needed for deriving T, N, M, or stage group, but provide the clinician with important information about the cancer. Some of these markers confirm the diagnosis, some help document the tumor volume, and some are of prognostic significance. Unless stated otherwise in the SSF, record the highest pre-treatment value for a tumor marker or lab value. If the field records the interpretation of the test, look for a statement by the clinician.

Examples of tumor markers and lab values collected in CS include:

In testicular cancer, **Alpha fetoprotein and human chorionic gonadotropin—AFP and hCG** measured before treatment are used to assess the histology of the tumor because various germ cell tumors will show positivity for either AFP or hCG or both, and this helps differentiate the type of tumor. Measured post-orchietomy, persistence of elevated tumor markers indicates residual testicular tumor and helps determine whether the patient should receive post-operative chemotherapy.

Carcinoembryonic antigen—CEA is a protein molecule found in many different cells of the body and is used as a tumor marker, especially for gastrointestinal cancers. Colorectal cancer is the most frequent cause for an increased/elevated CEA. CEA is also elevated by biliary obstruction, alcoholic hepatitis, and heavy smoking. The CEA level is most frequently tested on blood serum, but it may be tested in body fluids or biopsy tissue. An abnormally high CEA level prior to tumor resection is expected to fall following successful removal of the cancer. An increasing value indicates possible recurrence.

CA 19-9—This is another non-specific marker found in blood serum. It is an important tumor marker in the management of gastrointestinal and hepatobiliary malignancies. CA 19-9 is produced in excess by adenocarcinomas and released into the blood. It is elevated in pancreatic (70%–80%), hepatobiliary (60%), and gastric (50%–60%) malignancies. Levels above 1000 U/mL indicate the presence of metastases and probably unresectable tumor. CA 19-9 is also elevated in acute pancreatitis, cholangitis, cirrhosis, and other conditions, so it is not useful as a screening test but has value in monitoring for possible recurrence of known cancer. Unlike most tumor markers that are measured in nanograms per milliliter, CA 19-9 is recorded in Units per milliliter.

CA-125—This marker found in blood serum is not specific to ovarian or primary peritoneal cancer. CA-125 can be elevated in many diseases affecting the peritoneal lining of the abdominal and pelvic cavity, so it is not a screening test for women who have no history of cancer. Any value over 35 is highly correlated with cancer and about 80% of ovarian cancers show an elevated CA-125. However, a result in the normal range does not rule out cancer. Values up to 65 U/ml may be considered borderline, and values over 200 are unlikely to be due to a benign condition. CA-125 monitors for success of treatment and recurrence. After obtaining a baseline value prior to treatment, a lower result on a subsequent test indicates a response to treatment, and an increasing value indicates possible recurrence.

JAK-2, a gene found in all humans, is involved in the development of blood cells. If JAK-2 has mutated, the person is more susceptible to develop a myeloproliferative disorder (MPD). The JAK-2 mutation, which is acquired rather than inherited, is found in as many as 90% of patients with polycythemia vera (PV), about half of patients with essential thrombocythemia (ET), and slightly fewer patients with primary myelofibrosis (also known as agnogenic myeloid metaplasia and other terms).

A limited number of SSFs have been included for special interest or future research. The subjects covered in these items are generally of a very specific nature. While clinically significant, the tests may be infrequently performed or may be applicable only in limited circumstances. A few are being collected prospectively because the incidence of these cancers is rare and information gathered on a population basis will contribute to the understanding of these tumors.

Microsatellite instability is a pathology test that looks for a gene mutation associated with a particular type of hereditary colorectal cancer called HNPCC or Lynch syndrome. HNPCC is estimated as less than 5% of all colorectal cancers. A high level of microsatellite instability is suggestive of HNPCC. This test will not be performed

for every patient, and the field is not required by any of the standards-setting organizations. However, for patients with a family history of colon cancer, it is an important piece of information to obtain.

There is a “**schema discriminator**” field that tells the registry software program which schema to present to the coder. It is important to know how far from the esophagogastric junction is the center or midpoint of an adenocarcinoma. This field is left blank if the primary site code is something other than C16.1 or C16.2. The CSv2 algorithm defaults to the Esophagus GE Junction schema if the esophagus or GE junction is involved and the distance to the junction is unknown, and defaults to stomach if involvement of the esophagus is not stated.

Perhaps the most important thing to understand about the SSFs is that the registrar is not required to go looking for any site-specific data item that is not included in the pathology report or the medical record. The editors of the seventh edition *AJCC Cancer Staging Manual* acknowledge that certain types of information may not be available in some facilities, particularly those items of prognostic or research interest. Furthermore, both the clinicians and the American College of Surgeons recognize that it is not the registrar’s role to enforce practice standards. The CS Manual includes instructions on how to code missing information. The corollary to not finding information in the medical record is that the clinicians and pathologists may not realize that certain types of information are captured in the cancer registry. Furthermore, practice standards within facilities do change as new tests and equipment are acquired. Therefore, it is very important that the registrar communicate the ability to collect the SSFs and other data in a standardized manner to the cancer committee, oncology physicians, and the facility’s pathologists. It may be that the information is available but not in the medical record simply because no one has asked for it before. This is an opportunity for the registry to reinforce its ability to stay current and provide information of interest to clinicians.