physicians alike face the dilemma of knowing that most patients with DCIS do not benefit from adjuvant radiotherapy, but not knowing which patients can safely be spared treatment. Although the results of the modeling exercise presented by Soeteman and colleagues (1) are interesting, ultimately, the findings do not resolve this difficult and persistent dilemma.

Soeteman et al. (1) deliberately eschew the application of population-based utilities in their model and instead advocate for individualized discussion of the model results to aid patient decision making. To truly realize this goal, their next step should be to develop a user-friendly decision aid incorporating the findings of their model. As clinicians, where we will find these results most useful is in counseling patients who believe that mastectomy is necessary to maximize survival. After many years of decreasing, some evidence suggests that mastectomy rates have again begun to rise (11). The current study may help to stem this concerning tide by providing reassuring evidence of the safety of breast conservation for patients with DCIS.

References

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A Primary Approach to Cancers of Unknown Primary
Arnold M. Schwartz, Noam Harpaz

Most solid tumors are diagnosed in their organ of origin; however, approximately 20% of patients will present with a tumor identified in one or more metastatic sites. In the overwhelming majority of cases, a clinical history, physical examination, laboratory tests, functional and radiographic imaging (positron emission tomography/computed tomography), and histologic assessment will disclose the primary site, enabling site-directed chemotherapy. Yet, again, in approximately 20% of cases, the primary site eludes determination, even after examination of broad panels of immunohistochemical assays. These cancers of unknown primary organ (CUP), defined as metastatic cancers whose anatomic origin is clinically not detectable even after a thorough diagnostic evaluation, represent a heterogeneous group of malignancies and account for approximately 4% of cancer diagnoses (1,2). Interestingly, in our experience, even after postmortem examination, 20% of CUPs, or about 1% of all cancers, are never anatomically defined. Although these cancers present as metastases and represent a spectrum of biological behavior, oncologists have stratified them into favorable (approximately 20%) and poor (approximately 80%) prognostic groups based on such factors as clinical presentation, host factors, tumor histology, number and location of metastatic sites, and their sensitivity to chemoradiation treatment (1–3). In general, patients with CUP have an overall survival of 6 to 9 months, although the favorable prognostic group may have a median survival of nearly 36 months.

The pathologic diagnoses of CUPs in metastatic sites tend to be carcinomas, of which the majority are adenocarcinomas. The initial diagnostic approach seeks to exclude atypical but benign reactive process and then classify the malignancy as a carcinoma or other malignancies such as sarcomas, lymphomas, and melanomas. An immunohistochemical (IHC) panel can separate the majority of these tumor types. Histopathologic features combined
with histochemical mucin stains usually permit distinction between adenocarcinomas and other cancers, namely, squamous cell carcinomas, poorly differentiated carcinomas, germ cell cancers, neuroendocrine carcinomas, and the occasional mesotheliomas that mimic a sarcoma or adenocarcinoma. The increasing versatility of IHC panels based on the pairwise findings of CK7 and CK20, and the more refined organ-specific panels, have increased the pathologist’s ability to narrow the field of primary organ sites of cancer or in some cases to readily define it (1,3–5). Tumors with unique immunohistochemical signatures can provide high probability of primary sites such as the panel of CK7+, CK20+, CDX2+ for colorectal adenocarcinomas, and CK7+, CK20+, TTF-1+, Napsin-A+ for pulmonary adenocarcinomas. As more organ-specific and therapy-directed IHC markers (such as human epidermal growth factor receptor-2 and estrogen receptor) are introduced and validated, they should increasingly enable CUPs to be better defined and managed. Despite these advances, as a result of tumor heterogeneity, IHC only supports a differential diagnosis, and additional and alternative modalities for primary site designation are clearly needed. In this regard, several attempts at molecular profiling have been initiated that have focused on multiple gene expression profiles or microRNA signatures using sequencing, reverse-transcription polymerase chain reaction (RT-PCR), or microarray platform technologies. Some reports have claimed an 80% overall accuracy at organ-specific identification based on a focused group of tumor types (6–11). Commercial assays and reference laboratories advertise to help the oncologist in this endeavor and support the hypothesis that identification of the primary site will focus therapy and improve clinical outcome.

In this issue of the Journal, Greco and colleagues at the Sarah Cannon Research Institute in Nashville, Tennessee, have contributed to the clinical laboratory science of organ site prediction of CUPs based on a molecular profiling approach that complements the results of diagnostic pathology (12). Much of the work and the thrust of molecular tumor profiling (MTP) technology have already been published with the demonstration of the improved organ site identification over IHC findings (6,7). The authors generated a retrospective review of 171 CUPs and performed MTP using a proprietary technology (CancerTYPE ID, BioTheranostics, San Diego, CA) utilizing a 92-gene quantitative RT-PCR for 54 tumor classes on archival material. They compared the MTP results with clinical follow-up primary site identification and generic and focused IHC panels. The authors considered two patient groups: one consisting of 151 patients followed prospectively from 2008 to 2010, and a second prospective cohort of 24 patients whose primary sites were identified during clinical follow-up. Among these groups, the MTP assay was able to identify a single tissue of origin in 80%–90% of cases, compared with IHC, which could identify a single site in only 30%. Focusing on the cohort of 24 cases where the subsequent evaluation identified the anatomic primary site, MTP provided a single site in 22 cases and was correct in 18. IHC identified a single site in seven cases and was correct in six; in 16 cases, IHC offered a differential diagnosis and included the identified site in nine. Importantly, MTP is a multiparameter technique with a complicated algorithmic analysis, whereas IHC represents a set of binary decisions based on the staining characteristics. In a separate evaluation, 52 of 59 cases from the overall patient group in which IHC initially identified a single putative primary site and adequate tissue was available for MTP assay; the concordance was 77% (40 of 52 cases). In cases where IHC provided a differential diagnosis among several primary sites, there was agreement with the specific MTP results in 44% (43 of 97 cases), and, in the majority of these cases, clinical features supported the MTP diagnosis.

The results of Greco and colleagues (12) are encouraging and demonstrate that molecular profiling is capable of arriving at a correct single designation of the primary site in a large majority (80%) of cases. Interestingly, when IHC is definitive for a single site, it is also correct in a similarly high percentage of cases; however, it arrives at a single site in only the minority (30%) of cases. It is more likely that IHC provides a differential set of choices than a single identifiable site. The authors acknowledge that the current test characteristics of sensitivity and specificity need to be improved based on additional tumors for their test and validation assays. In addition, cost-effectiveness of the assays, standardization of the protocol algorithm for determination of the primary site, and the turn-around time need to be addressed. Currently, the National Comprehensive Cancer Network guidelines do not recommend the routine testing of gene expression profiles for the identification of tumor primary site (2).

The authors also appreciate that even with an improved assay protocol, tumor sufficiency will be a limiting condition preventing the utilization of fine-needle aspirations and needle core biopsies, material well suited for IHC. Even tissue from formalin-fixed, paraffin-embedded blocks will require pathologic determination for specimen adequacy and minimization of tumor necrosis. In their study, 13% of cases had insufficient tumor for assay diagnosis. Greco et al. have previously attempted to address the fundamental hypothesis of this endeavor—namely, that knowledge of the primary site will provide the correct treatment for improved clinical outcome—yet that study used historical controls and had some selection bias (13).

The primary site of malignant tumors represents a surrogate marker for oncological management. Further development of molecular modalities to determine chemotherapeutic sensitivity and resistance and targeted therapy can be expected to enhance management of CUPs. These cancers may be biologically different from their cognate primary tumors with predictable tumor progression and, consequently, identification of primary site of CUPs may be only one component of optimal cancer management.

References


**Cognitive Complaints After Breast Cancer Treatments: Patient Report and Objective Evidence**

Christina A. Meyers

The report by Ganz et al. in this issue of the Journal is an ambitious study that adds to the body of work assessing the neurocognitive effects of cancer and cancer treatment (1). Cognitive dysfunction, although frequently subtle, occurs in many cancer patients before, during, and long after diagnosis and treatment. There are now more than 12 million cancer survivors in the United States. One out of six people aged 65 years or older is a cancer survivor; 1.4 million of these survivors were diagnosed more than 20 years ago. With advances in early detection and treatment, cancer is becoming a chronic illness. However, cancer patients experience a number of adverse symptoms, including cognitive impairment, fatigue, pain, and sleep disturbance, most frequently in combination. This has been documented in a number of clinical human studies and animal models and has been investigated long enough to generate a number of meta-analyses and review articles (2–6). There are two issues to keep in mind regarding cognitive symptoms related to cancer treatment, which at first may seem contradictory. First, it is likely that scientific studies of this syndrome underestimate the true incidence in the overall cancer population. Second, applying these research data to individuals in the clinic with cognitive complaints is complex and requires a differential diagnosis.

As is always the case in studies that pool subject data, individual differences are obscured, suggesting that the true incidence of cognitive symptoms in cancer patients may be underestimated. First, a newly diagnosed person with cognitive impairment before treatment and a baseline evaluation may not experience much noticeable decline during therapy but still remain below their previous level of function. Second, as Ganz et al. acknowledged (1), the exclusion criteria for their study were extensive, including daily alcohol use (a glass of wine at dinner would have excluded many from their study), although their rigor was justified by their associated mechanistic biological endpoints. However, this suggests that their findings may not reflect the symptom burden of the larger population of cancer survivors who did not meet their criteria. Third, formal neuropsychological testing to confirm patient reports, as used in this article, is usually conducted in a one-on-one distraction-free setting, which is not representative of the individual’s real-world home and work environment. Thus, the cognitive test results may underestimate the effect of cognitive inefficiencies on the person’s daily routine.

Cognitive dysfunction in cancer patients is multifactorial, a result of the interaction between the cancer itself, individual (host) factors such as genetic susceptibility and immune reactivity, and the effect of specific treatments (7). In addition, the real-life impact of cognitive dysfunction on cancer patients depends upon their preillness level of function, the type of work they do, their developmental stage of life (eg, working parents with small children vs retired persons), and their overall ability to manage and cope with changing life circumstances. Furthermore, “chemobrain” is a diagnosis of exclusion because a number of factors may be responsible for or contribute to patient-perceived cognitive inefficiencies besides cancer treatment. These include the influence of systemic cancer on the central nervous system, central nervous system spread of disease, other cancer-related symptoms such as fatigue or pain, effects of adjuvant medications such as steroids and immunosuppressants, co- or preexisting neurologic and psychiatric illnesses, and even secondary gain. Thus, appropriate referrals and diagnostic work-ups are essential to guide treatment strategies.

Fortunately, symptom assessment is increasingly incorporated into clinical trials of new agents and routine patient care because cancer treatment can only be considered successful if these symptoms are managed. Successful management is guided in part by

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