that CoC-accredited hospitals can oversee community oncologists with hospital privileges, thus extending the reach of the standards.

Views Afield
Jimmie C. Holland, M.D., Wayne E. Chapman chair in psychiatric oncology at Memorial Sloan–Kettering Cancer Center in New York, was a member of the Institute of Medicine committee that wrote the 2007 consensus report, Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs.

The CoC standards for psychosocial distress are an amazingly helpful nudge, said Holland, who is founding president of both the American Psychosocial Oncology Society and the International Psycho-Oncology Society and is generally regarded as the founder of psycho-oncology.

“Nobody ever before has come to someone like me and asked, ‘What do we have to do to make sure we don’t lose our accreditation?’ So instilling a little fear, the stick, is going to be helpful to us because when there is no stick and there is no reimbursement to speak of, it is hard to get anyone to move, so I think this is going to be a helpful thing,” she said.

Holland added that the new standards incorporate three points: (1) distress screening as the standard of care for oncology patients; (2) development and implementation of a process to integrate and monitor on-site psychosocial distress screening and referral; and (3) consistency with the National Comprehensive Cancer Network guidelines that distress should be recognized, monitored, documented, and treated promptly in all stages of disease.

Otis W. Brawley, M.D., chief medical and scientific officer and executive vice president of the American Cancer Society, as well as author (with Paul Goldberg) of How We Do Harm: A Doctor Breaks Ranks about Being Sick in America (St. Martin’s Press, 2012), said that the American Cancer Society supports the new standards, especially the inclusion of patient navigation and supportive care.

“We need to think about the patient experience as the patient is being treated. So frequently we have just thought about what is good treatment and not about what is good care. And this is an effort that tried to look at care, which includes treatment, but also supportive services,” Brawley said.

He added that the standards may help patients overcome obstacles to getting complete care.

“I’m avoiding using the phrase ‘being more compliant,’” he continued, “since [we should not be] blaming patients for the fact that they were unable to get complete treatment—when the reality is, sometimes there are a lot of social issues that are beyond the patients’ control that prevent them from getting complete treatment.”

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C-Path: Updating the Art of Pathology

By Mike Martin

A n 84-year-old scoring technique pathologists use to diagnose and stage breast cancer is getting a 21st-century update from a computer model called Computational Pathologist (C-Path), which uses digital imagery and computer software to analyze more than 6,000 cell and tissue features faster and in more depth than the pathologist’s eye peering through a microscope.

“It would not replace human pathologists, but there are things a computer can do easier than a human,” said radiation oncologist Frances Wong, M.D., chief physician for the Fraser Valley (British Columbia) Cancer Centres. Wong did not participate in C-Path’s development, but she reviewed a study about it from research teams at Stanford, Harvard, the University of British Columbia (UBC), and the Academic Medical Center in Amsterdam.

According to a study in the November 2011 Science Translational Medicine, C-path generated prognostic scores that were “strongly associated with overall survival” in 576 patients from the Netherlands Cancer Institute (NKI) and Vancouver General Hospital (VGH).

The best histological predictors of patient survival are not from the carcinoma itself, but from adjacent stromal connective tissue. Women with worse breast cancer outcomes tended to have inflammatory and epithelial cells in distinct, thin cords infiltrating the stroma.

Oncology surgeon Paul Dale, M.D., chief of surgical oncology at Ellis Fischel Cancer Center in Columbia, Mo., said the latter finding was absolutely fascinating.

“This is a stand-alone result in its own right, and one of the more interesting research concepts to emerge from a recent paper,” explained Dale. “There have been reports about the importance of lymphocytes scattered in stroma around tumors, but nothing definitive that connects stromal observations with prognosis.”
From Old to New
Since 1928, pathologists have used qualitative microscopic analysis to stratify breast cancer patients into three prognostic groups. Using microscopic images, they stage the cancer and report to clinicians in a validated procedure that has changed little over the years.

“The information I get from morphology is the same information I received 20 years ago,” Dale explained.

C-Path is a new approach that analyzes quantitative features, explained C-Path codeveloper Andrew H. Beck, M.D., an assistant pathology professor at Harvard Medical School and Beth Israel Deaconess Medical Center in Cambridge, Mass. It could help reduce “considerable variability in histological grading among pathologists,” Beck said.

Radiologists learned the benefits of computerized technology long ago—one reason Dale depends more on radiology reports than on pathology reports.

“A typical mammography uses computerized analysis to zero in on problem areas. A mammogram can quickly tell you if something is abnormal ‘right here’ or ‘right there,’” Dale said. C-path has similar potential and could make pathology data useful for more than just routine diagnosis.

“If we had an automated system that could quickly clear a core sample, I could use that information to determine how much of a margin around the tumor I need to take out,” Dale said. “Accurate, quick margin status is a contribution I could see a machine like C-Path making.”

Getting Started
The researchers used hundreds of tumor microarrays (TMAs)—0.6-mm-diameter images—from patients both alive and dead after 5 years to develop C-Path’s prognostic model. Deliberately avoiding predefined sets of morphometric features, the team partitioned and classified the images via a three-stage analysis pipeline, explained UBC Genetic Pathology Evaluation Centre manager and study coauthor Samuel Leung, DO.

Digitized to allow the precise measurement of the intensity, texture, size, and shape of both epithelial and stromal characteristics, the TMA images “trained” the software to relate various features to patient prognosis such as typical or atypical nuclei, mean distance between epithelial and stromal nuclei, and distance between stromal regions. In all, the pipeline analyzed 6,642 cellular features, reminiscent of genomics studies with large data sets.

“This approach is similar to DNA or RNA analysis of tumors as part of an attempt to predict prognosis,” said Wong, formerly chief of the department of oncology at Surrey Memorial Hospital in British Columbia. “It is yet another way of analyzing more data by using computer technology.”

Once programmed, C-Path analyzed test samples from NKI and VGH. Researchers compared its performance with that of human pathologists.

One pathologist examined the NKI samples, which represented stage I or II breast cancers from women younger than 53 years. Several pathologists throughout the Vancouver community graded VGH samples, which represented more older women and women with advanced disease than did the NKI set.

Whereas human pathologist scoring yielded no significant association with survival, the C-Path score was significantly associated with overall survival, the group reported. The results don’t signal a move away from the traditional art of histological analysis, said Beck.

“But in the future, I do expect many tasks currently done manually will be performed with the aid of computational tools.”

Homing In on Stroma
With the standard qualitative method, pathologists examine three epithelial features to stage and grade breast cancer: tubule formation, atypical cellular nuclei, and mitosis.

But research suggests that epithelial cells don’t tell the whole story, Beck explained. The tumor’s surrounding microenvironment, including the stroma, can make substantial prognostic contributions. Technical challenges hinder stromal analysis, however, and “there are few well-established criteria for its qualitative visual interpretation,” he added. Consequently, he said, routine pathological assessment of breast cancer in clinical practice does not include stromal analysis.

The C-Path team decided to include it, analyzing and cataloguing stromal images.

Wong said that pathologists have long recognized the importance of the intercellular stroma. “That is the reason for building this stromal component into the computer algorithm.”

Having conquered the technical challenges, the team made C-Path’s most “striking finding: the significance of stromal features,” said codeveloper Daphne Koller, Ph.D., Stanford University Rajeev Motwani professor in the departments of computer science and pathology.

Breast cancer tissue with large, contiguous regions of stroma separated from large, contiguous epithelial regions—a finding associated with normal breast tissue—indicates improved outcomes. But thin cords of epithelial cells infiltrating stroma across the image predicts poor outcomes.

Other prognostically relevant features included presence of inflammatory cells in the stroma, the shape of stromal nuclei (round vs. spindle), and their relative abundance in stroma tissue, Koller explained.

“These findings will make everyone’s ears perk up,” said Dale. “Bad tumors do bad things. They grow, metastasize, and spread into the surrounding stroma. It
makes perfect sense that the stroma contains prognostic indicators.”

Preparing for Prime Time
Several limitations must be mitigated before C-Path becomes clinically available—most important, the use of whole-slide versus TMA images.

“Each TMA image captures only a minute portion of the full tumor volume, which is much smaller than the multiple whole-slide images used in routine diagnostic pathology,” explained study coauthor Ankur R. Sangoi, M.D., a Stanford University School of Medicine pathologist who practices at El Camino Hospital in Mountain View, Calif.

“It is likely that we could have derived a more powerful prognostic model by analyzing whole-slide images, because these might allow the generation of additional higher-level features such as measurements of tumor heterogeneity,” Sangoi explained.

Fortunately, C-Path is not specific to TMA image processing and can be adapted to whole-slide examination. Larger study participation at different institutions is also in the works, explained study coauthor Marc J. van de Vijver, M.D., Ph.D., who heads the NKI division of diagnostic oncology. To train C-Path at each new hospital, the team anticipates pathologists’ recalibrating the system with 50-60 hospital-specific images in about 1 hour. Samples specific to each institution will better reflect handling, sampling, and storage techniques that differ from place to place.

Along with more diverse study groups, the team hopes to improve C-Path’s ability to analyze breast neoplasia earlier than stage I and to integrate other important information with morphological data.

“We are working on several projects to incorporate molecular biomarker and genomics data into C-Path,” Beck explained. “Breast cancer biomarkers include HER2 and triple-negative status; relevant genomics data include copy number abnormalities and gene prognostic signatures.”

The last essential step for translating C-Path to clinical medicine will require a substantial contribution from the pathology community, van de Vijver explained. That step, which will help close the technological gulf between radiologists and pathologists, sounds simple, but it will take time and practice in using digital images.

“Even today, most pathology diagnoses are made from images viewed directly on a light microscope. Digital slide scanners are not routinely used,” van de Vijver said. “Innovative leadership among pathologists will be critical for facilitating widespread implementation of quantitative digital systems in pathology laboratories.”

Greater accuracy and automation can improve clinical pathology, both here and “in parts of the world where expert pathologists may be in short supply,” said study coauthor Torsten O. Nielsen, M.D., Ph.D., codirector of the UBC/VGH Genetic Pathology Evaluation Centre. Nielsen and his coauthors envision building a library of C-Path images from multiple cancer types, optimized to predict clinical outcomes and directly guide treatment decisions.

Improving the Outlook for Myelodysplastic Syndrome

By Vicki Brower

In his searing memoir, Swimming in a Sea of Death: A Son’s Memoir, David Rieff documents the painful battle his mother, writer Susan Sontag, waged with myelodysplastic syndrome (MDS) in 2004. Sontag’s treatment options were limited to the first and newly approved MDS drug, azacytidine; induction chemotherapy used to treat acute myeloid leukemia; and bone marrow transplantation—none of which worked.

Sontag died the same year in which she was diagnosed—when a wave of research on MDS was just beginning. For decades, doctors had only been able to offer patients supportive care, blood transfusions, and hematopoietic growth factors.

“Perhaps because MDS is neither an orphan disease nor a common cancer, in the past, it did not benefit from much funding, research, or hope,” said Joachim Deeg, M.D., professor of medical oncology at the University of Washington in Seattle. But that began to change about 5 years ago with the approval of azacytidine in 2004, lenalidomide in late 2005, and decitabine in 2006. Now MDS research is booming, with other compounds in early-stage trials, new combinations in testing, and evolving stem cell transplant regimens. Studies on the microenvironment and signaling pathways are also yielding clues about why hematopoietic cells in MDS do not differentiate and mature normally; die prematurely; and, later, resist apoptosis.

But what stands out most is what one researcher called a “veritable explosion” of genetic research published in the past year. Genetic sequencing technology has driven much of this new torrent of genetic studies, which is helping unravel the molecular basis and pathogenesis of MDS, said Benjamin Levine Ebert, M.D., Ph.D., assistant professor of medicine at Harvard Medical School.