DCIS Prognostic Markers: A Few New Candidates Emerge

By Nancy J. Nelson

Although survival rates for patients with ductal carcinoma in situ (DCIS) are excellent, managing the disease is difficult. Researchers have been slow to identify women whose DCIS is most and least likely to progress to invasive breast cancer. However, in the last few years, several prognostic factors have emerged as possible contenders to help stratify risk.

“If we could identify a molecular marker that could predict which DCIS would progress to invasive cancer versus which would stay DCIS forever, that would be an enormous clinical advance,” said Monica Morrow, M.D., chief of the breast service at Memorial Sloan–Kettering Cancer Center in New York. “That’s the big problem with DCIS,” she continued. “We’re treating DCIS not because DCIS per se causes any problems but because it is a major risk factor for the development of invasive cancer.”

DCIS, abnormal cells confined to the breast duct, makes up about 25% of breast cancers diagnosed in the U.S. The incidence of DCIS increased substantially through the late 1990s along with widespread mammography use. About 50,000 new cases were diagnosed in 2009 and an estimated 1 million women will be living with the condition by 2020. The good news is that with currently available therapies, the disease-free survival rates are between 97% and 98%.

“There is no DCIS associated with a high risk of dying,” said Morrow. “Regardless of how you treat DCIS, fewer than 2%–3% will die of breast cancer.”

Successful treatments—those that decrease the rates of subsequent disease—include lumpectomy plus radiation with or without tamoxifen and mastectomy with or without tamoxifen.

Managing DCIS

Describing the decision tree for managing DCIS, Morrow said that she first looks at how much of the breast is involved. “If the extent is too large to surgically remove with a margin of normal tissue around it, and get a decent cosmetic result, then the patient medically needs a mastectomy,” said Morrow. “Or if DCIS is in multiple areas of the breast, mastectomy is the treatment of choice. When DCIS is in a single area of the breast, the abnormal cells plus a margin of healthy surrounding tissue are removed.”

Matthew Goetz, M.D., a medical oncologist at the Mayo Clinic in Rochester, Minn., who sees patients after surgery, said that most patients undergo some sort of surgical treatment for DCIS because of the subsequent risk of invasive disease. “We don’t recommend any further treatment after mastectomy since the risk of recurrence following mastectomy is very low—in the 1%–2% range,” said Goetz.

“However, after lumpectomy, most women receive radiation because we haven’t been able to identify molecular markers that would tell us who should and shouldn’t receive radiation after lumpectomy,” said Goetz. The chance of recurrence with local excision and radiation is about 12%.

“The high survival rates of 98%–99% suggest that we are probably overtreating some patients,” said Goetz. “Treating patients with radiation, tamoxifen, or mastectomy can have a substantial impact on the patient’s quality of life.”

Overall, about 25% of DCIS patients choose complete mastectomies. Most, about 70%, opt for lumpectomy with or without some treatment such as radiation or hormones. Fewer than 5% chose to do nothing.

Current Prognostic Factors

Over the years, several factors have been statistically correlated with an increased risk of recurrent DCIS or subsequent invasive cancer. These include younger age at diagnosis, and features of the tumor such as large size, high nuclear grade, positive margins, and a pathology finding known as comedo necrosis. But, according to Stuart J. Schnitt, M.D., professor of pathology at Harvard Medical School, the magnitude of these effects is, at best, a doubling of the relative risk. The additional problems with standardization and reproducibility in evaluating margins, tumor grade, and size lead him to think that “we’ve gone about as far as we can go using traditional pathology to predict risk of local recurrence.”

Despite these shortcomings, the factors most strongly linked to recurrence were used to develop the Van Nuys Prognostic Index for DCIS in 1995. Its creator, Melvin Silverstein, M.D., professor of surgery at the University of Southern California in Los Angeles, and director of the breast program at Hoag Memorial Hospital Presbyterian in Newport Beach, Calif., used data from 1,500 cases of DCIS monitored for more than 7 years to create the index. It now relies on five factors to predict the risk of recurrence: tumor size, margin width, the presence of necrosis, nuclear grade, and age of patient. Each DCIS lesion receives a score that can vary between 4 and 12. The patients least likely to recur after conservative therapy have a score of 4 and include older women with small, low-grade, and well-excised...
lesions. Those most likely to recur have a score of 12 and are younger women with large, poorly excised, high-grade lesions.

Silverstein recommends watchful waiting after surgery for people who score 4–6, surgery plus radiation for scores 7–9, and mastectomy for anything higher. “I can tell you the people most likely to recur,” said Silverstein, “but I cannot predict who is going to recur with invasive cancer or DCIS. We’ve tried every trick, we’ve used every statistical method possible, we’ve subdivided in every way possible, and we can’t tell.”

Although the Van Nuys index scoring system is not widely used, its components do play a role in making decisions about DCIS, according to clinicians, including Henry Kuerer, M.D., Ph.D., director of the breast surgical oncology training program at the University of Texas M. D. Anderson Cancer Center in Houston. “In general I do not think it is used at all in the strictest sense as it was designed,” he wrote in an e-mail, “mostly because of the complexity . . . however, the concepts regarding the components of the [Van Nuys Prognostic Index] are discussed and thought about for each patient with a diagnosis of DCIS . . .”

**Looking for New Markers**

To help identify markers for invasive disease, some researchers turned to the lessons learned from invasive breast cancer. Gene expression profiling of invasive breast cancers has revealed five distinct subtypes, one of which is associated with aggressive disease and poor prognosis. It is known as the basal-like carcinoma or triple-negative subtype, because of the lack of expression of estrogen and progesterone receptors, and the absence of HER2 overexpression. Other genes such as basal cytokeratins, CK5/6, CK14, and CK 17, epidermal growth factor receptor, and c-kit are also expressed in this subtype.

A few laboratories have identified what appears to be a DCIS precursor with similar basal-like gene expression patterns. Chad Livasy, M.D., from the department of pathology at the University of North Carolina at Chapel Hill, and his colleagues analyzed
Laura C. Collins, M.D., a pathologist from Beth Israel Deaconess Medical Center in Boston, and her colleagues also identified four basal-like subtypes from a sample of 66 (6%) high-grade nuclear lesions.

Despite these promising results, Livasy said that no studies to date have analyzed whether a DCIS basal-like subtype has a higher risk of becoming invasive cancer than other subtypes.

Alteringations in various genes that regulate cell growth, development, and proliferation are tentative candidates for predicting poor outcomes. Most of the studies have been small, at single institutions, with short follow-up times and inconsistent results, according to Karla Kerlikowske, M.D., a physician at the University of California at San Francisco.

However, in a study published in this issue of JNCI, she and her colleagues, including Thea Tlsty, Ph.D., from the pathology department at UCSF, found alterations in genes associated with a high risk of subsequent invasive cancer. Their study looked at a subset of 1,162 DCIS patients who had been treated with lumpectomy alone. The subset consisted of 324 women who later developed either recurrent DCIS or invasive cancer. They found that the 8-year risk of subsequent invasive cancer was highest (19.6%) in women whose tumors expressed p16, COX-2, and Ki67 or whose tumors were detected by palpation. Women with mammography-detected lesions not expressing these markers had a 4.1% chance of subsequent invasive cancer.

“All DCIS lesions are not the same,” said Kerlikowske. “They’re actually very heterogeneous. Not only were we able to identify women at highest risk of invasive cancer, but we also can pinpoint those with quite a low risk...” For example, 17.3% of the cohort has a 4.1% chance of developing invasive cancer in 8 years and another 26.8% has an 8-year risk of 6.9%.

“This means about 44% of the cohort is at a pretty low risk of developing invasive cancer, so women in the lowest- and low-risk groups might consider not undergoing adjuvant radiation or hormone treatment, but undergoing follow-up with surveillance only,” she said.

Much work remains to be done, however. These findings are a long way from becoming a commercial assay for clinical use such as MammaPrint and Oncotype DX, the most commonly used gene expression assays for the management of invasive breast cancer patients. Both have undergone extensive validation studies in several large clinical trials to test their ability to predict survival and treatment benefit.

In the future, Kerlikowske plans to analyze another 2 years of follow-up data from the current cohort and to validate the results in another comparably sized cohort, which may include people that have been treated with lumpectomy plus radiation. That way she can see whether people with molecular signatures associated with high recurrence rates respond to therapy.