

# Can Some DCIS Patients Avoid Adjuvant Therapy? Still Unknown

By Charlie Schmidt

**A**mong patients with ductal carcinoma in situ (DCIS), adjuvant treatment with radiation, tamoxifen, or both cuts the risk of later invasive disease in the affected breast by more than half compared with lumpectomy alone. And invasive disease in the same breast is associated with a higher risk of death, according to a study in this issue of the Journal.

The new findings add to evidence that adjuvant treatments—because they reduce the risk of local recurrence—are warranted, said Irene Wapnir, M.D., lead author of the study and chief of breast surgery at Stanford University School of Medicine. The study also found that 35% of patients treated with lumpectomy alone—no adjuvant therapy—experienced a recurrence, in the form of either DCIS or invasive cancer. So for nearly two-thirds of 2,612 patients evaluated, adjuvant treatments were unnecessary, the authors conclude.

That finding speaks to one of the most tenacious questions in DCIS treatment today: Which patients can avoid adjuvant therapy without risk of recurrence? “We’d like to get to the point that we can identify patients who can be treated only with lumpectomy and reserve radiation or tamoxifen for those who need it,” said Wapnir’s coauthor, James Dignam, Ph.D., an associate professor of biostatistics at the University of Chicago. But right now, we don’t know how to reliably identify those patients who can forgo adjuvant treatments.”

This uncertainty has made the search for risk factors and prognostic markers that could help decide on follow-up to surgery a

priority in DCIS research, but so far there have been few results. Stuart Schnitt, M.D., professor of pathology at Harvard Medical School, said the last decade has produced virtually no progress on tailored treatments for DCIS. That’s in part because scientists know so little about why, or whether, DCIS becomes invasive in the first place, he said. Ever since DCIS became widely diagnosed in the wake of mammography (it now accounts for about 25% of all breast cancer diagnoses), clinicians have opted to remove it surgically. Consequently, little is known about DCIS’ “natural history,” or how it might progress to cancer without treatment.

“We’ve created a medical situation in which we immediately treat [DCIS] with the maximal therapy,” said Shelly Hwang, M.D., a professor of surgery at the University of California, San Francisco. “And that’s important because we often don’t know the biology of early diseases like DCIS; we think they’ll progress [to cancer], but not all of them go that way.”

Hwang said researchers assume that DCIS will progress to cancer because both conditions share similar genetic and epigenetic changes in individual patients (although those similarities aren’t generalizable across the population). Fundamentally, DCIS is not invasive. “However, the assumption is that cancerous changes have occurred at the in situ stage and that progression to invasive cancer is likely,” she said.

During the early 1980s, simple mastectomy was the treatment for most DCIS diagnoses. Now, treatment more commonly starts with image-guided needle biopsies followed by excision; lumpectomy; and, in

up to a third of cases (mostly when tumors are diffused throughout the breast), mastectomy. How many patients receive adjuvant radiotherapy isn’t clear, although data from the National Cancer Institute’s SEER (Surveillance, Epidemiology, and End Results) registry suggest that it’s at least 50% in the United States. Adjuvant tamoxifen treatments aren’t as common, but they are increasing in many countries, according to Nina Bijker, M.D., Ph.D. a radiation oncologist at the Academic Medical Center in Amsterdam, The Netherlands.

## Traditional Indicators

Researchers have tried to identify DCIS patients who might be spared adjuvant treatments by elucidating factors that predict local recurrence after surgery. Most of that research has focused on clinical factors, such as age and hormonal status, and pathological factors, such as tumor size, grade, and excision margins. From that research, scientists now know that tumor recurrence is more likely in younger women, although age thresholds haven’t been clearly defined, Schnitt said. So-called comedo-type tumors with high-grade nuclear features also recur more often, as do larger tumors and tumors with DCIS in the surgical margins.

Still, researchers routinely debate these parameters. For instance, Bijker said, some say that omitting radiation is safe when clear tumor margins exceed 1 cm. “But we don’t have prospective, randomized evidence for that,” she said.

Schnitt emphasized that tumor recurrence depends largely on how all these factors interact and that none of them should be taken in isolation. “But we’ve

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James Dignam, Ph.D.

basically pushed traditional clinical and morphological prognostic indicators as far as we can,” Schnitt said. “You can mix and match them in different ways, but one major problem is that most studies just lump DCIS and invasive cancer recurrence together, even though each may have different causes. So factors related to tumor burden, such as involved margins, might be predictive of DCIS recurrence, while other biological factors that we still don’t know about might be more associated with the development of invasive cancer.”

### Molecular Markers

In Schnitt’s view, researchers must now focus on molecular markers of recurrence, particularly markers intrinsic to the tumor’s microenvironment, such as the myoepithelial cells that surround breast ducts and the stroma. “It could be that invasion isn’t related as much to the DCIS cells escaping from the ducts due to their own intrinsic genetic or molecular changes as it is to a breakdown in the myoepithelial cells and other barriers that ordinarily block their release,” Schnitt said. “There’s some clinical evidence to suggest that myoepithelial and stromal cell markers can predict progression, but we’re a long way from using them in routine clinical practice.”

Larry Solin, M.D., chair of radiation oncology at the Albert Einstein Medical Center, in Pennsylvania, agrees that molecular markers will be key to stratifying patients for tailored DCIS treatment. Solin is principal investigator on a new trial sponsored by the NCI’s Eastern Cooperative Oncology Group ((NCT01132560), which aims to find biomarkers for ipsilateral local failure in DCIS, as well as for DCIS patients who develop cancer in the other breast. The study uses a modified version of the OncotypeDx recurrence score genetic assay, developed by Genomic Health in Redwood City, Calif. “In the context of other clinical and pathological parameters, gene expression profiling might allow individual patients and their doctors to make more informed decisions

about adjuvant treatments in DCIS,” Solin said.

According to Schnitt, clinical decisions in DCIS can be challenging for doctors and patients weighing risk reductions from adjuvant therapy against the real-life burdens of radiation and/or tamoxifen treatment. Women bring a range of concerns to these discussions, Solin said, including worries about local recurrence, cancer in the other breast, cosmetic results from treatment, and survival. “It’s remarkable that if you tell patients that risks for invasive cancer drop to 1.5% with adjuvant therapy from 3% without it some will view that as a big difference and others [will] not,” Schnitt said.

But although doctors can cite data showing that radiation and tamoxifen reduce local recurrence risks for either DCIS or invasive disease by 50%, just how those treatments influence survival isn’t clear. “The studies so far didn’t enroll enough patients to detect statistically meaningful differences in survival,” Solin said. “So for now, this must be considered an underpowered endpoint.”

According to the new study from Wapnir and colleagues, the absolute number of deaths is small. They obtained their data by looking at long-term outcomes from two randomized trials from the National Surgical Adjuvant Breast and Bowel Project. The B-17 trial compared lumpectomy only to lumpectomy and radiation, and the B-24 trial compared lumpectomy and radiation along with either tamoxifen or placebo. Of the 2,612 women that the two trials evaluated, 490 had a local recurrence—but only 263 of these recurrences were invasive, and only 22 women died from breast cancer.

“So that comes out to less than 1% of the patient population,” Wapnir said. “We’re showing relative risk reductions with adjuvant therapy, but what’s also important to understand is that the absolute numbers for DCIS-related mortality are very small.”

### Questioning Adjuvant Therapy

At a 2009 National Institutes of Health–sponsored state-of-the-science conference

on DCIS, expert panels concurred that removing the word *carcinoma* from DCIS might be appropriate, since the term evokes so much anxiety. The panels also emphasized that future research should focus on diagnosing DCIS patients who could achieve optimal outcomes with less therapeutic intervention. Schnitt concurs with the need for tailored treatments, but he counters that the term *carcinoma* doesn’t evoke anxiety so much as do routine DCIS treatments, including mastectomy and radiation.

Hwang, who says her views represent an emerging groundswell of opinion, questions the value of adjuvant treatment when its survival benefits appear so negligible. “Patients and their physicians need to discuss tradeoffs in order to determine whether 6 weeks of radiation treatment to drop a 1% mortality risk to 0.5% can be justified,” she said. “That’s something we need to consider carefully for each individual.”

Preliminary data from a study conducted at the University of California, San Francisco, Hwang said, suggest that DCIS can sometimes recede in response to non-surgical, hormonal blockade.

Hwang now plans to direct a clinical trial—opening next summer and coordinated by the NCI-sponsored Cancer and Leukemia Group B—to investigate surgery versus hormonal blockade (with tamoxifen and/or aromatase inhibitors) in women with hormone-sensitive DCIS, including disease that’s not amenable to lumpectomy. This focus is appropriate, Hwang said, because mastectomy is such a drastic response to a condition that may never be life-threatening.

“There’s a huge social health care drain that comes from treating DCIS,” Hwang said. “If it saves lives, then that’s great. But if it doesn’t, then future research might find that it is reasonable to follow some of these low-risk patients with active surveillance, much as we do in patients with prostate cancer.”