The Institute of Medicine has identified the management of ductal carcinoma in situ (DCIS) as one of the highest priority topics for comparative effectiveness research. With the rise of mammographic screening, the incidence of DCIS has increased dramatically, and currently about a quarter of all newly diagnosed breast cancers are DCIS. Although DCIS is by definition noninvasive, treatment is necessary because of the risk of development into invasive cancer. Therefore, most patients with DCIS face complex management decisions, including whether to undergo breast-conserving surgery or mastectomy, as well as whether to receive adjuvant radiotherapy and/or tamoxifen.

In this issue of the Journal, Soeteman and colleagues present an intriguing study using simulation modeling to evaluate the trade-offs in lifetime risks and benefits with various approaches for DCIS management (1). Specifically, they consider mastectomy (with or without reconstruction) and four options for native breast conservation (lumpectomy alone, lumpectomy with radiation, lumpectomy with tamoxifen, and lumpectomy with both radiation and tamoxifen). They compare predicted survival and breast preservation rates at three representative ages: 45, 60, and 70 years.

Perhaps the greatest contribution of the study is its finding that survival after mastectomy is similar to that after lumpectomy, radiation, and tamoxifen for all three patient ages. A randomized trial of mastectomy versus breast conservation for DCIS is extremely unlikely to be feasible. Therefore, it is useful to be able to refer to these model results to reassure patients that they do not have to sacrifice the native breast to maximize survival.

It is also interesting that the model suggests that radiation therapy yields a modest survival advantage. Although none of the randomized trials have demonstrated a difference in survival associated with the use of radiation, physicians have speculated how radiation therapy might, in theory, be lifesaving for a patient with DCIS. If radiation spares a certain number of patients invasive recurrences, some of which eventually lead to metastatic disease, it might indeed offer a survival benefit. However, given the relatively modest absolute reduction in invasive recurrence risk yielded by radiotherapy, and the fact that many recurrences can still be salvaged, the magnitude of any survival benefit would likely be too small to detect even with meta-analysis of all existing trials. The model results support the concept that radiation can improve survival, even for DCIS. Moreover, a survival benefit of a similar magnitude appears to result from the addition of tamoxifen in this setting.

Where the model seems weakest is in predicting rates of breast preservation. A critical model input is the assumption that all patients who receive radiation must have mastectomy upon recurrence, but that two-thirds of those who receive lumpectomy without radiation will undergo repeat breast-conserving surgery after recurrence. Soeteman and colleagues (1) cite as the basis for this critical assumption the findings of a small cohort study from Australia (2), in which 34 of the 56 patients with local recurrence after wide excision alone received repeat wide excision rather than mastectomy. Other studies have demonstrated rates of repeat breast conservation in a lower proportion of patients, ranging from 42% to 52% (3–5). For example, only 44% of patients experiencing local recurrences after wide excision alone in the Eastern Cooperative Oncology Group (ECOG) E5194 study received breast conservation as salvage therapy (4). Given that these are the most recent data from the United States, and that participants in a study of omission of radiotherapy would be expected, if anything, to have less risk aversion than the population more generally, we suspect that the majority of patients in the general US population would undergo mastectomy after recurrence, even if they had not previously received radiotherapy. Neither surgeons nor patients in the United States are likely to take in-breast recurrences, even noninvasive recurrences, in stride (6). The sensitivity analyses conducted by Soeteman and colleagues (1) suggest that lifetime breast preservation is improved with radiation if the rate of mastectomy at time of recurrence in an unirradiated breast exceeds 56%. Given substantial uncertainty about what that mastectomy rate would be in an unselected population of patients in this country, and the difficulty of any given patient predicting how she will wish to proceed if she does experience in-breast recurrence, we are not as confident that the baseline model provides clinically useful information regarding the impact of different treatment approaches on breast preservation likelihood. Moreover, rates of breast preservation after radiotherapy could be even higher if studies such as the Radiation Therapy Oncology Group (RTOG) 1014 are successful in identifying approaches to facilitate repeat breast preservation in previously irradiated patients.

Considerable controversy remains regarding the appropriate selection of patients for adjuvant radiotherapy after lumpectomy. Despite promising results from retrospective analyses (7), prospective studies have not yet been able reliably to identify a population at truly low risk of long-term recurrence after lumpectomy but without radiation for DCIS (4,8). The short-term results of RTOG 9804 are encouraging (9), as are steps toward molecular profiling to predict risk (10), but for now, patients and
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


Affiliations of authors: Department of Radiation Oncology (RJ, JH), and Center for Bioethics and Social Science in Medicine (RJ), University of Michigan, Ann Arbor.

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

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