Individualizing Follow-Up for Patients With Early-Stage Melanoma

Vernon K. Sondak, Moffitt Cancer Center; and University of South Florida College of Medicine, Tampa, FL
Sancy A. Leachman, Huntsman Cancer Institute; and University of Utah, Salt Lake City, UT

See accompanying article on page 4641

In this era of personalized medicine, in which every patient is supposed to be treated using a therapeutic plan that is tailored to provide the right care at the right time and in the right place, it is surprising how little attention has been paid to personalizing follow-up for patients after curative treatment of cancer. This is certainly true in localized cutaneous melanoma, for which there is little if any consensus with regard to standard follow-up strategies and virtually no guidance with regard to how to individualize follow-up on the basis of a patient’s estimated risk of requiring additional interventions. Should we (and our patients) care about this deficiency? Absolutely—given the time, effort, and expense that are involved in the follow-up of patients with localized melanoma when weighed against the relatively limited value derived per clinic visit, and the challenges that patients in many locations face with regard to obtaining appointments with dermatologists who are willing to perform comprehensive skin examinations and other aspects of melanoma follow-up.1,2 The numbers are sobering: in the article that accompanies this editorial, Turner et al3 report that for every 1,000 patients with stage I or II melanoma (primary invasive melanomas of any thickness with clinically and/or pathologically negative regional nodes), a typical follow-up schedule (visits every 3-6 months for 5 years, and then annually thereafter) will mandate more than 8,000 clinic visits during the next 10 years. The authors reported that, of that cohort of patients, 229 would be expected to develop recurrent melanoma and 61 to develop a new primary melanoma during that decade of follow-up. Is there any problem with observing all of those patients at that rate?

To put this in perspective, it should be recognized that many major melanoma centers see more than 1,000 new patients with localized melanoma in the course of a year, that it has been estimated that there are more than 800,000 survivors of melanoma in the United States alone,4 and that the incidence of melanoma continues to rise. In the course of a decade, 10,000 new patients could ultimately require as many as 80,000 15-minute follow-up clinic visits, filling five clinic rooms for 500 8-hour clinic days. Not only are there significant health care (and patient travel) costs associated with all of these visits, they consume finite clinic resources and thus threaten to delay the evaluation of new patients. Although Turner et al3 believe that an attenuated follow-up schedule that reduced visits to 5,221 per 1,000 patients would lead to only modest delays in the diagnosis of recurrent or new primary melanoma for those patients who are destined to experience recurrence,5 the question remains: are we providing the right care at the right time and in the right place to patients with melanoma?

Rapidity of detection does not have equal therapeutic significance for all recurrences. Curable recurrences (in melanoma, this means essentially those that are potentially resectable) and new primary tumors are clearly the most important to identify expeditiously. Even among unresectable recurrences, there are likely to be some important differences in outcome as a result of early detection (eg, finding brain metastases while they are few and small enough to treat with stereotactic radiation). To date, no studies have documented that surveillance of patients with early-stage melanoma with any imaging studies (including chest x-rays, positron emission tomography/computed tomography, or magnetic resonance imaging scans) or with laboratory studies are cost-effective, but nor have any of these studies tested best practices specifically to identify the type of resectable/treatable recurrences that would have most value. The results of follow-up in patients with stage III disease were recently evaluated and it was found that half of the recurrences were detected by patients, and that even in this high-risk cohort, “neither more intense nor more frequent follow-up is associated with discovery of resectable first relapses.”

Because patients with melanoma are at high risk for nonmelanoma skin cancer development, they are faced with regular visits to a dermatologist, in addition to whatever scheduled oncologic follow-up is prescribed. But what is the alternative? Can we do any better at providing the right care (close follow-up that identifies new primary melanomas of any thickness with clinically and/or pathologically negative regional nodes) or with laboratory studies are cost-effective, but nor have any of these studies tested best practices specifically to identify the type of resectable/treatable recurrences that would have most value. The results of follow-up in patients with stage III disease were recently evaluated and it was found that half of the recurrences were detected by patients, and that even in this high-risk cohort, “neither more intense nor more frequent follow-up is associated with discovery of resectable first relapses.”

Because patients with melanoma are at high risk for nonmelanoma skin cancer development, they are faced with regular visits to a dermatologist, in addition to whatever scheduled oncologic follow-up is prescribed. But what is the alternative? Can we do any better at providing the right care (close follow-up that identifies new primary
melanoma and nonmelanoma skin cancers and potentially curable nodal and soft tissue recurrences) at the right place (close to home) at the right time? We believe we can, but new concepts and collaborations are needed. Turner et al3 have begun to move us down the path toward data-driven, personalized follow-up guidelines. It seems clear, however, that the ultimate solution should and perhaps must involve shared follow-up with physicians in the community.

Shared follow-up with local dermatologists of patients with melanoma, after surgical treatment, would accomplish the primary goal of detecting skin, nodal, and soft tissue recurrences and new primaries (assigned to the local dermatologist or suitably trained primary care provider), and would simultaneously decrease the frequency of visits to the surgical or medical oncologist (relying instead on as-needed evaluations). Another potential solution to the challenge of providing follow-up for the growing number of patients with early-stage melanoma is the establishment of survivorship clinics that are tailored to the specific needs of this population. The staff of these clinics would require particular expertise in skin examination and biopsy techniques, but advanced practice professionals as well as primary care physicians, internists, dermatologists, and oncologists of all stripes could—with appropriate training—participate, perhaps on a rotating basis, to lessen the burden on any one specialist. These survivorship clinics would also provide an ideal setting for testing new surveillance strategies and evaluating the cost-effectiveness of current and proposed follow-up approaches.

Given that the majority of all melanoma recurrences and many new primary cutaneous malignancies are diagnosed first by the patient or the patient’s family, the shared follow-up concept should be extended to educate patients and families to maximize their ability to identify these findings and provide them with explicit instructions as to when and which clinician to notify if they arise. When the patient’s care is transitioned from postoperative monitoring into shared follow-up, a personalized discharge summary that includes information about how to perform skin and regional nodal examinations and on which areas to focus particular attention could facilitate a sense of partnership in the surveillance process and help convince patients and their families that as-needed evaluations at the oncology clinic are as good as regularly scheduled visits.

There are notable drawbacks of the shared follow-up approach: not all dermatologists and primary care physicians are as comfortable with or as skilled at examining lymph nodes as most oncologists, and many primary care physicians are not comfortable examining and biopsying skin lesions. So education needs to go beyond the patient and family, and melanoma centers may want to train and even certify providers in their catchment area. Patients should be willing to return to the melanoma center for evaluation of a suspected recurrence because properly diagnosing recurrence (eg, documenting nodal recurrence by needle aspiration cytology instead of open biopsy) is important to successful treatment. Importantly, we need to individualize the follow-up and identify which patients are best suited to have the bulk of their surveillance outside of the melanoma center and which patients should return more frequently.

The stage of the initial melanoma is obviously a major influence on any surveillance recommendations, but it is by no means the only one. Special situations, for instance, patients who become pregnant or who require therapeutic immunosuppression, necessitate individualized approaches, and we observe such patients much more closely in our own centers but in close conjunction with their other care providers. Patients with multiple atypical nevi (who may benefit from specialized imaging and longitudinal photography technologies), a history of multiple primary cutaneous malignancies, or extensive sun exposure require more detailed surveillance as well, but this may often be accomplished by a dermatologist outside of the melanoma center or in collaboration with community providers. Patients at the extremes of age also require individualized follow-up plans. We observe children and adolescents with melanoma closely (usually with twice-yearly visits to the melanoma center that are set up to coincide with winter and summer vacations to minimize missed school) in recognition of the uncertainty of their biologic behavior and the limited comfort most pediatricians and even dermatologists have with melanoma in this population. Elderly patients frequently have a much more difficult time making the trip to a melanoma center far from home, and likely benefit far less than younger patients from the detection of asymptomatic metastases—but determinations with respect to elderly patients (how old is old?) also need to be individualized. Finally, as diagnostic and treatment strategies evolve, new questions arise, among them: should patients who harbor germline p16 mutations, exhibit other cutaneous cancer syndromes such as xeroderma pigmentosa, or who are immunosuppressed and at risk of additional cutaneous malignancies be seen more frequently? Could BRAF mutation status influence the importance of early detection of metastatic disease?

The need is clear and the potential is there to decrease costs and inconvenience for the large (and increasing) number of survivors of melanoma without adversely affecting outcomes—indeed, with the prospect of improving them! To do so, we need to focus the lens of personalized medicine onto our follow-up strategies and be open to new partnerships and collaborations. If we do, we have a golden opportunity to deliver the right care to the right patients at the right time and in the right place.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None Consultant or Advisory Role: None Honoraria: None Research Funding: None Expert Testimony: None Other Remuneration: None

AUTHOR CONTRIBUTIONS
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES
In 1900, the life expectancy for Americans was 47 years, and when Franklin D. Roosevelt signed the Social Security Act on August 14, 1935, it was 62 years. Now it is 78 years. That is especially important because breast cancer is a disease of aging with an incidence rate of 82.2 new patients per 100,000 in women younger than age 65 years versus 403.8 per 100,000 for those age 65 years and older. The average age at diagnosis is currently 61 years and the average age at death is 68 years. Of the 207,000 new invasive breast cancers that were estimated to occur in 2010, 21% were projected to be in women age 75 years and older, accounting for about 43,000 patients. What may be even more important when it comes to breast cancer treatment is that 65- and 75-year-old women can be expected to live approximately 20 and 13 more years, respectively, if they do not die as a result of breast cancer. As the number of elders continues to increase—estimates are that 20% of the US population will be age 65 years and older in 2025—there will be more cancers of all types in elders. Making sure that these patients receive the best quality of care should be a major objective of all geriatricians and medical oncologists. Breast cancer is the most common cancer in women and the vast majority of patients, older and younger, present with local or locoregional disease that is amenable to cure. Metastatic breast cancer remains incurable regardless of age, but even in this disease, many endocrine, chemotherapeutic, and some biologic agents can be helpful when the goals of treatment are controlling symptoms, improving quality of life, and extending survival.

In the article that accompanies this editorial, Smith et al., using data from National Vital Statistics Reports and the Surveillance Epidemiology and End Results database of the National Cancer Institute, found that although both the rate of death as a result of breast cancer and the adjusted risk of death as a result of breast cancer in the population are decreasing (very good news), these improvements were much less for older patients. Their data show that for the general population, the rate of breast cancer death relative to 1990 decreased 2.5% per year for patients age 20 to 49 years, 2.1% per year for those age 50 to 64 years, 2% per year for those age 65 to 74 years, but only 1.1% per year for those patients age 75 years and older. Moreover, the adjusted risk of death as a result of breast cancer in patients newly diagnosed with breast cancer between 1980 and 1997 decreased by 3.6% per year in women younger than age 75 years compared with 1.3% per year for those age 75 years and older (P < .01). During this same time period the absolute 10-year risk of death as a result of breast cancer decreased by 15.3% for women age 50 to 64 years, but only by 7.5% for those age 75 years and older. Also noteworthy is that, although women age 75 years and older who were diagnosed between 1980 and 1984 had a lower risk of death as a result of breast cancer compared with those age 50 to 74 years, by 1995 to 1997, older women had a higher risk. In addition, the risk of dying as a result of breast cancer decreased 3.6% per year for white women of all ages, compared with 1.4% per year for African American women. This information should be of major interest to clinicians. Unfortunately, the news may be telling us that something is lacking in our care of older patients with breast cancer. The authors suggest that part if not all of these disparities might be a result of older patients not receiving state of the art care, with such undertreatment resulting in poorer survival.

What accounts for these overall improvements in survival? It is most likely the wider use of mammographic screening and adjuvant therapy. Annual and biannual mammographic screening has significantly improved breast cancer survival in women age 40 to 69 years, but there are limited data with respect to benefits in women age 70 years and older, and even less information for women age 75 years and older; randomized trials in this older age group are unlikely. Using available data, modeling has shown that mammography is likely to be cost effective in saving lives of older women, especially those in good health, yet data from the National Health Interview Survey in 2008 showed that the mammography rate for women age 65 years and older was 9% less than for women age 50 to 64 years (67% v 76%, respectively). Mammography is not without its downsides, including overdiagnosis, anxiety related to the procedure, false-positive results, and the potential high costs of a diagnostic work-up, especially in those age 80 years and older. However, we believe that a small part of the gap in survival for older women could be closed by the appropriate use of mammography for women age 75 years and older with reasonable life expectancy. Geriatricians should provide screening information to older patients and counsel them concerning mammography screening on an individual basis.

Major gains in adjuvant systemic therapy have also played a key role in improving survival, and these advances in breast cancer care are floating all boats up—survival is improving for all age groups. For instance, the majority of older patients with breast cancer present with curable disease, and most have hormone receptor–positive tumors. The meta-analysis of the Early Breast Cancer Trialists’