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OPINION ARTICLE

Staging and Follow-Up of Patients With Melanoma: Which Tests for Which Patients?☆

Estadificación y seguimiento de los pacientes con melanoma: ¿qué exploraciones y a qué pacientes?

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We routinely order chest x-rays, abdominal ultrasound imaging, and laboratory tests of all types for our patients at the time of melanoma diagnosis and during follow-up schedules of varying duration. Studies are done even in patients with tumors at low risk of recurrence. It is not unheard of to find a patient with a melanoma measuring less than 1 mm for whom a thoracoabdominal computed tomography (CT) scan was ordered merely to have a ''more complete'' diagnostic picture, not because there was clinical suspicion of further disease. Generally patients accept such testing agreeably, as they have the sensation that the physician managing their case is looking after them and will do everything possible to detect any problem related to the excised melanoma. But are such tests truly necessary? Should we not question our guidelines more, especially if they are inconsistent with recommendations being followed in other countries? In times of cutbacks, such as we are experiencing now, how much could be saved if we adopt more solid and up-to-date guidelines for ordering tests? And what would happen if we applied the savings to other areas, such as toward new treatments that target molecular pathways? This opinion article is based on the authors' experience and reading of numerous articles on the central topic. Our purpose is to encourage dialog on the need to revise existing guidelines in Spain in the interest of updating recommendations on the imaging studies and laboratory tests needed to fully diagnose and follow patients with melanoma.

Experts on the management of melanoma are in evident disagreement on how to diagnose and follow the disease, and specialists in different countries do not share the same ideas on what tests to order for either purpose.[1] There is also inconsistency in the frequency with which follow-up visits are scheduled: guidelines vary on this point even within Spain. However, the main discrepancies are found when we try to reconcile Spanish guidelines with the most recent ones published in other countries. The need for a uniform management approach to melanoma is justified from several points of view. On the one hand, clinicians who follow patients with melanoma require a review of current research and evidence-based recommendations. Such recommendations would affect the ordering of tests according to stage of disease, so that patients at low risk could avoid costly procedures, unnecessary inconvenience and discomfort, exposure to radiation, and anxiety while they wait for results. Furthermore, it is often the case that inconclusive test results, with values at the upper limit of normal, or the appearance of a benign lesion in images will entail further testing and additional imaging studies. Another reason why guidelines are needed is that many of our patients themselves possess very up-to-date information about their disease and fail to understand if the tests we order do not correspond to the ones described as necessary in the latest versions of guidelines they have consulted.

Appropriate decisions on the range of necessary laboratory and imaging studies can be approached from both clinical and economic perspectives. To understand the economic issues involved, we have to consider the number of melanomas diagnosed in Spain annually. Although there are

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no Spanish case registries on which to base an estimate of the incidence of melanoma, recent publications suggest that 8 to 9 cases are diagnosed per 100 000 inhabitants per year in this country.[2,3] According to current data from other countries, 70% of melanomas are diagnosed in stage I.[4] Roughly 3700 to 4100 melanomas are found in Spain annually and if 70% of them are in stage I, they would number about 2800. Dermatologists who see melanomas daily know that it is rare for patients with early-stage tumors to have abnormal test results on staging or follow-up studies. In fact, most cases of tumor recurrence (73%) are found by the patient or the patient's partner rather than by the physician following the case or through complementary imaging studies.[5] Therefore, the percentage of prompt detection of recurrence could very probably be increased through better education of the patient and relatives regarding early signs of new or reappearing melanomas. Regardless, another question to answer is whether we should continue to order, and even promote, the tests we presently use or instead introduce new ones.

The Spanish Academy of Dermatology and Venereology (AEDV) has not developed guidelines on diagnostic and follow-up testing for melanoma. Individual autonomous communities in Spain have produced some, and although we have not done an exhaustive search for all of them, we have reviewed those from the communities of Valencia[6] and Murcia,[7] the consensus paper of the network of melanoma centers of Catalonia and the Balearic Islands,[8] and the protocol for Hospital Reina Sofía de Córdoba.[9] Although we will not attempt to delve into any particular guideline in this article, we have taken them as a point of departure for our reflections. Starting with the guideline that affects us most, we find that the Community of Valencia recommends ordering laboratory tests, a chest x-ray, and abdominal ultrasound on the detection of a stage 0 (in situ) or stage IA melanoma.[6] For patients with a stage IA tumor, these tests are repeated annually for 5 years, along with ultrasound images of the region of lymphatic drainage. The guidelines for the Community of Murcia[7] describe a similar approach to staging and follow-up. In Catalonia and the Balearic Islands, however, laboratory testing and a chest radiograph are recommended on diagnosis, and laboratory tests are then repeated every 6 to 12 months for 2 years.[8] After that period, these tests are ordered along with a chest x-ray until 5 years after the diagnosis; abdominal ultrasound imaging is considered optional. At the Hospital Universitario Reina Sofía de Córdoba the protocol is the same as in Valencia and Murcia, but the follow-up period is 3 years.[9] Although these differing approaches to managing stage IA melanoma may give pause, there seem to be equally debatable discrepancies in the recommendations on performing thoracoabdominal or full-body CT scans every 6 months for 5 years in melanoma at stage IIB or higher.[6,8] As we know very well, CT exposes the patient to much higher radiation than simple radiography and CT is much more costly. Above all, we note that these recommendations seem not to be based on evidence in the literature.

Without wishing to disparage what seems reasonable based on findings in the individual patients we attend or on what we see in our more or less recent clinical guidelines, we think that routine decision-making ought to be more clearly guided by up-to-date evidence. The most advanced countries with high incidences of melanoma use evidence-based protocols to stage and follow patients with this disease. Recommendations issued in the United States,[10,11] the United Kingdom,[12] and Australia,[13] as well as those written by a group of European dermatologists specializing in melanoma[14] advise that patients with stage I or II tumors be followed mainly through clinical examination; imaging studies should be ordered only when signs of recurrence are detected or the patient reports suggestive symptoms. However, there is a certain degree of consensus about the appropriateness of ordering 2 imaging studies in 2 different contexts: for follow-up, ultrasound imaging of the region of lymph node drainage can be useful, and for the initial staging of high-risk (stage III) cases, positron emission CT (PET-CT) can be helpful. Studies have demonstrated the utility of ultrasound evaluation of regional lymph nodes.[15] These images offer more precision than palpation and some studies have shown that they are even superior to CT, PET, and PET-CT scans of regional lymph nodes.[16,17] Therefore, ultrasound examination might be considered as a complement to clinical examination in follow-up.[14] For evaluating high-risk (stage III) melanoma, both PET and CT have been found to be cost-effective: in 253 patients with stage III melanoma and palpable lymph nodes in one study, PET showed greater sensitivity and higher predictive value, whereas CT was more specific for the detection of distant metastasis.[18] A combination of PET and CT scanning or a modern PET-CT scan can offer the greatest diagnostic value for detecting distant metastasis, providing the highest sensitivity and specificity.[17,19] Based on these and other studies, the 2013 update of a National Comprehensive Cancer Network (NCCN) guideline for melanoma recommended that a baseline PET-CT scan be ordered for patients with stage III tumors and palpable nodes (and that one be considered in case of positive sentinel node biopsy).[10] Regarding laboratory tests, high lactate dehydrogenase levels are relevant in patients with metastatic disease because they warn of significant metastatic load and identify a subgroup (M1c) with the highest risk according to the most recent classification of the American Joint Committee on Cancer.[20] However, this marker has not proven useful for detecting metastatic disease in patients with stage I or II melanoma; therefore it should not be routinely ordered in such cases.[21] The usefulness of S100 protein detection is likewise undemonstrated in stage I and II melanoma; however, studies suggest that this marker indicates a poorer prognosis for a subgroup of patients with stage III disease.[22,23] Therefore, it seems reasonable to test for S100 positivity only in cases of stage III melanoma.

In 2012, 4 dermatologists met with other specialists under the auspices of the Spanish Society for Quality in Health Care (SECA) and the Spanish Multidisciplinary Melanoma Group (GEM) in an effort to contribute to systematizing diagnostic and treatment processes in cutaneous melanoma. The resulting position paper[24] gives recommendations that reflect the spirit of international guidelines and in certain aspects make use of concepts established in the new NCCN guidelines. The group agreed that it is unnecessary to order imaging procedures routinely for asymptomatic patients with localized melanomas (stages I and II). For patients with palpable nodes or in-transit metastasis, an initial PET-CT was recommended because it

is the most sensitive image for detecting distant metastasis. Afterwards, this guideline suggests, tests should be ordered based on the patient's signs and symptoms.

We cannot deny that health care savings constitute an argument for stricter, more rational use of additional testing. Studies have calculated the savings that would derive from establishing a protocol with fewer visits and less testing to manage early-stage melanomas; the same studies also led to proposals for more frequent visits and greater use of certain tests in patients with higher-risk tumors. A German study carried out between 2006 and 2008, using a 2004 price schedule for tests, estimated that a savings of €792.60 per patient with stage-I melanoma would accrue over 5 years of follow-up.[25] According to our calculations, based on the 2013 fee schedule for the Community of Valencia, the estimated savings would be €808.95 per patient with stage IA melanoma if follow-up were based on clinical examination without laboratory tests or imaging studies.[26] If we apply this amount to our estimate of the number of stage I melanomas found in Spain each year (2800), we can forecast annual savings of €2,265,060. Stage IB melanomas do not enter into that estimate, although the same tests are ordered for these tumors even more often than for stage IA tumors. Although the amount saved for patients diagnosed in a particular year should be distributed over the 5 years they will be followed and tested, in fact we must also remember that there would be savings accruing each year for patients newly diagnosed in each of the 4 years the first group is being followed. Therefore, the amount of our rough estimate would approximate the savings gained by eliminating routine testing in the follow-up of stage I melanoma. Evidently, the amount is theoretical. Many dermatologists and oncologists that manage melanoma do not actually order all these tests, but it is also true that we have not factored in the additional savings from further testing of those patients when anomalies are detected in radiographs, laboratory tests, or ultrasound studies; such extended testing does not generally reveal findings of any importance. Nor have we considered the savings that might be found by managing melanomas in other stages differently. Are such savings significant? The answer depends on how we approach the question. If the amounts were transferred to new therapeutic drugs that target molecular pathways (anti-BRAF and anti-CTLA4 agents), €2 million would pay for the treatment of 40 patients each year, at an annual cost of €50 000 each.

Melanoma groups in Australia have published what are probably the best studies on follow-up frequency. In 2011, Turner et al[27] studied 2 schedules for following patients with stage I or II melanoma. One was the established follow-up frequency in Australia at the time and the other was a study protocol requiring less frequent visits. The group found that for every 1000 patients followed under the conventional routine, 113 would suffer a delay of more than 2 months in the detection of tumor recurrence; in the group that followed the study protocol, detection would be delayed for 158 patients (45 more). Applying the study protocol would also result in more than 2 months' delay in the detection of new tumors in 9 additional patients (out of 1000 patients). Whether these increases are acceptable or not is a matter each health care system and community must decide. The authors of the Australian study argued that medical follow-up with frequent visits probably does not afford great advantages and they proposed more intensive patient education and self-examination.

It does seem clear that modern practice should make greater use of individualized management of risk: the minimum frequency of necessary visits should be established in guidelines but later modified according to a patient's situation and the type of melanoma.[28] Children, transplant recipients or other immunodeficient patients, those with a personal or family history of melanoma, and those who have multiple atypical nevi or for whom self-examination is problematic evidently require more frequent trips to the dermatologist. On the other hand, patients with stage I melanoma who are motivated to practice self-examination or have a family member ready to help could benefit from a more lax schedule of follow-up visits. Patients of advanced age with early-stage melanoma who have difficulty traveling to the doctor could also benefit from less frequent visits. Of great importance is showing the patient and the cooperating relative how to examine the skin to detect new pigmented or atypical lesions.

Our aim in this article has been to encourage more discussion of these issues in the hope that debate leads to more frequent periodic updating of guidelines for managing melanoma. We also hope for the advantageous adoption of Spanish guidelines for melanoma staging and follow-up. The effort will require multidisciplinary cooperation between dermatologists and other specialists, including our colleagues in oncology, of course. That there are controversies to resolve in the management of melanoma is clear. The coming years will probably bring new categories and melanoma typing that make use of molecular criteria. These advances will also affect approaches to follow-up. It is essential for us to be prepared for these changes.

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