High-risk cutaneous melanoma follow-up: time for more intensive surveillance?

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“There is now a need for a follow-up strategy for high-risk melanoma that reflects current staging and risk stratification and that facilitates the optimal use of a new generation of treatments.”

Systemic treatment options in melanoma have changed dramatically over the last 3 years, with new drugs now available that have the potential to substantially impact upon both quality of life and survival in advanced disease [1–5]. Guidelines for the follow-up of resected cutaneous melanoma have not kept pace with these changes. There is now a need for a follow-up strategy for high-risk melanoma that reflects current staging and risk stratification and that facilitates the optimal use of a new generation of treatments.

Current guidelines & existing evidence

In the UK, guidance from the British Association of Dermatologists for the follow-up of stage IIIb, IIIc and resected stage IV disease dates from 2010 and is based on regular clinical follow-up only [6]. Importantly, the use of imaging, both in terms of modality and frequency, is left up to the discretion of individual physicians and centers. A

similar emphasis on physician discretion in the identification of high-risk patients and use of imaging is also evident in the current National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) clinical practice guidelines [7,8]. This reflects the currently limited evidence that surveillance imaging improves outcomes [9]. However, this evidence is based mainly on studies that were undertaken at a time when treatments for systemic relapses of melanoma were limited to agents that were largely ineffective [10].

Use of surveillance imaging has also been contentious in other cancer types, with no overall survival benefit being shown in large screening studies [11]. This may be due in part to the fact that these studies have been based on the premise that in order to be effective, a screening program requires a ‘stage shift’ (i.e., an increase in the number of cancers identified at an early stage, where potentially curative surgery can be considered). In

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high-risk melanoma, advanced stage IV relapses are common [12], and such relapses will rarely be amenable to surgery with curative intent. Novel melanoma treatments, however, have the potential to confer long-term survival benefits to a proportion of these patients if such relapses are identified promptly and treatment is instituted in a timely manner.

Importance of early relapse detection in current clinical practice

The anti-CTLA4 monoclonal antibody ipilimumab is now licensed in Europe and the USA for the treatment of advanced melanoma at any line of therapy, and a number of trials of other immune-modulating therapies have had striking early results [13,14], suggesting that these drugs will have an increasing role in melanoma treatment in the future. As our understanding of the mechanisms of action and the patterns of responses seen with these drugs improves, it is becoming apparent that early identification of relapse and prompt treatment is important for their effective use. Unlike traditional cytotoxic agents, the timing and response patterns of anti-CTLA4 therapy can be variable and idiosyncratic. Delayed responses are common, and the phenomenon of tumor ‘flare’, with response preceded by an initial increase in tumor burden, is well recognized [15]. Long-term survival data from the two Phase III trials of ipilimumab have provided a better understanding of the characteristics of long-term responders, and it is patients with low-volume disease and a preserved performance status that tend to experience durable responses to therapy [16]. This is particularly pertinent to CNS disease, which accounts for 13% of first relapses in stage IIIC melanoma and is seen in a third of patients with metastatic melanoma overall [12]. Symptomatic CNS disease is distressing and debilitating for patients, and although ipilimumab can be effective in this situation [17], the associated impairment in performance status and need for high doses of steroids for symptom control may compromise its potential efficacy.

Similarly, with the BRAF-targeting agent vemurafenib there is evidence that those patients who are most likely to achieve prolonged responses have earlier-stage and less bulky disease [18]. This suggests that, as with immune-modulating therapies, the early use of targeted agents may result in the greatest clinical benefit. The purpose of cancer surveillance is to detect recurrence at a time

when an effective treatment can be offered. In modern melanoma practice this now means identifying relapsed disease at an early, low-volume, preferably asymptomatic point.

Defining ‘high-risk’ disease

The American Joint Committee on Cancer (AJCC) staging and classification system allows for precise evaluation of high-risk disease [19]. Taking into account clinicopathological factors relating to both the primary tumor and the pattern of regional metastatic spread, accurate predictions of 5- and 10-year survival can be made. For example, a thick, ulcerated T4b tumor is associated with a poorer prognosis than a stage IIIa tumor with micrometastatic nodal spread only, and the entry criteria for some recent adjuvant therapy studies now include ‘high-risk primary’ tumors, as well as resected stage III disease [20]. No formal definition of high-risk melanoma currently exists; however, if a cutoff based on a 5-year survival of less than 60% is used, this would include all patients with satellite, in-transit or macroscopic nodal disease, as well as T4b primary tumors.

Modality & frequency of imaging

The imaging modalities most studied to date in melanoma surveillance are ultrasonography, CT and PET [21]. Although ultrasonography has the highest sensitivity and specificity for the surveillance of regional lymph node involvement, given that many high-risk melanomas relapse systemically [12], it is not an appropriate tool for routine surveillance. PET-CT provides greater sensitivity and equivalent specificity when compared with standard CT alone for the surveillance of distant metastases. However, given cost and service considerations, standard CT of the chest, abdomen and thorax is still likely to be the most widely used imaging modality in many centers in the UK. In terms of CNS surveillance, MRI offers superior sensitivity and specificity at no radiation dose.

We have adopted a high-risk surveillance strategy using cross-sectional imaging, typically consisting of head MRI and chest, abdomen and thorax CT at baseline, followed by imaging every 6 months up to 3 years, then annually up to 5 years, involving a total of nine scans. As with all cancer follow-up, a balance needs to be struck between the potential benefit of imaging against the potential harms. A common concern is the risk of secondary cancers from

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the radiation exposure inherent in a schedule of frequent CT scanning. There are now good data regarding the average radiation doses of common medical examinations and their associated lifetime cancer risks stratified by age and gender [22,23]. For example, a chest, abdomen and thorax CT incurs an average radiation dose of 10 mSv, which, for healthy adults, equates to an additional lifetime cancer risk of approximately 0.05% per scan. A follow-up regime consisting of nine scans over 5 years therefore incurs a lifetime cancer risk of 0.45%, or approximately one in 200. When considered against an overall lifetime risk of cancer from all causes of approximately 40%, the low additional risk incurred over the follow-up period is likely to be acceptable to most, however must be taken into account and discussed with every patient to whom imaging surveillance is offered.

Conclusion

In our view, there is a need for a new consensus on the imaging surveillance of high-risk cutaneous melanoma. This consensus should be informed by the best available evidence, which ideally would come from a randomized trial

comparing more versus less intensive follow-up regimes. We would support this, but also think that carrying out such a trial would be challenging at present for a number of reasons, including the potential reluctance of patients to undergo randomization, the difficulty in defining end points and the risk that the rapidly shifting therapeutic landscape in melanoma could render the results uninterpretable by the time of reporting. Ultimately, however, in order to achieve the best from the currently available drugs for the treatment of advanced melanoma, we do not think it is justified to wait any longer before we change how we follow-up on high-risk patients.

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