Dermatology Practical & Conceptual

Melanoma Over-diagnosis: Historical Perspective and the Path Forward

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Themes emerging from the two opinion pieces regarding melanoma over-diagnosis (MO) include: melanoma in situ (MMIS) is the main problem, technology will mitigate the problem, and harms of MO are trivial compared to its resulting overtreatment.

To understand MO requires a historical perspective. Armed with evidence-based knowledge acquired in the 1970s showing that melanoma prognosis hinged primarily on tumor thickness, combined with the prevailing belief that primary cutaneous melanoma, if left untreated, would steadily grow until it metastasizes and kills the patient, heralded efforts aimed at early detection [1]. Then in the 1980s Doctor Ackerman promoted the concept that the earliest form of melanoma is when the 'malignancy' is confined to the epidermis [2]. In his editorial, 'No one should die of malignant melanoma', he implored all physicians to learn the morphologic features of flat (in situ) melanomas [2]. The intersection of evidence-based data, belief systems and influential physicians created the prevailing acceptance among clinicians, researchers, and epidemiologists that surveillance ought to save lives. And thus, the journey to detect melanoma as early as possible began. Investigations into the morphologic features of early melanoma gave rise to the ABCD mnemonic and the concept of the 'ugly duckling sign" [3,4]. The realization that biology of lesions is a sensitive indicator of melanoma heralded the importance placed on identifying change [5]. Technological advances including the ability to obtain baseline clinical images to assist in more objectively identify change led to use of baseline total body photographs [6]. Introduction of dermoscopy further enhanced our ability to identify otherwise difficult to detect melanomas including amelanotic and small diameter melanomas [7]. Today we have ever more sophisticated technology directed towards early melanoma detection including RCM, in vivo gene expression profiling, and artificial intelligence. I agree with the authors of the opinion pieces that technology, if used appropriately, will reduce unnecessary biopsies of nevi. However, any technology designed to detect melanoma cannot possibly reduce MO, as suggested by the authors.

The aforementioned efforts have delivered on the request of finding early melanoma, including MMIS. The presence of countless studies published over the past five decades now permits us to apply our 'retrospect-oscope' and realize that major flaws existed in our belief system. We are now aware

that some melanomas can grow very slowly, that factors other than tumor thickness impact prognosis, that MMIS may not be the monster we imagined it to be [8-10]. Given all the newly acquired insights it should not be surprising that both MMIS and invasive melanoma are prone to over-diagnosis [11]. However, as stated by Olsen and Whiteman we are living a 'tale of two epidemics'; one of potentially aggressive melanoma and another of indolent melanoma and perhaps even 'melanomas' that are not cancer in the first place [12,13]. Within the indolent group, MMIS appears to be the lowest hanging fruit that can be studied with respect to MO, as alluded to by the authors of the two opinion pieces. However, this should not be extrapolated to suggest that invasive MO is not a problem worthy of attention [14]. Furthermore, it should be underscored that over-diagnosis and overtreatment are two separate issues. The treatment of melanoma (based on our definition of what constitutes melanoma as a cancer) is dictated by trial outcomes. For example, invasive melanomas of yesteryear were over-treated by today standards with excision margins of 5 cm and elective lymph node dissection. It will require us to accurately define what lesions constitute a cancer of melanocytes based on their actual biology, to better understand the growth dynamics of 'indolent' melanoma and designing therapeutic trials to investigate alternative management approaches for lentigo maligna and thin invasive melanomas.

A point worth mentioning is that the harms from MO should never be trivialized. However, we should also not lose sight of the fact that lives have been saved because of our efforts directed towards early detection [15]. This raises the question of melanoma screening. Current epidemiological data does not support population-based melanoma screening, but individual patients at high risk for melanoma including those with multiple large nevi, CDKN2A mutations, BAP1 mutations, among others will likely derive benefits from screening programs.

So what are we to do? We must continue to strive to improve upon the current situation. We need to determine if MMIS is really a cancer, we need to investigate the features of MMIS that predict progression to bona fide invasive melanoma, we need to establish the clinical, histological, and molecular features that accurately differentiates indolent from aggressive disease. In addition, we need to improve on in vivo methods to increase not only sensitivity for melanoma detection but more importantly specificity. Until we have a method akin to the Gleason scoring system for prostate cancer, we have no choice but to address lesions that look like melanoma on our patient's skin and have no choice but to treat lesions diagnosed as melanoma. And on this we all agree.

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