Dermatology Practical & Conceptual

Overdiagnosis of Melanoma: Is It a Real Problem?

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"The best physician is also a philosopher"
Claudius Galen

Is Melanoma Over-diagnosis a Reality?

Overdiagnosis in cancer is the correct diagnosis of a cancer that, if left untreated, would never cause symptoms or morbidity. Over-diagnosis is caused by both over-detection (i.e. screening) and overdefinition (ie expanding disease definitions of diagnostic tests) [1]. The sine qua non requisite for establishing over-diagnosis of a cancer is a disproportionate increase in incidence without an accompanying increase in mortality (Figure 1).

All these conditions are met in the case of melanoma and explain to some extent the tremendous increase in incidence [2,3]: Evidence suggests that many melanomas grow slowly and might remain intraepidermal for a long period [4]. One of the most frequent subtypes, lentigo maligna (LM), might remain in the epidermis for several years or even decades, with only a small proportion (< 5%) evolving into invasive melanoma, making it an ideal paradigm of overdiagnosis [5,6]. Additionally, in last decades, early melanoma detection is considered a supreme task by healthcare systems worldwide and numerous efforts to increase screening and public awareness have been applied [7,8]. Furthermore, diagnostic tools evolved to allow earlier melanoma recognition. Dermatoscopy played a major role in changing practice, since the dermatoscope is a hand-held device available at any setting [9]. Finally, because of a diagnostic shift in the histopathologic diagnosis, tumors that were previously labelled as non-melanoma (i.e. 'dysplastic' nevi) are now classified as melanoma, usually in situ [3]. The latter is highlighted by the disproportionate incidence increase of melanoma in situ as compared to invasive melanoma [2].

Melanoma Over-diagnosis Exists. So What?

Considering all the above, there is little doubt that over-diagnosis of melanoma exists. In addition to causing an epidemiological artifact, over-diagnosis induces a vicious cycle of increased awareness, more screening, more biopsies and more over-diagnosis with significant impact on health

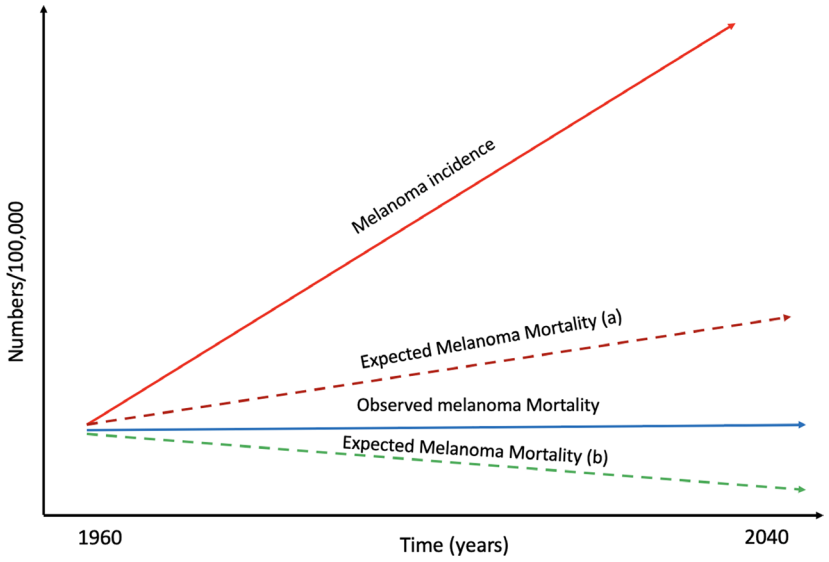

Figure 1. Evolution of melanoma incidence (red line) and melanoma mortality (blue line). Mortality has remained stable as incidence dramatically increases, characteristic of over-diagnosis. If there is a relevant increase in melanoma incidence, one should expect an accompanying increase in melanoma mortality (a, red dashed line). Should screening programs be effective, one should expect a decrease in mortality (b, green dashed line).

and insurance sources and possibly unneeded emotional stress [3]. Although these parameters should not be underestimated, the most relevant question is whether over-diagnosis has a negative impact on patients' health and if we should modify our clinical practice to address it.

The vast majority of the so-called 'over-diagnosed melanomas' are intra-epidermal or minimally invasive lesions and their definitive treatment usually implies a wide local excision with 5-10 mm margins, which usually translates into a small scar and almost zero morbidity [10]. Subsequently, these patients usually enter a prospective surveillance that allows an early detection of subsequent melanomas and other skin cancers that develop in a considerable proportion [11]. Overall, overdiagnosis does not cause any significant medical harm to the individual patients, probably the opposite.

Over-diagnosis or Over-treatment?

Let's go back to the "paradigm" of over-diagnosis, LM. LM typically arises on sensitive areas and any surgical treatment might cause aesthetic or functional concerns [12]. Additionally, LM tends to extend subclinically, which explains the increased recurrence rates when 5-mm margins are used [13]. For this reason, melanoma guidelines recommend wider margins or, ideally, staged excisions with margin control, that usually have significant requirements in time and costs [14]. All this for a tumor that has very low chance to invade the dermis even if left untreated [5]. To our understanding, the real problem results not from the 'early diagnosis' of LM, but from the exaggerated treatment for a tumor that is minimally aggressive. Recent data suggest that conservative surgery followed by adjuvant imiquimod allows for excellent cure rates, akin margin-controlled excisions, offering an example of how the problem of "over-diagnosis", which in fact is a problem of "over-treatment", could be partially addressed [15]. Similar considerations could be made for non-melanoma skin cancers, which although usually not biologically aggressive, are often treated with sophisticated and costly surgery [16].

Can We Do Something Else to Address Over-diagnosis?

Although not causing significant harm to the individual patients, the negative economic and emotional effects of over-diagnosis justify some efforts to address it, provided of course that these efforts will not put patient outcomes at risk. In the last decades, total body photography (TBP) and sequential digital dermatoscopy (SDD) are increasingly used [17]. In contrast to static examinations, these techniques provide information on the biologic dynamic of lesions, improve the sensitivity for melanoma diagnosis and reduce the number of excisions by revealing the biologic stability of lesions that might have been considered as suspicious at baseline [18]. A wider use of TBP and SDD might help to minimize over-diagnosis, but is limited by the significant requirement in time and expertise. Therefore, the use of these techniques is limited to individuals at very high risk, which restricts their impact [17]. The new generation of 2D TBP and the development of 3D TBP offer a fast documentation of the total skin surface at an unprecedented quality, and the addition of artificial intelligence (AI) has the potential

to improve the diagnostic accuracy of clinicians. This new era might allow a wider application of TPB and maximize its impact [19].

Other solutions proposed to address over-diagnosis are to downgrade the histopathologic terminology and increase the threshold for biopsy/excision of suspicious lesions.[3] Although re-labelling some in situ melanomas into terms like 'atypical melanocytic proliferations' would not solve the uncertainty on their biologic potential, it would indeed decrease the recorded melanoma incidence without causing significant harm, since they would have been excised anyway [20]. In contrast, the recommendation to return to an era when clinical diameter was used as a criterion to excise a lesion or not, is highly problematic in terms of medical ethics, since evidence suggests that melanomas < 6mm in diameter can already be invasive [3,21].

Although the aforementioned and other efforts may partially address over-diagnosis, a definitive solution is not feasible until the diagnostic gold standard procedure becomes more efficient [22]. Currently, the diagnostic gold standard for melanoma is histopathology, a purely morphological, subjective and static assessment that does not take into account the biologic course [22,23]. Ideally, melanoma diagnosis should involve a dynamic assessment of biology that would aim to spot those lesions with potential to invade the dermis, grow significantly and/or metastasize [23]. In the future, molecular or other tests, alone or combined with histopathology, possibly with the aid of AI, may improve baseline predictions on which melanomas will ultimately disseminate and threaten patients lives. Until then, histopathology remains our most effective method, but with significant limitations [22,23]. These limitations dictate that every melanoma is considered a potentially life-threatening tumor and explain the applied management at an individual basis.

Diagnostic and therapeutic medical care is not applied at a population, but at an individual basis; it is well stated that "we treat humans, not numbers". Therefore, the above discussion on epidemiology of melanoma and over-diagnosis has little value when it comes to medical decision-making for an individual patient. We believe that no clinician (and no patient) would ever take the risk not to excise a suspicious lesion just because of the epidemiologic problem of over-diagnosis, as long as available science and technology are insufficient to predict the biologic course of every single tumor.

Conclusions

In conclusion, over-diagnosis of melanoma is a fact explained mainly by our limited ability to predict the biologic course of melanoma. It has negative economic and emotional effects that justify some efforts to address it. The increased use of TBP and SSD and the re-consideration of treatment recommendations for minimally aggressive tumors seem reasonable for now, until more accurate tools to predict the biologic potential of individual tumors emerge.

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