Dermatology Practical & Conceptual

Biologic Gray Zone of Melanocytic Tumors, Fiction or Reality?

Harald Kittler[1]

1 Department of Dermatology, Medical University of Vienna, Vienna, Austria

Citation: Kittler H. Biologic Gray Zone of Melanocytic Tumors, Fiction or Reality? *Dermatol Pract Concept.* 2024;14(2):e2024148. DOI: https://doi.org/10.5826/dpc.1402a148

Accepted: March 12, 2024; **Published:** April 2024

Funding: None.

Competing Interests: None.

Corresponding Author: Harald Kittler, Department of Dermatology, Medical University of Vienna, Vienna, Austria.
E-mail: harald.kittler@meduniwien.ac.at

The so-called "gray zone", where the distinction between nevi and melanoma becomes blurred, continues to be the source of heated debates. Whether we like it or not, the "gray zone" is a reality due to the inherent complexity of melanoma biology and the limitations of our diagnostic methods. However, the concept of a "gray zone" can also be seen as fictional, as it leads to contradictory conjectures about the biological outcome of a specific melanocytic lesion. A lesion cannot be both benign and malignant simultaneously; one of these two assertions must be wrong. In practice, uncertain diagnoses present a challenge, as both doctors and patients seek definitive diagnoses and want solid treatment decisions. This quest for certainty is undermined by ambiguous terms such as "dysplastic nevus", "melanocytic tumor with uncertain malignant potential" or, more recently, "melanocytoma". These terms have the characteristic of eluding a precise definition and becoming loaded with all kinds of meaning, often leading to confusion. It is also unclear if these terms reflect biologic uncertainty ("the lesion does not know what it is") or diagnostic uncertainty ("the pathologist does not know what it is").

The idea of an intermediate biological state between nevus and melanoma is rooted in the broader concept of stepwise tumor progression, which in turn is based on the theory of evolution. It suggests a gradual transformation from benign to malignant states, reflecting a process of malignant transformation by accumulating oncogenic mutations and adaptation to the environment by selection. Early studies on melanoma, such as those by Ackerman in the late 1940s, introduced the idea that melanoma originates from preexisting nevi [1]. This was further supported by Allen and Spitz in 1953, who posited that all melanomas begin in a preexisting mole, particularly in an "active junctional nevus" [2]. These foundational beliefs have influenced melanoma diagnosis and management for decades. The introduction of the "dysplastic nevus" concept in the mid-1970s added complexity to this narrative. "Dysplastic nevi", characterized by architectural disorder and cytologic atypia, were proposed as intermediates in the transformation from nevi to melanoma [3]. From the start, this concept has been a source of debate, primarily due to the challenges in reproducibly identifying "dysplastic" features and assessing their true risk of progression to melanoma.

To enhance its utility in clinical practice and provide a clear target for intervention, the concept of the biological "gray zone" underscores the importance of identifying a specific lesion that embodies this gray zone. The "dysplastic nevus" offers a tangible example of this concept. However, the

stepwise tumor progression model, although supported by extensive research within and beyond melanocytic biology, does not always align with a clinically visible "intermediate" or "precursor" lesion. Sometimes, a clear precursor or intermediate lesion is absent, as for example in basal cell carcinoma (BCC). The lack of ambiguity in diagnosing BCC could be attributed to its distinct microscopic appearance, which facilitates straightforward identification, bypassing the need for the identification of intermediate, ambiguous stages. In the case of BCC, the absence of a diagnostic gray zone prevents speculation about a biological gray zone. This stands in stark contrast to the ambiguity encountered in diagnosing melanocytic proliferations.

The World Health Organization's (WHO) latest classification of melanocytic tumors acknowledges the complexity of classifying melanocytic proliferations into purely benign or malignant categories [4]. The new classification incorporates traditional histogenetic patterns, molecular alterations, and UV exposure within a pathway model that delineates nine distinct pathways. Each pathway traces the progression from benign precursor lesions to intermediate stages and, ultimately, to melanoma. The WHO classification concedes that, for some pathways, clear precursor or intermediate lesions remain unidentified, leaving open the possibility that such stages might not exist and could be fictional rather than real. The updated WHO classification also attempts to better define the concept of the intermediate lesion, introducing the term "melanocytoma" for this purpose. Examples include BAP1-inactivated melanocytoma, pigmented epithelioid melanocytoma, and Spitz melanocytoma. According to the WHO classification, these tumors are characterized by harboring more than one oncogenic mutation. Whether these tumors truly represent intermediate lesions, as suggested by the pathway concept, or are akin to the "dysplastic nevus"—essentially nevi with specific morphological features and a more complex array of somatic mutations that generally do not progress to melanoma—remains a matter of debate. My inclination is to support the latter interpretation.

Although there is the hope that molecular techniques will eliminate diagnostic grey zones, it is important to recognize that edge cases will persist. They may become less frequent but will not vanish entirely. Techniques like immunohistochemistry, in situ hybridization, and comparative genomic hybridization may offer crucial insights for "borderline" lesions. Yet, as most dermatopathologists know, usually these tools do not fully solve ambiguous cases. Even with cutting-edge methods like whole-genome sequencing, eradicating gray zones may remain unattainable. The unpredictable nature and individual variability of biological systems ensure that some level of uncertainty persists. Diagnoses are, in essence, conjectures. Biological processes, though seemingly deterministic, are influenced by chaotic elements. This concept, echoing chaos theory, suggests that minor differences in initial conditions—spanning from the specific set of somatic mutations to the microenvironment and the individual immune status—can significantly impact outcomes. In this sense, biology shares similarities with meteorology: making a diagnosis is more akin to forecasting the weather than to reading a clock.

In the context of medical diagnostics and treatment, the advent of Artificial Intelligence (AI), especially multimodal AI, holds the promise of significantly reducing the various diagnostic and biologic gray zones discussed so far. Multimodal AI, by integrating data from diverse sources such as imaging, genetic information, and electronic health records could offer a more nuanced and comprehensive understanding of cancer biology [5]. This integration could lead to more accurate diagnoses of melanocytic proliferations and vanishing gray zones. However, it is crucial to recognize that AI, regardless of its sophistication, cannot eliminate all forms of uncertainty. Even with technological advancements, the individual preferences of dermatologists and patients regarding the trade-off between sensitivity and specificity will continue to exist [6]. These preferences shape decision-making and treatment approaches, underscoring the importance of personalized care.

Ambiguity in diagnosis of melanocytic proliferations is an inescapable reality. Some of this ambiguity is a product of human interpretation, while the rest is deeply embedded in the complex biology of melanocytic tumors. Grey zones can be a source of anxiety, lead to delayed treatment, and, at times, result in unnecessary procedures. Therefore, navigating these uncertain waters with as much precision and clarity as possible is crucial. For us clinicians it is important to distinguishing between different types of gray zones. We should be aware that pathology reports may obscure diagnostic uncertainty with language that implies biological uncertainty instead. Recognizing these distinctions is vital for healthcare professionals in managing and communicating about "borderline" lesions. Finally, there is a silver lining: "Gray zones" also open up opportunities; they challenge us to refine our diagnostic methods and question our concepts and definitions. Furthermore, their existence reminds us as researchers that science never ends and forces us as clinicians to develop appropriate strategies in the face of uncertainty.

References

1. Ackerman LV. Malignant melanoma of the skin; clinical and pathologic analysis of 75 cases. *Am J Clin Pathol*. 1948;18: 602–624.
2. Allen AC, Spitz S. Malignant melanoma; a clinicopathological analysis of the criteria for diagnosis and prognosis. *Cancer*. 1953;6: 1–45.
3. Elder DE, Green MH, Guerry D 4th, Kraemer KH, Clark WH Jr. The dysplastic nevus syndrome: our definition. *Am J Dermatopathol*. 1982 Oct;4(5):455–60.
4. Ho J, Collie CJ. What's new in dermatopathology 2023: WHO 5th edition updates. J Pathol Transl Med. 2023 Nov;57(6):337–340.
5. Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical AI. *Nat Med*. 2022 Sep;28(9):1773–1784
6. Barata C, Rotemberg V, Codella NCF, et al. A reinforcement learning model for AI-based decision support in skin cancer. *Nat Med*. 2023 Aug;29(8):1941–1946.