A Holistic Approach to Firearm Legislation Is Needed

In reply to de Jager and colleagues

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We would like to thank de Jager and colleagues for their thoughtful commentary regarding our paper, "Wounding patterns based on firearm type in civilian public mass shootings in the United States."[1] The authors based their argument mostly on their own study, which examined FBI records of civilian public mass shootings (CPMS) to determine case-fatality ratio based on weapon type. However, that study grouped all events that involved multiple firearms in which 1 firearm was an assault weapon into the same group. The authors were not able to trace a particular gunshot wound to the actual weapon used to create it. This was the case in 65% of events. The authors commented that this is a limitation of the study and they also believed that another limitation of the study is their inability to account for specific injuries. Our study addressed both of these concerns (Table 1, Fig. 1).[1] By doing so, we were able to estimate the potentially preventable death rate as well and cross-reference that with the type of firearm used.

De Jager and colleagues also commented that our results are not congruent with past research on this topic. They quoted a study from 1992 by Coble and associates[2] that found that semiautomatic rifles are designed to accept high capacity magazines and fire high velocity bullets. We agree with the authors on this point, but more recent studies consistently report that handguns are now equipped with high capacity magazines and fire higher caliber missiles.[3-6] As such, Coble's findings from 1992 are not applicable in 2019. This is most likely the basis for Manley and colleagues' conclusion that "…any type of firearm can result in significant clinical injury and death, regardless of caliber or velocity designation."[3] It is also the basis for our call for "a holistic approach to gun legislation that addresses all types of firearms…"[1] as a means to make a significant impact on the probability of death after civilian public mass shooting events. Concentrating on assault rifles at the expense of minimizing the risk of death associated with handguns, magazines, and ballistics is not supported by the preponderance of evidence on this topic. As such, we stand by the conclusions of our study and join de Jager and colleagues in their original call for a centralized database from which we can study all aspects of firearm-related injury.

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Histogenetic Guidelines to Perform Sentinel Lymph Node Biopsy in T1b Melanomas of the 8th Edition American Joint Committee on Cancer

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In comparison with the 7th Edition, the 8th Edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma no longer considers the mitotic count in the a or b T1 categorization, but it adopts a sub-stratification based on Breslow depth: T1a $\leq$ 0.8 mm without ulceration and T1b $\leq$ 0.8 mm with ulceration or 0.8 to 1 mm with or without ulceration. Skin melanoma can be subdivided by Breslow depth into thin melanoma ($\leq$1 mm) or thick melanoma (>1 mm). According to the AJCC 8th Edition, a and b specifications are assigned based on ulceration and depth, which replace the mitotic count for square millimeter. From this assumption, an interesting question formulated by the authors appears very relevant[1]: should sentinel lymph node biopsy (SLNB) be performed for all T1b melanomas of the new AJCC 8th Edition?

According to our experience, the answer to this question lies in the histogenetic model of melanoma progression. In fact, at the onset, melanoma is characterized by a nontumorigenic radial growth phase (RGP), inside the epidermis

(intraepidermal) or within the papillary dermis (microinvasive), devoid of metastatic potential. This may be followed, early or late, by a tumorigenic vertical growth phase (VGP), with deeper extension into the dermis or beyond, nodular confluence, mitotic activity, and metastatic competence.[2-4] The only exception to this scenario is represented by nodular melanoma, in which either the RGP is rapidly over-run by the VGP, or the tumor arises directly from dermal melanocytes.[5] Today, Breslow depth remains the most important prognostic factor for clinically localized primary melanomas, allowing us to distinguish them as ultra-thin ($\leq$ 0.5 mm), thin ($\leq$ 1 mm), thick ($>$ 1 mm), or ultra-thick ($>$ 6 mm).[6,7] A systematic application of the histogenetic model to the Breslow depth permits an explanation of the debated issue of why some thin melanomas behave aggressively—because they possess an early tumorigenic VGP inside them.[8,9]

We believe that a renewed histogenetic approach to melanoma diagnosis deserves wide scientific dissemination, for a better stratification and clinical management of individual cases. The nontumorigenic RGP encompasses the intraepidermal lesions, namely, lentigo maligna and in situ melanoma, and the microinvasive forms (T1), ie ultra-thin melanoma and the vast majority of thin melanomas. Only a small quota of T1 melanomas, burdened by an aggressive biological behavior, show an early tumorigenic VGP; on the contrary, a late tumorigenic vertical growth phase is constantly present in all T2-T3-T4. In this regard, the terms *personalized medicine* or *stratified medicine* have just been introduced to describe the concept of a modern medicine ad personam, focused on decisions, practices, and interventions tailored to the single patient, and based on the calculation of individual risk for disease progression. To meet these demands, sentinel lymph node biopsy should be performed in all T1b melanomas of the AJCC 8th Edition, burdened by an early tumorigenic VGP inside them.

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Vertical Growth Phase and Sentinel Lymph Node Metastases

In reply to Roncati and Piscioli

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We appreciate the interest that Roncati and Piscioli showed in our recent publication, in which we evaluated the risk of sentinel lymph node (SLN) metastases in nonulcerated, T1b melanoma by the new 8th edition American Joint Committee on Cancer (AJCC) staging criteria.[1] The authors propose a model of melanoma progression based on the transition from a radial growth phase to a vertical growth phase (VGP) that can predict biologic aggressiveness and propensity to metastasize.

Based on their suggestions and on behalf of our coauthors, we reviewed the data available in the National Cancer Database (NCDB) with regard to growth phase. In the 6,894-patient cohort with T1b melanoma by AJCC 8th edition criteria alone (0.75 to 1.04 mm, nonulcerated), nearly 74% (5,087) had information regarding the presence or absence of a VGP; in 54% of patients, a VGP was present. The rate of a positive SLN biopsy was different between those with a VGP (6.4%) and those without a VGP (3.7%), for an unadjusted odds ratio of risk of SLN metastases of 1.78 (95% CI 1.37 to 2.32). In an adjusted multivariate model, adjusting for age, sex, thickness, and mitotic rate, presence of a VGP was an independent risk factor for a positive SLN biopsy (adjusted odds ratio 1.62, 95% CI 1.24 to 2.12); the other risk factors presented in our published model remained significant. This new model, with the additional VGP parameter, did not increase the predictive ability of