(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

the previous model (areas under the curve [AUCs] were not statistically different).

These findings are intriguing and likely warrant further investigation, either with registry data or multicenter collaboratives. The reliability of the VGP designation in the NCDB data needs to be better understood. Importantly, the absence of VGP did not predict a completely indolent melanoma, as the risk of SLN metastases in this cohort was nearly 4%. We again appreciate the comments of Roncati and Piscioli and hope this commentary inspires additional study in the peer-reviewed literature on the utility of VGP in predicting SLN metastases in thin melanoma.

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Reluctance to Operate on Pregnant Women

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The reluctance to operate on pregnant women is not new and is based on limited and flawed data.[1] We fear that the conclusions advanced in the recent publication by Fong and colleagues[2] may serve as unjustified support for such delay in surgery, exposing pregnant women to complications.

Our group recently reviewed the available literature on maternal and neonatal outcomes of nonobstetric surgery during pregnancy.[1] Indeed, the most feared complication of surgery in the third trimester of pregnancy is preterm delivery. However, data to support a cause and effect relationship of surgery and preterm delivery are nonexistent. Many studies, including the study by Fong and colleagues,[2] are confounded by the effects of the disease process itself. Pregnant women with an infectious or inflammatory intra-abdominal process would be expected to experience a higher rate of preterm delivery than pregnant women without such a process. Moreover, it is difficult to distinguish the physiologic and inflammatory effects of the disease process itself from the effects of surgery.

In the study by Fong and associates,[2] a comparison of the indication for cholecystectomy (ie symptomatic cholelithiasis, acute cholecystitis, gallstone pancreatitis, etc) between the groups should have been provided. It is possible that women with delayed surgery had a less acute or noninfectious process; an infectious and proinflammatory process (not the surgery) may have led to preterm delivery in the antepartum cholecystectomy group.

A recently published study evaluating pregnant women with acute biliary pancreatitis showed a lower rate of ERCP and cholecystectomy in pregnant women, as compared with nonpregnant women, and a higher risk of 30-day readmission for pregnant women.[3] This study exemplifies the potential dangers of delayed care resulting from the reluctance to appropriately treat pregnant women.

Finally, we are puzzled by the finding that eclampsia, a disease with a pathogenic basis on placental hypoperfusion and endothelial dysfunction, would be less common in women who have a gallbladder. This spurious observation highlights the inherent problems encountered when attempting to extract clinical information from administrative datasets, and casts doubt on the reliability of other conclusions in this study.

We applaud the authors on the large sample size of women undergoing a single type of abdominal surgery, but the study design limits the applicability of the results and cannot definitively answer the question of immediate vs delayed operation for women with such disease processes during pregnancy. In the absence of randomized data, and the knowledge that such a study is extremely unlikely, the decision to operate in pregnancy should continue to be individualized, with input from an experienced surgeon and an obstetrician or maternal-fetal medicine subspecialist.

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