Is Pregnancy-Associated Melanoma Associated with Adverse Outcomes?

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BACKGROUND: Melanoma is the most common malignancy encountered during pregnancy. Conflicting data have led to ongoing confusion regarding pregnancy-associated melanoma (PAM) in the media and among the public. The objective of this study was to better characterize both the clinical presentation of PAM and its prognostic implications.

STUDY DESIGN: Female patients of reproductive age, with stage 0 to IV cutaneous melanoma, were identified from our prospectively maintained database. Clinical and histopathologic factors were analyzed with appropriate statistical methods. Univariable and then multivariable analysis were used on matched data to compare disease-free survival (DFS), overall survival (OS), and melanoma-specific survival (MSS) for stage 0−III PAMs vs non-PAMs. Kaplan-Meier survival curves were then plotted for OS and MSS and compared using the log-rank test.

RESULTS: The clinical presentation of melanoma was similar for PAM and non-PAM patients. There was no significant difference in recurrence between the 2 groups; for PAM patients, 38.5% of patients had recurrence, as compared with 36.6% of non-PAM patients ($p = 0.641$). For PAM patients, median follow-up was 14.6 years (range 0 to 42.6 years) and 11.1 years (0 to 48.5 years) for the non-PAM patients. No significant differences in DFS, MSS, or OS were identified on univariable or multivariable analysis for PAM vs non-PAM patients in stage 0/I/II and stage III cutaneous melanoma, respectively ($p = 0.880$ DFS, $p = 0.219$ OS, and $p = 0.670$ MSS).

CONCLUSIONS: We observed no difference in DFS, OS, or MSS between the 2 groups. Pregnant patients should be screened for melanoma in a similar manner to nonpregnant patients and should be counseled that their survival is not adversely affected by their pregnancy. (J Am Coll Surg 2017;225:149−158. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Melanoma is the most common malignancy encountered during pregnancy, accounting for 31% of all malignancies in the intrapartum period.[1,2] For many years, pregnancy has been thought to have an adverse effect on the course of melanoma. Reports beginning in the 1950s suggested that pregnancy increased the risk of melanoma development, metastasis, and recurrence.[3-6] Since then, many hypotheses have been formulated, linking worsened outcomes to hyperpigmentation, relative immunosuppression, and hormone binding of melanocytes.[7-10] Given the overall increase in melanoma incidence in women of childbearing age in the US, this topic has become even more pertinent.[11,12] Editorials, systemic reviews, and media coverage of PAM persist, but fail to draw definitive conclusions despite many years of attention and underpowered studies.[13-21] Many of the adequately powered studies that do exist come from large, non-US based registries, with a resultant lack of granular detail and reliability.[22-25] The primary objective of this study was to query our large, single-institution melanoma database to

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Abbreviations and Acronyms
DFS = disease-free survival
HR = hazard ratio
MSS = melanoma-specific survival
OS = overall survival
PAM = pregnancy-associated melanoma

better characterize PAM, with particular attention to overall survival (OS) and melanoma-specific survival (MSS). Secondarily, we examined other clinical factors with regard to melanoma mortality, such as parity and gravidity, in addition to known prognostic factors such as age, stage, histologic type, Breslow thickness, and ulceration.

METHODS

Female patients of reproductive age (18 to 50 years), with American Joint Committee on Cancer (AJCC) stage 0 to IV cutaneous melanoma, were identified from the prospectively maintained John Wayne Cancer Institute melanoma database, between January 1971 and May 2016. All patient data were deidentified, and this study was independently confirmed to be exempt from Institutional Review Board review. Melanomas were staged by seventh edition AJCC criteria.[26-28] In order to ensure adequate staging, patients without lymph node staging for melanomas with Breslow thickness $\geq$ 0.75 mm were excluded from analysis (n = 540 non-PAM, n = 43 PAM). Pregnancy-associated melanoma is a field derived either from patient questionnaire responses (self reported) or direct physician queries (physician reported). The John Wayne Cancer Institute melanoma database defines PAMs by an affirmative response to, "Did melanoma develop during pregnancy?" This includes cases that developed de novo during pregnancy or melanomas that arose from pre-existing lesions that changed during pregnancy. We cannot exclude the possibility that some of these lesions were identified incidentally during prenatal visits. Laboratory pregnancy confirmation is incomplete in this dataset because patients receiving office-based excisions would not have routinely received urine or serum pregnancy evaluations. For this reason, we are not able to comment on the women who were deemed pregnant based on preoperative beta human chorionic gonadotropin alone. Clinical and histopathologic factors were examined between PAM and non-PAM groups, and *t*-test was used to analyze age at diagnosis, parity, gravidity, and Breslow thickness. The chi-square test was used for Clark level, anatomic site, ulceration, sentinel lymph node examination status, recurrence status, type of first recurrence, stage at diagnosis, and stage first seen at John Wayne Cancer Institute. A 1:1 matched pair sample was then created using pairs of PAM and non-PAM patients who were matched for Breslow thickness, age, stage, and ulceration status. With respect to age, we matched using the following categories: <25, 25 to <35, $\geq$35 years old. With respect to Breslow thickness, we matched for categories: $\leq$0.75, 0.75 to <2.00, 2.00 to $\leq$4.00, >4.00 mm and unknown. For stage at diagnosis, we matched using categories 0, I/II, and III. Finally, for ulceration, we matched using categories: yes, no, and unknown. Univariable and then multivariable analyses were conducted with the matched data to analyze DFS, OS, and MSS for patients with stage 0/I/II and stage III cutaneous melanoma at diagnosis. Due to the paucity of PAM patients with stage IV disease at diagnosis (n = 1), those patients were excluded from this analysis. Kaplan-Meier survival curves were then plotted for OS and MSS and compared using the log-rank test; SAS software, version 9.3 (SAS Institute) was used for all analyses. A 2-sided p value $\leq$ 0.05 was considered to indicate statistical significance.

RESULTS

Of the entire patient cohort (n = 2,025), 156 women (7.7%) with PAM were identified after selection criteria were applied. No cases of transplacental transfer of melanoma were identified. Clinical presentation of melanoma was similar for PAM and non-PAM patients, with no significant differences in Breslow thickness (1.30 mm vs 1.34 mm; p = 0.737), histologic type, or primary tumor site (Table 1). Age was greater in the non-PAM patients (36.8 vs 31.7 years; p < 0.001). There was also no significant difference in stage at diagnosis (Table 1). Parity was significantly increased in the PAM group (p = 0.010), as was gravidity (p < 0.001). At 10 years, disease-free survivals were 65.7% and 62.3% for the non-PAM and PAM groups, respectively (p = 0.8934). Mean disease-free survivals were also similar: 24.48 years in the non-PAM group and 20.65 years in the PAM group.

Matched pair sample

In an attempt to decrease potential biases associated with delay in diagnosis of PAMs, we created a matched pair sample. Each PAM patient was matched with a non-PAM patient by Breslow thickness, age, stage, and ulceration status. In this group of 310 patients (155 matched pairs), PAM patients had a median follow-up of 14.6 years (range 0 to 42.6 years), and non-PAM patients had a median follow-up of 11.1 years (range 0 to 48.5