Malignant Melanoma Arising During Pregnancy

A Study of 100 Patients

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Melanoma is often diagnosed in young adults, a significant proportion of whom are women of child-bearing age. The prognosis of women diagnosed with melanoma during a pregnancy continues to be debated. One hundred patients, ages 19 to 40 years, have been identified who were pregnant at the time of diagnosis of their melanoma. All were treated with local excision. Sixteen per cent underwent elective lymph node dissections. Immunotherapy was administered to 83% of patients. Mean follow-up was 6.8 years from the date of diagnosis. The patients were compared to an age-matched group of 86 women who were not pregnant at the time of diagnosis. Overall mortality during the follow-up period was 25% in the pregnant group and 23% in the control group. Among the pregnant group, there was an increased incidence of lymph node metastases during the follow-up period (39% *versus* 26%, p = 0.053). Among stage I patients, there was a significantly shorter DFI for the pregnant group (p = 0.039), with 50% of pregnant patients and 67% of control patients free of disease at 10 years. Similarly, among stage 1 patients, the time to development of lymph node metastases was shorter in the pregnant group (p = 0.021). Multivariate analysis demonstrated that pregnancy at diagnosis was significantly associated with the development of metastatic disease (p = 0.008), when controlling for tumor site, thickness, and Clark level. Patients who developed melanoma during pregnancy did not, however, have a significant decrease in survival.

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IN 1951, PACK[1] reported the unfavorable outcome of 10 patients diagnosed with melanoma during pregnancy. Since that time there have been many reports of the effects of pregnancy on the prognosis of melanoma. Shiu[2] reported decreased survival associated with pregnancy among patients with stage 2 melanoma. Sutherland[3] discussed the interaction of female hormones and melanoma and reported 67% mortality of 15 patients with stage 1 disease and of 3 patients with stage 2 disease. Reintgen et al.[4] reported that patients diagnosed during pregnancy had a significantly decreased disease-free interval (DFI) compared to the controls.

Others have failed to show a prognostic effect or association with pregnancy. Haughton et al.[5] showed no effect on survival when stage of disease and primary site were controlled. Ten of eleven recent studies on this subject failed to show a survival difference in pregnant patients compared to controls.[6]

A recent series was reported by Trapeznikov,[7] in which 102 cases of melanoma arising during pregnancy were compared to 599 nonpregnant women of child-bearing age. There was a significantly lower 10-year survival rate in the pregnant patients.

Despite disparate experiences with melanoma arising during pregnancy, however, there is general agreement that the development of melanoma subsequent to a completed pregnancy does not affect outcome.[2-4,8-10]

The purpose of the present study is to update our institution's experience with melanoma arising during pregnancy and to characterize further the distinguishing features of these patients. Five years have elapsed since the previous report on 58 patients. This interval has been associated with an increase in the number of patients available for study and in the length of follow-up. Specific goals of the study are to determine whether the previously reported difference in DFI has persisted and whether longer follow-up will show a similar difference in survival rates. Differences in the presentation and clinical course are also evaluated to understand better the characteristics of this group of patients.

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Materials and Methods

More than 7000 patients with melanoma have been evaluated in the Melanoma Clinic at one institution. Within this group, a subset of 100 patients have been identified as being pregnant at the time of diagnosis of their melanoma. These patients ranged in age from 19 to 40 years. A matched group of female patients aged 19 to 40 who were not pregnant at the time of diagnosis were selected. This control group contained 86 patients.

The clinical characteristics of these two groups are listed in Table 1. Mean follow-up has been 6 years since diagnosis. Almost 30 patients have been followed for more than 10 years.

All the patients were white women. The mean age at primary diagnosis was 29.3 years for the pregnant group and 29.5 years for the age-matched controls. The most frequent primary site was on an extremity.

The clinical and histologic parameters for the two groups were compared with chi-squared statistics and were comparable. The variables that differed significantly between the two groups were site of the primary tumor ($p = 0.016$) and age ($p = 0.002$). Despite similar age ranges and means, there were differences in the distribution of ages within those ranges. The percentage of patients within each of three age ranges (19 to 25 years, 26 to 30 years, and 31 to 40 years) were 20%, 40%, and 40%, respectively, for the patients diagnosed during pregnancy and 33%, 16%, and 51%, respectively, for the patients not diagnosed during pregnancy.

TABLE 1. *Population Characteristics: All Stages*

Characteristic	Pregnant	Not Pregnant
n	100	86
Age (mean years)	29.3	29.5
Range	19–40	19–40
Stage at diagnosis (%)		
1	88	92
2	10	6
3	2	2
Primary site (%)		
Trunk	40	52
Extremity	50	30
Head and neck	6	13
Other/unknown	4	5
Histology (%)		
LMM	0	2
SSM	69	63
Nod	18	23
Other/unknown	13	12
Clark level (%)		
I	2	1
II	9	10
III	49	50
IV	26	27
V	7	4
Unk/does not apply	7	8
Thickness (mm)		
Mean	2.17	1.52
Range	(0.26–16.8)	(0.39–5.40)
Median	1.40	1.20
Ulceration		
No	67 (74%)	50 (75%)
Yes	24 (26%)	17 (25%)
Unk	9	19

Ext, extremity; LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma; Nod, nodular melanoma; Unk, unknown.

Pathologic Review

A detailed pathologic study of the primary lesions was performed of the central cross-section cut along with step sections from each lesion. The review included histologic type, Clark level, Breslow thickness, the presence or absence of vascular and/or lymphatic invasion, ulceration, regression, mitotic rate, pigmentation, satellite lesions, peritumoral inflammation, and evidence of intradermal nevus.

Approximately one half were Clark level III, and one quarter were level IV. There was no significant difference (by chi-square analysis) in the distribution of values for the variables of ulceration ($p = 0.88$) or Clark level ($p = 0.724$). Tumor thickness was slightly greater for the pregnant patients by unpaired two-tailed t test ($p = 0.052$). One coauthor (RTV) reviewed all sections of the primary melanomas.

Statistical Evaluation

The total group of patients was first subdivided into the pregnant *versus* nonpregnant groups, and then divided again into three groups based on stage at the time of diagnosis. Further stratifications were performed, controlling for pathologic variables, in an attempt to identify those that influenced prognosis. Actuarial disease-free interval and survival curves were constructed for all subgroups using the Kaplan–Meier method.[11] A Cox-Mantel rank test[12] was used to test statistical significance, with a p value less than 0.05 considered significant. Thickness of the primary melanoma was used as a continuous variable in the multivariate analysis for the endpoint of disease-free interval and as a noncontinuous variable (less than 1.5 mm, 1.5 to 4.0 mm, and more than 4.0 mm) for the endpoint of survival. The p values reported refer to differences between survival distributions and do not refer simply to differences in median survival. Other stratifications were compared by chi-squared analysis when appropriate. All survival data are measured from the date of the histologic diagnosis of melanoma.

A multivariate analysis was performed on the total population and on selected subsets by using a Cox simultaneous proportional hazard model, with sequential elimination of variables lacking significance in the multivariate system.

Surgical Management

The primary lesions were excised with margins of at least 2 cm when anatomically possible. Among the patients with stage 1 disease at diagnosis, the initial surgical procedure performed for the two patient groups differed slightly. In the control group, wide local excision (WLE) was performed as the first surgical procedure in 82% and as the second procedure in 3%. The remaining patients underwent total excision. The pregnant group underwent WLE as the first procedure in 51% and as the second procedure in 30%, with total excision in 19%. In both groups, WLE was accomplished in 80% to 85% of cases, with the remainder managed with total excision.

Elective lymph node dissections (ELND) were performed for intermediate thickness lesions with principal lymphatic drainage to a single nodal basin. Therapeutic lymph node dissections were performed if regional nodes become palpable and if fine-needle aspiration cytology verified the presence of metastatic disease in the nodes. A total of 15 ELND were performed in the control group (17%) and 16 ELND in the pregnant group (16%). Eighteen therapeutic lymph node diessections (TLND) were performed in the control group (21%) and 23 TLND in the pregnant group (23%).

Specific Active Immunotherapy

Specific active immunotherapy is the subcutaneous injection of 2.5×10^7 irradiated allogeneic cultured melanoma cells, with Bacillus Calmette-Guérin (BCG) as an adjuvant.[13] The initial course is four monthly injections for stage 1 patients and seven monthly injections for patients with metastatic disease. Additional courses are repeated after each episode of recurrent disease whenever the recurrence can be surgically excised.

This adjuvant therapy was offered to each stage 1 patient whose primary melanoma had a Clark level of III or more and a Breslow thickness of 0.8 mm or more. It was also offered to patients with stage 2 disease, in addition to surgical resection of metastases. In the pregnant and control groups, 83% and 85% of the patients, respectively, were treated with specific active immunotherapy at some time during their course. In the remaining patients immunotherapy was not administered, because of either minimal disease or the presence of gross metastatic disease at diagnosis.

Chemotherapy

Patients with unresectable disease were principally treated with BOLD, a four-drug chemotherapeutic protocol including bleomycin, vincristine, (Oncovin) lomustine (CCNU), and dacarbazine (DTIC).[14]

Results

Patient Population

The age and clinical characteristics of the study group and of the control group are listed in Table 1.

A subset of the patients had stage 2 or 3 disease at the time of initial presentation. Excluding them from consideration, the interval from diagnosis to metastatic or recurrent disease was evaluated. The age and clinical characteristics of the patients presenting with stage 1 disease are listed in Table 2. The clinical course and the sites of first metastasis are listed in Table 3. Among the pregnant group, there was an increased incidence of nodal metastases during the follow-up period (39% *versus* 26%, chi-square = 3.777, p = 0.053) and as a first metastasis (71% *versus* 61% of patients who develop metastatic disease).

The overall mortality rate during the follow-up period was 25% in the pregnant group and 23% in the control group. The overall recurrence rates were 48% and 38%, respectively (chi-square = 1.74, p = 0.27).

Univariate Analysis of Prognostic Variables Associated with Mortality and Progression of Disease

Clinical Variables

Pregnancy. The interval to the first metastasis or recurrence (DFI), the interval to the first nodal metastasis, and the interval to the first distant metastasis were compared for 88 patients who were pregnant at diagnosis of

TABLE 2. *Population Characteristics: Stage 1 Patients*

Characteristic	Pregnant	Not Pregnant
n	88	79
Age (mean years)	28.9	29.6
Range	19–40	19–40
Primary site (%)		
Trunk	40	51
Extremity	52	33
Head and neck	7	13
Other/unknown	1	4
Clark level		
I	2	1
II	10	10
III	55	53
IV	25	25
V	2	4
Unk/does not apply	6	6
Thickness mean (mm)	1.87	1.45
Range	(0.26–16.8)	(0.39–5.00)
Median	1.30	1.20
Ulceration		
No	61 (75%)	47 (76%)
Yes	20 (25%)	15 (24%)
Unk	7	3

Ext, extremity; LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma; Nod, nodular melanoma; Unk, unknown.

TABLE 3. *Clinical Course of Patients with Melanoma*

	Pregnant	Not Pregnant
n	100	86
Mean follow-up (years)	6.0	7.7
Recurrence rate	48%	38%
Death rate	25%	23%
Site of first metastasis		
Nodes	71%	61%
Local skin	13%	18%
Lung	6%	12%
Liver	2%	6%
CNS	2%	3%
Other	6%	0%
Percentage who develop metastases in		
Nodes	39%	26%
Local skin	11%	10%
Distant mets	27%	26%

* Percentages are calculated for the subset who developed metastatic or recurrent disease.

localized (stage 1) melanoma and 79 patients who were not pregnant (Figs. 1 to 3).

There was a significantly shorter DFI for the pregnant group, with 51% of pregnant patients and 68% of control patients remaining disease free at 10 years (Fig. 1, p = 0.039).

The time to nodal metastases (Fig. 2) was significantly shorter (p = 0.021) for the pregnant group.

The intervals from diagnosis to the development of distant metastatic disease (distant disease-free interval [DDFI]) manifested by metastases other than to local skin or nodes were also compared (Fig. 3). The curves were separate until the 9-year follow-up, where they converged. The trend was toward a poorer prognosis for the patients diagnosed during pregnancy, but the difference was not significant (p = 0.265).

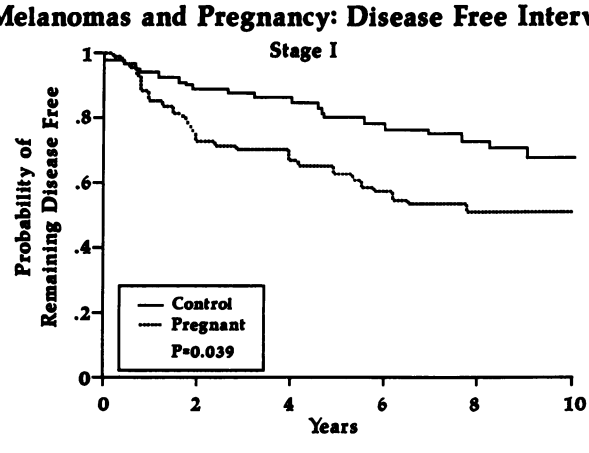

FIG. 1. The actuarial disease-free interval for patients (n = 88) who were pregnant at the time of diagnosis of localized (stage 1) melanoma is significantly less favorable than for age- and sex-matched controls (n = 79) who were not pregnant. p = 0.039.

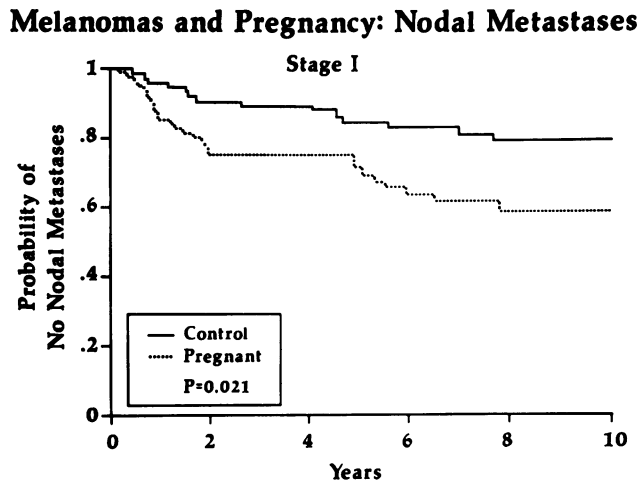

FIG. 2. The actuarial interval to the development of lymph node metastases for patients (n = 88) who were pregnant at the time of diagnosis of localized (stage 1) melanoma is significantly shorter than the interval for a series of age- and sex-matched controls (n = 79) who were not pregnant. p = 0.021.

Similar differences were found when all patients in both groups (n = 100 for pregnant patients, n = 86 for the nonpregnant group) were compared. The p values for DFI, time to nodal metastases, and DDFI were 0.028, 0.015, and 0.252, respectively.

Survival curves for all patients in the two groups were also plotted (Fig. 4). Again there was a trend toward a poorer survival rate for the pregnant group. That difference, however, was less than 5% at 10 years and, also, was not statistically significant (p = 0.320). When only stage 1 patients were compared, the p value was 0.299.

Stage at diagnosis. For the 186 female patients of childbearing age studied, the stage at diagnosis was strongly

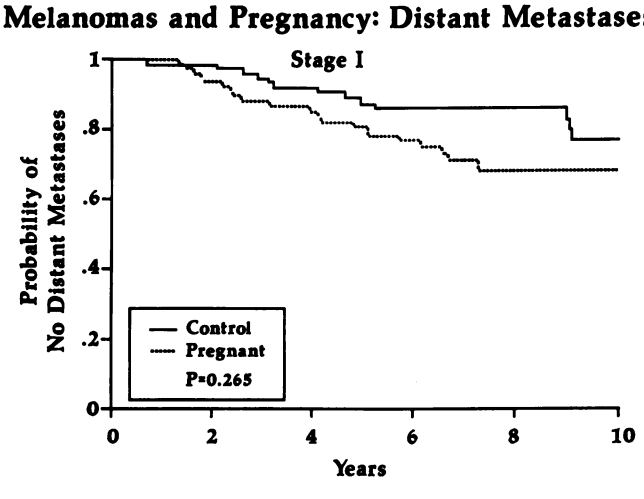

FIG. 3. The actuarial distant-disease-free interval for patients (n = 88) who were pregnant at the time of diagnosis of localized (stage 1) melanoma is not significantly different from that of a series of age- and sex-matched controls (n = 79) who were not pregnant. p = 0.265 (NS).

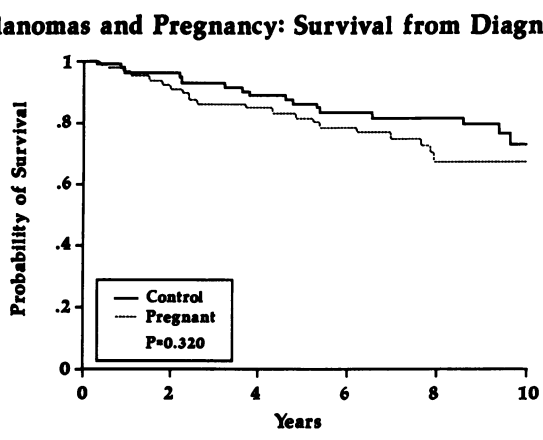

FIG. 4. The actuarial survival for patients (n = 100) who were pregnant at the time of diagnosis with localized (stage 1) melanoma is not significantly different from that of a series of age- and sex-matched controls (n = 86) who were not pregnant. The p value is 0.320 (NS).

associated with outcome. Actuarial 5-year survival rates of stage 1, stage 2, and stage 3 patients were 88%, 57%, and 25%, respectively. Patients diagnosed in stage 2 or stage 3 (with nodal or distant metastases, respectively) had significantly decreased survival rates compared to those diagnosed with stage 1 disease ($p < 0.001$).

Age. Among patients with stage 1 disease (combining the pregnant and control patients), the three age groups defined above were compared in terms of DFI and survival rate. There was no significant association between age and these outcomes. The p values for DFI for these three age groups were 0.17, 0.31, and 0.60, respectively. The p values for the survival curves were 0.30, 0.60, and 0.68, respectively.

Histologic Variables

Site of the primary melanoma. The primary sites were considered in three groups. DFI was longer in patients with extremity primaries than in patients with trunk primaries ($p = 0.026$), but the survival difference was not significant ($p = 0.534$). No significant prognostic significance could be demonstrated for the small number of cases of head and neck primaries.

Histology of the primary melanoma. The most common histologic types of melanoma were superficial spreading (SSM, n = 123), nodular (NM, n = 38), and unclassified (UNCL, n = 17). Other histologic types were found in less than five cases each. The disease-free interval was shorter in patients with NM than in those with SSM ($p = 0.017$) and those with unclassified histology ($p = 0.000$).

Survival was decreased for those with NM compared to those with SSM, but the difference is not significant ($p = 0.098$). The unclassified melanomas also had decreased survival ($p = 0.012$).

Ulceration of the primary melanoma. Ulceration of the primary melanoma was associated with slightly poorer patient outcome. In terms of DFI, the two curves were not statistically different ($p = 0.24$). The survival curves also showed a small, statistically insignificant difference ($p = 0.167$), with more deaths among the patients with ulcerated lesions.

Thickness of the primary melanoma. Patients whose primary melanomas were thicker than 4.0 mm had decreased survival compared to those with thinner primary melanomas ($p < 0.025$).

Multivariate Analysis

Endpoint: disease-free interval. The prognostic significance of diagnosis during pregnancy was further assessed by a Cox simultaneous proportional hazard multivariate analysis using patients from both groups (n = 186), segregated by stage at diagnosis. The numbers of patients with stage 2 or stage 3 disease at diagnosis were small. For those patients it was not possible to assess prognostic factors in a meaningful way. The multivariate analysis focused on the patients diagnosed with stage 1 disease (pregnant group: n = 88; control group: n = 79). The endpoints assessed were recurrent disease and death.

The variables included in the multivariate analysis were those associated with significant differences in the univariate analyses presented above.

When variables with p values greater than 0.05 were sequentially removed, the Clark level, the site of the primary lesion, the thickness of the primary lesion, and diagnosis during pregnancy were significantly associated with DFI (Table 4). When all four variables were included in the analysis, the p values were 0.003 for Clark level, 0.008 for pregnancy, 0.094 for site, and 0.098 for thickness. Both thickness and site were significant when only one of those two variables was left in the hazard equation. The combination of these variables, including pregnancy, resulted in a hazard equation with a p value of 0.001. These values are listed in Table 4.

Endpoint: survival. Multivariate analysis of variables associated with patient survival revealed significance only for the variable of thickness of the primary lesion. Three

TABLE 4. *Multivariate Analysis of Prognostic Variables for Melanoma in Women of Childbearing Age: Simultaneous Proportional Hazard Analysis (Endpoint: Disease-free Interval)*

	p Values for Three Alternative Models		
Variable	1	2	3
Pregnancy at diagnosis	0.004	0.022	0.008
Clark level of primary lesion	0.001	0.006	0.003
Site of primary lesion	0.050	—	0.094
Thickness of primary lesion	—	0.038	0.098
Significance of model	0.001	0.001	0.001

TABLE 5. *Multivariate Analysis of Prognostic Variables for Stage 1 Melanoma in Women of Childbearing Age: Simultaneous Proportional Hazard Analysis (Endpoint: Survival)*

Variable	p Values for Three Alternative Models		
	1	2	3
Pregnancy at diagnosis	0.339	—	0.283
Clark level of primary lesion	0.739	—	—
Site of primary lesion	0.613	—	—
Thickness of primary lesion	0.032	0.010	0.010
Ulceration of primary lesion	0.843	—	—
Significance of model	0.192	0.016	0.031

alternate hazard analyses are listed separately in Table 5. When considered simultaneously with the variables of Clark level, site, ulceration, and pregnancy, thickness alone was a significant predictor of survival. When considered alone, thickness alone had a significant prognostic significance and the prognostic model generated by that one variable alone was more significant ($p = 0.016$) than the model considering all five variables ($p = 0.192$). When only thickness and pregnancy were considered together, there was, again, prognostic value only for the tumor thickness.

Discussion

The effect of pregnancy on the clinical course of melanoma continues to be disputed. There are several studies that suggest that pregnancy has a negative impact on patients with melanoma, while others fail to show a difference. The present report identifies several characteristics of the presentation and clinical course of women with melanoma diagnosed during pregnancy.

The clinical course of patients diagnosed during pregnancy differed from that of matched controls: the pregnant patients had a significantly shorter DFI and a significantly decreased time to nodal metastases, based on comparison of actuarial curves. They were more likely to develop nodal metastases during their clinical course (39% *versus* 26%, $p = 0.053$), and were more likely to develop nodal metastases as their first metastases (71% *versus* 61% of those who developed metastases). The length of follow-up was slightly greater for the nonpregnant group (7.7 years *versus* 6.0 years); so the differences between the two groups are slightly underestimated by chi-squared analysis of the frequency of metastatic disease.

The previously reported association of pregnancy with shorter DFI[4] is supported in the current manuscript by longer follow-up and a larger cohort of patients. Univariate and multivariate analyses have shown the significance of pregnancy for the endpoint of recurrent or metastatic disease.

The shorter DFI of patients with melanoma during pregnancy was not reflected in poorer survival rates of those patients. Other known prognostic factors (ulceration, site, Clark level) also were insignificant in this analysis. Furthermore a relatively small number of patients died during follow-up (approximately 25%). Survival may not be as meaningful an endpoint as DFI in this population. In a different population, poorer survival rates for pregnant patients have been reported recently.[7]

The failure to document a survival difference between the groups may reflect a need for greater statistical power or may reflect similar patterns of metastases to non-nodal sites for the two groups. Distant metastases are more lethal than local or nodal metastases, and isolated nodal metastases are amenable to surgical management.

Patients who are diagnosed with melanoma during pregnancy should be informed of available prognostic data and should be advised of the following factors:

1. There is a shortened DFI, which can be explained by a decreased time to nodal metastasis.
2. The lymph node basins should be examined carefully on a regular basis because of an increased risk of nodal metastases. Pregnancy may be a relative indication for elective node dissection in appropriate patients.
3. Long-term survival approaches that of the normal population and is more likely to be predicted by standard prognostic factors, especially Breslow thickness, than by pregnancy alone.

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