Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study

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Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study

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Abstract

Background: The clinical features and the prognostic relevance of vitiligo lesions in melanoma patients are still controversial. This prospective observational study was designed to characterise the clinical features of melanoma-associated vitiligo, to analyse the association with other autoimmune manifestations and to ascertain whether the development of vitiligo lesions carries a prognostic relevance on the clinical course of melanoma. Materials and methods: A total of 2954 consecutive patients have been included; multivariate analyses of distant metastasis-free survival (DMFS) and overall survival (OS) were carried out to ascertain the independent prognostic role of vitiligo as a time-dependent covariate. Results: Vitiligo was demonstrated in 83 of 2954 melanoma patients (2.8%). A significantly higher percentage of autoimmune diseases was demonstrated in vitiligo patients (7 of 83) with respect to patients without vitiligo (80 of 2871) (P = 0.004). Multivariate analyses selected the time-dependent covariate vitiligo as the favourable independent prognostic variable associated to a longer DMFS in stage III and a higher OS in both stage III and stage IV. Conclusion: Melanoma-associated vitiligo should be considered as a distinct clinical entity, separate from vitiligo vulgaris, and identifies a subgroup of patients characterised by a high prevalence of immune-mediated diseases and by a favourable prognosis.

Key words: autoimmune diseases, melanoma, multivariate analyses, prognosis, vitiligo

Introduction

The development of vitiligo in melanoma patients is a well known even if puzzling and yet poorly understood phenomenon [1–7]. In fact, melanoma is a cutaneous malignancy originating from a proliferation of atypical melanocytes, while vitiligo is characterised by hypopigmented skin lesions pathogenetically derived from the loss of functional melanocytes from the epidermis.
The occurrence of vitiligo in melanoma patients has been reported for the first time 40 years ago [8]. Since then, this association has been mainly described in case reports and small patient series [5, 9, 10]. Only a few studies have been conducted in relevant cohorts of melanoma patients at different clinical stages [2–4, 11]. As a consequence, the reported incidence of vitiligo in patients affected by melanoma ranges widely between 1%–2% [12, 13] and 23%–43% [14, 15]. The risk for melanoma patients to develop vitiligo has been estimated to be 7- to 10-fold higher compared with the general population [4]. However, a cohort study carried out in patients with vitiligo found the presence of melanoma in only 3 of 1052 patients (0.3%) [7]. These controversial results could be due to different criteria used for the definition of vitiligo: some studies included peri-cicatricial vitiligo, leucoderma developing around cutaneous metastases and halo nevus, while others did not. Moreover, in recent years, vitiligo is increasingly reported in advanced metastatic melanoma patients treated by adoptive immune-based therapies with biological response modifiers and/or undergoing vaccine strategies [14–16].

Relevant issues concerning the association between vitiligo and melanoma are still controversial. The clinical differences between melanoma-associated and vulgaris vitiligo are not well defined: some authors consider them identical [17] while others found that melanoma-associated vitiligo has a more varied clinical spectrum of manifestations [1]. Conflicting results are reported also about the prognostic value of vitiligo in melanoma patients. Indirect evidences in animal models show that congenital melanoma spontaneously regresses in Sinclair swine after the appearance of generalised depigmentation [5]. Clinical trials of immune-based therapies in advanced metastatic melanoma correlated vitiligo with an improved clinical response, implicating an immune-modulating effect against metastatic disease [14, 15, 18–20]. Only two papers analysed melanoma patients at different clinical stages. Nordlund et al. [11] found that 67% of 51 stage I–III melanoma patients with vitiligo survived more than expected based on historical controls. Bystryn et al. [3] confirmed these results, showing that the 5-year survival of 46 stage I–III vitiligo patients was significantly better (86% versus 74%) than that expected on the basis of the risk factors.

The present study reports the results of a single-institution hospital-based prospective cohort study designed to (i) characterise the time of onset and the clinical features of melanoma-associated vitiligo; (ii) analyse the association with other autoimmune manifestations and (iii) ascertain whether the development of vitiligo has a prognostic relevance on the clinical course of melanoma.

**Materials and methods**

**patient population and follow-up**

This prospective observational cohort study recruited from January 1980 to June 2007 a total of 2954 consecutive patients with invasive melanoma diagnosed, treated and followed-up at our institution. The follow-up was ended on June 2008.

Inclusion criteria were as follows: (i) complete clinico-pathological and follow-up data of melanoma; (ii) detailed familial and medical history concerning vitiligo and other autoimmune diseases and (iii) date of onset, mapping and evolution of vitiligo. All the patients were reclassified according to the new American Joint Committee on Cancer (AJCC) staging system [21].

All the patients underwent clinical and radiological follow-up at our institutions, with assessment for the presence of vitiligo at every physical examination.
**stage I–II patients.** From 1980 to 2006, physical examinations were carried out every 2 months for the first 2 years after primary excision, every 3 months from the third to the fifth year, every 6 months from the 6th to the 10th year and yearly thereafter irrespective of Breslow thickness. Radiological procedures were done at diagnosis and yearly during follow-up [22, 23].

**stage III.** Lymph node dissection was carried out after the clinical demonstration of palpable adenopathy until 1998; from then on, patients with primary melanoma ≥1 mm, or <1 mm with Clark level IV–V, and/or ulceration and/or regression underwent sentinel node biopsy. Physical examinations were carried out every month in patients undergoing adjuvant treatment and then every 3 months. A computerised tomography (CT) scan was carried out every 6 months for the first 3 years, then once a year.

**stage IV.** Physical examinations were carried out every month before chemotherapy administration. CT scan was repeated after 3 months to assess the clinical activity of treatment and thereafter according to disease evolution.

**vitiligo definition and assessment**

Vitiligo diagnosis was based on the presence of the classic hypopigmented lesions and confirmed in doubtful cases by inspection with a Wood's lamp. Further clinical (diascopy) or laboratory tests (fungal scraping, biopsy) were used to differentiate vitiligo from other hypomelanoses in suspicious cases. A personal history about occupation, hobbies, home and workplace environment and exposure to specific chemicals was obtained in all cases to exclude chemical leucoderma.

Vitiligo was classified as localised or generalised according to the lesion distribution [11, 24]. Generalised vitiligo was further subdivided into acrofacial, vulgaris and mixed forms. Specific localised vitiligo expressions were considered in this study, besides the focal form, the presence of peri-cicatricial hypopigmented lesions and the halo nevi. Peri-cicatricial vitiligo was defined as the presence of hypopigmentation localised around the surgical scar of primary melanoma, locoregional nodal dissection or cutaneous metastasis excision, in the absence of scleroatrophic alterations.

The coexistence of autoimmune or immune-mediated diseases was derived from patient personal history, laboratory assays (serological tests, immune profiles and hormonal levels) and clinical/radiological data.

**statistical analysis**

Both parametric (χ² test and Student’s t-test) and nonparametric (Wilcoxon test and Mann–Whitney test) were used; only ‘P’ values of parametric tests were reported as the results of the two tests were similar. Overall survival (OS) was calculated separately for each stage from the surgical excision of melanoma (stage I–II) or from the date of first clinical/radiological evidence of locoregional (stage III) or distant (stage IV) metastatic disease to the date of death or last check-up for all patients. Disease-free survival (DFS) was calculated for stage I–II as the time from the surgical excision of the primary melanoma to either the date of relapse or last follow-up visit. Distant metastasis-free survival (DMFS) for stage III patients was calculated as the time from the radical node dissection to either the date of occurrence of distant metastases or last follow-up visit.

Patients with vitiligo before melanoma were included, while patients with unknown primary or choroidal melanoma were excluded from survival analyses.
In the univariate analyses, the product-limit estimates were derived by the Kaplan–Meier method [25] and the statistical comparisons were done by the log-rank Mantel–Cox test [26]. The median follow-up for the entire cohort of patients was 18.4 years (range 1–28). Two hundred patients (6.7%) were lost to follow-up, 101 of them (3.3%) after <5 years after primary melanoma excision.

Multivariate analyses using the Cox proportional hazards regression model [27] were carried out to evaluate the independent prognostic role of vitiligo on DFS, DMFS and OS. The presence of vitiligo was considered a time-dependent prognostic factor. The other prognostic factors used for variable selection were age, gender, Breslow thickness, ulceration and AJCC stage. Age was considered at the time of first melanoma diagnosis for stage I–II analysis, at the time of locoregional disease diagnosis for stage III analysis and at the time of development of distant metastases for stage IV analysis. AJCC stage was coded as IIIa, IIIb and IIIc for patients with locoregional disease and M1a, M1b and M1c for patients with distant metastases. All these factors were considered as non-time-dependent variables. Data were processed by the SPSS 15.0 software package (SPSS Inc., Chicago, IL).

Results

Clinical features

Vitiligo occurred in 83 of 2954 melanoma patients; the cumulative incidence was 2.8%. The median age of vitiligo occurrence was 53 years (range 20–79), with a female prevalence (Table 1). The median Breslow thickness was 2.2 mm (range 0.4–10 mm); four patients had a choroidal melanoma while the primary was unknown in three. The median follow-up of vitiligo patients from melanoma diagnosis was 17.4 years (range 2.3–28.5).

As to the time of onset, vitiligo was present from 2 to 45 years before melanoma occurrence in 17 patients, thus representing the 20.5% of the total melanoma-associated vitiligo cases; the cumulative incidence of vitiligo in patients who will develop melanoma is therefore 0.6%. The remaining 66 patients (79.5%) developed vitiligo after melanoma excision (median time 3.4 years, range 2 months–20 years). Thirty of 66 patients (45.5%) developed vitiligo after surgical excision of primary melanoma (28 stage I–II cutaneous and two choroidal melanoma), 28 of 66 (42.4%) after locoregional metastases (stage III) and 8 of 66 (12.1%) after distant metastases. Vitiligo occurred after treatment with biological response modifiers (interferon and/or interleukin-2, alone or in association with chemotherapy) in 16 of 66 patients (24.2%), corresponding to a value of 3% on the total of 528 patients treated with immunotherapy. Vitiligo was localised in 44 patients (53%) and generalised in the others (47%). Hypomelanotic lesions developed around cutaneous metastases in four patients. A characteristic site of hypopigmentation is represented by the surgical scar of melanoma (17 cases). Notably, 10 of them developed peri-cicatricial vitiligo after regional node dissection. No case of segmental or mucosal vitiligo was observed. Halo nevi were observed in six cases. Only two patients showed an extension of hypopigmented lesions.

In the majority of patients, hypomelanotic lesions were not well demarcated, showed irregularly shaped borders and pale colour and were mainly located on the face with a perioral or periorbital distribution and upper trunk. These features were peculiar of patients in whom vitiligo occurred after melanoma excision. On the other hand, the clinical picture was different in patients with vitiligo before melanoma. These patients tended to be younger (median age 38 years) and showed a prevalent generalised distribution (70.6% of vitiligo patients before melanoma with respect to 40.9% of vitiligo patients after melanoma), while the localised form was more frequent in patients with vitiligo after melanoma (59.1% versus 29.4%, respectively; χ² test: P = 0.029). Hypomelanotic lesions were usually well demarcated, round or oval in
shape, chalk- or milk-white in colour and predominantly located on the face, upper limbs and feet in patients with vitiligo before melanoma. A family history of vitiligo was revealed in three patients with vitiligo before melanoma but in no cases of vitiligo after melanoma.

**association with autoimmune diseases**

A significantly higher percentage of autoimmune diseases was demonstrated in vitiligo patients (7 of 83; 8.4%) compared with patients without vitiligo (80 of 2871; 2.8%) (P = 0.004). The most frequent diseases were thyreopathies (hyper- and hypothyroidism), which accounted for 58.6% of cases in both groups, followed by rheumatoid arthritis (10.3%), type 1 diabetes mellitus (10.3%) and inflammatory bowel diseases (5.7%).

**prognostic relevance**

No statistically significant difference was found in stage I (5-year survival 95.6% in patients with vitiligo and 95.4% in patients without vitiligo) and stage II survival (5-year survival 74.4% versus 68.8%, respectively). No differences were found in the DFS of stage I–II patients on the basis of the presence of vitiligo.

On the other hand, vitiligo was associated with a significant OS increase in stage III patients (5-year survival 65% in vitiligo patients versus 42.5% in patients without vitiligo; P = 0.03) (Figure 1A). The DMFS of stage III patients was significantly higher in vitiligo patients (5-year DMFS 52.4% versus 21.5% in patients without vitiligo) (Figure 1B). Vitiligo was associated with a significant survival improvement also in stage IV melanoma (median survival 14.4 versus 9.6 months; P = 0.0061) (Figure 2). The prognostic impact of vitiligo was independent from treatment in as much as the percentage of immunotherapy-treated stage III and stage IV patients was not statistically different in vitiligo compared with non-vitiligo patients (Table 2).

No survival differences were found according to the time onset of vitiligo, even if patients with vitiligo before melanoma showed slightly lower percentage rates compared with those with vitiligo after melanoma, not reaching a statistical significance (5-year survival 57% versus 66%, respectively). Similarly, the DMFS of stage III and the OS of stage III and IV were not statistically different between patients who developed vitiligo before and after melanoma.

The presence of autoimmune diseases other than vitiligo was not associated with a statistically significant different disease course; nevertheless, it is remarkable that all the seven patients (three stage II, three stage III and one stage IV) with autoimmune diseases in association with vitiligo are still alive and disease-free after a follow-up ranging from 3 up to 11 years from melanoma excision.

Multivariate analyses were carried out to evaluate the independent prognostic role of vitiligo (Table 3). The Cox regression analysis selected the time-dependent covariate vitiligo as a favourable independent prognostic variable associated to a longer DMFS in stage III (relative risk (RR) 4.634; 95% confidence interval (CI) 1.466–14.648) and a higher OS in both stage III (RR 7.547; CI 1.051–54.169) and stage IV (RR 9.158; CI 1.286–65.237). The other parameters selected by the stepwise procedure were ulceration and AJCC for DMFS, Breslow thickness, ulceration and AJCC for stage III OS and ulceration and stage IV M1c for stage IV OS.
Discussion

The results of this prospective hospital-based cohort study demonstrate that the presence of hypopigmented lesions identifies a small subgroup of melanoma patients (2.8%) characterised by a high prevalence of immune-mediated diseases and by a significant favourable prognosis in advanced stage. In fact, the presence of vitiligo was found to carry an independent significant prognostic relevance as time-dependent covariate on the DMFS of stage III and on the OS of stage III and stage IV patients.

Our study showed a cumulative incidence of vitiligo in melanoma patients (2.8%) similar to or slightly lower than that reported by previous studies (3.7% according to Schallreuter et al. [4]; 4.1% according to Bystryn et al. [3]). The incidence of vitiligo before (0.6%) and after melanoma (2.2%) is similar to that of normal subjects, in whom the prevalence is estimated from 0.5%–1% [28, 29] up to 4% in some South Asian, Mexican and American populations [30]. Another controversial issue is represented by the higher incidence of vitiligo reported in some series of advanced metastatic patients treated by biological response modifiers and/or undergoing vaccine strategies [14, 15] with up to 23%–43% of patients involved. We did not obtain such high percentages in spite of the inclusion as vitiligo of some hypopigmented lesions (peri-cicatricial, halo nevus). Our figures (3% on the total of 528 patients treated by immunotherapy) are similar to those of other studies [13, 16, 20] which reported vitiligo in a percentage of immunotherapy-treated patients between 2% and 7%. It is conceivable, therefore, that even if immunotherapeutic strategies can lead to the development of vitiligo as a consequence of immune activation, this does not represent the only or the most important pathway through which this phenomenon occurs. In our experience, in fact, hypomelanotic lesions appeared after a treatment with biological response modifiers in only 16 of all 66 vitiligo cases.

Conflicting results are reported in literature as to the clinical features of melanoma-associated vitiligo. Our data show that vitiligo occurring after melanoma is characterised by specific clinical features different from the vulgaris form and also by vitiligo occurring before melanoma. Vitiligo before melanoma developed in younger patients and was mainly generalised, as in the vulgaris form. Melanoma-associated vitiligo develops usually in middle-aged people without a family history of hypopigmented lesions, is less progressive than the vulgaris form, commonly localised and located on the face with a perioral/periorbital distribution and upper trunk. Our results are therefore in contrast with those reported by Hartmann et al. [17], who showed 75% of melanoma-associated vitiligo patients presenting with symmetrical bilateral lesions corresponding to classic vitiligo. We could not confirm also the results by Nordlund et al. [11] who reported a predominant involvement of the trunk with a subsequent centrifugal spreading to involve the face and extremities. Specific topographic variants are represented by the occurrence of vitiligo around cutaneous metastases and peri-cicatricial vitiligo. This latter form, which needs to be carefully distinguished from post-surgical scleroderatrophie or chemical leucoderma, occurred in a significant percentage of patients (25.7%) and could be interpreted as a Koebner phenomenon arising also long time from surgery. In addition, the morphology of cutaneous lesions in patients with vitiligo after melanoma, with not well-demarcated lesions, irregularly shaped borders and pale colour, is different from that of vulgaris vitiligo. On the other hand, hypomelanotic lesions were well demarcated, round or oval in shape, chalk- or milk-white in colour and predominantly located on the face, upper limbs and feet in patients with vitiligo before melanoma, a picture similar to that of the vulgaris form.

The main finding of our study is the demonstration of the favourable vitiligo prognostic role. Controversial data are reported in literature about this topic. The majority of studies were carried out on small cohorts of advanced metastatic patients treated by immunotherapeutic strategies and correlated vitiligo development after immunotherapy to an increased therapeutic activity and improved prognosis [14, 15, 18–20]. The
largest series was reported by Phan et al. [14] who showed the occurrence of vitiligo in 84 of 374 (23%) melanoma patients treated with high-dose interleukin-2: a response was achieved in 33% of them. Boasberg et al. [15] found a clear survival advantage (18.2 versus 8.5 months) in 21 of 49 metastatic patients who developed vitiligo during maintenance biotherapy. Only two papers published >20 years ago analysed melanoma patients at different clinical stages [3, 11] deriving the evidence towards a favourable vitiligo prognostic role only through the comparison with historical controls published by other institutions [11] or the expected survival on the basis of the risk factors [3]. In our paper, the OS of stage III and stage IV patients with vitiligo was significantly higher than that of patients with the same stage but without vitiligo. The prognostic advantage in stage IV was therefore confirmed not only for the patients who developed vitiligo after the demonstration of distant metastases and treatment with biotherapies, as indicated in the literature [14, 15, 18–20], but also for those patients who had developed vitiligo and showed subsequently a metastatic disease. The multivariate analyses clearly showed the prognostic independent role played by vitiligo as time-dependent covariate, on the DMFS of stage III and on the OS of stage III and stage IV patients, with unexpectedly high RR (4.634, 7.547 and 9.158, respectively).

In an attempt to better characterise melanoma-associated vitiligo patients, we analysed the frequency of immune-mediated diseases in patients with and without vitiligo. In fact, it is known that vitiligo is frequently associated with other autoimmune diseases, such as autoimmune thyroiditis, lupus erythematosus and insulin-dependent diabetes mellitus [31, 32]. Our study shows that melanoma patients with vitiligo are characterised by a higher frequency of immune-mediated manifestations than those without vitiligo. Even if the presence of autoimmune diseases ‘per se’ was not associated with a statistically different clinical course, nevertheless, all the patients with autoimmune manifestations and vitiligo shared a favourable prognosis also in the presence of metastatic disease. In fact, Gogas et al. [20] reported that the development of autoimmunity manifestations including vitiligo is associated to an increased survival in stage II and III interferon-treated melanoma patients.

An intriguing question is represented by the biological significance of vitiligo development in melanoma patients. Increasing evidences support the view that vitiligo results from an autoimmune response targeting the epidermal melanocytes [6, 33]. T-cell-mediated responses to normal melanocyte differentiation antigens (gp100, MelanA/MART-1, tyrosinase) were demonstrated in vitiligo patients [34] and CD8+ cytotoxic T cells recognising gp100 and tyrosinase were shown in vitiligo lesions [35]. Given the fact that the antigens recognised by cytotoxic T lymphocytes in vitiligo are shared by normal melanocytes and melanoma cells, vitiligo represents a marker of melanoma immunity and the selective impairment and destruction of melanocytes in vitiligo becomes the therapeutic goal to reach in melanoma treatment. A more comprehensive understanding of the immunobiologic mechanisms leading to vitiligo development could therefore improve the setting of vaccine-based and immunotherapeutic strategies.
references


Table 1. Clinical features of melanoma-associated vitiligo patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male (ratio)</td>
<td>49/34 (1.4)</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>33 (20-79)</td>
</tr>
<tr>
<td>Breslow thickness (mm median, range)</td>
<td>2.2 (0.4-10)</td>
</tr>
<tr>
<td>Vitiligo family history</td>
<td>5/83</td>
</tr>
</tbody>
</table>

Site of the primary
- Head/neck          3
- Anterior trunk     8
- Back               20
- Upper limb         12
- Lower limb         33
- Choroidal melanoma 4
- Unknown primary    3

Vitiligo lesion classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Vitiligo</th>
<th>No vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Segmental</td>
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<td></td>
</tr>
<tr>
<td>Mosaic</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Peri-olivartial</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Halo nevus</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td></td>
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<tr>
<td>Generalised</td>
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<td></td>
</tr>
<tr>
<td>Acral facial</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Vulgaris</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>


aAt the onset of vitiligo.
bAccording to Koga et al. [24] and Nordlund et al. [11].

dTable 2. Immunotherapy-based approaches in stage III and IV melanoma patients with and without vitiligo

<table>
<thead>
<tr>
<th></th>
<th>Vitiligo</th>
<th>No vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant IFN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (42%)</td>
<td>361 (49%)</td>
</tr>
<tr>
<td>No</td>
<td>23 (58%)</td>
<td>377 (51%)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>738</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Chemoimmunotherapy</th>
<th>Vitiligo</th>
<th>No vitiligo</th>
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<tbody>
<tr>
<td>Yes</td>
<td>12 (39%)</td>
<td>222 (45%)</td>
</tr>
<tr>
<td>No</td>
<td>19 (61%)</td>
<td>269 (55%)</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>491</td>
</tr>
</tbody>
</table>

aAs calculated on patients included in the univariate and multivariate analyses of survival.
bAdjuvant IFN administered to patients in stage III disease-free after surgery.
cIncludes different therapeutic schedules characterised by the association of chemotherapy and IFN/interleukin-2 administered to patients with stage IV metastatic melanoma.

IFN, interferon.
Table 3. Multivariate analysis of DMFS and OS Cox proportional hazards model in which vitiligo was entered as a time-dependent covariate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>RR</th>
<th>95% CI</th>
<th>Loss $\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III DMFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>0.651</td>
<td>0.102</td>
<td>1.918</td>
<td>1.597–2.342</td>
<td>40.989</td>
<td>&lt;0.001</td>
</tr>
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<td>Vitiligo</td>
<td>1.533</td>
<td>0.587</td>
<td>4.634</td>
<td>1.466–14.648</td>
<td>11.399</td>
<td>0.001</td>
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<td>AJCC IIIb</td>
<td>0.528</td>
<td>0.228</td>
<td>1.696</td>
<td>1.086–2.649</td>
<td>6.255</td>
<td>0.012</td>
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<tr>
<td>AJCC IIIc</td>
<td>1.080</td>
<td>0.250</td>
<td>2.944</td>
<td>1.802–4.809</td>
<td>21.739</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage III survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Breslow &gt;4 mm</td>
<td>0.351</td>
<td>0.111</td>
<td>1.420</td>
<td>1.142–1.765</td>
<td>9.697</td>
<td>0.002</td>
</tr>
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<td>Ulceration</td>
<td>0.672</td>
<td>0.105</td>
<td>1.958</td>
<td>1.593–2.406</td>
<td>40.397</td>
<td>&lt;0.001</td>
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<tr>
<td>Vitiligo</td>
<td>2.021</td>
<td>1.006</td>
<td>7.547</td>
<td>1.051–54.169</td>
<td>8.598</td>
<td>0.044</td>
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<tr>
<td>AJCC IIIb</td>
<td>0.420</td>
<td>0.217</td>
<td>1.523</td>
<td>0.995–2.331</td>
<td>4.217</td>
<td>0.050</td>
</tr>
<tr>
<td>AJCC IIIc</td>
<td>0.822</td>
<td>0.240</td>
<td>2.274</td>
<td>1.422–3.638</td>
<td>13.283</td>
<td>&lt;0.001</td>
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<tr>
<td>Stage IV survival</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>0.259</td>
<td>0.095</td>
<td>1.295</td>
<td>1.075–1.561</td>
<td>7.441</td>
<td>0.006</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>2.215</td>
<td>1.002</td>
<td>9.158</td>
<td>1.286–65.237</td>
<td>11.659</td>
<td>0.001</td>
</tr>
<tr>
<td>AJCC M1c</td>
<td>0.807</td>
<td>0.104</td>
<td>2.242</td>
<td>1.830–2.746</td>
<td>65.350</td>
<td>&lt;0.001</td>
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</tbody>
</table>

DMFS, distant metastasis-free survival; OS, overall survival; SE, standard error; RR, relative risk; CI, confidence interval.
Figure 1. Overall survival (A) and distant metastasis-free survival (B) according to the presence of vitiligo in stage III (patients with vitiligo, N = 40; patients without vitiligo, N = 738). Vitiligo patients included both patients who developed vitiligo after regional node dissection (n = 28) and patients who had vitiligo in stage I–II and subsequently progressed to stage III (n = 12).

Figure 2. Overall survival according to the presence of vitiligo in stage IV (patients with vitiligo, N = 31; patients without vitiligo, N = 492). Vitiligo patients included patients who developed vitiligo after visceral metastases (n = 3) and patients who had vitiligo in stage I, II and III and progressed to stage IV (n = 28).