Prognostic factors and survival of patients with primary cutaneous melanoma

Fatores prognósticos e sobrevida de pacientes com melanoma cutâneo primário

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ABSTRACT
Cutaneous melanoma has an aggressive clinical presentation with rapid growth velocity and metastatic dissemination. To evaluate prognostic factors and survival of patients diagnosed with primary cutaneous melanoma. Clinical-epidemiological and histopathological data from 102 patients diagnosed between 2004 to 2008, were retrieved from the archives of the Pathological Anatomy Service of the Araújo Jorge Hospital in Goiânia, Goiás, Brazil. For survival analysis, we selected patients who underwent a 60-month follow-up. Cutaneous melanoma affects mostly female individuals with the age of diagnosis ranging from 51 to 70 years. Regarding the clinical evolution of the patients 63.7% were alive during this study, and 25.5% died of melanoma. Metastasis were present in 47% of patients and 70.8% grew in the lymph nodes. The overall survival curve regarding the 5-year follow-up was 73%. The study group with Breslow index ≥2.1mm (p=0.0339), level of Clark IV and V (p=0.0007) and the presence of metastasis presented a lower survival rate. Early diagnosis emphasizing the significant prognostic factors of patients with cutaneous melanoma allows the definition of prognostic with a more reliable estimate and more survival probabilities.

Keywords: Melanocytes; Neoplasm Metastasis; Risk Factors; Skin Neoplasms.

RESUMO
O melanoma cutâneo apresenta apresentação clínica agressiva com rápida velocidade de crescimento e disseminação metastática. Avaliar fatores prognósticos e sobrevida de pacientes com diagnóstico de melanoma cutâneo primário. Dados clínico-epidemiológicos e histopatológicos de 102 pacientes diagnosticados no período de 2004 a 2008 foram extraídos dos arquivos do Serviço de Anatomia Patológica do Hospital Araújo Jorge de Goiânia, Goiás, Brasil. Para análise de sobrevida, selecionamos pacientes que foram submetidos a um seguimento de 60 meses. O melanoma cutâneo acomete principalmente indivíduos do sexo feminino com idade de diagnóstico variando de 51 a 70 anos. Em relação à evolução clínica dos pacientes, 63,7% estavam vivos durante este estudo e 25,5% morreram de melanoma. Metástases estavam presentes em 47% dos pacientes e 70,8% cresceram nos linfonodos. A curva de sobrevida global em relação ao seguimento de 5 anos foi de 73%. O grupo estudo com índice de Breslow ≥ 2,1 mm (p = 0,0339), nível de Clark IV e V (p = 0,0007) e a presença de metástase apresentaram menor taxa de sobrevida. O diagnóstico precoce enfatizando os fatores prognósticos significativos dos pacientes com melanoma cutâneo permite a definição de prognóstico com uma estimativa mais confiável e mais probabilidades de sobrevida.

Palavras-chave: Melanócitos; Metástase Neoplásica; Fatores de risco; Neoplasias Cutâneas.
1 INTRODUCTION

Skin cancer is the most prevalent neoplasia in the world. Cutaneous melanoma has an aggressive clinical presentation with rapid growth velocity and metastatic dissemination. Although it represents approximately 4% of all skin cancer, it shows a high lethality being responsible for 60% of all the deaths by cutaneous neoplasia (1,2). Shows a slightly higher frequency in females, which also presents a better prognosis and is uncommon in children, affecting predominantly middle-aged adults (3,4).

In most cases melanoma develops as an intraepidermal proliferation of neoplastic melanocytes that may be kept isolated in the epidermis or superficial dermis (5,6). At this stage of development, the melanoma has a high rate of cure through a proper surgical excision. The essential biological characteristics of the radial growth phase of melanoma appear slowly but with intense proliferation of atypical cells in the epidermis with possible neoplastic migration to the dermal papillae (7,8). In advanced stages, such as the vertical growth phase, the lesion may form nodules and infiltrate the reticular dermis reaching hypodermis (9,10). At this point, the lesions can metastasize and its prognosis is directly related to the depth of invasion (11,12).

The Breslow index is still the most important prognostic factor for melanoma (13). According to the tumor progression, from melanocyte hyperplasia to melanoma, there are five histologically distinct stages characterized by common nevi, atypical nevi, radial growth melanoma, vertical growth melanoma and metastatic melanoma (6). However, most cutaneous melanomas do not originate from melanocytic nevi, but as a de novo melanoma. This suggests that most melanomas do not follow this specific model of progression (1,9,11).

The knowledge of the epidemiology and pathogenesis of cutaneous melanoma provides subsidies for the application of primary and secondary preventive measures, which are fundamental to determine public health strategies. Melanoma may have a good prognosis if it is not thick, with cure rates approaching 100% for in situ melanomas Ferreira2016. When the diagnosis is made from the Breslow index and exceeds 4mm, survival falls to less than 50% in a five years’ time (14). Unlike most other tumors in which a tumor of 2mm to 3mm is at early stages, this size of tumor is already considered advanced regarding melanomas and show great lethality (8,15). In these cases, the surgical treatment after the early diagnosis is the only chance of cure. Therefore, this study evaluated the prognostic factors and survival of patients diagnosed with primary cutaneous melanoma.
2 METHODS

This is a retrospective study of clinical-epidemiological and histopathological data from 102 patients diagnosed with primary cutaneous melanoma. We retrieved data from the archives of the Pathological Anatomy Service of the Araújo Jorge Hospital (AJH) in Goiânia, Goiás, Brazil, during the period 2004 to 2008. For survival analysis, we selected patients who underwent a 60-month follow-up. We verified the death records from the Brazilian Mortality Information System and included patients whom melanoma was the cause of death.

Data were collected from medical records and histopathological reports with information regarding age, date of diagnosis, tumor location, family history of melanoma, histological type (superficial spreading melanoma, nodular melanoma, lentigo maligna, acral-mucosal melanoma or unclassifiable), regression, ulceration, peritumoral lymphocytic infiltration, mitotic index, microscopic satellites, Breslow tumor thickness, Clark level, regional lymph node involvement, margin involvement, distant metastasis and patient follow-up. We excluded incomplete medical records from the study. Tumors were classified according to the World Health Organization for cutaneous melanoma (International Classification of Diseases 10-C43).

The categories were found to be associated through the use of Chi-squared and Fisher’s tests. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. P< 0.05 was adopted as significant. SPSS® for Windows® (version 16.0) in order to perform statistical analysis. This study was submitted and approved by the Associação de Combate ao Câncer em Goiás (ACCG) and Universidade Federal de Goiás (UFG) Ethics and Research Committee.

3 RESULTS

The study population consisted of 62.7% females (64/102) and 37.3% males (38/102). The mean age observed for men was 63.1 years (SD ± 17.0) and women was 57.2 years (SD ± 17.3). The age difference between the groups and the most prevalent age group ranged from 51 to 70 years old (44.1%) (p<0.0026). However, there was a patient diagnosed at the age of 13 years old. We found statistically significant difference regarding the gender of the patients and the age group at the time of diagnosis (p<0.023) (Table 1).

The torso was the primary site most affected by cutaneous melanoma, affecting 32.3% of patients. Regarding the family medical history 70.6% of patients reported no
cases in the family and 10.8% reported cases of melanoma in the family. We found that superficial spreading melanoma was present in 52.9% of patients. The Breslow index (thickness of the tumor), the highest prevalence was ≤1.0mm, present in 39.2% of the cases, followed by injuries deeper than >4.0mm, present in 23.5% of patients. According to the Clark level, 29.4% of patients were level IV and 25.5% were level V. Ulceration was present in 45.1% and absent 54.9% of the samples. Tumor regression was observed in 11.8% and absent in 82.2%. The mitotic index was present in 91.2% of the samples and the peritumoral lymphocyte infiltration in 91.2%. Microscopic satellite was absent in 87.3% of the tumors evaluated and histopathological evaluation showed that 98% were tumor-free margin (Table 2).

Metastasis occurred in 47% of the cases. Regarding the clinical evolution of the patients, 63.7% were alive during this study, 25.5% died of melanoma and 10.8% died due from other causes, such as acute myocardial infarction (Table 2). Distant metastasis was present in 47% of patients during the five years period of the study (60 months) and 70.8% grew in the lymph nodes, 27.1% in the lungs and skin, 18.8% in the brain, 10.4% in the bones, 6.3% in the liver and the remaining 4.2% in the stomach (Figure 1). The sites of metastasis repeated two or three times in different locations such as lymph node and skin, lymph node, lung and brain.

The overall survival curve regarding the 5-year follow-up (60 months) was 73% (Figure 2). Survival rate for patients with cutaneous melanoma compared to the Breslow index ≤2mm was 82.3% and 64.1% for index ≥2.1mm (p=0.0339) (Figure 3). The survival rate for patients with cutaneous melanoma regarding the Clark level was 91.3% for levels I, II and III, and 62.5% for levels IV and V (p=0.0007) (Figure 4). The survival rate for cutaneous melanoma patients according to the development of metastasis was 58.3% for patients who develop metastasis and 90.7% for those who did not (p=0.0007) (Figure 5).

4 DISCUSSION

Melanoma prognosis is based on clinical and histopathological factors. The first step in developing strategies for disease prevention is to assess the magnitude of the problem and the characteristics of the affected population (1,6). In Brazil, epidemiological data are scarce.

According to the Brazilian National Cancer Institute (INCA) there are 6,260 new cases per year with 2,920 men and 3,340 women with cutaneous melanoma in Brazil in
2018 and 1,547 cases of death (903 men and 644 women) (16). The population-based cancer registries in Brazil, the city of Goiânia has the highest percentage of cases calculated by the standardized incidence coefficient (SIC) for invasive cutaneous melanoma among men (8.1/100,000). Among women, the highest SIC for invasive cutaneous melanoma is found in Goiânia (6.1/100,000) (1,17).

In this study 62.7% of the patients were female. The number of patients was more restricted due to 60-month follow-up within the period 2004-2008. Most melanoma studies performed in Brazil showed a prevalence of women patients, although few studies comprised a group of patients where males were more prevalent (1,15,18,19,20,21,22). Other studies did not found difference regarding gender and cutaneous melanoma in a study conducted in Goiânia, Goiás, Brazil (23).

The different study period may justify this change in the incidence of melanoma between men and women. Moreover, women seek medical attention more often, especially regarding dermatological care. This fact may be a possible explanation for the predominance of women in the sample group. Also, social inequalities and health policies explains the difference of health policies directed to women in Brazil and along with the lower participation of men in healthcare, generate important differences (9,10,12).

Brazil is a tropical country, with high temperatures during most of the year, thus it is expected that there will be greater sun exposure of people during life (15,17). Goiania is located in Brazil’s Midwestern region, at an average altitude of 749 meters and latitude - 16°40’43’’. It’s observed to have high and very high ultraviolet radiation rates in the fall and in the winter, and extreme ones in the spring and in the summer, according to National Institute for Space Research (INPE) (12).

In Brazil, skin cancer is the most incident, and melanoma is more aggressive than other types of this cancer. In the world, the cutaneous melanoma types are registered in countries with Caucasian population, while lower rates are commonly found in South American countries, where and Afro-American populations and pardos (triracial descendants of Europeans, Native Americans, and West Africans) predominate, as in Brazil (12,17).

The age of cutaneous melanoma diagnosis is related to prognosis and the higher the age the lower the survival of the patient (20). The mean age observed in this study was 57.2 years for women and 63.1 years for men (p<0.0026), and the age of diagnosis ranged from 51 to 70 years (44.1%). The mean age of cutaneous melanoma diagnosis in Goiânia was found averages of 54-60 years old. Despite the consistency of the results, it
is unclear why melanoma shows a tendency to increase the rate of diagnosis in middle-aged adults (1,15,21,23,24). A possible explanation is the cumulative effect of solar radiation besides deterioration of the immune system, DNA damage and DNA repair failures (10,25,26).

The primary site most affected by cutaneous melanoma was the torso (32.3%), followed by the lower limbs (24.5%). This confirms the relationship between the occurrence of cutaneous melanoma and exposure to solar radiation since its higher incidence affect areas more exposed to sun radiation. Most authors consider the torso the site of melanoma occurrence with the worst prognosis (19,27,28). Melanoma located in the head, neck and torso show the worst prognosis, and a lower survival rate of patients with lesions in their hands and feet (4,5,8).

A family history of melanoma is an important risk factor. Patients with cutaneous melanoma in first-degree relatives have twice the risk of developing cutaneous melanoma, while three or more family members with melanoma may increase the risk by 35 to 70 times (8,9,24,25). A family history of melanoma was present in 18.6% of patients.

The histological type of cutaneous melanoma most found was the superficial extensive melanoma (52.9%) followed by nodular melanoma (25.5%) associated with thicker tumors. Superficial extensive melanoma is predominant in Caucasians, followed by the nodular type, the lentigo maligna and the acral type (12,20). However, some studies show a predominance of the nodular type over the superficial extensive melanoma likely due to the ethnic differences of the extensive miscegenation in the Brazilian population (9,29).

The Breslow index, the highest incidence was tumors ≤1mm (39.2%) followed by lesions >4mm (23.5%). Considering the depth of the lesion, a large number of tumors showed thickness above 4mm. Araújo Jorge Hospital is a reference in oncology in the State of Goiás and the most serious and complex cases are referred to this institution. Studies found an increase in the incidence of thin melanoma (up to 1mm thick) compared to thick melanomas (greater than 3.5mm) (5,11,30). The increased incidence of thin melanoma is due to an early diagnosis, which leads to an improvement in survival rates (13). In Goiânia, Sortino-Rachou et al. found 2.8% melanoma in situ, and Fernandes et al. showed lower rates of in situ melanoma diagnosis (2.5%), which corroborates our results (23,31).
Today, a new concept that the density of melanoma cells at the position where Breslow thickness is measured is a morphological prognostic biomarker, which called Breslow density. This represents a novel morphological prognostic biomarker that is independent of Breslow thickness and has prognostic value for overall survival (2,11,13). In this study, the level of Clark IV corresponded to 29.4% followed by level V with 25.5%. The Clark level was initially an independent prognostic factor, such as the Breslow index. The American Joint Committee on Cancer (AJCC) stated in 2002 that the Clark level evaluate the prognosis of lesions when the Breslow index is <1mm. Currently, Clark’s level evaluates thin melanomas (≤1mm) only when information on the mitotic index is not available (5,32).

Ulceration is a histological feature associated with the strong aggressiveness of cutaneous melanoma. Ulceration was present in 40.2% of the analyzed samples. The survival rate of patients with ulcerated melanoma is proportionally worse compared to those without ulceration. The rate of ulcerated melanoma is about 35% for patients with localized disease and 6% for thin melanoma (32). Melanoma staging was the variable that most influenced the 10-year survival in patients with localized melanoma based on Breslow thickness and ulceration.

The mitotic index was present in 91.2% of the samples. Borges et al. showed the presence of mitoses aggravates the prognosis of patients with melanoma (20). A multivariate analysis of 10,233 melanoma patients reported that mitotic index is the second most important prognostic factor and tumor thickness based on Breslow index is the primary factor (32,33). The most significant correlation with survival was at a rate of at least one mitosis per cubic millimeter. The presence of mitoses is correlated with the reduction of disease recurrence time (28). Mitotic index influenced tumor thickness and ulceration but was not significant to patient survival.

About the distant metastasis onset 47% of the patients developed metastasis within the five-year follow-up period. Among, 70.8% of metastasis were in the lymph nodes, 27.1% in the lungs and skin, 18.8% in the brain, 10.4% in the bones, 6.3% in the liver and 4.2% in the stomach (figure 1). Approximately two-thirds of the initial metastasis will be limited to the drainage area of lymph nodes, making them the most common site of better metastatic cells survival. Distant metastasis may have a non-visceral character affecting skin, subcutaneous tissue and non-regional lymph node or a visceral character affecting mainly lungs (18-36%), followed by liver (14-20%), brain (12-20%), bone (11-17%) and gastrointestinal tract (1-7%) (14,32).
Non-visceral metastasis usually has a better prognosis when compared to visceral metastasis. Metastatic melanoma of an unknown primary site accounts for 2% to 5% of the cases and in 60% of the times lymph nodes are involved. Other sites affected are skin and subcutaneous tissue, less frequently the lung, brain and gastrointestinal tract (4,7,34). For metastatic disease, the presence and characteristics of lymph nodes and distant metastases are the major factors impacting survival.

About the clinical evolution of the patients in this study 25.5% died from melanoma. Studies there is an improvement in the survival rate of patients with cutaneous melanoma in recent years, which is attributed to an early diagnosis (6,33,35). Mortality rates declined in men and women younger than 65 years but increased for older individuals with cutaneous melanoma (6.6% for men and 0.6% for women) (34,35,36).

The overall survival curve with a 5-year follow-up of patients was 73%. Other studies with melanoma patients in Goiânia found an equal result (73% and 81.4%) (23,37). The patients evaluated in this study were observed from the moment of diagnosis, which was confirmed by histopathological report, until the moment they left the study either by death or by last outpatient contact (12,17). Further analysis including more years and more patients is required.

In the present study, mortality rate was higher with for higher Breslow index, Clark’s level and the presence of metastasis. Statistical analysis was significant when comparing melanoma mortality between the different levels of Breslow (p=0.0339), Clark (p=0.0007) and metastasis (p=0.0007), revealing a higher severity of the disease among patients. Survival rates for cutaneous melanoma patients compared to the Breslow index ≤2mm were 82.3% and 64.1% for Breslow index ≥2.1mm (p=0.0339). The risk increased linearly with tumor thickness up to a depth of 6mm from when the risk reaches a plateau (11,13,36,38).

In this study Clark level increase was directly related to the risk of death. The Clark levels I, II and III were 91.3% and levels IV and V were 62.5% (p=0.0007). Increasing Clark levels influenced the occurrence of melanoma deaths in patients with localized tumor, regardless of age, location of tumor, ulceration and tumor thickness. The level of Clark IV and V was associated with an increased risk of metastasis in the sentinel lymph node in patients with thick melanomas (>4mm) (38,39). Clark level V melanoma showed a 14-fold greater risk of death over 10 years than those with Clark level I melanoma (p<0.0001) (38).
In melanomas with thickness between 1mm and 2mm, the Clark level did not influence the occurrence of lymph node metastasis, the distance of metastasis neither the survival rate of patient (39). The survival rate of the individuals with and without metastasis was 58.3% and 90.7%, respectively (p=0.0007). Metastasis indicate a worse prognosis, with survival estimates assessed in months. Several studies found a shorter survival rate in individuals with metastatic melanoma (40,41,42,43,44).

5 CONCLUSION

Data from Brazil of melanoma patients and prognostic factors remain scarce. In this study cutaneous melanoma affects mostly female individuals with the age of diagnosis ranging from 51 to 70 years. The study group with Breslow index ≥2.1mm, level of Clark IV and V and the presence of metastasis presented a lower survival rate. This study shows that Brazilian melanoma patients experienced a lower survival rate than the current worldwide average. Evidencing the importance of an early diagnosis and emphasizing the significant prognostic factors of patients with cutaneous melanoma investigated in the present study allows the definition of prognostic groups with a more reliable estimate and allowed the calculation of survival probabilities. The increasing number of qualified professionals, prevention campaigns and sun protection tend to provide better early detection rates of the disease. This study showed an analysis of the population seen in our hospital, which is reference for the treatment of melanoma in Goiânia, Goiás, Brazil.

REFERENCES


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Figure 1: Distribution of the main sites of distant metastasis among patients with cutaneous melanoma.
Figure 2: Kaplan-Meier curves illustrating overall 5-year (60-month) survival rate of cutaneous melanoma patients.

Figure 3: Kaplan-Meier curves illustrating 5-year (60-month) survival rate regarding the Breslow index for patients with cutaneous melanoma.
Figure 4: Kaplan-Meier curves illustrating 5-year (60-month) survival rate regarding the Clark’s level for patients with cutaneous melanoma.
Figure 5: Kaplan-Meier curves illustrating overall 5-year survival (60 months) rate regarding metastatic development for cutaneous melanoma patients.

Table 1: Distribution of melanoma cases according to gender and age of the patients at the time of diagnosis in an oncological reference center.

<table>
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<tr>
<th>GENDER</th>
<th>FEMALE</th>
<th>MALE</th>
<th>TOTAL</th>
<th>p</th>
</tr>
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<tr>
<td>n (%)</td>
<td>64 (62.7)</td>
<td>38 (37.3)</td>
<td>102 (100)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Average age (±SD)</td>
<td>57.2 (±17.3)</td>
<td>63.1 (±17.0)</td>
<td>59.4 (±17.3)</td>
<td>0.023</td>
</tr>
<tr>
<td>Age group at diagnosis</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
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<tr>
<td>10-30</td>
<td>7 (10.9)</td>
<td>0 (0)</td>
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<tr>
<td>31-50</td>
<td>17 (26.6)</td>
<td>5 (13.2)</td>
<td>22 (21.5)</td>
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<tr>
<td>51-70</td>
<td>22 (34.4)</td>
<td>23 (60.5)</td>
<td>45 (44.1)</td>
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<tr>
<td>71-90</td>
<td>17 (26.6)</td>
<td>10 (26.3)</td>
<td>27 (26.5)</td>
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</tr>
<tr>
<td>91-100</td>
<td>1 (1.5)</td>
<td>0 (0)</td>
<td>1 (1.0)</td>
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</table>
Table 2: Clinical and histopathological characteristics of patients diagnosed with cutaneous melanoma, in an oncological reference center.

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<th>VARIABLES</th>
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<td>Primary local</td>
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<td>32.3</td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td>Face / Scalp</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>13.8</td>
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<td></td>
<td>Palmoplantar</td>
<td>9.8</td>
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<td></td>
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<td></td>
<td>Yes</td>
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<tr>
<td>Family history of melanoma</td>
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<td>70.6</td>
</tr>
<tr>
<td></td>
<td>No information</td>
<td>18.6</td>
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<tr>
<td></td>
<td>Extensive Superficial</td>
<td>52.9</td>
</tr>
<tr>
<td></td>
<td>Nodular</td>
<td>25.5</td>
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<td>Histological type</td>
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<td></td>
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<td>Unclassifiable</td>
<td>4.9</td>
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<tr>
<td></td>
<td>In situ</td>
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<tr>
<td>Breslow’s index</td>
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<tr>
<td></td>
<td>1.01 a 2.0 mm</td>
<td>21.6</td>
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<td></td>
<td>2.01 a 4.0 mm</td>
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<tr>
<td></td>
<td>II</td>
<td>23.5</td>
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<td>Clark’s level</td>
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<td></td>
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<td></td>
<td>V</td>
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<td>Regression</td>
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<td></td>
<td>Absent</td>
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<td>Mitotic Index</td>
<td>Present</td>
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<tr>
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<td>Absent</td>
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</tr>
<tr>
<td></td>
<td>Present</td>
<td>91.2</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>---------------------</td>
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<td>Peritumoral Lymphocyte Infiltration</td>
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<td>Microscopic Satellite</td>
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<td>Positive margins</td>
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<td>47</td>
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<td>Metastasis</td>
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<td>Progression</td>
<td>Died from melanoma 25.5</td>
<td>Died from other causes 10.8</td>
</tr>
</tbody>
</table>