Original article

Cutaneous malignant melanoma in situ: A Danish cross-sectional study on patient and tumour characteristics in 144 cases
Population-based cross-sectional study

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ABSTRACT

Introduction: Cutaneous malignant melanoma in situ (MIS) has not been subject to much attention or investigation. Little is known of the characteristics of patients and tumours. The aim of this study was to elucidate important tumour characteristics in patients treated for MIS.

Methods: Based on data from the Danish Melanoma Register, patient and tumour characteristics were evaluated in a cross-sectional study including all patients diagnosed with cutaneous malignant melanoma in Health care Region Zealand between 2012 and 2013.

Results: A total of 144 patients were identified with malignant melanoma in situ; more females were affected than males, and the males were older than females. Patients with lentigo maligna were older than patients with superficial spreading MIS, which were predominantly found in the head and neck region. Among patients treated for MIS, 28% were previously treated for other skin malignancies.

Conclusion: The anatomical distribution of MIS differed with patient age and tumour subtype. The anatomical distribution was different in comparison to invasive malignant melanomas, and...
MIS cases were generally older. This suggests a non-linear relation between malignant melanoma in situ and invasive malignant melanoma.

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Introduction

Cutaneous malignant melanoma in situ (MIS) is thought to be a precursor to invasive cutaneous malignant melanoma (CMM). However, all MISs may not progress to CMM. In Denmark, MIS is treated according to guidelines from the Danish Melanoma Group, which implies local radical excision at 5-mm distances to the tumour, and a profound resection of a superficial part of the subcutaneous fat, ensuring complete removal of the dermis in the affected area.

Patients with MIS have an increased risk of developing a subsequent MIS. In addition, they have 4.6 times increased risk of developing subsequent invasive CMM compared with the general population. An annual increase in the MIS incidence rates of up to 15% has been reported in Australia, USA and Sweden. The highest incidence rates of CMM in Europe are found in Northern and Western countries (Scandinavian countries, the Netherlands, UK and Ireland) and the lowest incidence rates have been observed in Spain and Portugal. World Health Organisation (WHO) Globocan reports that the Danish female population has the third highest risk of melanoma in the world (First is New Zealand, with Australia in the second place), and the Danish female population aged 15–39 years had the highest incidence of CMM in the world. In 2006, Denmark showed the highest incidence rates across Europe (both genders), and different studies have suggested a continuous annual increase in the incidence rate of more than 3%. Whereas CMM only represents approximately 4% of all skin cancers, the disease is responsible for approximately 80% of all skin cancer-related deaths.

Over the years, the people of Denmark have changed from a culture of avoiding the sun to seeking it instead. Furthermore, during the 1960s, artificial sun devices were introduced in Denmark, and a cross-sectional study by Koster et al in 2009 showed that 29% of all Danes aged 15–59 had used sunbeds within the past 12 months. Among female children and adolescents aged 15–19 years, 59% had used sunbeds within the past 12 months. As a consequence of the altered sun exposure pattern, in addition, we hypothesize that the patient and tumour characteristic may have changed during the past decades. In order to improve targeted examination and intervention, the main aim of this study was to describe patient and tumour characteristics in a cohort of Danish MIS.

Method

Study design and setting

This was a cross-sectional study based on the entire population living in the Health care Region Zealand (approximately 800,000 inhabitants) in Denmark. Data were obtained from the national Danish Melanoma Registry (DMR), which holds prospectively collected information on patients diagnosed with MIS or CMM in Denmark. Reporting to DMR is mandatory for all departments involved in the diagnosis and treatment of malignant melanoma. The recorded data include specific information on disease characteristics, treatment and follow-up. Patients are registered in DMR after a histological confirmation of the MIS.

Participants

This study included patients diagnosed with primary MIS between January 2012 and December 2013, residing in the Health care Region Zealand (a governmental administration unit comprising the
islands Zealand (except the Copenhagen capital area), Lolland, Falster and several minor islands with a total population of approximately 810,000 inhabitants corresponding to 14% of the entire Danish population (2013)). The study excluded patients with unknown tumour thickness and Clark level due to limitations in biopsy material and patients with otherwise incomplete set of data who could not be supplemented from the patient records.

Variables

The histological examination was conducted at the Department of Pathology, Roskilde University Hospital, which is a highly specialized facility investigating all melanocytic tumour biopsies from Region Zealand. All patients were treated at the Department of Plastic Surgery, Roskilde University Hospital, which is a centralized and highly specialized facility treating all patients in the Region Zealand suspected or diagnosed with melanoma.

We obtained data on patient characteristics (gender, age), anatomical tumour location and tumour characteristics. In addition, we supplemented the data with information on previous malignant tumours from the national Danish Pathology Registry (DPR), which holds information on all pathological examinations in Denmark. Although it contains some information from as early as 1970, reporting to DPR has been mandatory since 1997.15

Statistics

Number and proportions were used to describe patient and tumour characteristics. In variables that were not normally distributed, median values were used with minimum and maximum values. Non-parametric Mann–Whitney statistical test was used to test for difference in these cases. Differences in tumour site, age groups, MIS tumour type and other skin cancer types were tested using chi-squared test (Fischer’s exact). Level of significance was set at $p = 0.05$. All statistical methods were computed using the dedicated statistical software InStat (version 3) and Prism (version 5), GraphPad, USA.

Results

Participants

A total of 151 patients of MIS were identified. Seven patients were duplets and subsequently excluded as only the first MIS of each patient was used in the following comparative analysis. A total of 144 patients with MIS (Clark level 1) were thus included in this study (Table 1).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>144 (100)</td>
<td>78 (54)</td>
<td>66 (46)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median age (range) (years)</td>
<td>66 (26; 98)</td>
<td>63 (26; 98)</td>
<td>68 (28; 89)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Tumour site (no, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>59 (41)</td>
<td>29 (37)</td>
<td>30 (45)</td>
<td>0.08</td>
</tr>
<tr>
<td>Trunk</td>
<td>38 (26)</td>
<td>17 (22)</td>
<td>21 (32)</td>
<td></td>
</tr>
<tr>
<td>Upper extremities</td>
<td>19 (13)</td>
<td>11 (14)</td>
<td>8 (12)</td>
<td></td>
</tr>
<tr>
<td>Lower extremities</td>
<td>22 (15)</td>
<td>17 (22)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>6 (4)</td>
<td>4 (5)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Tumour type (no, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>80 (56)</td>
<td>45 (58)</td>
<td>35 (53)</td>
<td>0.32</td>
</tr>
<tr>
<td>Acral lentiginous</td>
<td>2 (1)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>62 (43)</td>
<td>31 (40)</td>
<td>31 (47)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>
Of the 144 patients included for analysis, 78 (54%) were female and 66 (46%) were male patients. Overall median age was 66 years (median age; males: 68 years vs. females: 63 years, \( p < 0.05 \)).

Both genders had MIS predominantly localized in the head and neck region (41% of all MIS) followed by trunk (26% of all MIS). There was no statistical difference in anatomic localization between the genders, \( p = 0.08 \). Of the 144 MIS, superficial spreading malignant melanoma (SSM) in situ accounted for 56%, lentigo maligna (LM) 43% and acral lentiginous melanoma (ALM) in situ 1%, respectively. There was no statistically significant difference between the genders, \( p = 0.32 \).

We found the median age to be significantly higher among patients with LM in comparison to SSM in situ – 71 years (range: 46–98) versus 59 years (range: 26–93), respectively, \( p < 0.001 \). We compared the anatomical localization between age groups (age <21 years (\( n = 0 \)), 21–40 years (\( n = 8 \)), 41–60 years (\( n = 39 \)), 61–80 years (\( n = 81 \)) and >80 years (\( n = 16 \)) and found a significant difference in anatomical distribution between the age groups, \( p > 0.001 \) (Figure 1). While 49% of the tumours in the age group '61–80 years' were located in the head and neck region, the '>80 years' age group had 75% of the tumours located in the head and neck region. In contrast, the '41–60 years' age group had tumours located on the trunk (46%), with 13% located in the head and neck region. We compared the anatomical localization of LM (\( n = 61 \), one missing data on tumour localization) and SSM in situ (\( n = 75 \), five missing data on tumour localization) and found an overall significant difference in the anatomical distribution (\( p < 0.001 \)) as patients diagnosed with LM, 82% were located in the head and neck region and only 3% were located on the trunk. In comparison, 48% of SMM in situ were found on the trunk, and 22% were found in the head and neck region.

Furthermore, we investigated the historic prevalence of previous skin cancer and actinic keratosis (considered to be a precursor for squamous cell cancer) in the patients’ data retrieved from the Danish Registry of Pathology. Among the 144 patients diagnosed with MIS, we found 41 (28%) with prior (all time) one or more malignant skin tumour type (no difference was found between genders; \( p = 0.85 \)) (Table 2). The previous skin tumour types comprised non-melanocytic skin cancer in 32 patients (78%) and melanocytic skin cancer in nine patients (22%) (all \( \geq \) Clark level 2). In total, nine patients were diagnosed with more than one (two to three) additional different skin tumour types.

Discussion

Melanocytic malignancies of the skin are recorded in three different registries in Denmark: (1) Danish Melanoma Registry administered by the Danish Melanoma Group, (2) Danish Cancer Registry (DCR) and (3) the DPR administered by the Danish Society of Pathology. Whereas DCR contains more general information (ICD-10 and tumour, node, metastasis (TNM) classification), DMR and DPR

Figure 1. Comparison of the anatomical localization of malignant melanoma in situ in age subgroups among 144 patients diagnosed between 2012 and 2013 in Health care Region Zealand.
contain more specific data on tumour subtype and histologic characteristics. We based our study on data from DMR and DPR, as these two registries combined covered our requirements. Health care Region Zealand and its inhabitants are comparable to the other four health-care regions in Denmark, and therefore we believe that our results to a large extent are representative of the entire population of Denmark. Although all treatment and diagnostics were conducted at a single institution (Roskilde University Hospital), all clinical procedures and pathological examination strictly followed the national guidelines provided by the Danish Melanoma Group. This study population reflects the Danish population, which is generally well educated, ethnically homogeneous (Caucasians) and benefiting from a uniform public health-care system covering all citizens, and thus limiting the generalizability to other populations with different health-care systems, demographics or treatment protocols. We attempted to increase the completeness of our data set by validating all data which included identifying irregularities and rectifying the data by reviewing the histological examinations and clinical reports. However, the cross-sectional design of our study precludes conclusions on causality and analyses changes in variables over time.

The median age in our study population was 66 years. More females were diagnosed with MIS in comparison to males, 54% versus 46%, respectively. SSM in situ accounted for 56% of the lesions, while LM and NM (nodular melanoma) 1% accounted for 43 and 1%, respectively. We found no difference in tumour type or tumour localization between genders. When comparing age groups (21–40, 41–60, 61–80, >80 years) to the anatomical site of the lesion, we found that tumours were more likely to be found on the head and neck region among the oldest patients (>61 years), whereas they were more likely to be found on the trunk among the younger patients (41–60 years, \( p < 0.001 \)). Patients diagnosed with LM were older in comparison to those with SSM in situ (median age 71 vs. 59 years, respectively; \( p < 0.001 \)). In addition, we found that LM was predominantly found on the head and neck region, whereas SSM in situ was predominant on the trunk (\( p < 0.001 \)). This suggests that there are two subgroups consisting of SSM in situ and LM with rather different patient characteristics within the MIS population. In this study, nine (6%) patients had previously been diagnosed with melanoma skin cancer (MSC), all of them with invasive CMM. In addition, 22% of the patients had previously been diagnosed with non-MSC (NMSC). On the basis of these results, in order to identify additional skin tumours, we suggest that the diagnosis of MIS should lead to a thorough clinical examination of the body surface.

Compared to the 520 patients diagnosed with CMM in the same period (Reference: Accepted for publication in Danish Medical Journal, June 2015), patients with MIS were significantly older (CMM median age 61 years vs. MIS median age 66 years; \( p < 0.01 \)).

For both genders, MIS was predominantly located on the head and neck region followed by the trunk, whereas CMM was predominantly located on the trunk and lower extremities (Figure 2). The difference in anatomical localization between MIS and CMM was significant, \( p < 0.01 \). The identified differences in anatomical distribution and in median age between MIS and CMM contradict the general assumption that MIS is a simple precursor of CMM. But, as described earlier, the MIS group appears to consist of two

<table>
<thead>
<tr>
<th>Table 2 Prevalence of other skin malignancies among 144 patients diagnosed with cutaneous malignant melanoma in situ.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>Other tumour types (no, %)</strong></td>
</tr>
<tr>
<td>Yes (one or more)</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>Tumour types (no, %)</strong></td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Square cell carcinoma</td>
</tr>
<tr>
<td>Actinic keratosis</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Melanoma skin cancer</td>
</tr>
<tr>
<td>Invasive cutaneous malignant melanoma (≥Clark level 2)</td>
</tr>
<tr>
<td>Malignant melanoma in situ (Clark level 1)</td>
</tr>
</tbody>
</table>
subgroups, of which the ‘SSM in situ’ group shows patient characteristics similar to CMM (tumour localization predominantly on the trunk in both groups and median age 59 years vs. 61 years, respectively). It has been shown that patients who had a primary MIS on body sites other than the head and neck have a significantly higher risk of developing a subsequent primary CMM compared with patients who had their primary MIS on the head and neck — in particular if the lesion was located on the lower extremities.4 These observations support the fact that LM has less potential for malignant transformation in comparison to SSM in situ, and thereby tends to weaken the general association between MIS and CMM.

In a recently published study based on data from Danish Registry of Pathology between 1997 and 2011, Toender et al found an overall fourfold increase in the incidence rate of MIS in Denmark from 1.97 to 8.7 cases per 100,000 person years with a threefold increase among females (2.6–8.1) and a fourfold

**Figure 2.** Comparison of the anatomical localization of tumours in patients diagnosed with malignant melanoma in situ (144 patients) or invasive malignant melanoma (517 patients) between 2012 and 2013 in Health-care Region Zealand.

**Picture 1.** An 80-year-old male was referred with a brown tumour localized on the auricular helix measuring $7 \times 4$ mm (Picture 1). The element was treated with a wedge excision of 5-mm excision margins. The histological examination confirmed the diagnosis of lentigo maligna (LM). Although the boarders of the tumour appeared to be relatively well defined, the initial excision was not radical, and a subsequent wedge excision was done. This case report illustrates that determining the extension of LM can be challenging.
increase among males (1.4–5.6).\textsuperscript{19} Furthermore, the highest increase was found for the latest 5-year period (2007–2011) in the time period investigated. As this study is a cross-sectional study, we cannot draw conclusions on incidence (see Figure 1).

In a population-based study from Sweden, they found the peak incidence rate of MIS to be at 75–84 years among males and 60–64 years among females. In addition, they found that males develop MIS on the head and neck, while the female population develop MIS at the lower extremities.\textsuperscript{17}

In a recently published Australian study,\textsuperscript{4} it was found that more males in comparison to females developed MIS (54\% vs. 46\%, respectively) and that more elderly people (>65 years) developed MIS. They found an anatomical distribution for the first MIS as follows: head 30\%, trunk 28\%, upper extremities 24\%, lower extremities 15\% and not specified 2\%. MIS was found to be significantly more likely to appear in the head and neck region compared with CMM. All these reported findings are in line with our results.

Conflict of interest

None.

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None.

Approvals

This study was approved by the Danish Data Protection Agency, reference number 2008-58-0020/12-000179.

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