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ORIGINAL ARTICLE

Metastatic melanoma mortality in Malta

Liam Mercieca, Kristie Tonna, Alexandra Betts, Susan Aquilina

Background

There are currently no studies looking specifically at the characteristics of the primary melanoma in patients who died of metastatic melanoma in Malta. This retrospective study looks at the demographics of these patients and the characteristics of their primary melanoma.

Method

Mortality data secondary to metastatic melanoma between 2007 and 2016 was gathered from the Malta National Mortality Registry. All patients whose death certificates had metastatic melanoma as the cause of death were included. Further data on histology and imaging was gathered from the Malta National Cancer Registry and the hospital electronic database.

Results

There were 87 recorded deaths (45 male; 42 female) in Malta secondary to metastatic melanoma between 2007 and 2016, with an average age at diagnosis of the primary melanoma of 64.3 years (range 23-92 years), average age at death of 67.9 years (range 28-96 years) and an average duration of survival after diagnosis of primary melanoma of 34.7 months (range 1-180 months). The commonest histological subtype of the primary cutaneous melanoma was nodular. The commonest site for the primary cutaneous melanoma was the back. The mean Breslow thickness was 4.23mm (range 0.3-13mm). The commonest site of metastasis was to distant lymph nodes, followed by the skin, liver and lung.

Conclusion

Mortality secondary to metastatic melanoma is prevalent in the over 60 age group, with the back being the commonest site of the primary melanoma. Identification of patients who are at higher risk of death from melanoma in Malta allows for their more effective targeting in local melanoma screening and education campaigns.

Liam Mercieca MD, MRCP*
Dermatology Department
Mater Dei Hospital
Msida Malta
liam.mercieca@gmail.com

Kristie Tonna MD, Dip Derm
Primary Health Care Department
Floriana, Malta

Alexandra Betts BChD, MPhil, FRCPath
Pathology Department
Mater Dei Hospital
Msida, Malta

Susan Aquilina MD, FRCP
Dermatology Department
Mater Dei Hospital
Msida Malta

**Corresponding author*

Introduction

Melanoma is the most serious form of skin cancer, due to the significant risk of metastasis and death. Risk factors for cutaneous melanoma include sun exposure, increasing number of moles on the skin, the presence of atypical moles, fair skin, family or personal history of melanoma, immunosuppression and increasing age.[1] The ABCDE (asymmetry, border, colour change, diameter, evolution) pattern and the ugly duckling sign are useful educational tools to help the general public pick up any warning signs for melanoma.[2]

The Maltese islands have a high UV index for several months of the year with the population being exposed to intense sunlight particularly in the spring and summer months. The majority of the population is of skin phototype II to IV.[3] This means that a significant percentage of the population is susceptible to skin burning when exposed to the sun, which is a risk factor for the development of melanoma. In Malta, melanoma incidence has been on the increase over the past twenty years,[4] a trend which has been observed in white populations worldwide.[5-8] The standardised incidence for primary invasive cutaneous malignant melanoma in Malta increased from 3.7 per 100,000 population per year for males and 5.1 for females between 1993-1997, to 10.1 per 100,000 population per year for males and 12.1 for females in 2017.[4] Despite this, mortality from melanoma has remained stable between 2007 and 2017,[4] presumably because the increased incidence is mainly for thin melanomas of low metastasizing potential.[6]

Established bad prognostic factors indicating a higher risk of death in patients with cutaneous melanoma include increasing tumour thickness (Breslow thickness), ulceration, mitotic rate, number of metastatic nodes, clinically apparent nodal metastasis and visceral metastasis.[9]

Traditionally, the treatment of cutaneous melanoma has involved surgical excision with narrow margins, followed by wider surgical excision with margins guided by the Breslow thickness (Table 1).[10] Sentinel lymph node biopsy (SLNB), performed at the time of the wider excision,[10] is offered to patients depending on the Breslow thickness (>1mm) and other high risk factors. SLNB for melanoma has been offered in Malta since May 2010. Further investigation (blood tests, ultrasound, CT, PET scans etc) would be indicated according to the prognosis of the patient; most patients with thin melanomas (Breslow thickness <1 mm) would be treated only with surgery and close clinical follow up.

Table 1 Recommended excision margins of a primary melanoma depending on depth of invasion.

Breslow thickness, mm	Recommended excision margin, cm
In situ	0.5
≤ 1.0	1
1.01-2.00	1-2
2.01-4.00	1-2
> 4.0	2

There are no studies looking specifically at the demographics of patients dying of metastatic melanoma in Malta, or the characteristics of their primary melanoma. This retrospective study aims to look at these factors, to help identify the patients who are at a higher risk of death from melanoma in Malta, so they may be targeted more effectively in local melanoma screening and education campaigns.

Methods

Data for this study was collected retrospectively from the Malta National Mortality Registry. All patients whose death certificates listed metastatic melanoma as the cause of death between 2007 and 2016 were included in the study. Further data on histology and imaging was gathered from the Malta National Cancer Registry and the hospital electronic database when available. Data collected included demographic details, date of diagnosis of the primary melanoma, date of death, melanoma histological subtype, site of primary melanoma, Breslow thickness, Clark's level, presence of ulceration, lymph node involvement including sentinel lymph node biopsy result and site of distant metastasis when imaging was available.

Results

There were 87 recorded deaths (45 were male and 42 were female) secondary to metastatic melanoma in the ten-year period between 2007 and 2016. The primary melanoma was identified histologically in 57 cases (66%), whilst 24 cases (27%) had confirmed metastatic melanoma on histology and imaging, but the primary melanoma was not identified. The remaining 6 cases (7%) originated from an extra-cutaneous primary site. The commonest histological subtype of the primary cutaneous melanoma was nodular followed by superficial spreading and acral melanoma (Table 2a). The commonest site for the primary melanoma was the back, followed by the hands and feet (acral), followed by the legs (Table 2b).

Table 2a Histological subtype of the primary melanoma

Melanoma histological subtype	Percentage (number of cases,n=87) Male(M), Female (F)
Nodular	25% (*n*=22; M16:F6)
Superficial spreading	17% (*n*=15; M8: F7)
Acral lentiginous	15% (*n*=13; M3:F10)
Other (balloon cell ,mucosal, desmoplastic, choroidal)	7% (*n*=6; M2:F1)
Not available/Primary not identified	36% (*n*=31; M15:F16)

Table 2b Site of the primary melanoma

Site of primary	Percentage (number of cases, n=87) Male(M), Female (F)
Back	22% (*n*=19; M13:F6)
Acral	15% (*n*=13; M10:F3)
Legs	13% (*n*=11; M5:F6)
Arms	9% (*n*=8; M4:F4)
Head and neck	7% (*n*=6; M5:F1)
Chest and abdomen	5% (*n*=4; M3:F1)
Choroidal (eye)	2% (*n*=2; M0:F2)
Genital	2% (*n*=2; M1:F1)
Paranasal sinus	1% (*n*=1; M1:F0)
Oral	1% (*n*=1; M1:F0)
Lung pleura	1% (n=1) (M0:F1)
Anal	1% (n=1) (M1:F0)
Not available/Primary not identified	21% (n=18)

The average age at diagnosis of the primary melanoma was 64.3 years (range 23-92 years, median 65 years), the average age at death was 67.9 years (range 28-96 years, median 69 years) and the average duration of survival after diagnosis of the primary melanoma was 34.7 months (range 1-180 months, median 19 months).

Table 3 shows the Breslow thickness and Clark's level in the 57 cases (66%) where histology of the primary melanoma was identified. The mean Breslow thickness was 4.35mm (range 0.3-13mm). Ulceration was present in 21 cases. Five patients who died of metastatic melanoma had a primary cutaneous melanoma with a Breslow thickness <1mm. Their characteristics are shown in Table 4.

A sentinel lymph node biopsy result was available in a total of 30 cases; 28 of these were positive while 2 were negative. The 2 cases that presented with a negative sentinel lymph node biopsy and eventual metastasis had their primary melanoma on the back and a Breslow thickness of 3.5 mm and 12 mm respectively. The commonest sites of distant metastasis were to distant lymph nodes, liver and skin (Table 5).

Table 3 Breslow thickness and Clark's level of the primary melanoma

Breslow thickness	Percentage (number of cases, n=57)
In situ	0% (*n*=0)
0.1 – 1.0mm	8% (*n*=5)
1.01 – 2.0mm	18% (*n*=10)
2.01 – 4.0mm	32% (*n*=18)
>4.0mm	42% (*n*=24)
Clark level	**Percentage (number of cases, n=57)**
1	0% (*n*=0)
2	4% (*n*=2)
3	25% (*n*=14)
4	56% (*n*=32)
5	15% (*n*=9)

Table 4 Data for patients with a Breslow thickness between 0.1-1mm (*n*=5)

Sex	Months between diagnosis and death	Melanoma type	Primary Melanoma Site	Breslow Thickness	Clark's Level	Ulceration present (Y/N)	Site of documented metastasis
F	39	Superficial spreading melanoma	Left foot	0.3	2	N	Leg
M	7	Superficial spreading melanoma	Left leg	0.7	3	N	Brain
F	138	Not available	Chest	0.8	3	N	Axillary lymph node
F	15	Invasive superficial spreading malignant melanoma	Right leg	0.93	3	N	Inguinal lymph node
F	38	Invasive superficial spreading malignant melanoma	Left flank	0.93	3	N	N/A

Table 5 Documented sites of metastasis (The same patient might have had two or more distant metastasis sites. Data on the site of metastasis was not available in 39 cases)

Site of metastasis	Number (*n*=48)
Distant lymph nodes	33
Liver	8
Skin	7
Lung	6
Bone	5
Brain	2
Bowel	2

Discussion

Our study shows that death from melanoma in Malta, as seen in other countries, is more common in the older age groups, with an average age at death of 67.9 years, occurring within an average of 34.7 months of diagnosis of the primary melanoma. Older people also show a higher incidence of melanoma, in Malta as well as worldwide, where melanoma incidence (age standardised) rates peak at the seventh and eighth decades of life.[11]

The commonest histological type of melanoma causing metastasis and death in our cohort was nodular melanoma, followed by superficial spreading and acral melanoma. This does not come as a surprise as, although superficial spreading melanomas are the commonest form of melanoma, they tend to be diagnosed at less than 1 mm thickness, as opposed to nodular melanomas that tend to be thicker than 2 mm at the time of diagnosis and would therefore be associated with a worse prognosis.

The back was the commonest skin site for the primary melanoma leading to death in our cohort. Among Caucasian populations, including the Maltese population, melanoma is more frequently reported on the backs and shoulders in men and on the lower limbs in women.[5-6,11] The back should be emphasized in educational campaigns so that patients ensure that this part of their body is checked regularly by other family members, their doctor or friends, or else with the use of a mirror. Mole mapping in selected cases can be useful as a baseline photographic record for long-term screening in order to allow objective comparison and early detection of any changes in pigmented lesions, especially in areas that are difficult to monitor. The primary melanoma leading to metastasis was never identified in 27%(*n*=24) of cases. This could be due to regression of the primary tumour or due to patients presenting at a terminal stage or the melanoma occurring in an inaccessible site.

As expected, thick primary melanomas correlated with an increased risk of death. The mean Breslow thickness in our cohort was 4.35mm and we had no patients dying of

metastatic melanoma who had presented with an *in situ* primary melanoma. However, 8% of the total deaths due to melanoma in our cohort had a primary melanoma with Breslow thickness of only 0.3 to 1 mm and showed no ulceration. Internationally, patients with a primary melanoma with Breslow thickness <1 mm have a 95% 5-year survival rate.[12] Our results do remind us that patients in the thin melanoma category may – rarely – still develop metastases and die from them.

Sentinel lymph node biopsy carried out in our cohort was positive in 38 cases and negative in only 2. Several international large-scale studies have reported a relatively high false-negative rate for SLNB (5.6-21%).[13] The false negative rate of SLNB biopsy in Malta cannot be determined from this study as we only studied patients who died of melanoma. However, our results do highlight the small possibility of a false negative result with a SLNB biopsy, which should be communicated to the patient.

A limitation of the study is the small number of patients, despite including the whole population on the islands over a 10-year period. Data on the primary melanoma was unavailable in about one fourth of cases since these patients were diagnosed at the metastatic stage. Patients included in the study had metastatic melanoma as the primary cause of death on their death certificate. However, co-morbidities which may have contributed to death were not taken into account in this study. The site of metastasis was unavailable or undocumented in a number of cases and patients may have had undocumented metastases elsewhere.

In recent years, the management of melanoma has undergone some very important changes. Up to a few years ago, due to the absence of effective systemic therapy options, surgery was viewed as the only potential curative treatment. A big leap in the treatment of metastatic melanoma occurred with the advancement of new systemic therapies, including immunotherapy with cell cycle checkpoint inhibitors (e.g. nivolumab and pembrolizumab) and targeted therapies aimed at BRAF and MEK mutations (including dabrafenib and trametinib), which may also be used in the adjuvant setting. These treatments became available in Malta in recent years. There has also been a move away from performing complete lymph node dissection in patients with a positive sentinel lymph node (clinically occult disease), as no overall survival benefit was shown over observation with nodal basin ultrasound surveillance in two large prospective randomized phase III studies (MSLT-II and DeCOG).[14] These patients would now be offered adjuvant therapy, so the role of SLNB is changing from that of a prognostic indicator to one that influences access to adjuvant treatment.[15] The American Joint Committee on Cancer (AJCC) published the eighth edition of its staging system for melanoma in 2017,[12] to move towards a 'more personalized' approach to the treatment of melanoma. It is hoped that future studies on melanoma mortality in Malta will reflect the positive influence of these new management strategies.

Finally, local campaigns to advise the public not to overexpose their skin to the sun should also be continued and promoted, together with campaigns to encourage earlier detection and treatment of melanomas when they present on the skin or accessible parts of the body. With this three-pronged approach of primary prevention of melanoma, early detection and treatment, and improved management of patients with metastatic

melanoma, we hope that as few patients as possible will succumb to this cancer.

Conclusion

This study has provided more local data on melanoma to help in the fight against this cancer. It confirms that death from melanoma is highest in patients over 60 years of age. It also highlights the importance for individuals to have their backs checked since this is the commonest primary melanoma site leading to mortality.

Summary Box

What is known:

- Melanoma causes significant mortality
- Early diagnosis is key
- Latest guidelines on staging updated
- New treatments available

New findings:

- There has been a rise in melanoma incidence but not mortality in Malta over the past 10 years
- Death from melanoma in Malta is commonest in the over 60 age group.
- The characteristics of the primary melanoma leading to metastatic melanoma in Malta have been identified. The commonest site for the primary was the back, with nodular melanoma being the commonest histological type.

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