

Analysis of prognostic factors for melanoma patients

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Introduction. Melanoma is the most dangerous form of skin cancer. Morbidity from melanoma is increasing every year. Previous studies have revealed that there are some demographic and clinical factors having effect on melanoma survival prognosis.

Aim of the study. Purpose of our study was to assess melanoma survival depending on prognostic factors, such as age, sex, stage, depth, histology and anatomical site.

Materials and methods. We investigated melanoma-specific survival up to 10 years in 85 primary cases of melanoma from diagnosis at the National Cancer Institute in 2006. Analysis was performed for one-, five-, and ten-year survival. The data were processed with Microsoft Excel, data analysis was conducted using SPSS[®] software.

Results. Melanomas diagnosed at stage IV or thicker than 4.00 mm had lower survival (five-year survival: 12.5% and 26.66%, respectively). A significant survival difference was observed among the different stages ($p = 0.003$) and different depths ($p = 0.049$) of melanoma. Ten-year survival was 32% for men and 61% for women, but melanoma-specific survival dependent on sex did not have a statistically significant difference ($p = 0.121$). In persons diagnosed at the age of 65 or older, ten-year survival was lower than in those of 40–64 years of age and in the age group of 15–39 years (44.44% and 26.66%, respectively), but melanoma-specific survival in different age groups did not have a statistically significant difference ($p = 0.455$). Back/breast skin melanoma had lower ten-year survival (37.03%) than other anatomic sites. Nodular melanoma had the poorest five-year and ten-year melanoma-specific survival among histological subtypes (51.67% and 38.75%). The differences between melanoma localizations ($p = 0.457$) and histological types ($p = 0.364$) were not statistically significant.

Conclusions. Lower melanoma-specific survival rates were observed among patients diagnosed at a late stage, older age, and when melanomas were thicker than 4.00 mm. Female and younger patients had better melanoma-specific survival than men and older people, and these differences were statistically significant. Melanoma diagnosed at an early stage and of a small depth had higher survival rates. Back/breast skin melanoma had poorer prognosis than other anatomic sites. Nodular melanoma had the lowest melanoma-specific survival, while superficial spreading or lentigo maligna had the best prognosis among histological subtypes. However, differences in melanoma survival in different sex and age groups, localizations and histological types were not statistically significant.

Keywords: melanoma, survival, histology, anatomic sites

INTRODUCTION

Diagnosis, prognosis, and treatment are the three core elements in the art of medicine. Modern medicine pays more attention to diagnosis and treatment but prognosis has been part of medical practice much longer than diagnosis. Cancer is a heterogeneous group of diseases characterized by growth, invasion, and metastasis. To plan the management of an individual cancer patient, the fundamental knowledge base includes the site of the origin of the cancer, its morphologic type, and the prognostic factors specific to that particular patient and cancer. Most literature references describe factors that directly relate to the tumour itself. However, many other factors not directly related to the tumour also affect the outcome. Some prognostic factors are essential to decisions about the goals and treatment choice.

The incidence of both non-melanoma and melanoma skin cancers has been increasing over the past decades. Currently, between two and three million non-melanoma skin cancers and 132,000 melanoma skin cancers occur globally each year (1).

According to the Cancer Statistics Report compiled by the Cancer Registry of the National Cancer Institute, more than 300 people are given the diagnosis of melanoma in the Lithuania every year.

Skin melanoma is the most aggressive form of skin cancer. Although it accounts for less than 5% of all skin cancer cases, deaths from melanoma account for more than 70% of deaths from all skin tumours. In some countries melanoma is the main cause of death from cancer in the cohort of young people (25–29 years of age). It is the second most common cancer after breast cancer causing deaths of women in the cohort of 30–35 years of age.

Detection and surgical treatment of the early-stage disease seem to prevent progression in most cases. However, patients with deep primary tumours or tumours that metastasize to regional lymph nodes frequently develop distant metastases. Median survival after the onset of distant metastases is only 6–9 months, and the five-year survival rate is less than 5% (2).

Two-thirds of patients with melanoma are female. Melanoma-related morbidity in Lithuania is lower than in other European countries, but its rate is increasing.

Over the past three decades, the prevalence of melanoma in the world has more than doubled. In

European countries, the highest incidence of melanoma is observed in the Scandinavian countries and the lowest in the Mediterranean region.

In addition to the stage of melanoma at diagnosis, previous surveys (3–6) have found that other prognostic factors such as age, sex, histology, and location are related to melanoma survival. In this investigation, we analyzed the data from the Cancer Registry to research melanoma-specific one-year, five-year, and ten-year survival dependent on the demographic and clinical factors. Also, these prognostic factors are essential in making decisions about the choice of treatment and its goals.

METHODS

We analyzed the data from the Cancer Registry of the National Cancer Institute (NCI) in Lithuania. The Cancer Registry (V zio registras) is a population registry that aims to maintain the records of malignant tumours across the whole territory of Lithuania. The purpose of the registry is to record the registry objects, to collect, accumulate, process, systemize, keep, make use of, and supply the register data. The Cancer Registry is a member of the International Association of Cancer Registries and of the European Network of Cancer Registries.

In 2006, 93 cases of melanoma were diagnosed at the NCI. We eliminated one case of melanoma in situ; three melanoma cases which were primary tumours found in rare sites such as the anus, rectum and an eye; four cases of an unknown depth. Our final study population included 85 primary invasive melanoma cases. All patients with melanoma were identified using the International Classification of Diseases for Oncology, Tenth edition (C43.0–C43.9). We analyzed melanoma-specific survival dependent on the demographic factors (age, sex) and clinical factors (stage, depth, histology, and localization of melanoma). We compared survival rates between men and women from 27 to 86 years of age. Patients were divided into three age groups: below 39, 40–64, and over 65 years of age. To evaluate the melanoma stage, we used the American Joint Committee on Cancer (AJCC) Staging System. The depth of melanoma was divided as less than or equal to 1 mm, 1.01 to 2.00 mm, 2.01 to 4.00 mm, and thicker than 4.00 mm. All cases were classified by melanoma histological

subtype (superficial spreading, lentigo maligna, acral lentiginous, nodular, and other). Melanoma localization was categorized by the anatomic sites such as head/neck, lower limb/hip, upper limb/shoulder, back/breast, and trunk. We present one-year, five-year, and ten-year melanoma-specific survival. The data were processed using Microsoft Excel; data analysis was conducted using SPSS® software.

RESULTS

In this investigation we analyzed 85 cases of invasive melanoma diagnosed in 2006 at the National Cancer Institute of Lithuania. The main aim of the study was to describe melanoma-spe-

cific survival by demographic and clinical factors. Overall, the one-year, five-year, and ten-year melanoma-specific survival was 94.12%, 55.29%, and 47.06%, respectively. The study involved 51 women (60%) and 34 men (40%). The average age was 58 years. The youngest person diagnosed with melanoma was 27 years old, and the oldest – 86 years old. The average age of women was 58 years and that of men 59 years. The youngest woman was 27 years old and the oldest was 86 years old. The youngest man was 34 years of age and the oldest was 82 years old (Table 1).

In this study we established sex and age significance to the survival rate. Females had better one-year (88.24%), five-year (69%) and ten-year

Table 1. Correlation of demographic and clinical factors with survival in melanoma patients

Characteristic	Melanoma-specific survival, %				
	No.	Percentage	1 year	5 years	10 years
Overall	85		94.12	55.29	47.06
Sociodemographic					
Sex					
Male	34	40	85	38	32
Female	51	60	88.24	69	61
Age at diagnosis, years					
<39	8	9.42	100	88	75
40–64	50	58.82	94	50	46
≥65	27	31.76	96.29	59.25	44.44
Clinical					
Stage at diagnosis					
I stage	27	31.76	100	84	80
II stage	31	36.47	93.10	65.51	51.72
III stage	18	21.18	88.23	29.41	23.52
IV stage	9	10.59	62.5	12.5	0
Depth, mm					
0.01–1.00	18	21.18	100	93.75	87.5
1.01–2.00	19	22.35	100	66.66	61.11
2.01–4.00	18	21.18	94.11	58.88	47.05
>4.00	30	63.54	83.33	26.66	16.66
Histological subtype					
Superficial spreading	39	45.88	95.51	88.43	79.32
Lentigo maligna	8	9.41	96.29	89.28	78.61
Acral lentiginous	3	3.53	92.14	72.34	48.54
Nodular	11	12.94	89.76	51.67	38.75
Other	24	28.24	93.45	77.33	64.19
Anatomic site					
Head/Neck	14	16.47	92	62	46
Lower limb/hip	26	30.58	92.30	61.53	57.69
Upper limb/shoulder	8	9.41	100	50	50
Back/breast	27	31.76	92.59	44.44	37.03
Trunk	10	11.78	100	75	62.50

(61%) survival than men (85%, 38%, and 32%, respectively). However, melanoma-specific survival dependent on sex did not have a statistically significant difference ($p = 0.121$). Irrespective of the gender, as the time from diagnosis increased, we observed diminished melanoma-specific survival (Fig. 1).

Men and women given the diagnosis at the age of 65 and older had lower ten-year survival than those at the age of 40 to 64, and of 15–39 years of age (44.44 vs. 46 and 75%). The five-year melanoma-specific survival was 50% for cases diagnosed at the age of 40 to 64, which was lower than for

the cases diagnosed at the age of above 65 years (59.25%) and the youngest age category (88%), but melanoma-specific survival in different age groups did not have a statistically significant difference ($p = 0.455$) (Fig. 2).

Stage I melanoma had 100% one-year survival, but despite early detection there were still deaths during ten years from diagnosis (ten-year melanoma-specific survival 80%). Unfortunately, diagnoses at late stages had lower melanoma-specific survival (one-year survival 88.23% (stage III) and 62.5% (stage IV)). As the time from diagnosis increased, so the melanoma-specific survival became worse

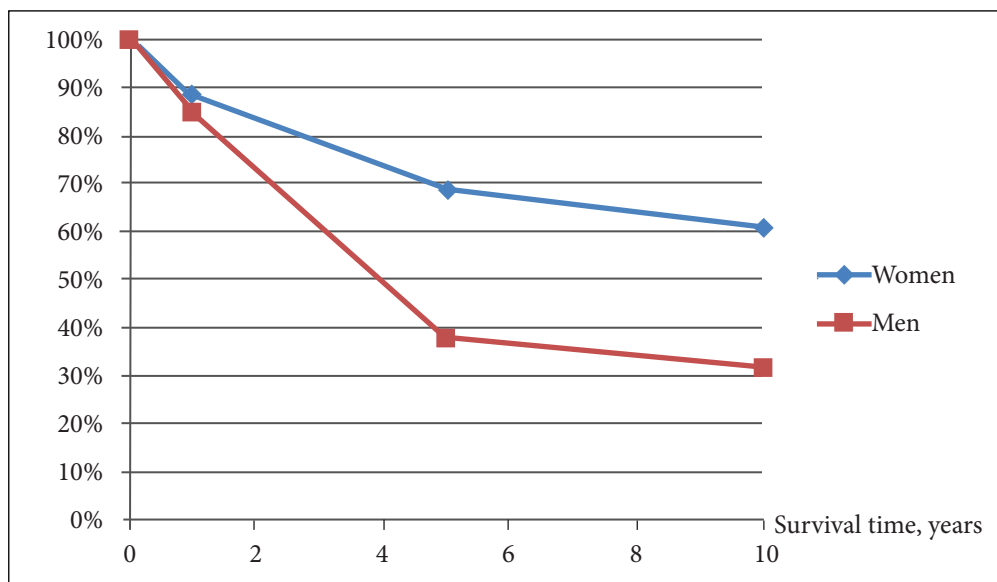


Fig. 1. Melanoma-specific survival curves by gender

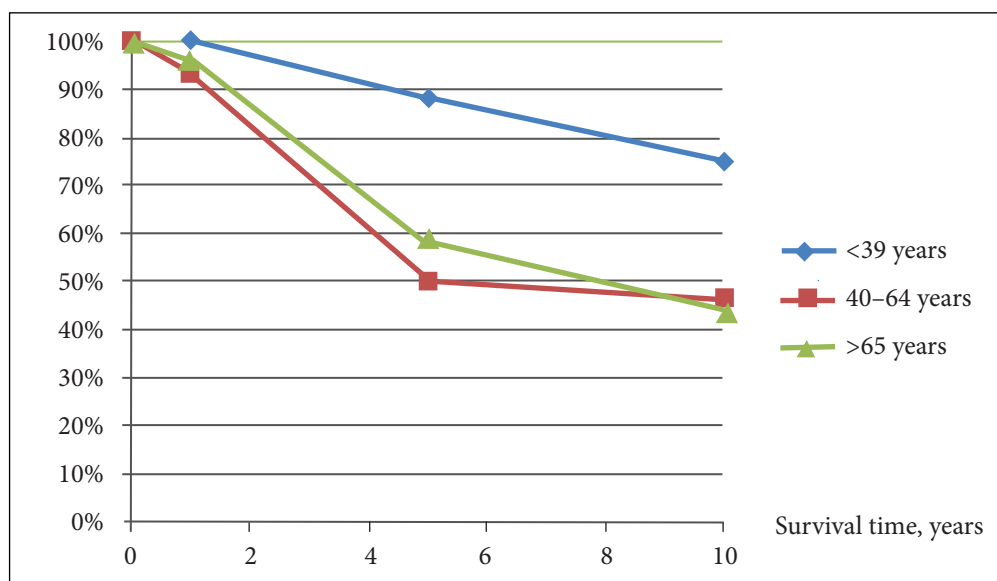


Fig. 2. Melanoma-specific survival curves by age at diagnosis

depending on the stage of the disease. Men and women given the diagnosis at stage IV had the poorest melanoma-specific survival: unfortunately, none of them survived ten years. Melanoma survival dependent on the stage at diagnosis had a statistically significant difference ($p = 0.003$). The most melanoma cases (31 cases, or 36.47%) were diagnosed at stage II and the least at stage IV (9 cases, or 10.59%) (Fig. 3).

The depth of melanoma had a statistically significant impact on melanoma survival ($p = 0.049$). Lesions less than 1.00 mm had ten-year melanoma-specific survival of 87.5% while the ten-year survival for lesions of 1.01–2.00 mm was 61.11%;

2.01–4.00 mm – 47.05%, and for lesions thicker than 4.00 mm, ten-year survival was only 16.66%. As the time from diagnosis and the depth of lesions increased, the melanoma-specific survival became worse. Sadly, many of the melanoma cases had lesions above 4.00 mm in depth (30 cases, or 63.54%) (Fig. 4).

Most melanoma cases were diagnosed as superficial spreading (39 cases, or 45.88%). Two histological melanoma subtypes having similar survival were superficial spreading and lentigo maligna (one-year 95.51 and 96.29%, five-year 88.43 and 89.28%, and ten-year 79.32 and 78.61%). Nodular melanoma had

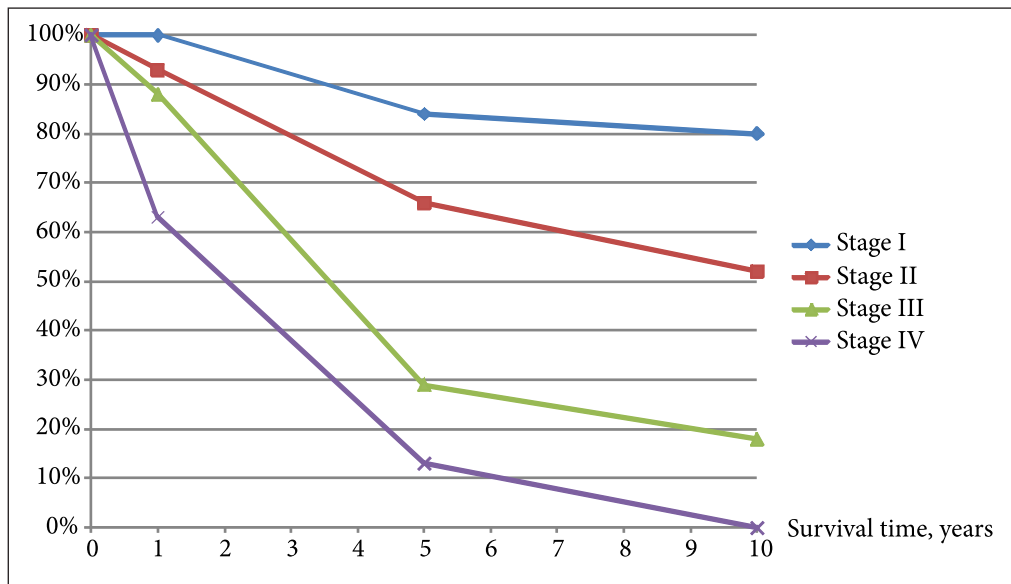


Fig. 3. Melanoma-specific survival curves by the stage at diagnosis

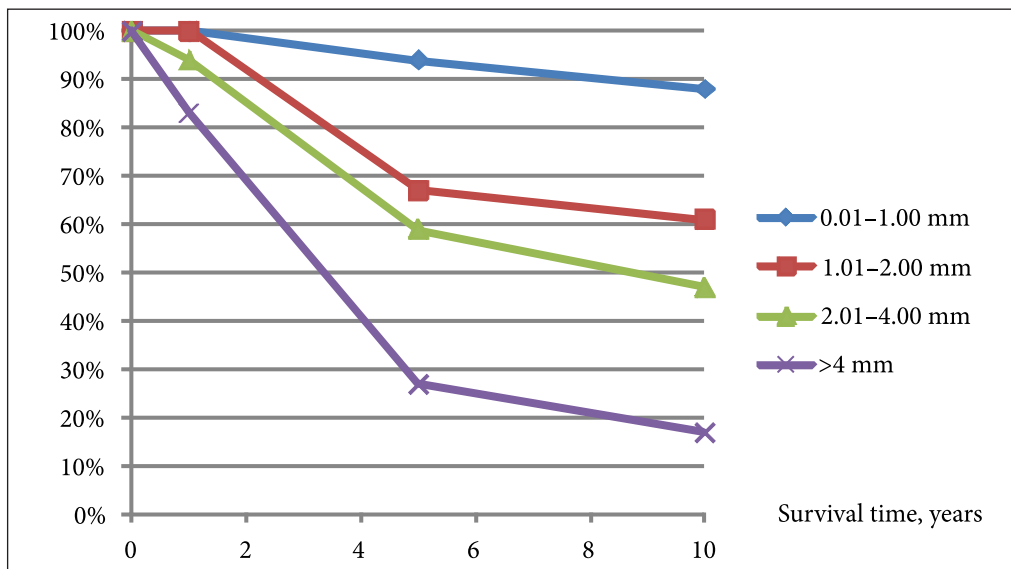


Fig. 4. Melanoma-specific survival curves by the depth of melanoma

the poorest five-year and ten-year prognosis among histological subtypes (51.67 and 38.75%, respectively). Acral lentiginous melanoma had five-year melanoma-specific survival of 72.34%, and ten-year survival of 48.54%. Melanoma survival in different histological subtype groups did not have a statistically significant difference ($p = 0.364$) (Fig. 5).

In most cases (27 cases, or 31.76%) melanoma was diagnosed on the back and in the breast region, less (26 cases, or 30.58%) on the skin of lower limbs and hips. The best survival depending on the anatomic site was for melanoma on the trunk skin (one-year – 100%; five-year – 75%; ten-year – 62.50%).

Similar five-year survival was observed for melanoma diagnosed on the skin of the head/neck and the skin of a lower limb/hip (62% and 61.53%, respectively), but poorer ten-year melanoma-specific survival for melanoma on the head/neck skin (46%) than melanoma on the skin of a lower limb/hip (57.69%). Melanoma diagnosed on the skin of the back/breast had the worst survival depending on the anatomic site (one-year – 92.59%, five-year – 44.44%, and ten-year – 37.03%). However, melanoma-specific survival dependent on the anatomic site did not have a statistically significant difference ($p = 0.457$) (Fig. 6).

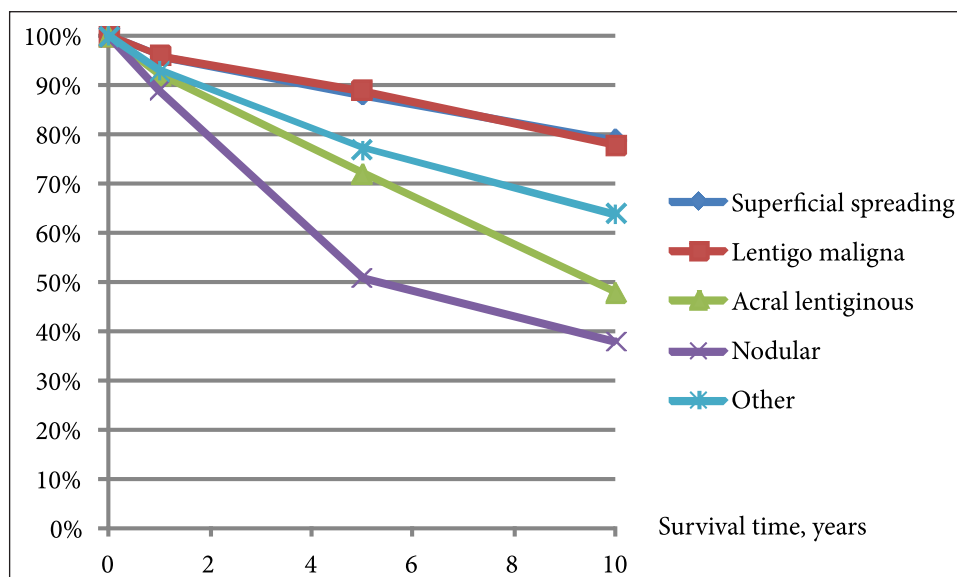


Fig. 5. Melanoma-specific survival curves by the histological subtype

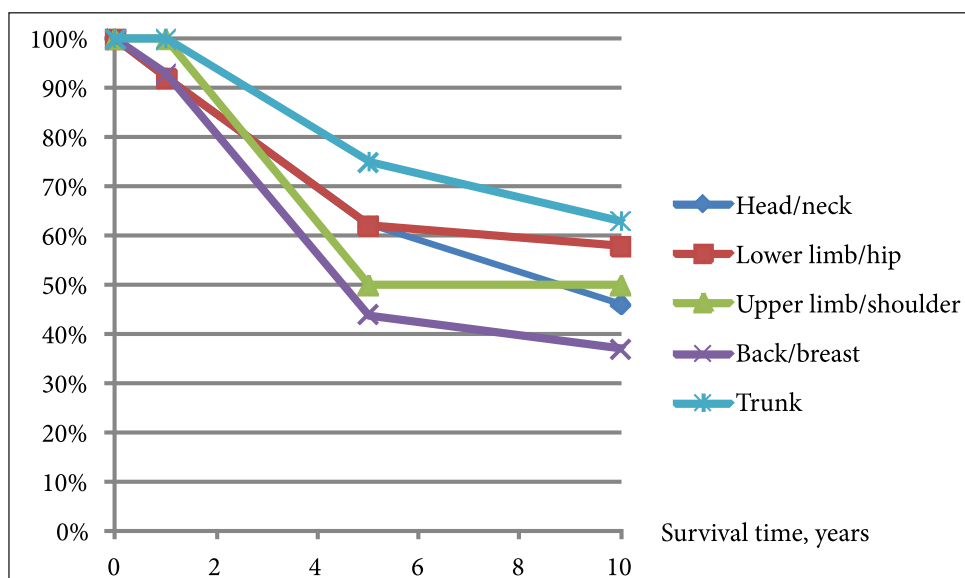


Fig. 6. Melanoma-specific survival curves by the anatomic site

DISCUSSION

The study included 85 cases of invasive melanoma diagnosed in 2006 at the NCI. The data was analysed using the NCI Cancer Registry. The incidence of melanoma was distributed by demographic and clinical characteristics and by one-, five-, and ten-year melanoma-specific survival. Overall, the one-, five-, and ten-year melanoma-specific survival was 94.12%, 55.29%, and 47.06%, respectively. Our survival results were appreciably lower compared to previous studies (15). This might be explained by the small population of patients involved in the investigation.

More women (60%) than men (40%) were included in the study, which indicates more frequent diagnosis of melanoma in women compared to men. We can observe the same tendency in others studies (5, 7).

The average age of melanoma manifestation was 58 years. The average age of women was 58 years, and of men 59 years. Our results also prove that melanoma is more frequent among middle-aged people (according to the American Skin Association, the median age of melanoma diagnosis is 59) (10). Some studies suggest that more melanomas appear *de novo* and the risk for transformation of a single nevus into a melanoma may increase with age (11). It could occur as a slowdown of metabolism and cumulative sun exposure. Harmful ultraviolet (UV) rays were the cause of 90% of melanoma cases. Nowadays people tend to spend their holidays in southern countries where the UV Index is higher than in the northern countries. Previous studies have shown that more than 40% of people got sunburnt during their holiday. It is worth mentioning that sunburns are associated with a doubling of the risk of melanoma because of the development of mutations in melanocytes (9). Ultraviolet rays cause mutations in skin cells and an accumulation of cancer-causing mutations leads to more cases of cancer in older compared to younger people. Mutations affect normal tissue cells, which results in proliferation of abnormal cells. Healthy cells in young bodies quickly outcompete cells with cancerous mutations. In old tissue healthy cells are no longer a perfect fit and mutations might help a cancer cell adapt and multiply in the organism (12). This may lead to the highest incidence of melanoma in older people than in younger.

Sex and age at diagnosis made an impact on survival. Females had better one-, five- and 10-year survival than men. The results of our study show that 19 cases (55.89%) of melanoma in men was diagnosed at late stages and 15 cases (44.11%) at early stages. Meanwhile, most of melanoma cases in women were diagnosed at early stages (39 cases, or 76.47%), and only 12 cases (23.53%) at late stages. Poorer survival among men compared to women could be due to late stages of melanoma at the time of diagnosis. Women more often perform self-examination or tend to contact dermatologists for screening than men (13). It is reported that melanoma is rare before puberty, it tends to be more invasive during pregnancy, and decreases during post-menopausal years. This might signal the importance of hormones in melanoma development. It could also explain why males have higher death rates of melanoma (5, 14).

Men and women given the diagnosis at the age of 65 and older had a lower ten-year survival than those at the age of 40 to 64 years, and 15 to 39 years. Thus our study shows that as the age at diagnosis increases, so does the melanoma prognosis become poorer. Since elderly people often have one or more chronic diseases (heart diseases, diabetes, and others) beside melanoma, they have weakened immune systems and lower survival rates of melanoma. Additionally, elderly people rarely perform self-examination or visit dermatologists for screening (13). As a consequence, melanoma is diagnosed at a late stage and greater depth, which impacts the prognosis of the disease.

Even stage I melanoma had a 100% one-year survival; however, even despite early melanoma diagnosis there still were deaths after five and ten years after diagnosis. In contrast, late-stage diagnoses had poor prognoses. Patients given the diagnosis at stage IV had the poorest melanoma-specific survival: unfortunately, none of them survived ten years. It happens because at stage IV melanoma has travelled to more distant areas of the body. Metastases of melanoma could be found in vital organs such as lungs, abdominal organs, brain, and bone, as well as in soft tissues such as skin, subcutaneous tissues, and distant lymph nodes. This results in bad melanoma prognosis. Our study and previous studies have shown the same results: as the stage of melanoma at diagnosis increased, the survival rates became worse (15, 20).

The depth of melanoma has an impact on melanoma survival. Lesions thinner than 1.00 mm had better melanoma-specific survival compared to lesions deeper than 4.00 mm. Sadly, numerous cases of melanoma had lesions deeper than 4.00 mm. Previous studies have demonstrated that thinner lesions are more often found by dermatologist (3). Patients have a tendency to visit health care specialists when they notice symptomatic (mostly bleeding) lesions, which are related to a more advanced stage and depth of melanoma with a poorer prognosis (16, 17). Our study demonstrated the need for public education about early detection of melanoma by performing self-examination and regular screening done by a dermatologist.

Various studies, including ours, have shown that most of melanoma cases were diagnosed as superficial spreading. The nodular melanoma had the poorest survival among another histological subtypes (20).

In most cases melanoma was diagnosed on back and breast skin and less on lower limbs and hips. Our study revealed that melanoma was mostly diagnosed on the shanks in the women's group (21, or 41.18%) and on the back in the men's group (17 cases, or 50%). The best survival depending on the anatomic site was for melanoma on the trunk, and the worst survival was recorded for melanoma diagnosed on back/breast skin. Previous studies have shown that head and neck melanoma were associated with chronic sun exposure while other sites of body melanomas were associated with periodic sun exposure. Also, melanomas which are not on the body sites usually exposed to the sun (for example, the back) are mostly associated with a high quantity of nevus (5, 18). So, depending on the geographical position, Lithuanians get seasonal sun exposure resulting mostly in the manifestation of back and breast melanoma. As the back is the least self-examined site of the body, skin alterations here are very often overlooked, especially by elderly patients (19). Therefore melanoma on back had poorer prognosis because it was diagnosed at late stages and bigger depth. Unfortunately, we can deny the discrepancy between our results and other studies because of the small population of patients involved into investigation. However, these results are intermediate so we are tend to continue our study further.

CONCLUSIONS

Our study of prognostic factors for melanoma patients concludes:

1. The tendency of melanoma morbidity: two-thirds of patients are female and one-third male.
2. The average age of patients with melanoma is 58–59 years.
3. Melanoma-specific survival is better for women (however, melanoma-specific survival dependent on sex did not have a statistically significant difference ($p = 0.121$)) because of lifestyle factors (self-examination and screening) and biological factors (hormones).
4. With the increasing age at diagnosis, the melanoma prognosis was becoming poorer, but melanoma-specific survival in different age groups did not have a statistically significant difference ($p = 0.455$).
5. Melanoma survival in different histological subtype groups did not have a statistically significant difference ($p = 0.364$); the best survival prognosis was for superficial spreading and lentigo maligna, and the poorest for nodular melanoma.
6. As the stage ($p = 0.003$) and melanoma depth ($p = 0.049$) at diagnosis increased, melanoma survival rates became lower.
7. In most cases melanoma was diagnosed on the skin of the back and breast, and less on the skin of lower limbs and hips.
8. The best survival depending on the anatomic site was for melanoma on the trunk, but melanoma-specific survival dependent on the anatomic site did not have a statistically significant difference ($p = 0.457$).

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PACIENTŲ, SERGANČIŲ MELANOMA, PROGNOSTINIŲ VEIKSNIŲ ANALIZĖ

Santrauka

Įvadas. Melanoma – pati grėsmingiausia odos vėžio forma. Sergamumas šia liga kiekvienais metais didėja. Ankstesni tyrimai parodė, kad yra keletas demografinių ir klinikinių veiksnių, turinčių įtakos melanomos išgyvenamumo prognozei.

Darbo tikslas. Tyrimo tikslas buvo įvertinti sergančiųjų melanoma išgyvenamumo priklausomybę nuo prognostinių veiksnių, tokių kaip amžius, lytis, melanomos stadija, gylis, histologinis tipas ir lokalizacija.

Darbo metodika. Tyrėme pacientų, sergančių melanoma, išgyvenamumą iki 10 metų nuo diagnozės nustatymo. Tyrime dalyvavo 85 pacientai, kuriems Nacionaliniame vėžio institute 2006 m. buvo diagnozuota pirminė melanoma. Išanalizuota 1, 5 ir 10 metų melanomos išgyvenamumo perspektyvos atsižvelgiant į prognostinius rodiklius. Duomenys apdoroti Microsoft Excel, duomenų analizė atlikta naudojant SPSS® kompiuterinę programą.

Rezultatai. IV stadijos arba storesnės nei 4,00 mm melanomos lėmė mažesnę pacientų išgyvenamumą (atitinkamai 5 metų išgyvenamumas 12,5 ir 26,66 %). Skirtingų melanomos stadijų ($p = 0,003$) ir skirtingo gylio ($p = 0,049$) stebimas statistiškai reikšmingas pacientų išgyvenamumo skirtumas. 10-ties metų vyrų išgyvenamumas siekė 32 %, moterų – 61 %, tačiau tarp lyčių statistiškai reikšmingai nesiskyrė ($p = 0,121$). Asmenų, ku-

riems melanoma diagnozuota 65 metų ar vyresniems, 10 metų išgyvenamumas buvo mažesnis nei 40–64 ir 15–39 metų amžiaus pacientų (44,44 %; palyginti su 46 ir 75 %), tačiau tarp skirtingų amžiaus grupių išgyvenamumo skirtumai nebuvo statistiškai reikšmingi ($p = 0,455$). Pacientų, sergančių nugaros / krūtinės odos melanomomis, 10 metų išgyvenamumas (37,03 %) buvo mažiausias, palyginti su kitomis melanomos lokalizacijomis. Mazginė melanoma lėmė prasčiausią 5 ir 10 metų išgyvenamumą tarp histologinių tipų (51,67 ir 38,75 %). Skirtumai tarp skirtingų melanomos lokalizacijų ($p = 0,457$) ir histologinių tipų ($p = 0,364$) nebuvo statistiškai reikšmingi.

Išvados. Mažesnis išgyvenamumas nustatytas tarp sergančių melanoma pacientų, kuriems ši liga diagnozuota vėlyvose stadijose, vyresnio amžiaus žmonių ir kai melanomos gylis buvo daugiau nei 4,00 mm. Moterų ir jaunesnių pacientų melanomos prognozė buvo geresnė nei vyrų ir vyresnio amžiaus žmonių. Melanomos, diagnozuotos ankstyvoje stadijoje ir su nedideliu gyliu, lėmė geresnę išgyvenamumo prognozę, ir šie skirtumai buvo statistiškai reikšmingi. Nugaros / krūties odos melanomos prognozė buvo blogesnė nei kitų anatominių vietų. Mazginė melanoma pasižymėjo prasčiausiais pacientų išgyvenamumo rezultatais, o paviršiumi plintanti ar *lentigo maligna* iš histologinių tipų išsiskyrė geriausia prognoze. Tačiau sergančiųjų melanoma išgyvenamumo rodiklių skirtumai tarp skirtingų lyčių, amžiaus grupių, lokalizacijų ir histologinių tipų nebuvo statistiškai reikšmingi.

Raktažodžiai: melanoma, išgyvenamumas, histologija, anatomicinės sritys