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Survival and disease–free interval of malignant melanoma patients in relation to the prognostic factors

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In the present study 236 patients with malignant melanoma of the skin treated at the Institute of Oncology in Ljubljana during the years 1970–1983 were included, 100 males and 136 females, with mean (and median) age of 54 years, ranging from 16 to 92 years. Overall 5-year survival for the whole group was 57.5%, and median survival 108 months; 5-year survival by sex was 66.4% for females and 38.5% for males, thus being markedly better in the former group of patients. Therefore, female sex can be regarded as a favourable prognostic factor. Mean disease–free interval (DFI) for all patients was 56 months, whereas 5-year DFI was 48.6%. For the female patients 5-year DFI was 52.6%, and for males 26.3%; their median DFI was 81 and 20 months respectively. Obviously better DFI observed in female patients indicate that female sex represents a favourable prognostic factor for DFI. Using univariate analysis of the influence of sex and investigated clinical and pathohistological variables on the survival in our group of patients, a statistical significant difference was established so for sex as well as for the extent of invasion by Clark levels. In order of relevance, these parameters were followed by the stage of the disease at diagnosis, the type of the primary tumor excision and patients age at diagnosis. Survival was better in the group of patients with lower grade of invasion, localized disease, as well as with radical excision off the primary tumor and younger age at diagnosis. Irrespective of sex, a statistically significant better survival was found in the group of patients with thinner melanoma. Data on preexisting nevus or other skin alterations, localization of the primary tumor and pathogenetic type of melanoma were not found to be statistically important prognostic factors for the survival and DFI.

Key words: melanoma; skin neoplasms; prognosis

Introduction

In the world, patients with malignant melanoma (MM) represent aproximately 1% of all cancer patients. The incidence of MM has been rapidly increasing, reaching its double value every 6-10 years, and likewise, also MM-related mortality has been exhibiting a trend of constant increase. Also in Slovenia, the yearly incidence of cutaneous MM by sex shows tendency of slow in-

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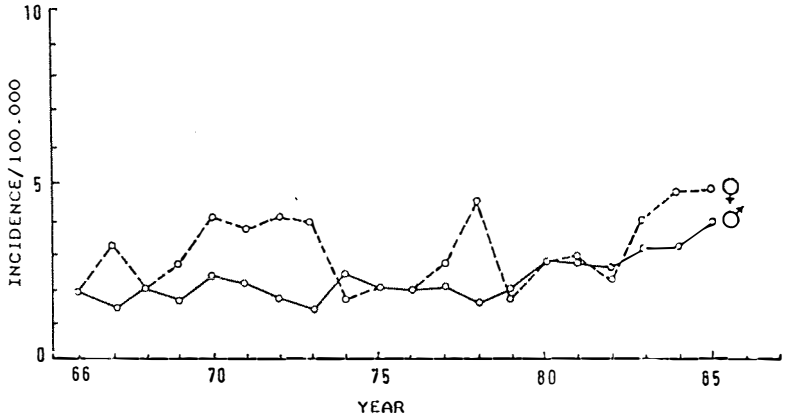

Figure 1. Annual incidence of malignant melanoma of the skin in Slovenia from 1966 to 1985 (Cancer Registry of Slovenia 1985)

crease (Figure 1) which is slightly more evident in women. In 1986, the respective rate for men was 4.7 and for women 6.1 new cases per 100.000 inhabitants, with the highest frequency of appearance evident in the middle age group[1] whereas the disease is less frequent during childhood and adolescence. Basically, MM is a rare tumor and its course is frequently unpredictable, ranging from spontaneous regressions to rapid disseminations ending in the fatal outcome, which can be partially explained by the numerous biological properties of the tumor.[2]

Considering the high mortality rates observed in patients with metastatic MM as well as ineffective treatment of the advanced disease, several authors worldwide have been investigating the natural course of MM, trying to explain the role of clinical and pathohistological characteristics as prognostic factors in evaluating the survival and disease-free interval (DFI) in order to predict the course of disease and enable sensible treatment planning. Factors influencing the survival of MM patients are associated with the stage of disease[3,4] according to TNM classification, depth of invasion and tumor volume, which are considered to be the most relevant prognostic factors. However, clinical practice and numerous publications show that the old system[5] classifying the disease into Stage I (localized disease), Stage II (regional progression) and Stage III (distant – systemic dissemination) is used more frequently.

The greatest influence of prognostic factors has been noted in Stage I MM, i.e. in the phase when the disease is still curable by surgery. These factors are as follows:

A) *Pathohistologic properties of the primary tumor:*

– tumor thickness according to Breslow,[6] classified by Balch et al.[7] into four classes with regard to their influence on prognosis and survival; greater tumor thickness is associated with worse survival[8-16]

– depth of invasion according to Clark,[17,18] which highly correlates with the survival[10-13, 19-20] and represents an additional information to »tumor thickness«;[21, 22]

– intensive growth period (radial, vertical);

– histogenetic type: superficially spread (SSM), lentiginous (LM), nodular (NM), and acral lentiginous (ALM); there SSM, LMM and ALM are associated with a better prognosis owing to their long radial phase of growth and late metastasizing, for the difference from NM which has got only the vertical phase of growth and shows tendency of early metastasizing;[10,11,19,23] generally, the subclassification of MM exhibits minor correlation with the survival, except perhaps in the cases of LMM;[2,24]

– mitotic activity, where a lower speed of cell division is associated with better survival;[11,15,25]

– ulceration: its presence in the primary tumor represents an unfavourable prognostic sign;[8,10,11,15,24,25]

– immune response;[2,11,15]

– tumor cell type (epitheloid-, spindle-cell, mixed);[2,15]

– vascular invasion;[2,11]

– microscopic satellites;[2]

– histologic signs of MM regression: a majority of authors failed to establish any correlation between the latter factor and survival.[8,10-12,15,26]

At this time, investigations such as the determination of DNA aneuploidy,[27] estrogene receptors[28] and MM cell phenotype changes[29,30] are being used only for research purposes, and therefore their prognostic relevance for predicting the course of disease has not been confirmed by clinical practice yet.

B) *Clinical factors:*

– age: younger age at diagnosis is associated with a better survival prognosis;[9-11,24, 31-33]

– sex: in a majority of studies, female sex has been considered a favourable prognostic factor;[9,10,31-33] Shaw et al.[34] have reported more MM sites on the extremities, a higher proportion of tumors of lesser thickness, and a higher proportion of patients under the age of 50 years among women, all of which is believed to be associated with a more favourable prognosis and may explain better survival rates in women.

– site: in comparison with the extremities, primary tumor sites on the trunk are considered prognostically less favourable in both sexes; the most frequent MM site in women is the lower extremities, which can partially explain their better survival;[9,10,24,25,31,33-36] lesions in the scalp have worse prognosis than those situated on the face and neck.[12,14]

The more advanced the stage of malignant disease (St. II, St. III), the lesser is the prognostic value of pathohistologic characteristics of MM (ulcerations, tumor thickness[7] for patients survival, and the higher the value of the number of metastatically involved lymph nodes,[8,14,23,37] distant metastatic sites,[23,24] tumor volume and cell kinetics[38]).

As to the numerous previously mentioned prognostic factors by different stages of malignant disease, which were reported to be of varying prognostic value for survival and DFI of MM patients, practical clinical value was confirmed for some of them only, i.e. pathohistologic characteristics of MM in the stage of localised disease (tumor thickness, depth of invasion, intensive growth period, histogenetic type), whereas of clinical variables, relevance was established with age at diagnosis, sex and MM site.

Considering better survival results in patients with localised MM, i.e. in the stages when the disease is still curable by surgery, and taking into account ineffective treatment of metastatic disease with consequentially high mortality rates, our study was aimed at following the survival and DFI of MM patients diagnosed and treated in the period 1970-1983 at the Institute of Oncology in Ljubljana, and the prognostic factors which to the largest extent influence them. We also tried to establish possible correlation between individual factor and compare our results with those reported in literature.

Patients and methods

The study represents a retrospective analysis of data on 258 MM patients diagnosed in the period from January 1, 1970 to December 31, 1983 at the Institute of Oncology in Ljubljana. The duration of follow up was till the patient's death or at least five years after the inclusion of the last patient. The last follow up examinations and the patient condition data collected at that time dated back to the first months of 1990.

Of the total 258 patients, 22 were excluded from further analysis owing to unreliable MM histology, insufficient data, or because they were lost to follow up or had »in situ« MM (Clark I), so that the number of included patients totalled to 236 (100 males and 136 females; median and mean age 54 years, range 16-92 years). Their survival and disease-free intervals were assessed in correlation with different prognostic factors

such as age, sex, stage, depth of invasion, tumor thickness, histogenetic type, cell type, extent of surgery (radicality), MM site and anamnestic data on previous nevus.

The data were processed using univariate analysis and stratified by means of BMDP 1 L statistic program[39] for survival curve calculation and difference testing. Survival curves and DFI for individual groups of patients were calculated by the method of limit product,[40] whereas the comparison and evaluation of possible statistically significant differences between the groups was done by means of log-rank test[41] or Mantel-Cox statistic test with statistical significance at $p < 0.05$.

Results

Five-year survival for all patients was 57.5%, and median survival 108 months. Following surgical removal of MM, in 129 patients dissemination or recurrence appeared within a certain period of time, i.e. they presented with DFI, whereas 84 patients were without evidence of the disease on the last follow up examination. Five year DFI was 48.6%, median 56 months.

Tables 1 and 2 present the distribution of patients according to the observed clinical and pathohistological variables and the calculated values of 5-year survival, median survival and p-values by comparing the survival curves in different subgroups of patients.

Distribution by sex shows for one third higher rate of female patients which is associated with an almost 5-times longer median survival and statistically significantly better survival than in males (5-year survival 66.4% vs. 38.5%) (Figure 2).

Five-year DFI for females was 52.6% and for males 26.3%, i.e. statistically significantly better for the former. The surviving male patients are considered free from the risk of death due to MM when they have managed to survive over 10 years, whereas the same can be said of female patients only after 16 years when they are regarded as practically cured.

Table 1. Analysis of 5-year and median survival in patients with malignant melanoma according to the sex and age distribution

	No of pat.	Survival 5-year (%)	median (months)	
SEX				
males	100	38.5	38	
females	136	66.4	175	p=0.001
AGE				
< 39	46	66.0	193	
40 – 49	50	63.6	125	
50 – 59	49	52.0	78	
60 – 69	41	33.0	39	
> 70	50	50.0	82	
< 54	120	61.4	125	
> 55	116	46.3	58	p=0.01
males				
< 54	52	48.5	49	
> 55	48	26.6	33	p=0.006
ALL	236	57.5	108	

Table 2. Analysis of 5-year and median survival in patients with malignant melanoma according to the level of invasion (Clark), tumor thickness and stage of the disease.

	No of pat.	Survival 5-year (%)	median (months)	
Clark level				
males II	5	40.0	38	
III	18	50.9	–	
IV	37	47.0	60	
V	20	27.5	17	p < 0.0001
females II	6	83.3	–	
III	43	94.7	–	
IV	26	83.4	175	
V	21	32.5	21	p < 0.0001
Thickness (mm)				
< 0.75	6	100.0	–	
0.76 – 1.50	15	85.0	–	
1.51 – 4.00	28	88.7	–	
< 4.00	22	57.3	175	p=0.003
Stage				
localized	180	63.5	141	
regional	45	22.7	11	p < 0.0001
disseminated	11	30.3	12	
ALL	236	57.5	108	

By distributing the patient into two larger age groups according to the median age (54 years) in order to assess their survival in relation to age at diagnosis, a significantly longer median survival 125 vs. 58 months) and a longer DFI, as well as

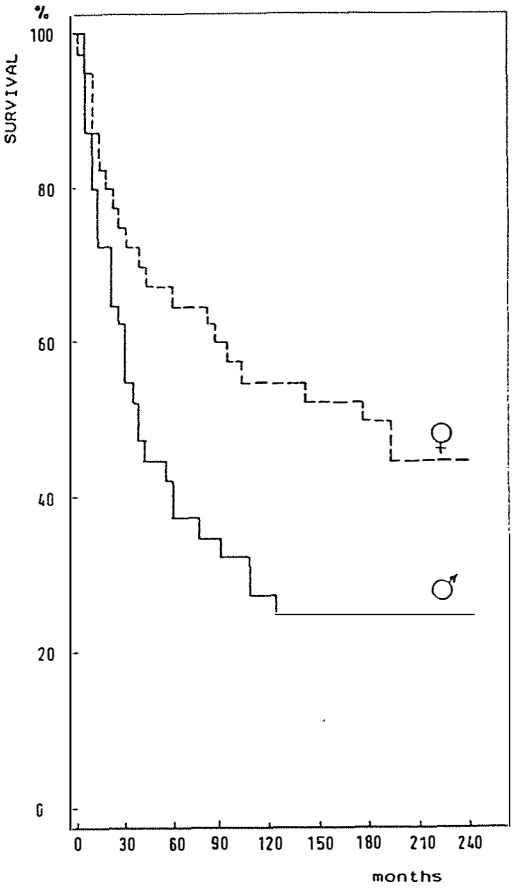

Figure 2. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to sex distribution.

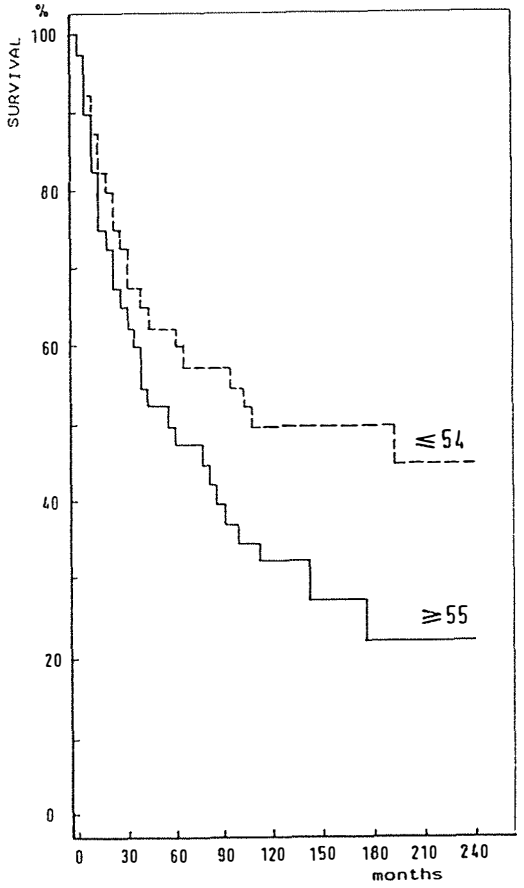

Figure 3. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to the median age.

statistically better survival and DFI were established in the younger age group (Figure 3).

Also,stratification by sex and age showed a better 5-year survival (71.6% and 48.5% for the younger, and 61.0% and 26.6% for the older age group) as well as DFI in the younger group of patients of both sexes, whereas in the same age group a better DFI was observed in female patients in comparison with males; the differences were statistically significant.

In 73% of patients with history of previous pigmented nevus a better survival and DFI were registered, though they were not statistically significant.

In 107 patients MM was situated on the extremities, in 93 on the trunk in 36 on the head and neck, whereas after stratification by sex, in males 66% of MM were found on the trunk and only 25% on the extremities, in opposition to females who had 60% of MM on the extremities and 23% on the trunk, which can partly explain the worse survival of male patients.

In males the best 5-year survival was found with MM situate on the extremities; this site was followed by the head and neck where survival results were somewhat worse, and the trunk with 29.5% survival rate; in females the 5-year survival for all three localizations ranged between

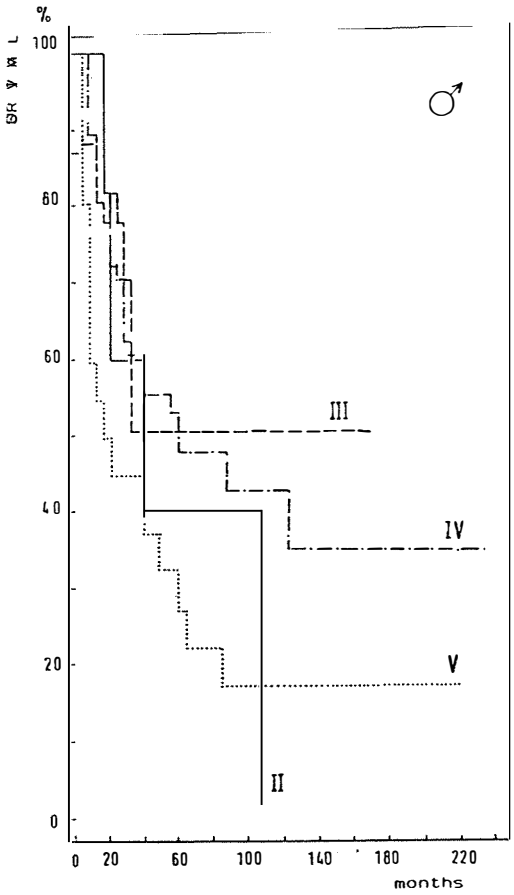

Figure 4. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to the level of invasion (Clark), group of female patients.

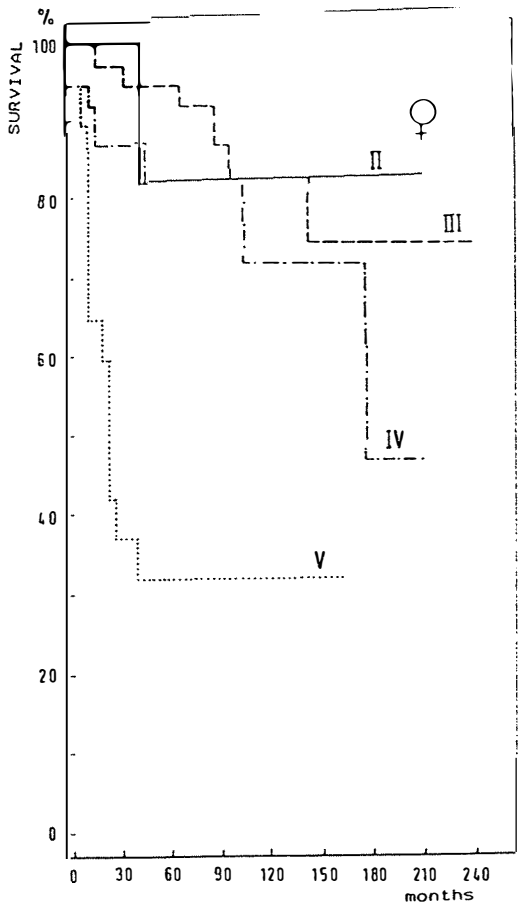

Figure 5. Survival of malignant melanoma patients treated at the Institute of Oncology in Ljubljana from 1970-1983 according to the level of invasion (Clark), group of male patients.

58-69%, without statistically significant differences in the survival curves for both sexes; the same findings applied to DFI as well.

The depth of invasion according to Clark gradation was determined in 176 of 236 patients. After data stratification by sex, a significantly better survival was established in lower grades and female patients. Thus, marked differences were seen in Clark IV and V, with respective survival rates of 47.0% and 27.5% in males, and 83.4% and 32.5% in females. The latter also presented with a higher rate of MM with lower grade of invasion (Clark III) which can be regarded as a favourable prognostic factor believed to be responsible for better survival of female patients (Figures 4 and 5). When disregarding the factor of sex owing to the insufficient number of cases, increasing Clark grade was directly associated with a decrease in 5-year DFI; the differences were statistically significant (Figure 6).

Tumor thickness according to Breslow was determined in 71 of 236 patients only, which rendered the analysis of stratification by sex meaningless. The survival (Figure 7) and DFI (Figure 8) of patients with lesser MM thickness

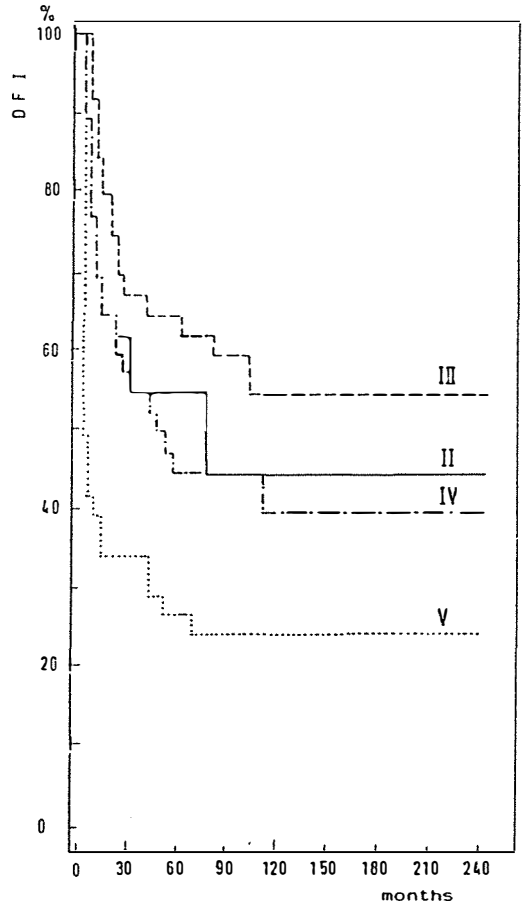

Figure 6. Disease-free interval (DFI) in malignant melanoma patients according to the level of invasion.

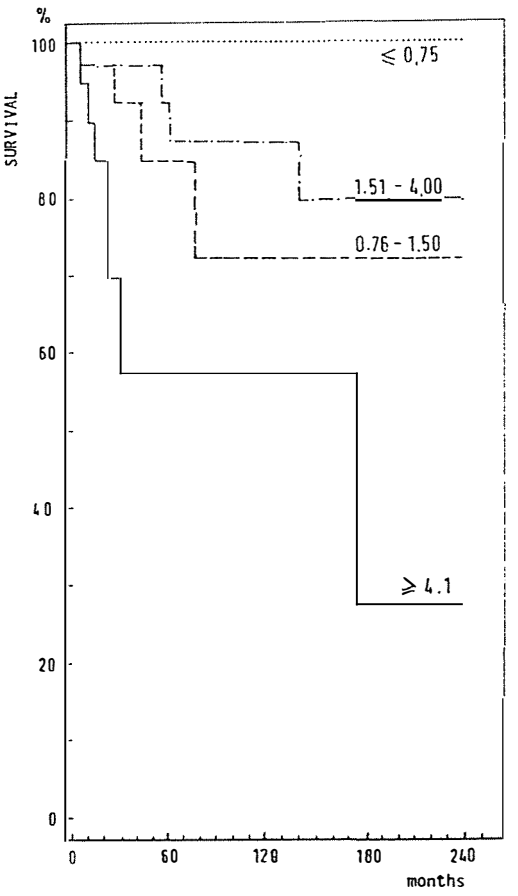

Figure 7. Survival of malignant melanoma patients according to the tumor thickness.

was significantly better; the difference is particularly evident with thickness exceeding 4.1 mm.

The stratification of patients by sex and stage of disease pointed out a statistically significant better survival in the stages of localized disease where 5-year survival for females was 76.6% and for males 45.5%. The rate of female patients with St. I MM was 80%, and of male 71%, which could partly explain generally better survival observed in all women. Males are considered to be cured after 10 years, whereas women are regarded as such only after 16 years.

Cell type of MM was determined in 19 patients only, and therefore our results pointing out a better survival of patients with epitheloid cell type vs. spindle cell type are not statistically significant.

Discussion

Univariate and stratified analysis of possible clinical and pathohistological prognostic factors enabled us to identify those which to the largest extent influenced the survival and DFI. The factors were as follows: sex, age at diagnosis, type of surgery, depth of invasion (Clark), tumor thickness (Breslow), and stage of disease at

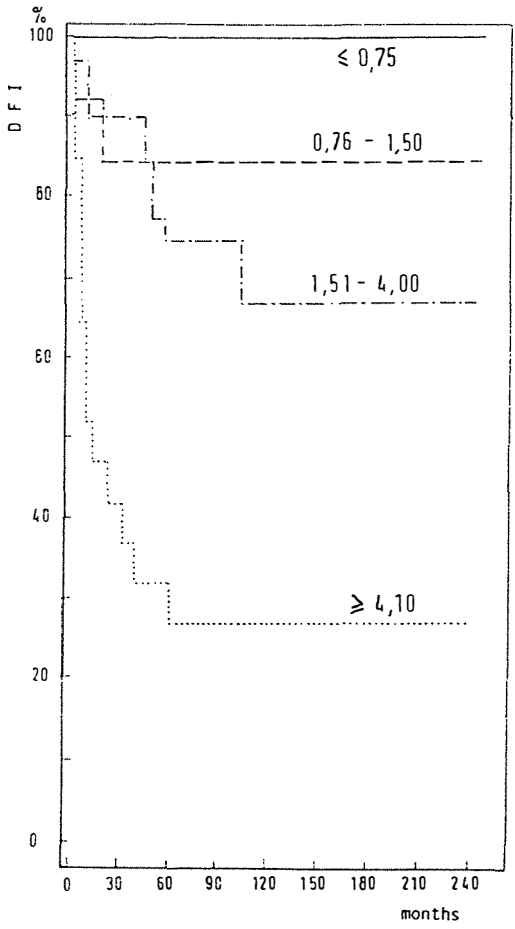

Figure 8. Disease-free interval (DFI) in malignant melanoma patients according to the tumor thickness.

diagnosis. Anamnestic data on previous pigmented nevus, site of primary tumor, pathogenetic and cell type of MM were not found to be statistically relevant prognostic factors.

The comparison of our results with the findings of other national studies and clinical trials carried out by foreign authors showed no controversion of the results; thus, female sex, younger age, lesser thickness of MM, lower depth of invasion, primary tumor site on the extremities, pathogenetic type of SSM and lower stage at diagnosis are associated with better survival and DFI.

The findings of earlier studies on the influence of sex and age on patients' survival were controversial[7,9,35] because the investigated groups of selected patients were small and non-homogeneous by age, the follow up was too short or incomplete, and the registration of the cause of death other than MM was inaccurate.

Some later large-scale national studies such as e.g. an American study covering 10% of American population,[32] as well as a Swedish national study[33] and a Finish national study,[31] which were based on population registry data, have confirmed a better survival in younger patients, and a more favourable course of disease in females. These findings are in accordance with the results of our study.

The advantage of large-scale national studies over hospital ones is in the large number of randomized patients, long follow-up period, and 100% following of the patients till the end of study.

Similar conclusions on statistically significantly better survival in females and patients younger then 50 or 60 years were obtained also in a study carried out at the Cancer Center in Arizona,[10] and in the West Canadian Study,[11] apart from some other prognostically relevant factors (MM thickness, ulcerations and selected regional lymph node removals).

There is no definitive explanation for better survival of female patients. It is well known, however, that in females MM is more frequently situated on the extremities and face, which is associated with a better prognosis, whereas MM site on the trunk more frequently seen in males prognosticates a worse survival,[7,24,34,35] which has been confirmed also by our analysis. Also, MM in females are to a lesser extent exulcerated[24] and have lesser thickness at diagnosis;[11,36] this finding applies to our female patients as well.

Better survival of women in different age groups, which has been established by our analysis, points out that there is no direct correlation between sex hormones and survival. A higher prevalance of estrogene receptors found in women is associated with a less malignant course of MM and accordingly also a better prognosis for survival.[28]

The established better survival in younger patients[24,31,33] could be attributed either to the fact that older patients search surgical help in more advanced stages of disease, or to a decreased immune response in advanced age,[42] though all these explanations are just hypothetical as none of them is based on any substantial biological facts.

Female sex and younger age are associated with a better prognosis for survival of MM patients, which points out the existence of age – and sex-specific factors influencing the course of growth and dissemination of MM.[33]

The distribution of MM sites by sex is in agreement with the findings of other authors;[33,35] the prevalence of lesions on the trunk in males, and on the extremities in females could be associated with different exposure to UV rays.[43]

An increased number of head and neck lesions, particularly in women, associated with a relatively high proportion of LMM type situated on the face[44] was established in a number of studies.

Site on the extremities usually represents a more favourable prognosis than trunk or head & neck sites;[9,25,31,34-36] this finding has been confirmed also in our male patients though the differences were not statistically significant, which is in agreement with the results obtained by Worth et al.[11]

In our study, NM type associated with worse survival and DFI – in men more obvious than in women – prevails, however, without statistically significant differences. In a majority of other studies, the prevailing type is SSM which is associated with more favourable prognosis for survival[10-12] sometimes even significantly better.[19]

In our study, the increasing depth of invasion was found to correlate with worse survival and DFI in both sexes; particularly unfavourable prognosis was associated with Clark grade V. There were more lesions with lesser depth of invasion found in women, which can partially explain better survival of female patients. Better survival with lower Clark grades was established also by other authors.[9-16,19]

The increasing thickness of MM statistically significantly correlates with worse prognosis, particularly the thickness exceeding 4mm, which is in agreement with the results of a study performed in Arizona;[10] in the latter study, some other critical points for survival were associated with tumor thickness.

Many authors in their analyses found a highly significant influence of MM thickness on survival; the significance was even more evident than that established for the depth of invasion.[8,12-15]

At the time of diagnosis, a majority of our patients of both sexes presented with localised stage of the disease – women more frequently than men. Their survival was statistically significantly better in comparison with the stages of regional or systemic dissemination. Similar results were obtained also by Wanebo et al.[12] and by the authors of Finish National Study.[31]

A better survival, though insignificant, established in patients with epitheloid-cell MM type, is of no statitical value in our analysis owing to insufficient data. In the West Canadian Study,[11] the prevailing cell type failed to correlate with survival.

The extent of surgery for MM, which was in our study found to have favourable influence on the prognosis, was not considered in a majority of other studies. Most other authors also have not studied DFI in correlation with prognostic factors.

Conclusion

The prognosis in patients with MM of the skin, and related to it survival and disease-free interval, depends on a number of clinical, pathohistologic and immunohistochemical factors, the so-called prognostic factors. Only some of which, however, proved to be of practical clinical value. It has not been explained yet why findings of different authors on the relevance of individual prognostic factors are sometimes controversial. Using univariate and stratified analysis of possible prognostic factors, we have identified those believed to be of statistically significant prognostic value for the survival and DFI; thus, better

prognosis was associated with female sex, younger age at diagnosis, radical surgical removal of primary tumor, lower grade of invasion depth, leser tumor thickness, and stages of localized disease vs. regional and systemic dissemination (the latter applies to survival only).

Though tumor site on the extremities, history of previous pigmented nevus and SSM subtype were found to correlate with a more favourable course of the disease, the finding lacked statistic significance. Nevertheless, the results are in agreement with those reported by other authors.

Unfavourable prognostic factors were used to identify the gropus of patients at risk requiring a special follow-up regimen and additional treatment.

It has been found that the proportion of patients with localized disease at the time of diagnosis is approximately 75%, and is higher in women than in men. The distribution of MM sites by sex is in agreement with the findings of other authors, the prevailing site in men being the trunk, and in women the extremities. According to our data, the proportion of NM subtype is twice as high as that of SSM type, though in some other studies the SSM type is reported to be prevailing. A history of previous pigmented nevus has been registered in 73% of patients, whereas a higher number of lesions with lesser depth of invasion has been found in women than in men; tumors exceeding 1.50 mm of thickness were prevailing.

With respect to the findings on better survival and DFI in patients with a lesser tumor thickness and a lower grade of invasion depth, more efforts should be directed into the organization of general and professional education in order to increase the level of primary and secondary prevention.

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