Analysis of prognostic factors in patients with cutaneous malignant melanoma

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Ph.D. Thesis

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Contents

Publications of the author related to the thesis

Original articles

I. **Oláh J.**, Korom I., Dobozy A.:
A melanoma malignum klinikuma és kezelése.
LAM 5: 412-416, 1995.

II. Hammer H., Tóth-Molnár E., **Oláh J.**, Dobozy A.:
Cutaneous dysplastic naevi: risk factor for uveal melanoma.
Lancet i: 255-256, 1995.

III. Hammer H., Tóth-Molnár E., **Oláh J.**:
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Szemészet, 133: 45-46, 1996.

IV. Hammer H., **Oláh J.**, Tóth-Molnár E.:
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Malignus tumorok bőráttéteiről.
Bőrgyógy. Vener. Szle. 72: 193-198, 1996.

VI. **Oláh J.**, Szolnoky Gy., Korom I., Kapitány K.:
Nyálkahártya melanoma.
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VII. Korom I., **Oláh J.**, Gyulai R., Varga E.:
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VIII. **Oláh J.**, Gyulai R., Baltás E., Nagy Sz., Korom I.:
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IX. Tóth Molnár E., Hammer H., **Oláh J.**:
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X. Tóth Molnár E., Hammer H., **Oláh J.**:
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Őrszemnyirokcsomó-biopsziával szerzett tapasztalataink melanoma malignumban.
LAM 11: 536-41, 2001.

XII. **Oláh J.**, Dobozy A.:
A melanoma malignum új TNM beosztása.
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XIII. Altmayer A., Korom I., **Oláh J.**, Dobozy A.:
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XIV. **Oláh J.**, Dobozy A:
A melanoma malignum új TNM-beosztása
Magyar Onkol 47: 2003 (közlés alatt)

XV. **Oláh J.**, Kovács R., Korom I., Kemény L., Dobozy A.:
Pigment anomaly caused by calcipotriol in a subject with melanoma
JEADV (accepted for publication)

XVI. **Oláh J.**, Gyulai R., Korom I., Varga E., Dobozy A.:
Tumour regression predicts higher risk of sentinel node involvement in thin cutaneous melanomas
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XVII. **Oláh J**, Korom I., Kapitány K., Dobozy A.:
The presence of dysplastic nevi predicts the appearance of melanoma at a relatively young age (submitted for publication to Melanoma Research)

Book chapters

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Abstracts

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Is tumor thickness alone a sufficient criteria for indication of sentinel node biopsy in melanoma?
Mel. Res. 11. S78, 2001.

Abbreviations

CMM	cutaneous malignant melanoma
UM	uveal malignant melanoma
DN	dysplastic nevi
SN	sentinel node
LN	lymph node
SNB	sentinel node biopsy
SNB0	SNB not done
SNB-	SNB histologically negative
SNB+	SNB histologically positive
ELND	elective lymph node dissection
DLND	delayed lymph node dissection
SLND	selectively lymph node dissection
RLA	radical lymphadenectomy
LMM	lentigo maligna melanoma
SSM	superficial spreading melanoma
NM	nodular melanoma
ALM	acro-lentiginous melanoma
AMM	amelanotic melanoma
TNM	Tumour-Node-Metastasis
IFNα	interferon alpha
t.i.w.	three times per week
S.C.	subcutaneous
MU	Million Unit
DTIC	dacarbazine
LC	lymphoscintigraphy
MCi	milliCurrie
DN+	dysplastic nevi bearing CMM patient
DN-	DN-free CMM patient
AJCC	American Joint Committee on Cancer

Introduction

Once considered a rare tumour, cutaneous malignant melanoma (CMM) is now recognised as a leading cause of morbidity and mortality, and its frequency is rapidly increasing. It can occur on any cutaneous surface, as well as in eyes and on mucous membranes [1;2]. Although it is considered a very aggressive tumour, its biological behaviour is heterogeneous.

The incidence of invasive CMM among Caucasians in the United States is about 11 cases per 100 000 inhabitants per year and in Europe 3-14 [3].

The risk of melanoma is inversely related to distance from the equator: in England there are only three new cases per 100 000 inhabitants per year, and the highest reported rate 46 per 100 000 is from Queensland, the most equatorial of Australian States [1; 2; 4]. Fair skinned Caucasians are at grater risk, than those who have darker skin. The lower risk is found among black and Asian populations [5]. The incidence of melanoma has increased dramatically over time. The rapid rise in incidence among recent birth cohorts has led to a relative predominance of melanoma among young adults [6]. CMM rarely occurs prior to puberty but when it does occur about 50 % of cases arise in giant congenital nevi [7].

Mortality rates have also been analysed in many countries, and the findings parallel those of incidence.

In CMM, the most commonly identified mutation is found in the tumour suppressor gene family. Recessive germline *CDKN2A* mutations have been found in 30% to 50% of members of melanoma kindred, in 8% to 15% of individuals with multiple primary melanomas and in some sporadic CMM. Mutations in the cyclin-dependent kinase *CDK4* has also been identified in a few melanoma families. However, at least 60% of melanoma families have neither of these mutations [8-10]. Many studies have characterised the phenotypic features of individuals who are at increased risk for developing CMM [11; 12]. Melanoma is five times more common in individuals with fair or red hair, blue eyes and fair skin and markedly more frequent in those people, who react to sunlight by burning rather than tanning [13-17]. Congenital and many common acquired nevi are also associated with higher risk for susceptibility of cutaneous melanoma [18-25]. By far the strongest association is with the presence of atypical or dysplastic nevi (DN).

The DN is both a precursor of and a very important risk factor for melanoma. The dysplastic nevus syndrome (DNS) was described by Clark [26] and Lynch [27] related to the familial melanoma. Since its first description, it has been a subject of controversy, the main areas of argument being the exact clinical and pathological criteria required to make the

diagnosis [28]. These nevi may be seen in patients in a sporadic or a familial setting, and their true biological significance is still under debate. The sporadic form [29] is more common.
In 1984 a NHI Consensus Conference [30] suggested that patients with DN could usefully be divided into four categories on the basis of personal and family involvement (Table I.). This is a useful working classification as the risk of malignant melanoma is raised very little above baseline in the A category but by several hundredfold in the D category.

TABLE I. Melanoma risk related with personal and family history

Multiple DN Patient	***Personal history of CMM***	***Family history of multiple DN***	***Family history of CMM***
A	***No***	***No***	***No***
B	***No***	***Yes***	***No***
C	***Yes***	***No***	***Yes***
D	***Yes***	***Yes***	***Yes***

The clinical feature of DN is characteristic (Fig. 1). They may have an irregular shape with indistinct border and asymmetric pigmentation. Within the macular lesion an eccentric nodule may be palpable. The size and number of lesions are variable. They can be localised on any part of the skin surface. Predilection sites are the upper trunk and especially the back. Characteristic feature is the involvement of the non-sun exposed areas such as the buttocks and scalp (Fig. 2) [21]. DN, usually compound, is identified on histological examination by the presence of architectural atypia (lentiginous melanocytic hyperplasia, bridging of junctional nests and focal elongation of epidermal rete ridges) and by cytological atypia of the nevus cells (Fig. 3).

In our previous studies we have determined that the frequency of atypical moles is increased not only in cutaneous, but in uveal melanoma patients: DN patients are at increased risk of developing both cutaneous and uveal melanoma [31-35]. We have also found that uveal melanoma patients with DN are at increased risk developing prognostically worst (epitheloid/mixed) histological forms of uveal malignant melanoma [36; 37]. Ophthalmic examinations of our DN bearing patients revealed markedly more frequent pigmented ocular alterations among individuals harboring cutaneous dysplastic nevi compared to non-dysplastic population [38]. The prognostic importance of the presence of DN in the course of CMM is not clarified.

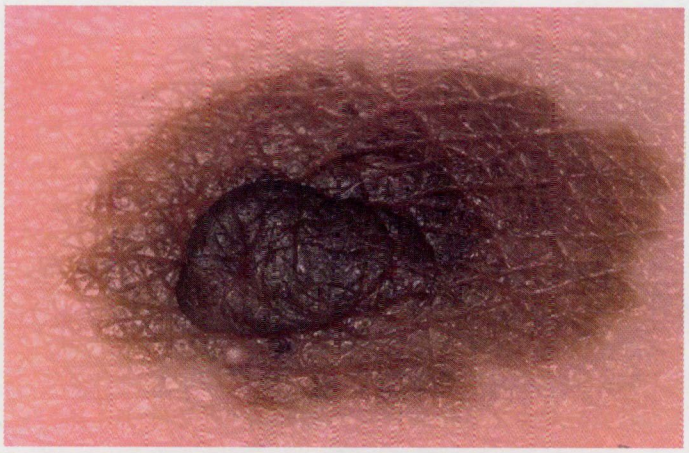


Figure 1. Characteristic clinical picture of the dysplastic nevi.

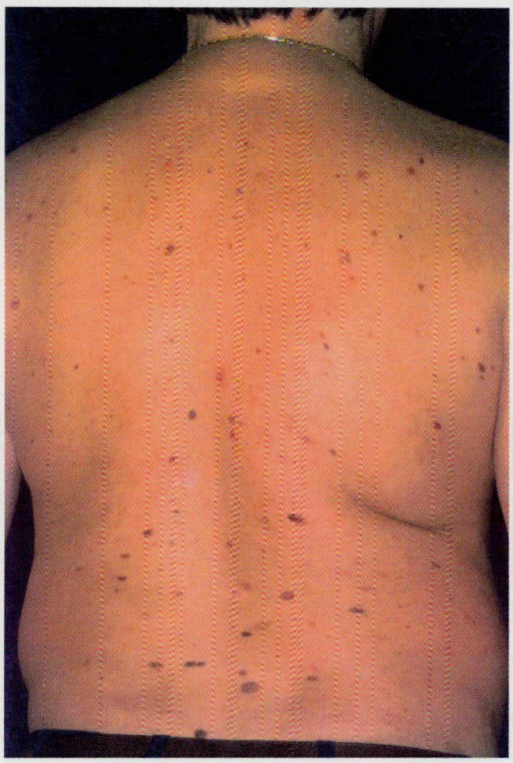


Figure 2. Multiple dysplastic nevi appeared on the back of a patient with dysplastic nevi syndrome (DNS).

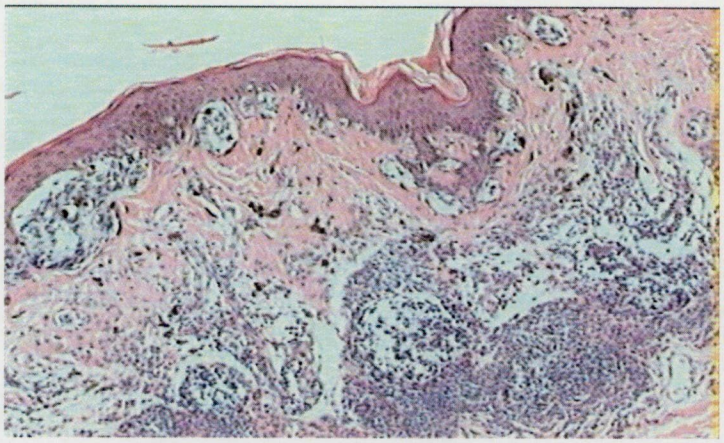


Figure 3. Malignant transformation of a DN with histological signs of regression (H&E) (5 x objective)

Early recognition and prompt excision of primary CMM is the course of action most likely to improve the patient's survival prospects. If CMM is diagnosed when it is an early melanoma (<1mm) the cure rate is close to 100 %, in contrast with advanced diseases, where the life prospect is close to 0% [22; 39-43]. The course of malignant melanoma is characterised by early dissemination. Metastasis usually occurs at first through the lymphatics into the surrounding skin or into the regional lymph nodes. The recurrences are developed in distant sites by haematogenous route in one third of metastatic cases.

At present, there is no agreed view on the optimal procedure for treating melanoma. Generally, the position is that malignant melanomas should be treated by surgery.

As far as possible, extensive three-dimensional surgical removal of the primary tumour is performed with resection margin into the healthy tissue and down to the fascia, which is not excised. Over the past decade the recommended resection margins for melanomas of varying thickness have been reduced (Table II.) [40; 44-46].

TABLE II. Tumour thickness and safety margin

Tumour thickness (mm)	***Safety margin (cm)***
In situ	**0.5**
<2mm	**1**
>2mm	**2-3**

Surgery remains the only effective option in the treatment of nodal metastasis from CMM since chemotherapy and radiotherapy do not achieve the same cure rate in patients with nodal disease. However, the indication for performing an elective lymph node dissection

(ELND) or a delayed one (DLND) is contested [47]. Morton et al. [48] therefore developed a minimally invasive, intraoperative lymphatic mapping technique that should allow more precise pathologic staging before deciding to perform radical dissection [49-52]. Using this diagnostic procedure, patients could be distinguished with clinically occult nodal disease from those whose lymph nodes are tumour-free [53; 54]. Radical lymphadenectomy (RLA) is then confined to those in the former group, introducing in this way the concept of selective dissection (SLND) in contrast to ELND and DLND of the past. The lymphatic mapping technique uses a blue dye and subsequently this dye together with a radioactive agent to trace the path of lymph, as it flows from the primary to nodes in the regional lymphatic drainage basin. If the melanoma has metastasised, tumour cells are most likely to be found in the lymph node on the lymphatic drainage channel closest to the site of the primary melanoma. The "sentinel" node (SN) is the first in the regional basin to stain as the dye enters the lymphatic basin. It can then be removed for immediate pathologic staging before decision is made to go ahead and perform RLA [49; 50; 52; 55].

Accuracy and safety of this technique are now largely documented. All the reported experiences indicate that the SN is the lymph node most likely to harbour metastatic melanoma [53; 54; 56]. The precise indication of SNB in CMM and biological evidence of the nodal micrometastasis are questionable.

The treatment modalities have not been dramatically changed in the past decades in metastatic melanoma. Various approaches have been used in treating of distant metastases [57-59]. All four major therapeutic modalities- surgery, chemotherapy, immunotherapy and radiation therapy-may be helpful in appropriate circumstances, but most patients with advanced disease die from the internal organ involvement.

Excellent prognostic information can be obtained from clinical features and histological examination of CMM (Table III.). Advanced age and male gender have been associated with an adverse prognosis [60; 61]. Anatomical site is an important clinical prognostic determinant. Histological types are usually correlating with survival.

TABLE III. Histological types of CMM

1. LMM	lentigo maligna melanoma (Fig. 4. A1)
2. .SSM	superficial spreading melanoma (Fig. 4. A2, Fig. 5.)
3. NM	nodular melanoma (Fig. 4. B1)
4. ALM	acro-lentiginous melanoma (Fig .4. B2)
5. AMM	amelanotic melanoma (Fig. 4. C2)

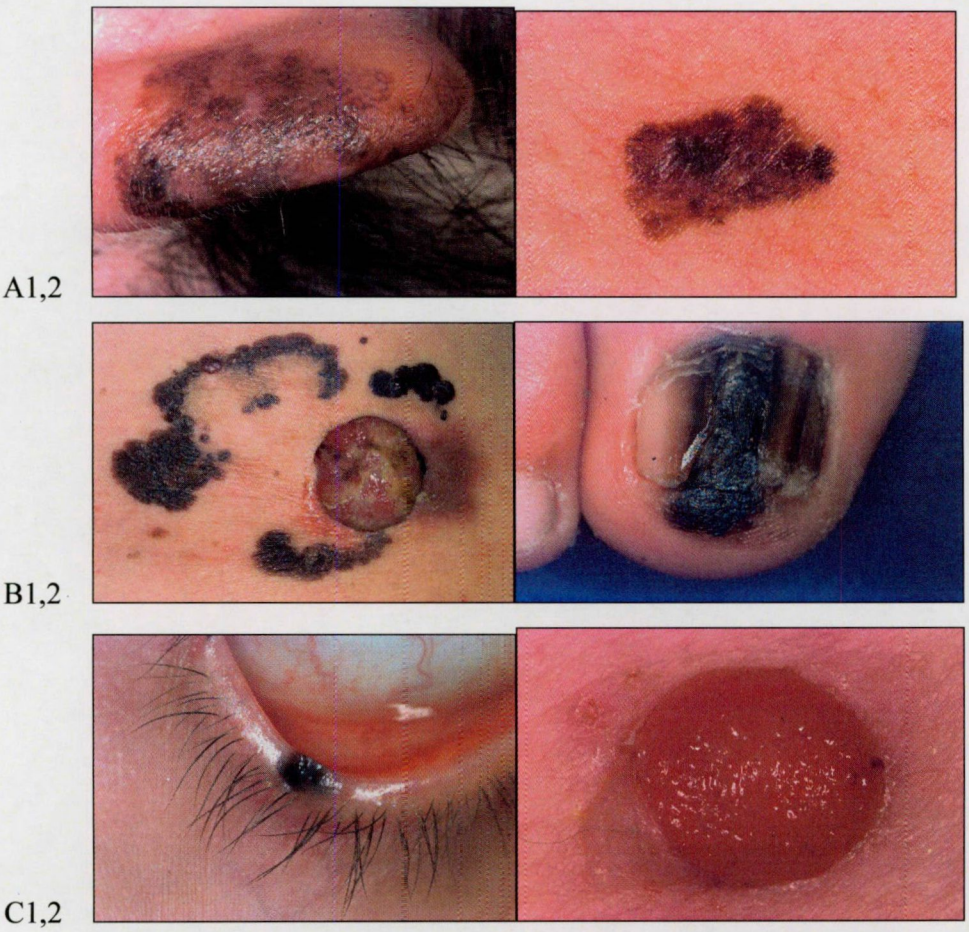


Figure 4.

A1 LMM on the ear

A2 Early SSM

B1 SSM with nodular part

B2 ALM on the toe

C1 NM on the lower eyelid

C2 AMM on the trunk

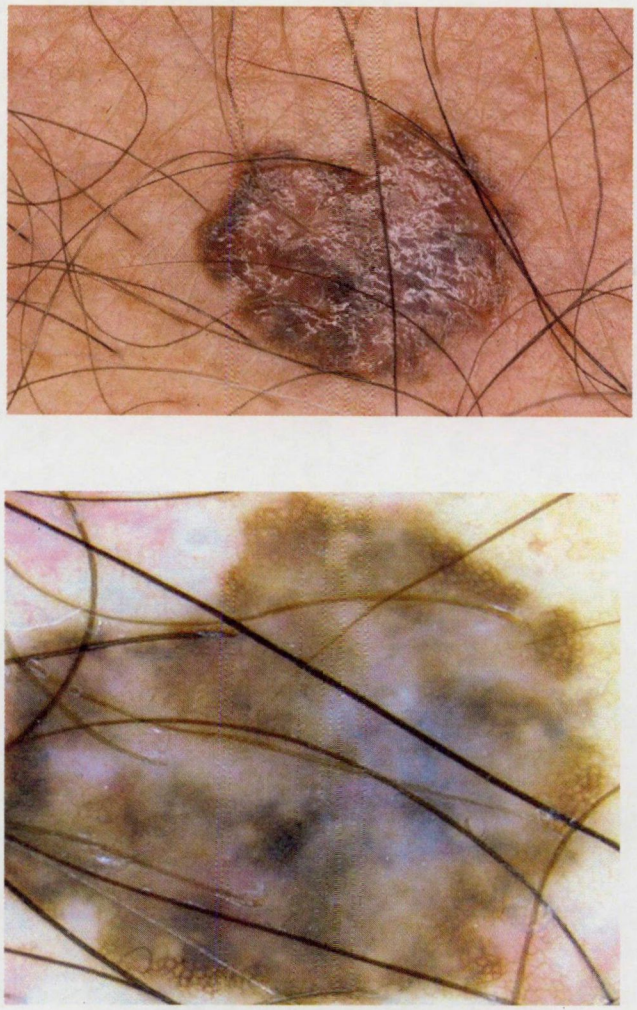


Figure 5. Clinical (A) and dermatoscopical (B) picture of the SSM with regression

The Breslow thickness, the most important single predictor of prognosis, is defined as a distance between the granular layer of the epidermis and the deepest melanoma cells. The relation of thickness to survival has been expressed in inverse ratio [62; 63]. The Clark level reflects the depth of invasion [64]. In most cases the invasion correlates well with the thickness. Increased mitotic rate and ulceration of the primary tumour are poor prognostic signs. Microscopic satellitosis and vascular invasion of tumour cells have also been associated with unfavourable prognosis.

Definition of tumour regression and lymphocytic reaction has been variously defined by different pathologists [65]. Lymphocytic infiltration of vertical growth phase of the tumour may indicate a favourable prognosis, whereas complete regression of a portion of the tumour may associate with a relatively poor survival rate. Recently it was determined, that beside the tumour thickness, the regional lymph node involvement is the most powerful predictor for the

disease outcome in CMM. This fact has induced the changing of Tumour-Node-Metastasis (TNM) classification in 2002. The new TNM defines the pathological staging of the regional lymph nodes [66; 67].

Despite of all these well-known classical prognostic factors CMM is an unpredictable disease with a capricious biologic behaviour.

Regarding the mentioned serious consequences of the disease, considerable efforts has been made to identify the intrinsic end extrinsic risk factors and prognostic markers to determine the most endangered population. Despite the presently available selection of the risk population it is important to further clarify new powerful predictors, which could influence the therapy and the disease outcome in CMM.

Aims of the study

I. To characterise the main classical prognostic factors and the course of the disease in our melanoma patient population:

gender
age of onset of melanoma
location of the primary tumours
histological types
invasion rate
thickness of the tumour
clinical stages of the disease
second malignancies
survival

II. To compare the main prognostic factors and survival in melanoma patients with or without dysplastic nevi.

III. To study the main prognostic factors and course of disease in melanoma patients in relation with the histology of sentinel nodes.

IV. To clarify the predictive value of different tumour parameters for the risk of sentinel node involvement in melanoma cases.

Patients and methods

I. Evaluation of main prognostic factors in all CMM patients treated between 1970 and 2000

General management of CMM patients

The study group consisted of 1803 patients with CMM, who were treated between 1970 and 2000 at the Department of Dermatology and Allergology, the University of Szeged. Dermato-oncological Program computerised database was acquired to retrospectively identify the data of patients.

The following data were recorded:

A. Demographic

- Age at onset
- Gender
- Home address

B. Clinical findings

- Location of the primary tumour
- Palpable lymph nodes

C. Surgical

- Method of primary tumour removal
- Lymph node dissection

D. Histological findings

- Histological type
- Tumour thickness
- Invasion rate
- Lymph node involvement

E. Dissemination rate: stage of the disease by using TNM classification UICC 1987. (Table IV.)

F. Course of disease and survival

- Second malignant tumours

The clinical diagnosis was histologically verified in every case. The majority of these patients underwent wide local excision of the primary CMM. Until late the 90s, the safety zones were 3 cm in impalpable lesions and 5 cm were in thick (palpable) tumours with skin

grafting. Intraoperative frozen-section biopsies were histologically examined in questionable cases.

Usually we have performed the operations under general anaesthesia. Our previous concept in the treatment of non-palpable regional lymph nodes was to apply ELND. Initially we have performed ELND in all of those patients who had primary CMM of 1.5 mm or thicker and/or infiltrating the reticular dermis (Clark level III). Palpable nodes were indication for RLA (Fig. 6) We have changed our therapeutic management of CMM based on new data in the literature (Fig. 7). The safety margins were decreased for 1-2 cm related to the risk of melanoma (Table II). Excision margins were based on clinical assessment of tumour thickness. Our current policy in surgical treatment of regional nodes is to use SLND (see in part of SNB technique). The technique of SLND is presented as a rational and practical technical alternative to ELND or wait-and-watch treatment of patients with medium/high risk melanoma without palpable nodes.

The majority of the histologically node positive cases were treated with dacarbazine (DTIC) monochemotherapy. The drug was given in a dose of about 250mg/m^2 body surface for 5 days at 4 weeks intervals by intravenous route.

BOLD regimen (bleomycin, oncovin, lomustine/carmustine, DTIC) was used to treat patients with metastatic disease in other organs. Other polychemotherapies, and chemoimmunotherapy (DTIC-Fotemustine, DTIC- cysplatin,DTIC-Bleomycin DTIC-IFNα) were applied in several cases. In the last decade, immunotherapy was used in selected cases with nodal involvement or high-risk primary tumour without metastasis. Interferon alpha (IFNα) 2a and 2b were given in different dosages based on the indication of the therapy and tolerance of patients (3-10 MU s.c. t.i.w. during half to 2 years).

TABLE IV. TNM classification of malignant melanoma (UICC 1987)

Stage I A	**pT_1**	**N_0**	**M_0**
Stage I B	**pT_2**	**N_0**	**M_0**
Stage II	**pT_3**	**N_0**	**M_0**
Stage III	**pT_4**	**N_0**	**M_0**
	all pT	**$N_{1,2}$**	**M_0**
Stage IV	**all pT**	**all N**	**M_1**

Management of melanoma at the Department of Dermatology and Allergology, University of Szeged

(1970-1998)

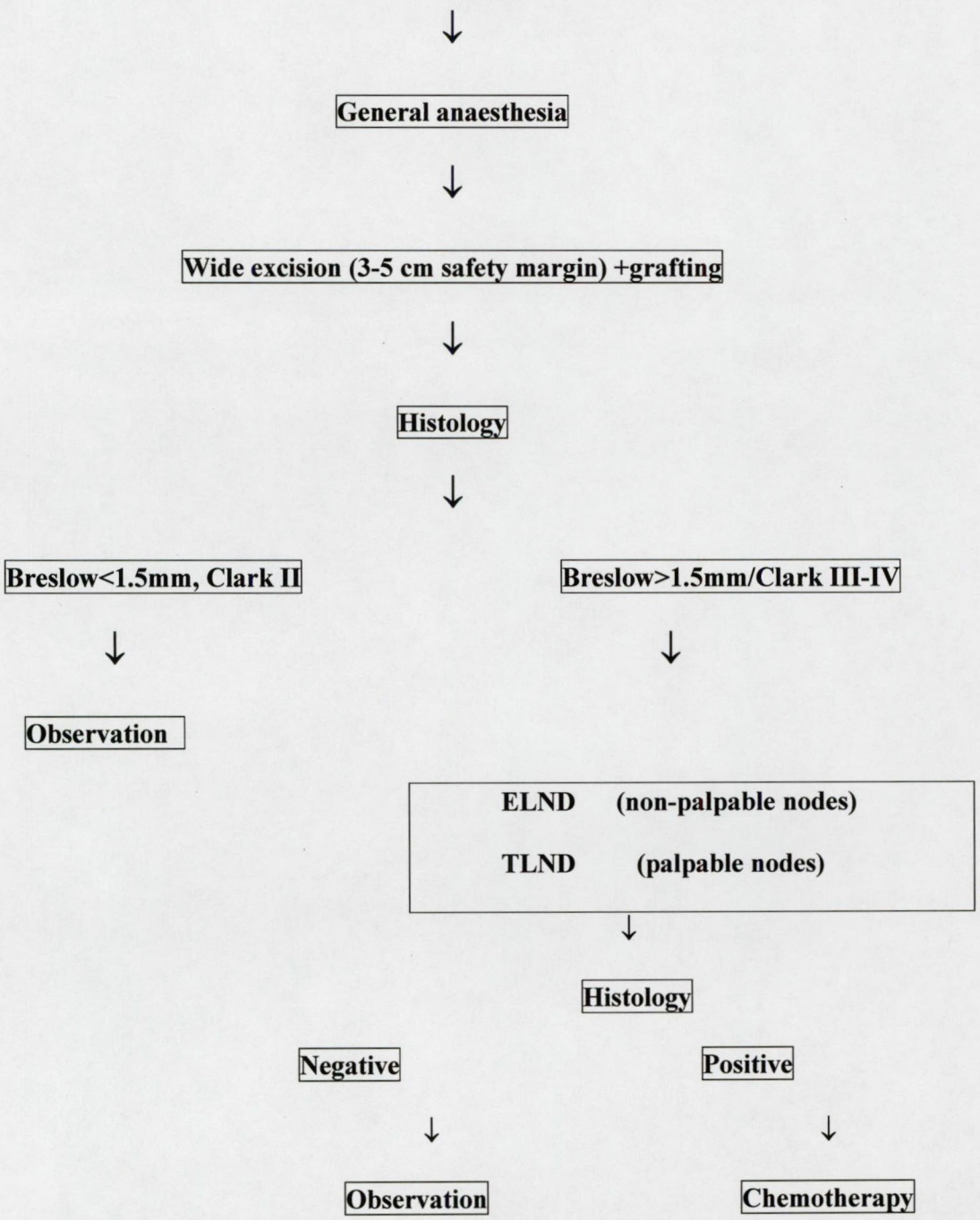


Figure 6.

Management of melanoma at the Department of Dermatology and Allergology, University of Szeged

After 1998

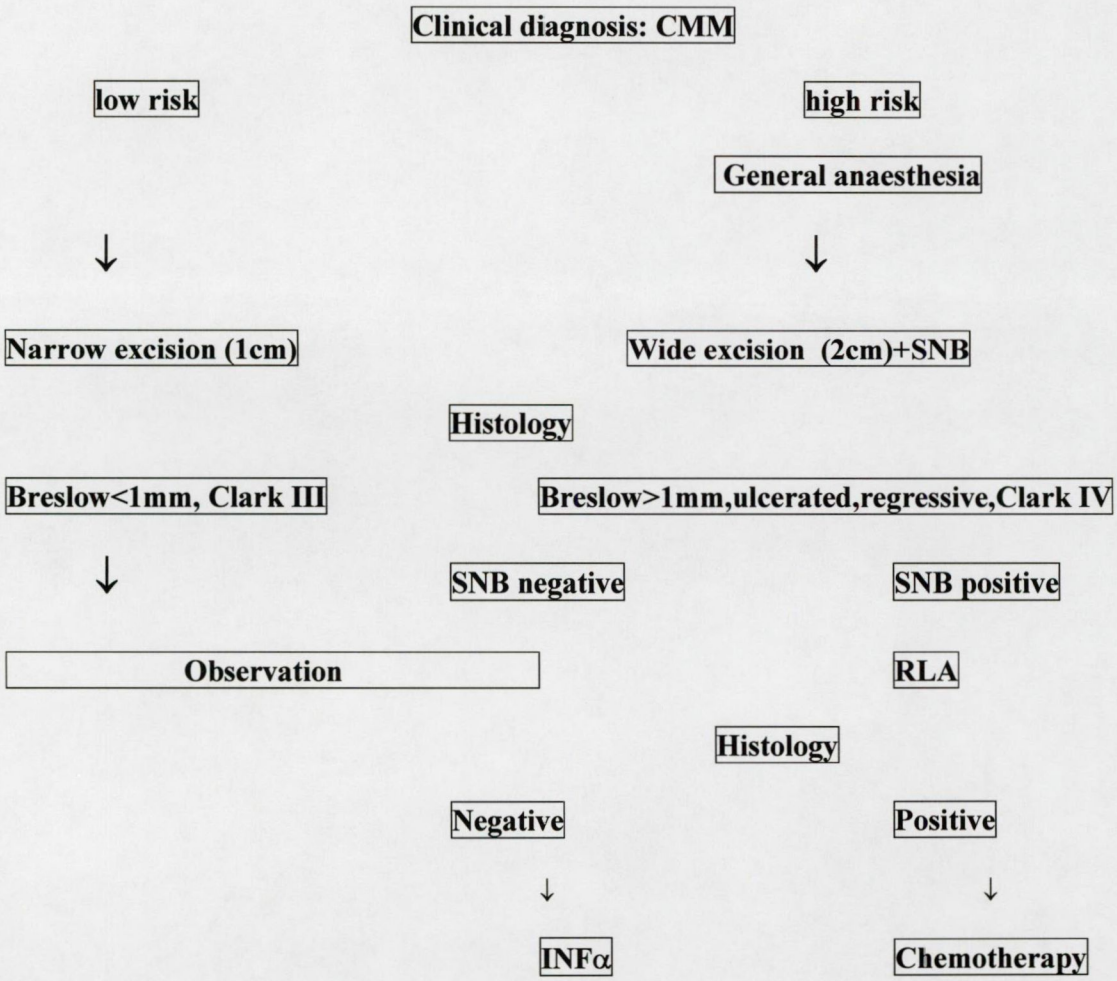


Figure 7.

II. Evaluation of prognostic value of cutaneous DN in CMM patients

This part of the dissertation consists the analysis of 665 selected CMM patients treated between 1990 and 1997 at our department. The same data were recorded as in part I and completed with personal and family history of DN.

Clinical diagnosis of DN in patients with CMM

DN was diagnosed with clinical inspection that included the dermatoscopy and skin surface microscopy (epiluminescent microscopy) in all patients with melanoma, who were treated after 1990 at the Department of Dermatology. Our criteria for diagnosis of DN were: irregular border, asymmetry, irregular pigmentation, macular part within the pigmented lesion, size bigger than 0.5 cm [26; 27; 29]. Dermatoscopical examination enabled us to differentiate DN from thin melanomas or other benign melanocytic nevi [68; 69]. Dermatoscopy allows examination of pigmented lesions in vivo on the body surface at a moderate magnification of 10-to 100x, using oil to render the surface epidermis translucent.
Those patients classified as DN-bearing patient, who had 10 or more atypical moles. We have distinguished two groups within the DN+ cases based on family history of DN.
In several cases the clinical diagnosis of DN was confirmed by histological examinations.

III. Predictive value of different tumour parameters for the risk of SN involvement in melanoma patients

In the third part of the dissertation 244 CMM patients treated between 01/01/1999 and 31/12/2000 were evaluated. During this time SN was removed together with primary tumours of 1 mm or thicker, ulcerated or regressive, based on clinical appearance, in 120 melanoma cases. Our database was completed with the histological findings about the ulceration and regression of the primary tumours and the SN examination for this period.

Surgical removal of the SN

The SNB technique is currently used by many melanoma centres to evaluate the presence of clinically inapparent microscopic metastases in the first draining lymph node in a nodal basin.

-Preoperative dynamic lymphoscintigraphy (LC) was done in every patient who underwent SNB (Fig .8) It was helpful to define lesions with more than one draining nodal basin. This was carried out by intradermal, perilesional injection of 0,5 mCi Tc-99 labelled sulfur colloid (Amersham Shorin). Continuous imaging with a large field view gamma camera was performed, depending on location of the CMM, for up to 2.5 hours for axial tumour sites with potentially equivocal lymphatic drainage [50; 70].

-Under general anaesthesia 0,5-2 ml of blue dye (patent blue 50 mg sulpharum coeruleum, Byk Gulden) was injected intradermally around the lesion or into the site of the primary tumour. (Fig. 9)

-A hand-held gamma probe was used to identify the greatest radioactivity within the draining lymphatic basin over which the skin excision was made. The primary indicator of SN was the visual blue colour.

SNs were considered those, which appear dyed by the tracer or those which counts were 15 to 20 fold the counts of background tissues. When significant residual activity was registered in the operating field, additional SNs were searched for.

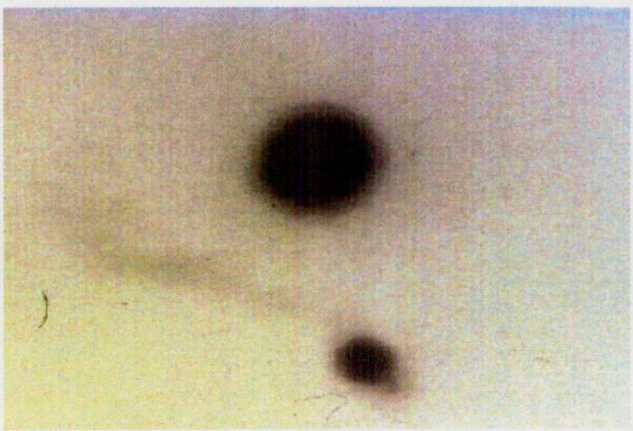


Figure 8. Praeoperative lymphoscintigraphy

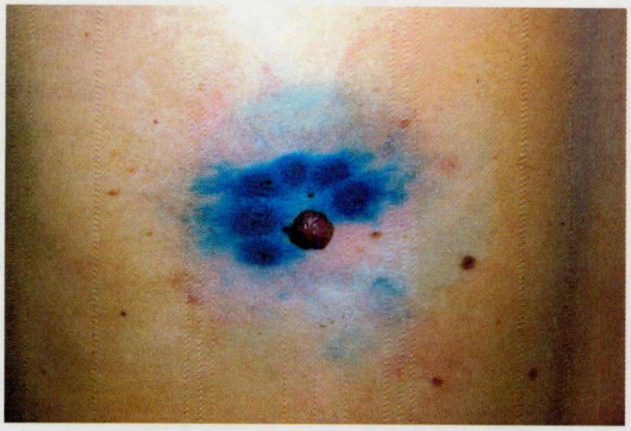


Figure 9. Intracutaneous patent blue injection around the primary tumour

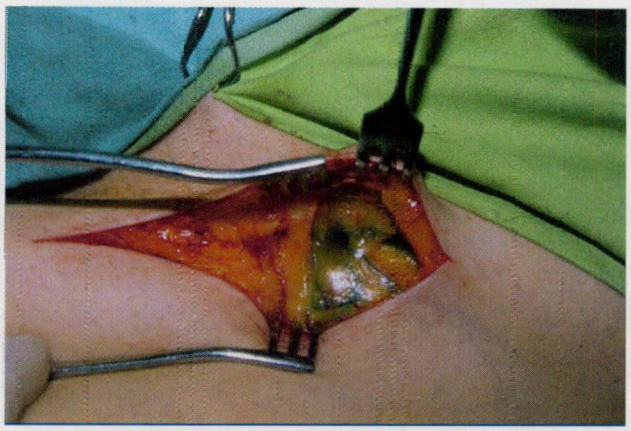


Figure 10. Intraoperative picture of the blue sentinel node

Histological examination of SN

Once the SN was removed, it was fixed in buffered 10% formalin for paraffin embedded sections to stain with Hematoxylin and Eosin (H&E) (Fig. 11). Lymph nodes negative for metastasis by this analysis had additional sections stained with immunohistochemical markers to S 100 (DAKO) (Fig. 12), HMB 45 (DAKO) (Fig. 13) and/or Melan A (DAKO). Histologically, melanoma as small aggregates of single cells or group of cells appeared in subcapsular location in most cases. These cells were then by careful cytologic evaluation differentiated from nevus cells and by immunohistochemical staining from macrophages. S-100 positive dendritic cells can be recognised by their dendritic appearance and benign nuclear characteristics. SN with evidence of metastasis by light

microscopy or immunohistochemical analysis were considered positive, and SLND was performed (or recommended) on the involved basin(s). In our cases the PCR technique was not applied for evaluation of metastatic cells [50].

IV. Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) biostatistical computer program.

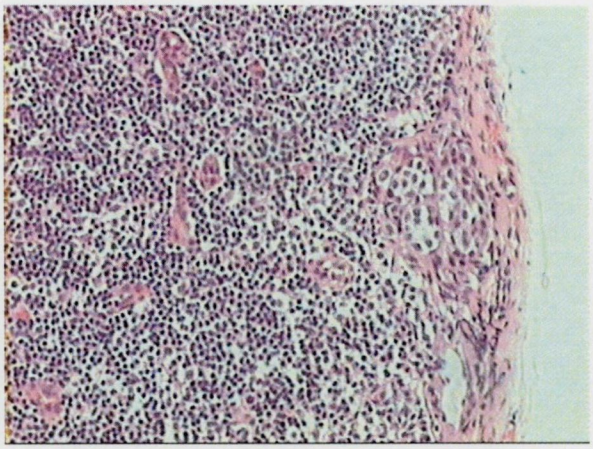


Figure 13. Melanoma metastasis in sentinel node (H&E staining) (5x objective)

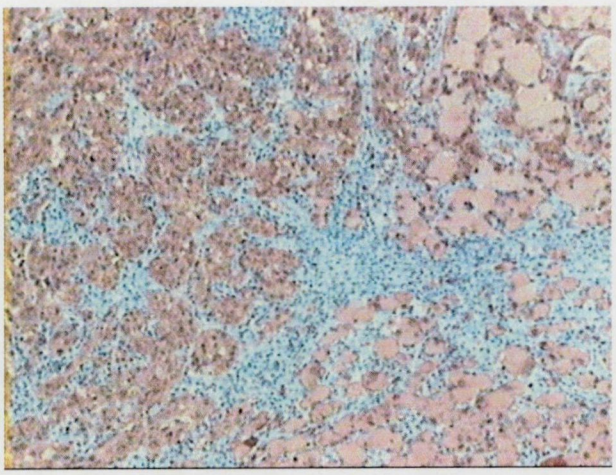


Figure 14. Melanoma metastasis in sentinel node by immunohistochemistry with S-100 (5x objective)

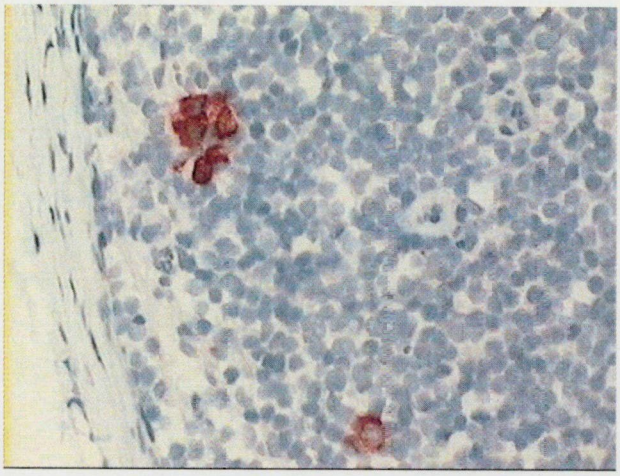


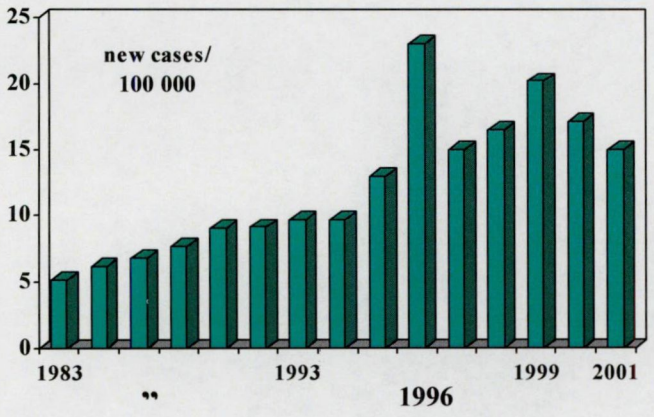
Figure 15. Groups of metastatic melanoma cells in the sentinel node by immunohistochemistry (HMB-45) (10x objective)

Results

I. Evaluation of main prognostic factors in all CMM patients treated between 1970 and 2000

In the last three decades 1802 CMM patients were treated at our Department. Among these cases 777 were male and 1025 were female. The mean age of the CMM patient population was 53.6 years (range, 13-98 years). The current increasing incidence of CMM can also be observed in our region in Hungary. Figure 16 demonstrates well that in the last three decades the increase in incidence was about eightfold in Szeged. We have relatively exact data in our town. In the last year 17 new CMM cases were diagnosed per 100 000 inhabitants. As can be seen on the diagram, there was a peak in 1996 probably because awareness and screening programs were initiated at that time.

Figure16. Incidence of CMM in Szeged (n=414) („:1985-1989 data are not presented)



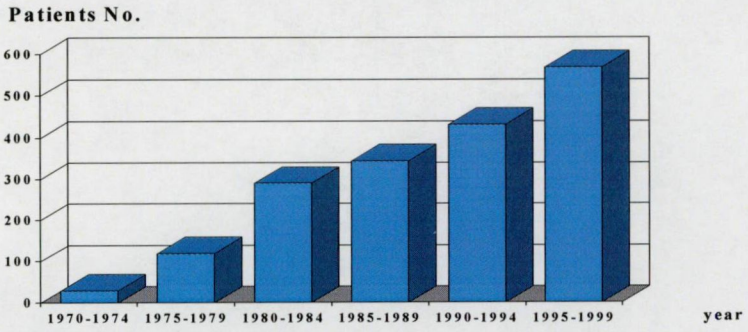


Figure 17. Number of CMM treated between 1970 and 2000 in periods of 5 years

The absolute number of the treated patients has also increased dramatically over the time. Distribution of CMM patients treated in 5-year periods is shown in Fig. 17.

The locations of primary tumours in both sexes are shown in Fig. 18. The most frequent site of primaries in the male population was the trunk in contrast with females, where the majority of CMM localised on the lower limbs.

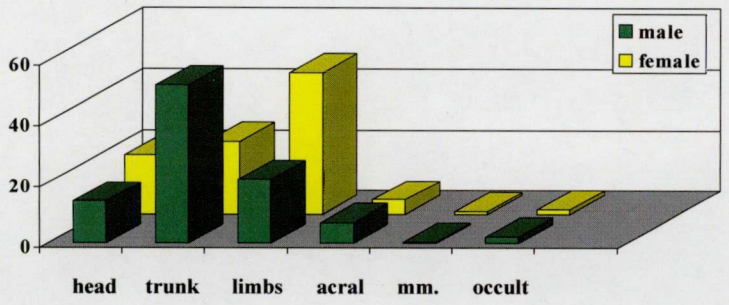


Figure 18. Locations of the primary tumours in patients with CMM (n=1802) (%)

The frequencies of the different histological types of primary tumours are shown in Fig. 19. The dominant histological type of primary tumour in both sexes was the SSM, however numerous NM were also found.

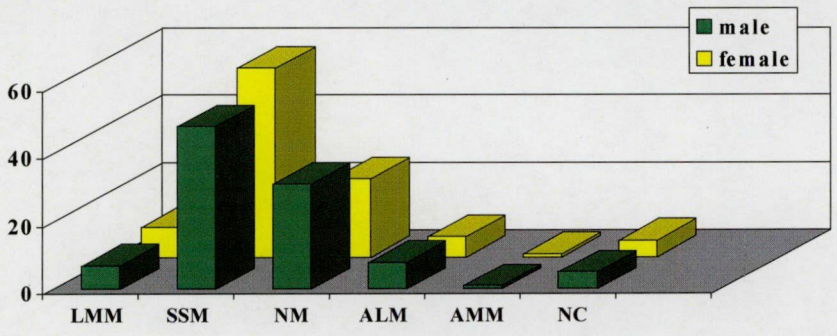


Figure 19. Distribution of histological types of CMM (n=1802) (%)

The maximum thickness of primary melanoma varied as can be seen in Fig. 20. About two-thirds of the tumours were thicker than 1.5 mm, which had medium or high risk for the development of metastases.

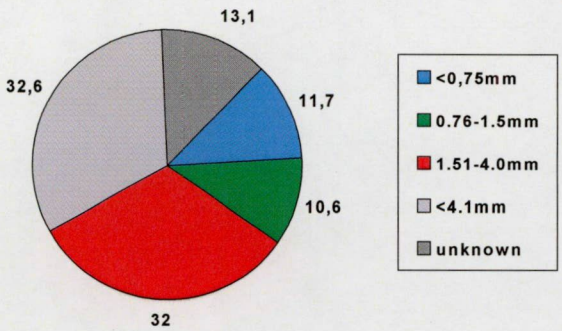


Figure 20. Distribution of Breslow thickness in CMM patients % (n=1802)

Primary tumours were also classified on the basis of the depth of tumour invasion in both sexes. These groups are shown in Fig 21. Most tumours have infiltrated the reticular dermis or invaded deeper elements of the cutaneous / subcutaneous tissues.

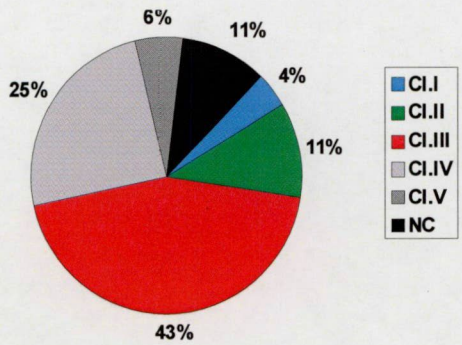


Figure 21. Distribution of invasion rate of CMM patients (%) (n=1802)

The stage distribution (according to TNM classification, UICC 1987) of melanoma cases is demonstrated on Fig 22. As can be seen in this diagram, the typical stage was stage III in both sexes. At present, among the 1802 cases 941 patients lives 559 patients were deceased and another 302 are lost to the follow up. The least follow up period was one year.

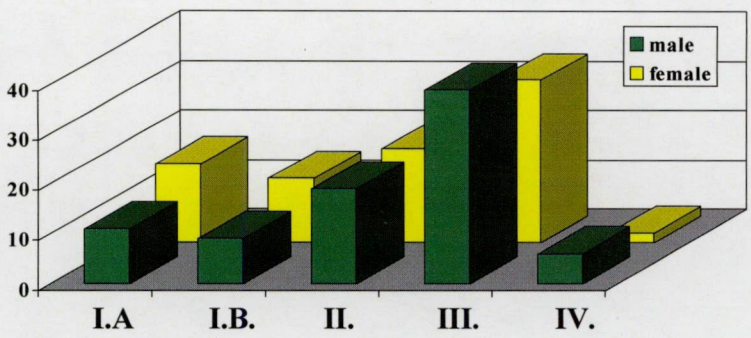


Figure 22. Stage distribution of CMM patients (n=1802)

Stage related survival rates are demonstrated on Figure 23, 24 and 25. Among those patients whose primary tumour was thinner than 4 mm without nodal or distant metastasis the overall survival was about 90 %. On the other hand, with regional nodal involvement (stage III) or distant metastasis (stage IV) the survival rate were found much worse (58 to 10 %).

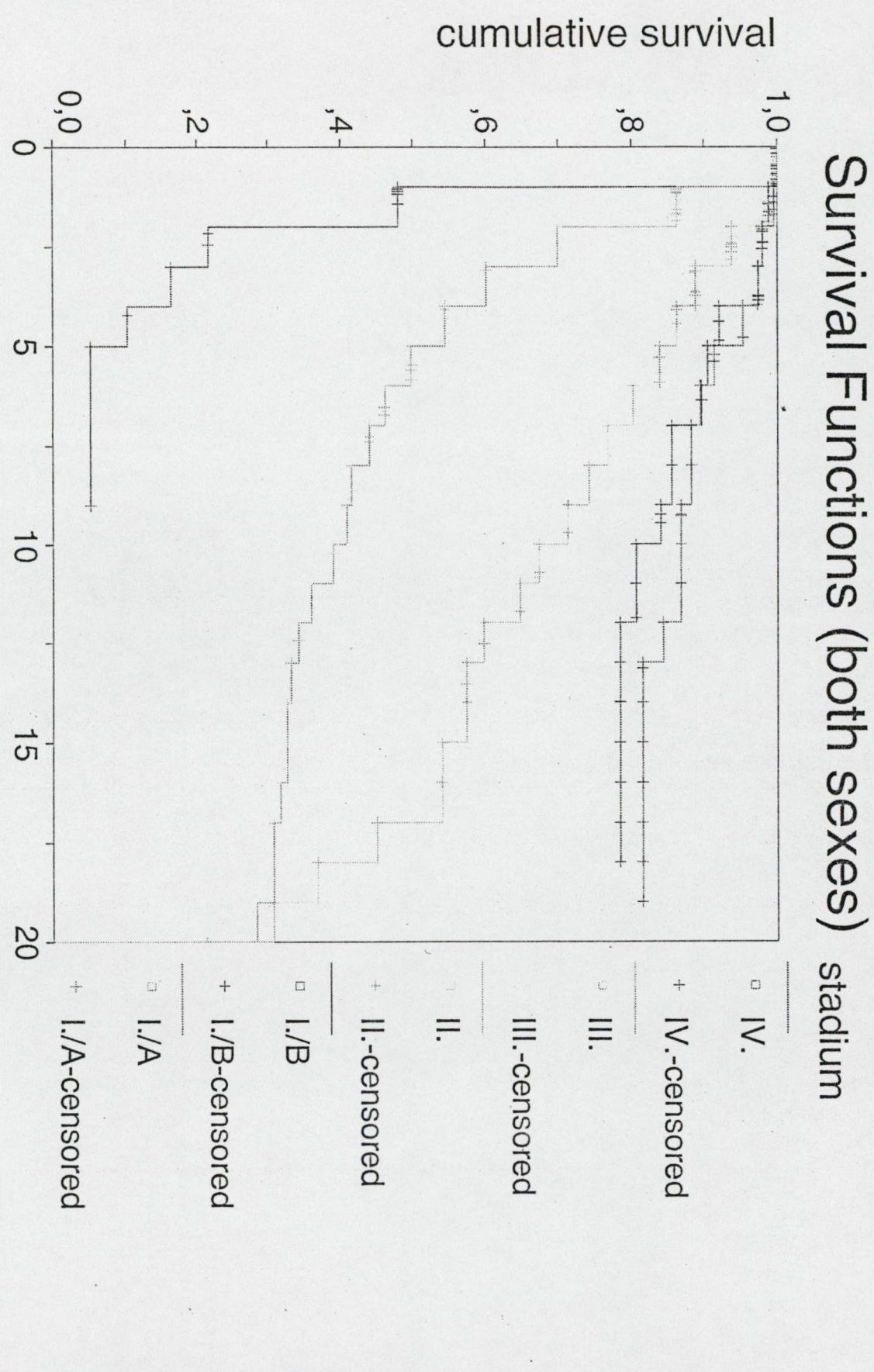


Figure 23. Survival of patients with CMM (n=1802)

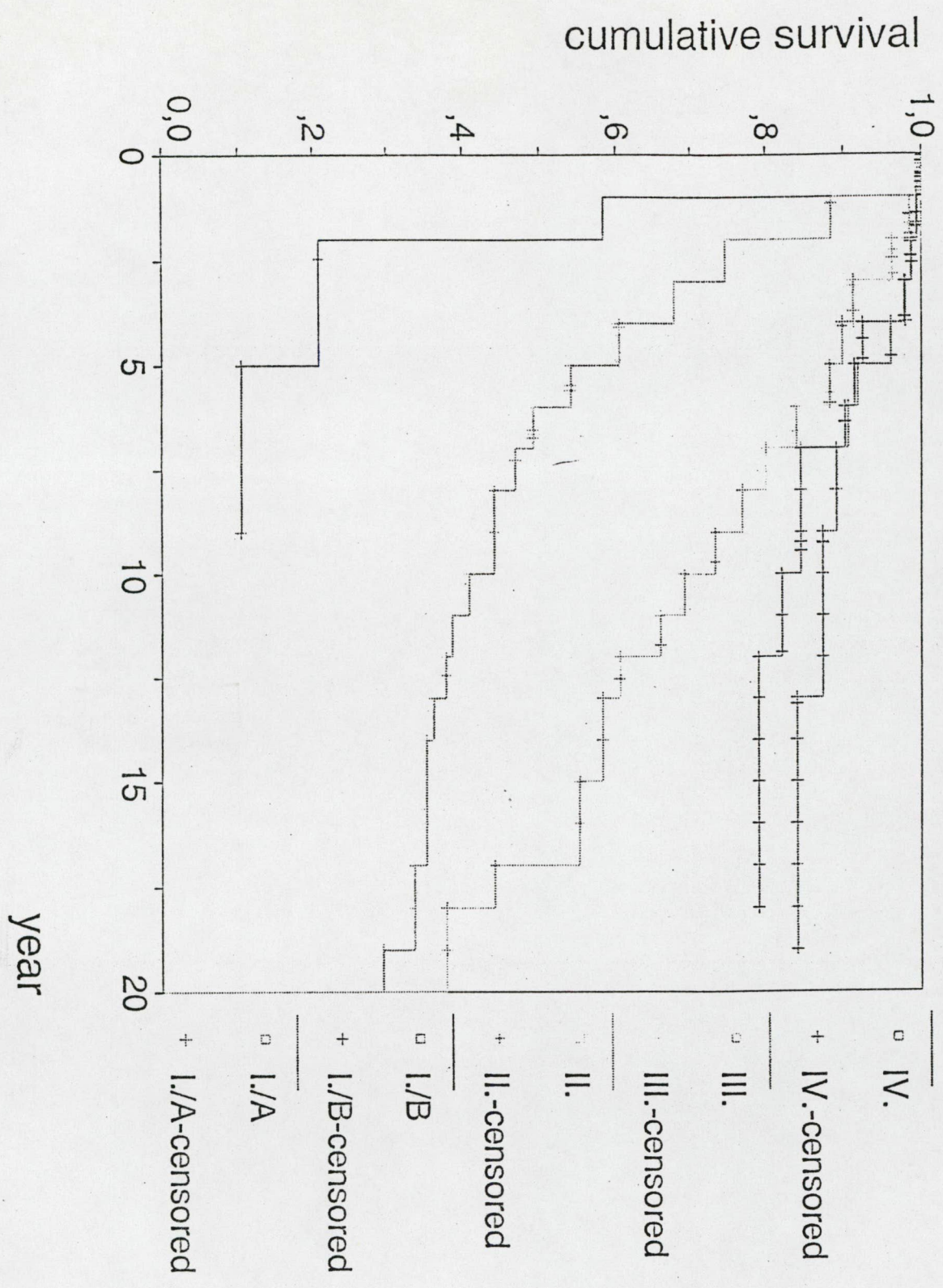


Figure 24. Survival of female patients with CMM (n=1025)

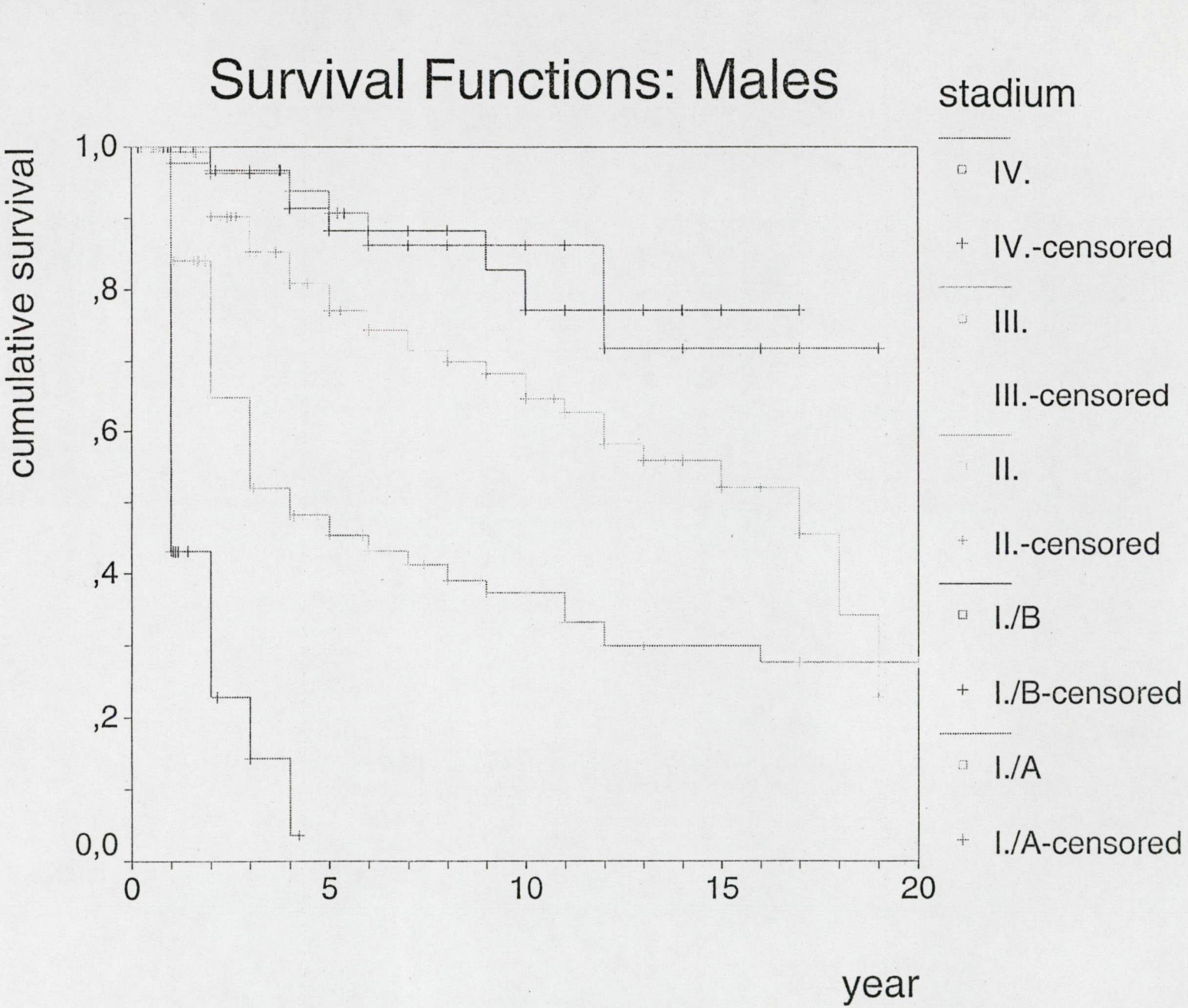


Figure 25. Survival of male patients with CMM (n=777)

II. Evaluation of the prognostic value of DN in CMM patients

In order to investigate the prognostic value of cutaneous DN, the age, location, dissemination rate, second primary tumors and survival were compared in CMM patients with or without DN. The study group consisted of 665 selected patients (393 female and 272 male), treated between 1990 and 1997, whose data were collected retrospectively from our computerized database. The mean age of these cases was 55.57 years (range 14-94 years). From a minimum of 10 to 100 DN were found in 148 (22,25 %) of the 665 cases, and 15 patients (2.25%) had more than 100 cutaneous DN. These 163 patients were considered to be DN-bearing individuals. Within this DN+ group, only 25 patients (15.33%) had a positive family history for DN without CMM occurring in the family. The difference between the ages

of onset of tumour in the compared groups was significant in both sexes. Both the DN+ females and males were much younger (by 19.34 years for the females and 9.19 years for the males) than the DN- group at the time of detection of CMM (Table V). Both univariate analysis and the Mann-Whitney test indicated that the differences were significant ($p<0.001$).

TABLE V. Age of onset in CMM patients with and without DN

Gender	DN-bearing CMM patients	Mean age of onset of CMM (yrs ± SD)	Number of patients
Male	**DN-**	**60.28 (13.55)**	**197**
	DN+	**50.36 (14.58)**	**75**
	***DN+ 1**	**51.45 (13.90)**	**67**
	****DN+ 2**	**41.25 (17.90)**	**8**
Total		**57.54 (14.51)**	**272**
Female	**DN-**	**58.53 (14.36)**	**305**
	DN+	**39.18 (13.58)**	**88**
	***DN+ 1**	**39.78 (13.66)**	**81**
	****DN+ 2**	**32.29 (11.27)**	**7**
Total		**54.20 (16.32)**	**393**
Both sexes	**DN-**	**59.22 (14.06)**	**502**
	***DN+ 1**	**45.06 (14.91)**	**148**
	****DN+ 2**	**37.07 (15.36)**	**15**
Total		**55.57 (15.68)**	**665**

DN-: Dysplastic nevi absent

DN+: Dysplastic nevi present

*DN+ 1: number of DN 10-100

**DN+ 2: number of DN >100

SD: standard deviation

The other prognostic factors were analyzed in 619 patients (360 female and 249 male) from among the 665, whose follow-up time was at least 5 years.

CMM was located on the trunk more frequently in the DN+ females than in DN- females (Table VI), in whom the characteristic location was the lower limbs ($\chi 2$ $p<0.001$).

TABLE VI. Location of primary tumors in female DN- and DN+ CMM patients

		Location of the primary CMM						
DN-bearing of CMM patients		**H**	**T**	**L**	**A**	**M**	**Unknown**	**Total**
DN+	**No.**	**6**	**41**	**27**	**1**	**0**	**2**	**77**
patients	(%)	7.8	53.2	35.1	1.3	0	2.6	100
DN-	**No.**	**56**	**70**	**133**	**15**	**3**	**6**	**283**
patients	%	19.8	24.7	47.0	5.3	1.1	2.1	100
Total	**No.**	**62**	**111**	**160**	**16**	**3**	**8**	**360**
	%	17.2	30.8	44.4	4.4	0.8	2.2	100

DN+ = DN present, DN- = DN absent

H = head & neck, T = trunk, L = limbs, A = acral, M = mucosal

($\chi 2$ $p<0.001$)

In contrast, essential differences were not found between the location of CMM in the DN- and DN+ male groups (Table VII)

TABLE VII. Location of primary tumors in male DN- and DN+ CMM patients

DN-bearing of CMM patients		Location of the primary CMM H	T	L	A	M	Unknown	Total
DN+	**No.**	**1**	**47**	**13**	**1**	**0**	**2**	**64**
patients	%	1.6	73.4	20.3	1.6	0	3.1	100
DN-	**No.**	**29**	**106**	**42**	**4**	**1**	**3**	**185**
patients	%	15.7	57.3	22.7	2.2	0.5	1.6	100
Total	**No.**	**30**	**153**	**55**	**5**	**1**	**5**	**249**
	%	12.0	61.4	22.1	2.0	0.4	2.0	100

DN+ = DN present, DN- = DN absent

H = head & neck, T = trunk, L = limbs, A = acral, M = mucosal

Figs 26. and 27. demonstrate that significant differences were not found in the distribution of the CMM stages (UICC 1987) in the compared groups for either males or females ($\chi 2$ $p>0.05$).

However, analysis of the frequency of non-skin second malignancies revealed an extremely large difference between the DN+ and DN-free groups. 14.1% of the DN+ patients had second malignant tumors, as compared with 3.3% of the DN- patients (Table VIII). The most frequent second tumor in the DN+ patients was CMM, in contrast with the DN- cases, whose second malignancies (with only low incidence) were other solid tumors. Double primary melanomas were found in 17 of the 148 DN+ patients, in 3 further cases more than 2 CMMs were diagnosed. A 28-year-old male had 8 SSM, and 2 males suffered from triple melanoma.

Comparison of the stage-related survival rates demonstrated the survival benefit of the presence of DN. The subgroups consisted of relatively small numbers of patients with DN, which did not allow conclusions of great statistical significance. These data were also difficult to compare because of the extremely large difference in the mean ages of the groups.

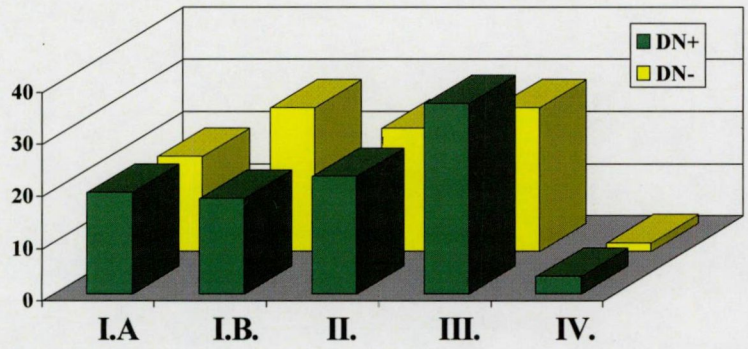


Figure 26. Distribution of stages in female CMM patients with and without DN (%) n=360

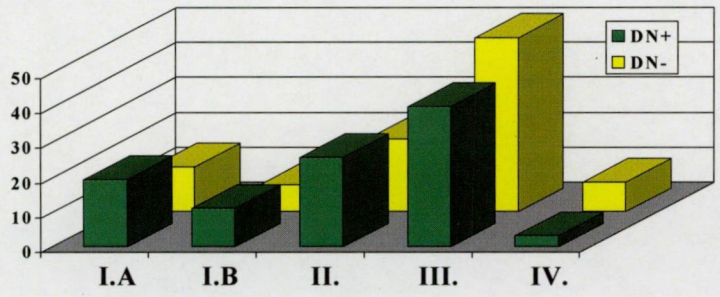


Figure 27. Stage distribution of DN+ and DN- male patients with melanoma (%) n=259

TABLE VIII. Second primary tumours in melanoma patients with or without DN

Patients		Melanoma	Other malignancies
DN+	163	21 (12.88%)	2 (1.22%)
DN-	502	1 (0.20%) (* p<0.001)	16 (3.18%) (*p>0.05)

*Fischer's exact test

III. Predictive value of different tumour parameters for the risk of SN involvement in melanoma patients

In the present study the data of 244 selected patients with CMM treated between 01/01/1999 and 31/12/2000 were analysed retrospectively. In the past two years we have removed the SNs together with primary tumours of 1mm or thicker, ulcerated and regressive, based on clinical appearance, in 120 melanoma cases. The thickness, ulceration and regression of the primary CMM in relation with the histology of SNB were evaluated. The distribution of the histological types of the primary CMMs is demonstrated in Table IX.

TABLE IX. Distribution of the histological types of melanomas.

	LMM	SSM	NM	ALM	AMM	OTHER	OCCULT
Patients	21	134	51	12	3	18	5

In the histological findings the regression and ulceration were graded as present or absent. All patient had non-palpable regional lymph nodes by clinical examination. During this study period at least 1 SN was successfully localised and harvested in all of the cases. Among the 120 cases with CMM 128 SNs were considered. The locations of SNs and the primary CMMs are shown in Table X and XI.

TABLE X. Location of the primary melanomas and the histology of sentinel nodes

	H	T	UL	LL	A	MM	Other	All
Patients								
SNB 0	32	31	20	25	5	6	5	124
SNB -	2	23	11	24	1	0	1	62
SNB +	1	34	12	9	1	0	1	58
All	35	88	43	58	7	6	7	244

H = head, T = trunk, UL = upper limbs, LL = lower limbs, A = acral

TABLE XI. Location of sentinel nodes and their histology

SNB	Axillar	Inguinal	Other	Total
SNB -	**35**	**34**	**1**	**70**
SNB +	**34**	**19**	**5**	**58**
Total	**69**	**53**	**6**	**128**

Of the 120 patients 58 (48,3%) had involved SN with metastatic cells. As can be seen in table XII, our data demonstrates a significant positive correlation between SNB positivity and increasing tumour thickness ($\chi 2=62.595$; df=8.$p<0.001$)

TABLE XII. Correlation between tumour thickness (mm) and the histology of sentinel node(s)

	Thickness				
Patients	**0,001-1 (mm)**	**1,001-2 (mm)**	**2,001-4 (mm)**	**4< (mm)**	**Other**
SNB 0	**63**	**14**	**11***	**17***	**19**
%	70.7	31.1	22	42.5	95
SNB –	**15**	**20**	**20**	**7**	**0**
%	16.9	44.4	40	17.5	0
SNB +	**11**	**11**	**19**	**16**	**1**
%	12.4	24.5	38	40	5
Total	**89**	**45**	**50**	**40**	**20**
%	100	100	100	100	100

* Patients with palpable lymph nodes or distant metastasis and/or serious concomitant diseases

Ulceration required the localised total absence of epidermis. Among the 224 primary CMMs 84 (37,5%) were ulcerated. The histological sign of ulceration was more frequent in thicker tumours, therefore correlated well with SN positivity (Table XIII)

TABLE XIII. Correlation between sentinel node positivity, tumour thickness (mm) and ulceration

	Ulcerated		**Non ulcerated**		**Total**
Tumour thickness	**0,001-2**	**2,001<**	**0,001-2**	**2,001<**	
SNB0/-	**9**	**45**	**103**	**10**	**167**
SNB+	**3**	**27**	**19**	**8**	**57**
Total (%)	**12** (5.4)	**72** (32.1)	**122** (54.5)	**18** (8)	**224*** (100)

* 5 occult primary melanoma and 15 unclassified for ulceration

By our criteria the definition of regression to have prognostic significance must include the presence of a zone of tumour-free epidermis and dermis, in which there is fibrosis, often along with inflammation and dilated vessels, flanked on one or both sides by tumour. After the histological examination of the primary tumours the signs of regression were found

among the patients with thin (<2mm) CMM (n=134, Table XIV). The relative risk for the involvement of SN in patients with regressive CMM was near tenfold higher compered to the cases with non-regressive tumours (Relative risk: 9.779, 95% Confident interval: 3.560-26.862)

TABLE XIV Correlation between sentinel node positivity and histological signs of regression

	Regressive	**Non-regressive**	**Total**	%
SNB 0/-	**8**	**95**	**103**	76
SNB +	**14**	**17**	**31**	23
Total (%)	**22** (16.4)	**112** (83.6)	**134**	100

In cases of histologically positive SN we have recommended for the patients the lymphadenectomy of the basin. Of 58 SNB positive patients in 52 cases SLND were performed. Among the 52 patients who underwent SLND additional nodal involvement were found in 24 (46,15%) cases.

These results are summarised in Table XV.

TABLE XV. Number of positive lymph nodes (LN) in patients with selective lymph node dissection

LN number	**1 LN**	**2 LNs**	**2<LNs involvement**
Cells/group of cells	5	8	4
Metastasis≥ 2mm	3	3	1

Although the follow up period is very short, of the 62 SN negative patients only 3 cases have developed metastasis. The clinical characteristics of these three patients are listed in Table XVI.

TABLE XVI. Characteristics of sentinel node negative patients with tumour progression

Number of patients	**1.**	**2.**	**3.**
Sex/Age (year)	**F/36**	**F/56**	**F/50**
Localisation of the primary tumour	**leg**	**leg**	**arm**
Histological type	**SSM**	**SSM**	**SSM**
Invasion rate	**II**	**III**	**IV**
Thickness (mm)	**0,89**	**1,56**	**2,97**
Ulceration	**0**	+	+
Regression	**0**	**0**	+
Site of recurrence	**RLN**	**in transit**	**RLN**

Discussion

Ad 1.

CMM represents a significant and growing public health burden worldwide. Approximately 42 000 cases of CMM and 40 000 cases of in situ CMM were diagnosed in 2000 in the United States [1; 2; 4; 22]. In the 1930s, the lifetime risk of an American developing invasive CMM was 1 in 1500. Currently, that risk is 1 in 74. Hence, this neoplasm is responsible for the loss of more years of life than might be expected on the basis of its associated mortality.

According to the reorganised Hungarian Cancer Registry there were about 1000 new melanoma cases at the same period in Hungary. The calculated incidence rate of CMM was about 10 per 100 000 inhabitants in 2000 in Hungary. In contrast, in our database we have revealed 17 new CMM cases in Szeged at the same period. Though the annual number of hours of sunshine is the highest in Hungary (it is more than 2000 hours), this itself can't account for the relevant difference between these two values. Among our patients the proportion of in situ primary tumours was absolutely low. In our previous studies the relatively low incidence of CMM observed in south eastern Hungary during a 20-year period between 1970 and 1990 may be a consequence either of a poorer diagnosis of early cases, or a truly lower incidence [71; 72]. Because of the dramatically increasing incidence in the last decade worldwide and the great proportion of high-risk tumours at presentation in Hungary we believe that a considerable number of primary tumours in an early stage are probably missed, and therefore the relatively low incidence observed in Hungary is not realistic.

Many authors have reported female preponderance of CMM. The male to female ratio of 1:1.319 in our series is only slightly greater than the overall sex ratio for CMM in the general populations in other part of the world. The mean age at first diagnosis in our series was 53.6 years. This is similar to previous reports of CMM [67].

Early recognition and immediate treatment have resulted in a rise in the overall five year survival rate for all stages of disease from 60% in 1960 to 1963 to 83% in 1977 to 1982 in the United States. Considering that in Hungary 360 patients have died of melanoma in 2000, and the 1000 new diagnosed CMM, our results of five-year survival rate for all stages is approached approximately 60% [57; 67; 73].

At the first clinical examination, most patients were free of palpable nodal involvement or distant metastases, but the proportion of thick, deeply invading primary tumours was high, greater than 60%. The majority of our cases were in stage III, which means, that most of our cases had thicker tumours than 4 mm and/or had the regional nodal

involvement. Balch et al. reported the prognostic factor analysis of 17 600 patients with CMM. In that multi-institutional series about 70% of all cases had 2 mm or thinner tumours [67]. Several other authors have demonstrated similar data. These findings also indicate a deficiency in the early recognition of CMM in Hungary [22; 74].

The most frequent anatomical locations of the primary tumours in man were the back and acral regions, while in women it was the leg. These data and the distribution of histological types of primary tumours are similar to the observations of several other authors [43; 67].

Comparison of the stage related survival rates of our CMM cases and the data of other cancer centres have not revealed considerable differences in stage I A-B and Stage IV. Survival rates in stage II and III were more favourable in our cases [43; 67]. In our previous clinical practice, the implementation of ELND has given an accurate pathological selection between node negative and node positive CMM patients. This upstaging has resulted an apparent survival benefit both in stage II and in stage III. Previously, Szekeres et al. have reported similar data about the importance of ELND in patients with primary CMM with intermediate risk (tumour thickness between 1.5 and 4 mm) [71]. Our department has participated in an international multicenter randomised trial that was carried out by the WHO Melanoma Programme from 1982 to 1989 [47]. The trial included patients with trunk melanoma 1.5 mm or more in thickness. Multivariate analysis showed that routine use of ELND had no impact on survival, whilst the status of regional nodes affected survival significantly. The patients with regional nodes that became clinically and histologically positive during follow up had the poorest prognosis. Node dissection offers increased survival in patients with node metastasis only. These data have suggested the therapeutic benefit of SLND.

Ad 2.

In the improvement of the early recognition of CMM it is fundamental to screen the risk population. At the same time that we are seeing a rise in the incidence of CMM, there is a growing awareness that many or most melanoma deaths may be prevent by the screening of individuals at high risk. The purpose of screening high-risk individuals is twofold: to remove or closely monitor high-risk, pigmented cutaneous lesions that are potential precursors of melanoma and to diagnose melanoma in an early phase, before metastases have developed.

It is well known that one of the most relevant and sensitive phenotypic markers of increased melanoma risk is the presence of DN, but numerous other potential risk factors have also been cited. Included among these are acute and blistering sunburn, certain phenotypic factors, immunosuppression, prior therapy with psoralen with UV A light, UV exposure at tanning beds, elevated socio-economic status and history of CMM in a first-degree-relative [7; 13-17; 75-79]. Furthermore, people who have had one CMM are at higher risk of developing another.

In our previous studies we have found that the relative risk for uveal melanoma in patients with DN was similar to the relative risk of CMM in patients with DN. These results suggest that the presence of DN may be used as a sign of the gene carrier status not only for skin but also for uveal melanoma [34-37].

In the present study, the prognostic factors and the survival times of melanoma patients with and without DN were compared. Melanoma developed 19.34 years, and 9.19 years earlier in female and male DN+ patients, respectively. 21 of the 163 DN+ patients, while only 1 of the 502 DN- patients suffered from multiple primary melanomas [80].

Analyses of the prognostic factors of patients with multiple primary melanomas have been published by other groups [10; 81-86]. In all of these studies it was reported that the group with DN was approximately 10 to 21 years younger than the group without DN. The frequency of DN in patients with multiple melanomas in previously reported studies was between 38% and 48%. Our results also demonstrate a significant difference between the mean ages of DN- and DN+ patients with CMM, and a high frequency of multiple melanomas in the DN+ groups. Thus, DN should be considered a risk factor for the development of melanoma at a relatively young age.

In conclusion, our findings confirm that patients with DN syndrome are indeed genetically disposed to develop CMM. Special emphasis should therefore be placed on the early and regular screening of patients with this important risk factor.

Ad 3.

The AJCC recently proposed major revisions of the TNM categories and stage groupings for CMM using evidence-based methodology. The proposed staging system better reflects independent prognostic factors that are used in clinical trials and in reporting the outcomes of various melanoma treatment modalities. Major revisions include:

(1) melanoma thickness and ulceration to be used in T category but not the level of invasion (except for T1 melanomas);

(2) the number of metastatic LN to be used in the N category rather than their gross dimensions and the delineation of clinically occult (microscopic) versus clinically apparent (i.e. macroscopic) nodal metastases;

(3) the site of distant metastasis and the presence of elevated serum lactic dehydrogenase (LDH) to be used in the M category;

(4) an upstaging of all patients with stage I to III when the primary tumour is ulcerated;

(5) a merging of satellite metastases around a primary CMM and in transit metastases into a single staging entity that is grouped into stage III disease

(6) a new convention for defining clinical and pathological staging so as to take into account the new staging information gained from intraoperative lymphatic mapping and SNB [66; 67; 87].

In this new AJCC melanoma staging system Balch et al. have confirmed that the metastatic involvement of regional lymph nodes is the most powerful prognostic predictor in CMM.

After the controversial elective lymph node dissection (ELND) and delayed lymph node dissection (DLND) the implementation of the novel technique sentinel lymph node biopsy (SNB) should make it possible to better select the high-risk patients for nodal involvement. The SNB has become widely established in several countries as a technique for prognostic assessment. The surgical procedure is not complicated and has a relatively low morbidity, however, the indications for SNB are still a matter of debate.

The decision to surgically stage regional LNs should be based on several factors, including sensitivity of the diagnostic procedure, the likelihood of finding occult metastasis, the impact of such findings on treatment, and other clinical and psychosocial issues. The questionable populations among the CMM cases are the patients with thin melanomas. Although metastatic involvement in patients with thin primary melanoma is rare, there have been several reported cases [88; 89]. Previous reports have suggested using SNB in patients with

primary tumour 1 mm or thicker, ulcerated and deeply invasive (Clark level IV.) [46; 50; 53; 54; 56; 70; 90-97].

Our policy was to use SLND in those patients who had primary tumours 1 mm or thicker, ulcerated or regressive on clinical appearance. After the learning phase the rate of successful SNs localisations increased to 100% using the combination of preoperative lymphoscintigraphy and intraoperative lymphatic mapping with both vital blue dye and radio colloid.

In our series the sentinel node positivity rate was 48,3%. This is much higher than the findings of other groups [98-100]. The positive correlation of SNB positivity with tumour thickness is expected and generally has been observed. Other groups have found ulceration of the primary tumours between 10% and 25%. In our study we have found ulcerated CMM in 37.4%. The high rate of nodal involvement in our series could be associated both with the precise pathological examinations and the grater proportion of high-risk tumours with ulceration.

Melanomas showing histological evidence of regression are in some cases to be associated with worse clinical course than similar but non-regressing tumours [90; 101]. Partial regression of primary tumours has been documented in up to 20 % of the cases, even complete spontaneous regression has been observed. The regression may be decreasing the thickness of the tumour, which becomes relatively thinner, but as it seems the survival correlates with the original tumour thickness. The definition and judgement of regression are debated, whilst the precise pathomechanism of regression is unknown. It seems to be an immunological reaction of the host against the tumour. These reasons may explain the controversy of this area both in pathology and immunology.

Our findings have revealed high rate SN involvement also in the group of patients with thin, but regressive melanomas. We found the predictive value of tumour regression in thin tumours for the risk of nodal disease significantly high.

134 melanoma patients with a primary tumour thickness of 2.0 mm or less were treated at the Department of Dermatology, University of Szeged, from January 1, 1999, through December 31, 2000. Following preoperative lymphoscintigraphy (Tc-99m nanocoll) and lymphatic mapping, sentinel nodes were successfully identified in all cases using both blue dye and radiolabelled colloid with a gamma probe. Both primary tumours and sentinel nodes were analysed histologically on paraffin embedded specimens on serial sections using haematoxylin and eosin staining and immunohistochemistry with HMB 45 and S-100 antibodies by two well-trained dermatopathologists independently. By our criteria the definition of regression must include the presence of a zone of tumour-free epidermis and

dermis, in which there is fibrosis, often along with inflammation and dilated vessels, flanked on one or both sides by tumour (the estimated specificity and sensitivity were over 90%).

Among the one hundred and thirty-four melanoma patients (primary CMM is less than 2mm thick) thirty-one patients (23%) had positive SNB. There were eighty-nine patients with CMM less than 1 mm thick, of which twelve (13.5%) had positive sentinel node (specificity 99% and sensitivity 96%) The patients in our study underwent follow-up visits every three months. The median follow up was 36 months (range: 24-48 months).

Sentinel node metastases were found in a significantly greater proportion among patients with primary tumours showing histological evidence of regression: 14/22 (63.6%) vs. 17/112 (15.2%) positive cases in patients with regressing and non-regressing melanomas, respectively. The relative risk of sentinel node-positivity for patients with regressing tumours was 9.779 (95% CI 3.56-26.862) as compared to patients with non-regressing tumours. Furthermore, of the 14 sentinel node-positive patients with regressing melanomas, 11 had tumours thinner than 1.0 mm (mean 0.682+ 0.20, range between 0.380 and 0.912 mm), and none of these ulcerated or infiltrated deeper than the papillary dermis (Clark's level II).

These findings indicate that early in their disease course, patients with relatively thin but regressing melanomas are at an almost ten times higher relative risk of developing regional lymph node metastases than are patients with non-regressing melanomas. It is tempting to speculate that histological regression results in a decreased Breslow's thickness measurement, and thus in some cases an erroneously more favourable prognostic estimate. Although melanoma regression has been reported to be associated with higher metastatic potential [88], to date no direct evidence has been published to the effect that histological regression predicts increased risk of nodal involvement. Currently for patients with primary melanoma less than 1.0 mm thick, SNB is only indicated if ulceration or deep infiltration (Clark's level IV-V) is present [50].

Our results suggest that patients with thin melanomas showing histological signs of regression should be considered as potential candidates for sentinel lymph node biopsy.

Conclusions

1. CMM represents a significant and growing public health burden in Hungary just as it does worldwide. Our findings reveal that our CMM patients have thicker primary tumours and more advanced disease than the CMM patients in western countries. These findings indicate a deficiency in the early recognition of CMM in Hungary. Prevention and early detection remain the primary goals in the war against this cancer. Professional education, public awareness, patient education and research advances should and must improve the survival prospects of our patients.

2 To achieve early recognition of CMM, the most important strategy is to screen the high-risk population both for cutaneous and uveal melanoma therefore, the DN+ melanoma patients have to be included in the focus of our interests since they represent an increased clinical risk population. Our results indicate that DN is the most significant factor that warrants increased surveillance of such patients to detect and treat melanoma in its early and curable stage. Our findings revealed that the DN bearing melanoma patient population is much younger at the time of first diagnosis of CMM compared to the DN free individuals. Multiple CMMs were also more frequent among the DN+ melanoma cases. These patients should be warned of the potential hazards of sun exposure, educated in methods of protecting themselves and their children from the sun, and encouraged to do monthly skin self-examinations. Total skin examinations at regular intervals should be performed by a trained dermatologist at least once a year and should be continued for life in all of DN bearing individuals.

3 The presence or absence of nodal metastasis is a very sensitive predictor of the outcome of melanoma. With the implementation of SNB technique it is possible to select melanoma patients with occult nodal disease at an early stage. We have found a great proportion of SN positive patients among those cases who had thick, ulcerated and/or regressive melanomas regardless of tumour thickness. Our findings indicate that tumour regression should be included as a new parameter in the criteria of the indication for SNB in patients with thin melanomas.

Summary

Cutaneous malignant melanoma (CMM) represents a significant and growing public health burden in Hungary just as it does worldwide.

The aims of this study were to characterize the main common prognostic factors, tumour parameters and survival in our patients treated with cutaneous malignant melanoma. These factors were also compared in those melanoma patients who had dysplastic nevi.

Our findings reveal that melanoma patients in Szeged, Hungary have thicker primary tumours and more advanced disease than the melanoma patients in western countries. These findings indicate a deficiency in the early recognition of the melanoma in Hungary.

We have found that the dysplastic nevi bearing melanoma patient population is much younger at the time of first diagnosis of melanoma compared to the dysplastic nevi free melanoma patients. Multiple cutaneous melanomas were also more frequent among the dysplastic nevi bearing melanoma cases. Our results indicate that dysplastic nevus is the most significant factor that warrants increased surveillance of such patients to detect and treat melanoma in its early and curable stage

The presence or absence of nodal metastasis is a very sensitive predictor of the outcome of melanoma. With the implementation of sentinel node biopsy (SNB) technique it is possible to select melanoma patients with occult nodal disease at an early stage. We have found a great proportion of sentinel node (SN) positive patients among those cases who had thick, ulcerated and/or regressive melanomas regardless of tumour thickness. Our findings indicate that tumour regression should be included as a new parameter in the criteria of the indication for SNB in patients with thin melanomas.

To achieve early recognition of CMM, the most important strategy is to screen the high-risk population both for cutaneous and uveal melanoma that includes patients who carry dysplastic nevi on their skin, since they represent an increased clinical risk population. Prevention and early detection remain the primary goals in the war against this cancer. Professional education, public awareness, patient education and research advances should and must improve the survival prospects of melanoma patients.

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