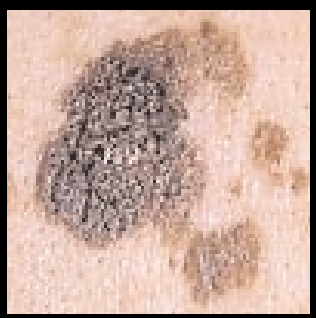
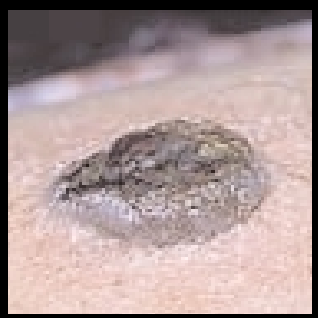
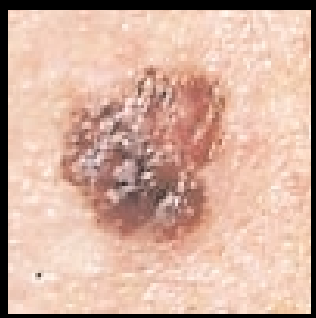
Malignant melanoma in Denmark in the period 1985-94

By Lone Bak Hansen







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CONTENTS

Preface

The study was carried out at the Department of Plastic Surgery and Burn Unit, Copenhagen University Hospital (Rigshospitalet), and the Department of Cancer Epidemiology of The Danish Cancer Society. The study is based on data on patients with malignant melanoma, which were accumulated prospectively by the members of the Danish Melanoma Group (DMG) in the period from 1985 until 1994. In the period February 2000 until August 2002 the following hospitals have been visited in order to verify the data on patients included in the DMG-database: Århus Kommunehospital, Odense Universitetshospital, Roskilde Amtssygehus, Gentofte Amtssygehus, and Herlev Amtssygehus.

My supervisors were Chief of Department, dr. med. Krzysztof T. Drzewiecki, Department of Plastic Surgery and Burns, Copenhagen University Hospital (Rigshospitalet) and Chief of Department, dr. med. Jørgen Olsen, Department of Cancer Epidemiology, The Danish Cancer Society. I wish to thank them for sharing their great knowledge.
Kasper D. Hansen assisted with the statistical analyses, which he did profoundly and at a highly professional level.

K.T. Drzewiecki gave permission to use tables and graphs of the studies from the period 1964-82.

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Special gratitude and love should be aimed at my boyfriend Flemming, my parents Jonna and Ejgil, my sister Ulla, her husband Jan, and their 3 kids for their never failing support and believing in me and in my skills.

I also wish to thank the chartered surveyors Klavs Petersen and Karina Christiansen for the production of the map of Denmark, where regions and cities involved in DMG were depicted, and graphic designer Christel Franke for designing and producing the front page.

Abbreviations

AJCC	American Joint Committee on Cancer
ALM	Acral lentiginous melanoma
CPR	Person identification number. A number consisting of 10 characters uniquely identifying every person in Denmark. The first six characters are the date of birth "ddmmyy" and the last 4 characters are an identification code. If the last character is even, the patient is female, if the last character is uneven the patient is male. An example of a CPR: (240554-2420). The patient is female because the last character is 0, and she is born 24th of May 1954. If a patient is foreigner, the four last numbers in the CPR contain one or more letters.
CR	The Danish Cancer Registry
DMG	The Danish Melanoma Group. The group consists of experts within the specialities plastic surgery, pathology, epidemiology, dermatology, oncology, and others. DMG has existed since 1984 and has prospectively accumulated data on Danish melanoma patients according to registration protocols. Data is collected from all over the country except the Southern and Northern part of Jutland.
DMG-83	The Danish Melanoma Group registration protocol set up in 1983
DMG-89	The Danish Melanoma Group registration protocol revised in 1989
DMG-92	The Danish Melanoma Group registration protocol revised in 1992
CDR	The Danish Cause of Death Registry
GE	Gentofte Hospital (Gentofte Amtssygehus)
HE	Herlev Hospital (Amtssygehuset i Herlev)
HH	Hvidovre Hospital
LMM	Lentigo malignant melanoma
MM	Malignant melanoma
NM	Nodular melanoma
OD	Odense University Hospital (Odense Universitetshospital)
RH	Copenhagen University Hospital (Rigshospitalet)
RO	Roskilde Hospital (Roskilde Amtssygehus)
SSM	Superficiel spreading malignant melanoma
TUM	Thickness unclassified melanomas
ÅR	Århus Hospital (Århus Kommunehospital)

Introduction

Objective of this PhD study was 1. To validate the completeness and quality of registration in the DMG-database by internal validation, by a comparison with the Danish Cancer Registry, and furthermore by a sample test of 100 cases chosen randomly from the database. 2. To provide descriptive analysis and survival analyses of the population of Danish melanoma patients diagnosed and treated in the period 1985-94 on basis of the DMG-database. 3. To investigate if the type of initial diagnostic procedure, either excision biopsy, incision biopsy or curettage, influenced overall - and recurrence-free survival. 4. To provide the means that will allow allocating thickness unclassified primary melanomas in proper TNM-classification. The consequence of a sub-optimal primary initial diagnostic procedure is impairment of sufficient pathological classification, especially due to the ability of measuring the tumour thickness. In Denmark the treatment of thickness unclassified melanomas is wide excision and since the late 90´ies sentinel node biopsy is performed on these patients; however it has not been investigated whether this is the optimal treatment in all cases. The thickness unclassified melanomas were in this study categorised according to other important prognostic factors than tumour thickness (level and ulceration) and the survival rates of these categories was compared with those of the staging categories calculated by American Joint Committee on Cancer (AJCC). This comparison enabled to suggest a proper TNM-classification and thus an optimal surgical treatment for the thickness unclassified melanomas.
This treatise is written in a way that the reader can choose to follow subject by subject; e.g. background, materials and methods, results, and discussion within the subject validation, followed by descriptive analysis of the Danish melanoma population etc.

Background

During decades malignant melanoma has been the type of cancer showing the most rapid increase in incidence compared to any other type of cancer in Denmark and other countries as well (1, 2, 3); the survival has improved during the period (4, 5), the mortality has been rising as well (1, 3). The highest melanoma incidence in Denmark occurred in 1995 (Fig. 1) with 998 malignant melanomas. From 1996 the incidence of malignant melanoma seemed to be levelling off for both sexes. A comparable levelling of in the incidence has also been seen in other populations (6, 7). However, in 1999 another increase in incidence seemed to be on its way (Fig. 1) (8), according to age adjusted incidence rates it was mostly pronounced in males (9).

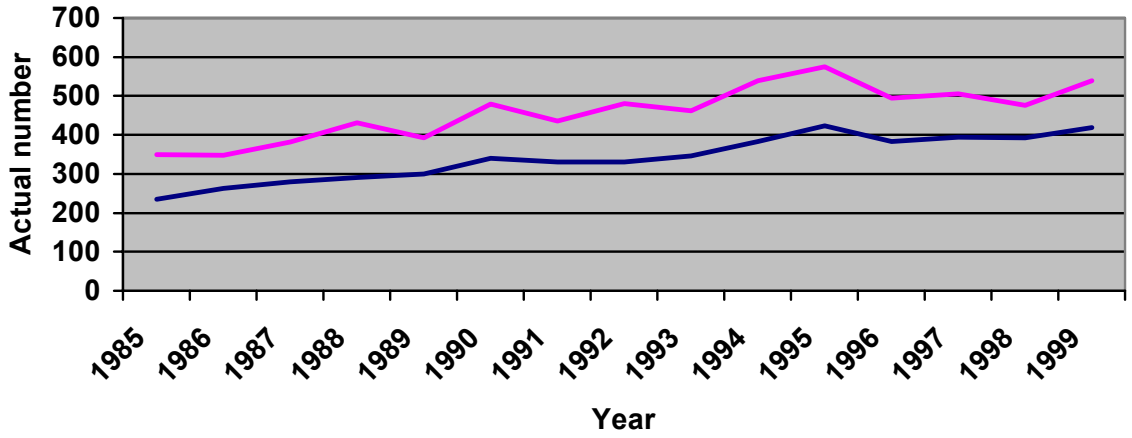

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Fig. 1. Incidence of malignant melanoma in Denmark in the period 1985-99 according to sex (—males, — females) Data from the Danish Cancer Registry (8).

Validation of the database

An increased use of registries, databases, information systems and other studies based on secondary data is seen, presenting both advantages and disadvantages (10, 11, 12, 13, 14). An advantage is that the data already exists; the time spent on the study and the loss of data is therefore considerably reduced compared with the studies using primary data collection. Other advantages include the size of the sample, its representativeness for the population studied, and the reduced likelihood of bias due to e.g. recall, non-response, and effect on the diagnostic process of attention caused by the research question.

Disadvantages of using secondary data are lack of control by the researcher of selection, quality, and the methods of collection. It is therefore important to validate secondary data (15, 16, 17). Factors affecting the value of secondary data to be taken under consideration are outlined by Sørensen in his thesis (15):

1. Completeness of registration of individuals:
    a. Comparing the data source with one or more independent reference sources such as other registries or databases
    b. Comprehensive records review, which are used particularly in hospital discharge systems. It comprises investigation on variations in coding, errors in coding and incompleteness in coding (18).
    c. Aggregate methods, which comprise comparison of total number of cases in the data source to the total number in other sources.
2. The accuracy and degree of completeness of variables:
    a. Precision, which implies estimation of amount of missing values.
    b. Validity, which include assessment of random and systematic errors.
3. The size of the data sources, which implies description and number of variables as well as of the population.
4. Registration period.
5. Data accessibility, availability and cost
6. Data format, whether it is paper records or computerized.
7. Record linkage. Description of linkage to other data sources.

(If you wish to follow this subject, turn to page 17)

Descriptive analysis of the Danish melanoma population

A vast majority of the malignant melanomas develop in the skin at the junction of epidermis and dermis. The tumour arises from the melanocytes in the basal layer of the epidermis. Characteristics describing a malignant melanoma include assessing of the tumour type, the level of invasion in the skin, description of presence of ulceration and measurement of the tumour thickness. Melanoma types are divided in superficial spreading melanomas (SSM), nodular melanomas (NM), lentigo maligna melanomas (LMM) and acral lentigenous melanomas (ALM). The dept of invasion in the skin layer is divided in five levels, level I-V, where level I is an in situ lesion and level V is a deep invasion through stratum reticulare into the subcutis.

The total number of benign melanocytic naevi, presence of freckles, presence of 3 or more clinically atypical melanocytic naevi and a history of three or more episodes of severe sunburns or tendency to burn are thought to be contributing factors in the development of the malignant melanoma disease (19, 20, 21).

Descriptive of the Danish melanoma population 1943-87:
Drzewiecki *et al* (22, 23) has described the melanoma population on basis of a patient registry (including 648 and 714 cases, respectively) at Odense University Hospital for the period 1964-82. Østerlind (20) described in her thesis the Danish melanoma population in the period 1943-87 on basis of the Danish Cancer Registry, which included a case-control study of the melanoma population of the eastern part of the country in the period 1982-85 of 551 melanomas.

More females than males were found to develop malignant melanoma (20, 21, 22, 23, 24). In the period 1958-87 the average age at time of diagnosis was 52-54 years (20, 21, 22). The anatomical localisation was different in the two sexes. Drzewiecki *et al* found that the most frequent anatomical sites of melanomas on males were the trunk (50%) and the head/neck (24%), whereas the most common sites in females were the lower leg (35%) and the trunk (20%). The same distribution was found by Østerlind except for males who had melanomas on the lower leg (22%) more frequently than in the head/neck region (14%) (20, 23). SSM represents between 65-76% of the incidences of malignant melanoma, followed by NM representing 18-19%. Unclassifiable melanomas represent 9-10%, ALM represents approximately 6%, and LMM represents 5% (20, 22, 25). In the period 1964-72 Drzewiecki *et al* found a median tumour thickness of 2.3 mm; in the period 1973-82 it decreased to 1.5 mm (22). During the period (1964-82), Drzewiecki *et al* found the following distribution of level: level II 13%, level III 44%, level IV 35% and level V 8%. (22); in the subsequent period (1982-85) Østerlind (20) found the following distribution of level: Level I 5.3%, level II 35.7%, level III 29.4%, level IV 25.4% and level V 4.3%.

In her thesis Østerlind (20, 26, 27, 28) has investigated the connection between malignant melanoma and the occurrence of other malignant diseases, the influence of dietary intake, smoking, the use of hair products and hormonal and reproductive factors in women. A slightly higher incidence of chronic lymphatic leukaemia for males and of endometrial cancer for women was seen, but the reason for this increase was found to be due to incidental occurrence. No connections were found between the other above-mentioned variables and the malignant melanoma disease. Swerdlow *et al* (29) also studied the risks of second primary malignancies in the Danish melanoma patients in the period 1943-89. They found no increased risk of developing secondary non-skin

malignancies in both sexes. A statistically significant increased incidence of oropharyngeal cancer in both sexes combined was found; increased incidence of chronic lymphocytic leukaemia in males and in both sexes combined and increased brain and nervous system cancers in females and both sexes combined was found. According to both sexes separately and combined a statistically significant increase was found of non-melanoma skin cancers. In a study of the melanoma population in the City of Hope, California (30), an increase in risk of developing a subsequent melanoma and bladder cancer was found.

A description of the pathological - and clinical variables in the DMG-database of the period 1985-94 was carried out. Time trend analyses were carried out on basis of the descriptive variables of this study and a former study of Drzewicki *et al* (23), which included the periods 1964-82 and 1985-94.

(If you wish to follow this subject, turn to page 23)

Survival analyses of the Danish melanoma population

The survival of the Danish melanoma population has been investigated. Univariate analyses of the survival calculated by the actuarial method for different prognostic variables were published by Drzewiecki *et al* (22, 31) (Table 1).

	5-year[1] (%)	10-year[1] (%)
Sex		
Males	76	64
Females	85	75
Anatomical region		
Legs	85	75
Arms	84	71
Head and neck	81	72
Trunk	78	74
Thickness		
< 0.76 mm	98	97
0.76-1.49 mm	91	87
1.50-2.49 mm	78	56
2.50-3.99 mm	73	52
≥ 4 mm	58	58
Ulceration		
No	92	84
Yes	65	51
Level		
II	97	97
III	88	80
IV	73	54
V	57	53

	5-year [2] (%)	10-year [2] (%)
Type		
SSM	75	52
NM	55	32
Thickness		
< 2 mm	88	66
> 2 mm	54	31
Ulceration		
No	87	64
Yes	52	29
Level		
I - III	84	65
IV - V	62	35

Table 1. [1]Actuarial survival data for melanoma patients treated in Denmark 1964-82 (22).
[2]Actuarial survival data for melanoma patients treated in Denmark 1964-73 (31).

They showed that females have better 5- and 10-year overall survival compared to males (Table 1). This was also found by Carstensen, and Østerlind and Kjems in 1993 (4, 5). They published survival analyses based on data from the Danish Cancer Registry, which show a 5-year survival rate of localized disease of 70.1% in males and 82.3% in females, and a 10-year survival rate of 55.3% in males and 69.8% in females for the period 1978-87. It is noteworthy that in all three studies the 5-year survival rate of the males was similar to the 10-year survival rate of the females. Engeland A *et al* (32) studied the survival of cancer patients in the Nordic countries. For malignant melanoma no differences was found in survival between the Nordic countries. The highest Scandinavian age-adjusted mortality rates were found in Norway, followed by Denmark, Sweden, and Finland; this distribution in mortality was estimated to continue in the future (33, 34).

In the period 1964-82 patients with melanomas on the trunk (Table 1) were found to have the poorest prognosis with a 5- and 10-year survival of 78% and 74%, respectively. Intermediate survival rates were seen in the head/neck region (81% and 72%), the arms (84% and 71%). The best prognosis was seen when melanomas were located on the legs with a 5- and 10-year survival rate on 85% and 75%, respectively (22, 23).

In previous studies of the Danish melanoma population patients with NM have the poorest prognosis, whereas patients with LMM have the best (23, 35). The thicker and deeper the invasion is into the skin, the poorer the prognosis is for the patient. Localization at the mucous membrane, ulceration, growth into the vessels and presence of epithelioid cells are all poor prognostic signs (22, 23).

Only very few studies studied the recurrence pattern and the survival following recurrence in the Danish melanoma population. In 1988 Lock-Andersen *et al* (36) described the patterns of the first lymph node metastases of patients with malignant melanomas of axial localisation. In 1989 a case report by Lock-Andersen *et al* (37) described a metastasizing thin melanoma of a young female, and in 1993 Andersson *et al* (38) described the recurrence pattern and prognosis after relapse from head and neck melanoma. They found that first recurrence was local in 27%, regional in 49% and distant in 24% of the cases. In the period of the study 1949-86 the survival after recurrence of head and neck melanomas was markedly decreased, the 5-year survival following local, regional and distant metastases was 30%, 27% and 4%, respectively. Factors that influenced the survival following first recurrence were localisation of the first recurrence and presence of ulceration of the primary tumour.

(If you wish to follow this subject, turn to page 24)

Initial diagnostic biopsy procedure and survival analyses

The recommended initial diagnostic procedure is excision biopsy, because it gives the possibility to establish a satisfactory diagnosis for the further treatment (39, 40, 41, 42, 43, 44, 45, 46). However, in very large lesions or lesions placed at surgically difficult areas it is sometimes indicated to perform incision biopsy. Curettage, which is a superficial shaving of the epidermis with a "curettage" instrument, superficial skin biopsy by scalpel shaving, and scissors biopsy, which is removal by elevating the element with a pair of tweezers and cutting it off with a pair of scissors, are contraindicated in the initial diagnostic procedure, because these methods likely do not provide

adequate tissue for sufficient histological analysis, including determination of the tumour thickness (39).

The procedure punch biopsy is a punch of the pigmented element by a circular scalpel of different diameters. Excision biopsy is excision of a pigmented lesion *in toto* with a 2-5 mm clinical visually free resection margin.

Different studies have investigated the survival according to the initial diagnostic biopsy (47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60). The joint conclusion of these studies is, that type of initial diagnostic procedure does not significantly influence the overall survival (47, 48, 49, 50, 52, 54, 55, 59, 60). Few studies, though, stated that survival was decreased when incision biopsy was performed. Rampen *et al* (51) showed a possible decreased survival in a study where incision biopsy had been carried out on 14 patients, Austin *et al* (53) claimed higher mortality following incision biopsy of head and neck tumours in 48 patients. Fitzpatrick *et al* (56) and Pitt (57) found decreased survival when incision biopsies were performed; however none of the studies were stratified or adjusted for thickness, presence of ulceration, level or histological subtypes.

Only one study was found that investigated the recurrence-free survival according to type of primary biopsy. Bagley *et al* (55) reviewed 147 patients, where incision biopsy was performed in 22 of the patients, and they neither found evidence of increased incidence of recurrence, nor any influence on the 5-year survival.

(If you wish to follow this subject, turn to page 25)

Unclassified malignant melanomas; problems related to TNM-classification

In the late 1990ies a new melanoma classification system, the TNM-classification was developed by the American Joint Committee on Cancer (AJCC) that included clinical and pathological factors that more accurately reflected the biology of the disease. The classification system was developed on basis of melanoma populations from major melanoma centres in the United States, Europe and Australia. Major revisions included melanoma thickness and ulceration to be used in the T category but not level (except for T1 melanomas) and number of lymph nodes with metastases both microscopically and macroscopically to be used in the N category. Furthermore the site of distant metastases, the presence of elevated serum lactic dehydrogenase (s-LDH), and upstaging in some categories when ulceration is present, is among some of the major revisions in the new classification system. In March 2000 the new classification system was published in Cancer for the first time and in 2001 the "Final version of the American Joint Committee on Cancer staging

system for cutaneous melanoma" was released (61, 62). Many countries including Denmark have implemented this classification system. The classification system defines TNM categories (Table 2) and clinical and pathological stage groupings (Table 3). As an example of classification according to the TNM-classification system a T2bN2bM1a melanoma is an ulcerated melanoma 1.01 – 2.0 mm thick with macrometastases to 2-3 regional lymph nodes and metastases to distant skin, distant subcutaneous tissue, or distant lymph nodes; s-LDH is normal (Table 2). A T1aN0M0 melanoma is a thin non-ulcerated melanoma (≤ 1.0 mm) with no micro- or macrometastases to the regional lymph nodes and no distant metastases (Table 2).

T classification	Thickness	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and level II/III
		b: with ulceration or level IV/V
T2	1.01- 2.0 mm	a: without ulceration
		b: with ulceration
T3	2.01 – 4.0 mm	a: without ulceration
		b: with ulceration
T4	> 4.0 mm	a: without ulceration
		b: with ulceration
N classification	**No. of Metastatic Nodes**	**Nodal Metastatic Mass**
N1	1 node	a: micrometastasis*
		b: macrometastases†
N2	2-3 nodes	a: micrometastasis*
		b: macrometastases†
		c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	
M classification	**Site**	**Serum Lactate Dehydrogenase**
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table 2. The New Melanoma TNM Classification (62)

The clinical and pathological stage groupings in the new TNM-classification system are presented in Table 3 (T_{is} is melanoma in-situ) to visualise that the thickness unclassified melanomas are not implemented. Staging implies microstaging by sentinel node biopsy. The pathological stages are differentiated in stage 0 to stage IV, there is no stage III, instead the group is divided in the

subgroupings IIIA, IIIB and IIIC. The clinical stages are differentiated in stage 0 to stage IV; there are no stage III subgroupings. Stage I and II is localized melanoma, stage III is melanoma disease with regional metastases, and stage IV is melanoma disease with distant metastases.

	Clinical Staging*			Pathological Staging†		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III‡	Any T	N1	M0			
		N2				
		N3				
IIIA				T1-4a	N1a	M0
				T1-4a	N2a	M0
IIIB				T1-4b	N1a	M0
				T1-4b	N2a	M0
				T1-4a	N1b	M0
				T1-4a	N2b	M0
				T1-4a/b	N2c	M0
IIIC				T1-4b	N1b	M0
				T1-4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	Any M1	Any T	Any T	Any M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

†Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

‡There are no stage III subgroups for clinical staging.

Table 3. Clinical and pathological stage groupings for cutaneous melanoma (62)

According to the new melanoma TNM and staging categories survival rates on cause-specific survival have been calculated by AJCC (62). Table 4 presents a summary ($T_{1a-4b}N_0M_0$ melanomas). The survival rates of this table were used for comparison with the survival rates of the present study.

Pathologic Stage	TNM	Thickness (mm)	Ulceration	No. of Patients	5-Year Survival ± SE	10-Year Survival ± SE
IA	T1a	≤1	No	4,510	95.3±0.4	87.9±1.0
IB	T1b	≤1	Yes or level IV, V	1,380	90.9±1.0	83.1±1.5
	T2a	1.01-2.00	No	3,285	89.0±0.7	79.2±1.1
IIA	T2b	1.01-2.00	Yes	958	77.4±1.7	64.4±2.2
	T3a	2.01-4.00	No	1,717	78.7±1.2	63.8±1.7
IIB	T3b	2.01-4.00	Yes	1,523	63.0±1.5	50.8±1.7
	T4a	>4.0	No	563	67.4±2.4	53.9±3.3
IIC	T4b	>4.0	Yes	978	45.1±1.9	32.3±2.1

Table 4. Summary of survival rates for melanoma TNM and staging categories calculated by AJCC (62).

The primary pathological parameters that classify a melanoma according to the T-category of the TNM-classification system are assessment of the tumour thickness as the most important prognostic parameter, but also presence of ulceration, and in thin melanomas level (61, 62).

A precise pathological classification of a malignant melanoma is essential, because the measured thickness of the malignant melanoma decides the extent of surgical treatment, eventual adjuvant therapy, and it is the strongest known prognostic predictor.

However, insufficient primary biopsy, pronounced regression or pronounced ulceration of the tumour, special histological characteristics of the tumour, and incorrect handling of the specimen before fixation can impair a precise classification (39, 42), and the melanoma is categorized as a thickness unclassified malignant melanoma. In the literature the definition of unclassified malignant melanomas is ambiguous. Often the unclassified malignant melanomas are a mixture of missing values and melanomas not properly classifiable. In the TNM-classification system unmeasurable malignant melanomas are classified as $T_xN_{0-3}M_{0-1c}$ (61, 62).

In many countries guidelines have been developed to recommend the optimal treatment of the malignant melanoma disease. The Danish guidelines for melanoma treatment (42, 63, 64) and also guidelines from many other countries (39, 43, 65, 66, 67, 68, 69) recommend extent of surgical treatment of a malignant melanoma according to the measured tumour thickness. However, recommendations of optimal treatment of thickness unclassified malignant melanomas are not

present in any of the guidelines. In Denmark the tradition has been to treat unmeasurable melanomas as "worst case" (tumour thickness > 4 mm), independent of the classification of other prognostic parameters.

(If you wish to follow this subject, turn to page 32)

Aim

Prospective of this study was:

1. To validate the data in the DMG-database in the period 1985-94.

2. To perform a descriptive analysis and survival analyses of the Danish melanoma population based on the DMG-data, and to compare the results with former studies of the same population in a time trend analysis.

3. To investigate whether type of primary biopsy influenced overall and recurrence-free survival by using a Cox proportional hazard model with and without imputation.

4. To characterize the unclassifiable malignant melanomas, according to prognostic parameters besides melanoma thickness and their impact on survival.

Materials and methods

Validation of the database

The DMG-database was validated according to the following paragraphs described in the thesis by Sørensen (15):

1. Completeness of registration of individuals
    a. Comparing the data source with one or more independent reference sources
    b. Comprehensive records review
    c. Aggregate methods
2. The accuracy and degree of completeness of variables
    a. Precision
    b. Validity
3. The size of the data sources
4. Registration period
5. Data accessibility, availability and cost
6. Data format
7. Record linkage

1. Completeness of registration of individuals

Comparison of two data sources:

Estimate of the degree of completeness of the data can be obtained by comparing the data source with one or more independent reference sources in which the total or a part of the target population is registered (12, 15, 16). The comparison is made case by case. The DMG-database (data source 1) was compared with the Danish Cancer Registry (data source 2).

	Data Source 2		
Data Source 1	Registered Cases	Non-registered Cases	
Registered Cases	a	b	a+b
Non-registered Cases	c	d	c+d
	a+c	b+d	a+b+c+d

Table 5. Comparison of two data sources

Terminology in relation to evaluation of data source 1 is visualised in Table 5. Data source 2 is used for comparison (70).

The completeness rate of data source 1 is calculated as a/(a+c).

External record linkage between registers reveals the possibility to estimate the true population of a disease by Capture-Recapture analysis (15, 70, 71). Independence between the two involved registers should be assumed before using the Capture-Recapture analyses.

Capture-Recapture analysis:
The true incidence of a total population (where p_{MLE} is the maximum likelihood estimate of the total population) was calculated as (70, 71):

$$p_{MLE} = (a+c)(a+b)/a$$

d is the estimate of the population not included in any of the two registers and was calculated as:

$$d_{MLE} = bc/a$$

2. *Accuracy and degree of completeness of variables*

Calculations on the accuracy and degree of completeness of the variables include an estimation of random errors and systematic errors and estimation of extent of missing data.
The random errors were estimated by performing a test sample of 100 melanoma cases from the DMG-database and comparing them with the information from the patient files.

A possible systematic error was investigated; it was claimed from the southern region of Denmark (Fig. 2) that a portion of the patients with trunk melanomas, the thick melanomas and the metastasized melanomas from the northern region were referred and treated in the southern region, which might give a poorer survival rate in this region compared with the other regions of Denmark; because a potential unequal distribution of melanomas (according to prognosis) between regions of the country was present. To determine whether this claim was true a comparison of median tumour thickness, the number of trunk melanomas and the overall survival was carried out between the different regions of the country.

To estimate the extent of missing data of the DMG-database a table visualising the amount of missing data within the different variables was calculated.

Pathologists outside DMG examined some of the melanomas. However, all samples were revised by DMG pathologists, who also always filled out the pathological part of the registration forms. In that way all registration forms were filled out by experienced pathologists.

The quality of the DMG database has been assessed in a previous study of intra - and interobserver variation among pathologists by Lock-Andersen *et al* (72).

Test sample

The registration forms of the patients were completed by a great number of different doctors. After completion of the DMG registration forms, copies of these were sent to the DMG secretariat, where they were registered in the computerized database by the different secretaries of the DMG secretariat staff.

Mistakes could be made during this process; the treating doctors could register wrongly if they were insufficiently informed of the DMG protocol, and further the DMG staff could register wrongly in the database.

To obtain estimate of the random errors and the quality of the data in the DMG database a test sample of 100 cases was procured. The forms were selected randomly by a simple number procure software program and were generated by case number "Project number". All case numbers were included because the registration forms were registered randomly. If a case number was selected and date of radical operation was not from the period 1985-94 it was discarded and a new case number was chosen. This procedure was repeated until 100 cases within the relevant time period was obtained. The strategic variables to be validated were as follows:

- CPR
- DMG treatment centre
- Anatomical localisation
- Melanoma type
- Melanoma thickness
- Date of operation
- Cause of off study
- Off study date

Revision of the DMG database

The data of the DMG database was optimized by obtaining missing clinical and pathological information from the patient files by travelling to the different DMG hospitals and searching for missing data in the file archives.

Examination of the patient files of the test sample revealed a significant number of recurrent mistakes in off study forms concerning both the causes of off study and the dates off study.

Furthermore it was revealed that a substantial part of the data was lacking. Due to this discovery, all the off study cards in the DMG office were compared to the content of the DMG database, concerning off study registration, and the mistakes in the database were corrected. If the information of an off study card was insufficient or lacking the patient file was procured, correct information was obtained and subsequent registered in the DMG database.

3. The size of the data sources

The project was based on a prospectively accumulated clinical database, which consisted of patients treated of malignant melanoma in Denmark.

In the period of the study data was not collected from the northern and southern part of Jutland (Fig. 2). The amount of missing data was estimated to comprise around 10% of the total Danish melanoma population. Furthermore, some patients could be treated by private practitioners and therefore were never referred to a DMG-treatment centre; the size of this patient group is not known, but it is thought to be small.

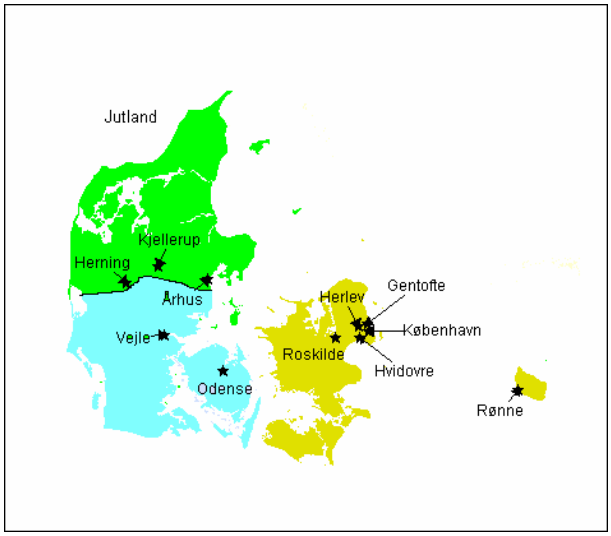

Fig. 2. Map of Denmark with regions and cities that participate in DMG-registration.

Regions: North, South, East.

Data was collected on basis of three different forms; the primary "registration" form, the "flow-sheet" form and the "off study" form. Data from the "flow-sheet" forms was not used in this study, and therefore is excluded in the following description of the database. The relevant part of the database consisted of a total of 106 different "registration" form variables and 40 "off study" form variables. Most of them were clinical and pathological, and related to the melanoma disease.

From the first release of the DMG protocol in 1984 until now the protocol has been revised twice; in 1989 and in 1992. The number of variables has been adjusted. The definition of the different variables has not been changed except for the size of excision margin, which has been adjusted from 5 to 4 cm according to the DMG-92 protocol, and the definition of clinical stage I, where the allowed distance of satellites from the primary tumour changed from 3 to 4 cm (3 cm in DMG-83 changed to 4 cm in DMG-89 and DMG-92). Due to adjustments the DMG-83 "registration form" consisted of 97 variables, the DMG-89 "registration form" consisted of 42 variables and the DMG-92 "registration form" consisted of 53 variables.

The distribution of the different registration forms (due to protocol revisions) was as follows:

Registration Form	No. of Cases (%)
DMG-83	4079 (81.8%)
DMG-89	215 (4.3%)
DMG-92	690 (13.9%)
Total	4984 (100.0%)

Table 6. The distribution of the 3 different registration forms

Seven DMG-treatment centres participated in the sending of the registration forms. In the eastern part of Denmark the treatment centres were Rigshospitalet (RH), Hvidovre Hospital (HH), KAS-Gentofte (GE), Herlev Hospital (HE) and Roskilde Amtssygehus (RO). In the southern part of Denmark the treatment centre was Odense Universitetssygehus (OD), and in the northern part the treatment centre was Århus Kommunehospital (ÅR) (Fig. 2).

Other departments sending flow-sheets and off study forms were Kjellerup Sygehus and Herning Centralsygehus from the northern part, Vejle Sygehus from the southern part, and Bornholms Centralsygehus from the eastern part of Denmark (Fig. 2).

4. Registration period

All melanoma cases within the 10-year period 1st of Jan 1985 – 31st of Dec 1994 selected by date of operation were included in the project.

Three time intervals were used in the survival analyses:

a. The number of years between date of operation and date of off study, where cause of off study was defined in the DMG protocol
b. The number of years between date of operation and death until 25th of July 2001 according to the CPR Registry (a unique personal registration number assigned at birth to all Danish inhabitants by the Danish CPR-Registry, see page 23)

c. The number of years between date of operation and death until 31st of December 1998 according to the Danish Cause of Death Registry (see next page)

5. Data accessibility, availability and cost

The DMG-database is owned and run by the Danish Melanoma Group. The group consists of plastic surgeons, pathologists, oncologists, epidemiologists, and others with interest in the treatment of malignant melanoma. The statutes of DMG define that any use of the DMG data should be accepted by the DMG executive committee.

The DMG database is approved by the Danish "Datatilsynet" and it fulfil regulations according to this. Permission of comparison to the different public registers was implied in the approval.

6. Data format

The database was based on the software program Microsoft Access, which is a relation database; it consisted of 1 key file (Patient) and 2 data files (Project and Off study):

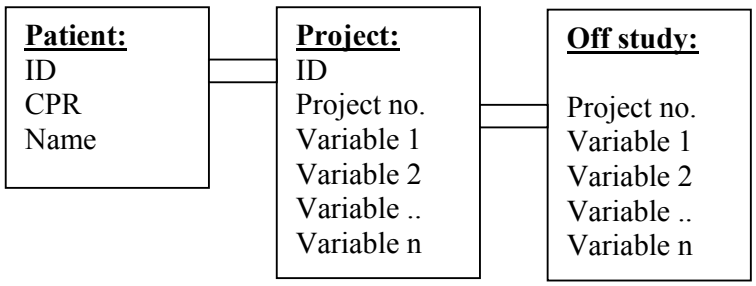

Fig. 3. Structure of data in the DMG-database

The data files consisted of information from the clinical and pathological variables ("Project") and the off study variables ("Off study"). The key file consisted of information on an "ID" number, the CPR, and the name. The data files were connected to each other by the key variable "Project number" and the data file "Project" was connected to the key file "Patient" by the variable "ID".

7. Record linkage

In Denmark there are unique possibilities for epidemiological studies. Partly because of a well functioning CPR Registry, where all people in Denmark are registered with a unique personal number, and partly because of other very complete and well-functioning registries as the Cancer Registry and the Danish Cause of Death Registry among others. The CPR-numbers are used in all

registries concerning public - and health related conditions, which gives the possibility to compare the different registries. To this project the CPR Registry, the Danish Cause of Death Registry, and the Cancer Registry have been used:

CPR Registry
The CPR Registry was established by the Ministry of Internal Affairs in 1968. The registry administrates the assignment of CPR-numbers to newborns and to immigrants, so that all persons resident in Denmark are provided with a unique CPR-number. Furthermore the CPR Registry receives information on among others births, deaths and immigration. The Registry is updated weekly.

The Cancer Registry
In 1942, as the first place in the World, a population based registry with all cancer cases in the country was established. Since 1943 reports have been received from all hospital departments (private or public), and from general practitioners, who diagnose cancer cases. The pathology departments report cancer cases found at section, if these are not earlier diagnosed, and furthermore the registry is supplied with information from other registries as the "Landspatient" Registry, which is a registry that contains information on all discharges from hospital departments (except psychiatric departments), and from 1995 also from out-patient departments. Furthermore the Cancer Registry receives information from the The Danish Cause of Death Registry, which is described below. The Cancer Registry has been estimated to contain approximately 95-98% of all malignant melanomas in Denmark (73).

The Danish Cause of Death Registry
The Danish Cause of Death Registry was established in 1973. It is run by the National Health Service of Denmark. It contains information on cause of death by diagnose codes (ICD-7 and ICD-10), death date, age at death, and the patients´ municipality address.

(If you wish to follow this subject, turn to page 35)

Descriptive analysis of the Danish melanoma population

Inclusion and exclusion
All melanoma cases within the 10-year period 1st of January 1985 – 31st of December 1994 selected by date of operation were procured from the DMG database; in total 5426 cases after the revision of

the database. The following cases were excluded: Level I melanomas, which were 410 (7.6%) cases, because they do not have metastatic potential, if the pathology identification number was not present and could not be procured (4 cases), or the CPR-number was with letters (1 case), which was the case if the patient was not Danish inhabitant; if the CPR-number was incorrect and could not be procured (3 cases), if the anatomical region of the primary tumour was unknown (16 cases), or the melanoma was totally regressed (8 cases). In all 4984 cases fulfilled criteria and were included in the descriptive part of the study.

Data on descriptive variables of earlier time periods (1964-82) of the Danish melanoma population was procured and compared to the present study. In the time trend graphs the period with lacking data was visualised by punctuating the lines. The parameters included in the time trends analyses were anatomical site, tumour thickness, and presence of ulceration (Fig. 6, Fig. 7, Fig. 8, Fig. 10). Influence of diagnostic drift (whether changes were due to e.g. altered diagnostic methods or treatments instead of changes over time) due to these parameters was not considered of importance because the methods of assessing tumour thickness and presence of ulceration had not changed significantly during the involved decades.

Independent T-tests, Mann-Whitney Us test and chi-square tests were used to evaluate differences within the descriptive data (74).

(If you wish to follow this subject, turn to page 40)

Survival analyses of the Danish melanoma population

The following criteria were used to select the population for the survival analyses:

Patients 90 years old and older were excluded (32 cases). Only patients in clinical stage I were included (265 cases excluded) (Clinical stages defined by the DMG-protocol (42); clinical stage I: Localised melanoma with eventual satellites not exceeding 3 (or 4) cm from border of primary tumour. The TNM classification system was not implemented in the period of this study); if clinical stage was missing the cases were excluded (13 cases), as well as missing date of radical operation (13 cases). Patients only occurred once, and patients with more than one melanoma only occurred with the first melanoma. If the patient was treated for more melanomas at the same time as first occurring melanoma, the thickest melanoma was included; the others were excluded (in all 88 cases excluded). Three cases were excluded due to a negative number of days between date of operation and off study date. If less than 28 days were present between date of radical operation and

recurrence the case was considered as having recurrence at the date of operation and the case was excluded (275 cases).

136 cases were lacking information on cause or date of off study; they were excluded in the recurrence-free survival analyses. It was decided to include these latter 136 in the overall survival analyses even though date of off study was not known, and less than 28 days between date of radical operation and recurrence could occur (which indicated that the melanoma disease was not localized at the time of operation), because the number of cases of incorrect inclusion was expected to be very few. Furthermore, no difference was found in the results, whether the cases were excluded or not in the analyses.

Information on date of eventual death of all causes was procured from the CPR-registry and was used as event in the univariate survival analyses.

An outcome estimate in the recurrence-free survival analyses should be interpreted as the chance of not developing recurrence at a certain time point measured from the date of re-excision (radical operation). In that way a high recurrence-free survival rate should be interpreted as low incidence of recurrence, and opposite a low rate should be interpreted as high incidence of developing recurrence. Event in the recurrence-free analyses was recurrence of all kinds.

(If you wish to follow this subject, turn to page 48)

Initial diagnostic biopsy procedure and survival analyses

The initial diagnostic procedures were differentiated in "excision biopsy", "incision biopsy", and "curettage". The procedures were carried out at the primary healthcare, or in a DMG treatment centre.

Curettage was defined as a superficial shaving of the skin with a "curettage" instrument; only dermatologists performed this kind of biopsy. Incision biopsy was defined as an incomplete elliptic biopsy of the pigmented lesion at the thickest portion of the tumour; punch biopsies (a punch of the pigmented element by a circular scalpel of different diameters), shave biopsies (superficial shaving of element with a scalpel), and scissors biopsies (element elevated by a pair of tweezers and cut off with a pair of scissors) were included. Excision biopsy was defined as excision of a pigmented lesion *in toto* with a 2-5 mm clinical visually free resection margin. If an excision biopsy by pathological examination was found to have tumour infiltrated resection margins, it was in this study re-classified as an incision biopsy.

In the overall material the number of unknown (missing) prognostic values was very small. However, in the population of incision biopsies and curettage the number was substantial; which was problematic since the analyses were constructed to investigate exactly this sub-population. A way of dealing with this problem was to construct a Cox proportional hazard model with interaction between type of primary biopsy and tumour thickness (whether the tumour thickness was classifiable or unclassifiable); in that way two analyses were performed to make it possible to include the unclassified malignant melanomas in the analyses. However, a better option was using a model with imputation (75). The principle of this method is to make the computer simulate "reasonable" values of the missing values in selected applicable parameters (by random assignation of a value with regard to the calculated distribution probabilities in the overall melanoma population), and after that take into account, that the values are simulated. The parameters tumour thickness, level, ulceration, and tumour type were selected for imputation.
Survival analysis on basis of imputation is not yet a conventional method. Therefore both the traditional (which was not traditional because of the interaction) and the analyses with imputation were carried out, to compare the results. Analyses were carried out according to both overall - and recurrence free survival.

In the overall survival analyses information on date of death was procured from the CPR-registry. Event in the overall survival analyses was death of all causes. Survival times were calculated from date of radical operation (re-excision) and were censored for patients who were alive at the date 25th of July 2001. Death of all causes was chosen because data from the Danish CPR registry are of very high quality.
All melanoma patients were offered standardized follow up according to the DMG-protocol. They were followed 5 years at the DMG treatment centres and after that they were followed further 5 years at the primary healthcare. During the first 2 years the patients were controlled every 3 months; during the following 3 years the controls took place every 6 months. After 5 years the patients were followed once a year at the primary healthcare until 10 years following primary treatment (42).

According to the DMG protocol the patients were registered as off study by the following causes (appendix e):

a. The patient does not want follow up

b. Recurrence (location of metastases stated at the off study form)

c. Termination of follow up after 10 years (5 years at hospital, 5 years at general practitioner)

d. Other malignant disease (except non-melanoma skin cancer)

e. Death

f. Termination of follow up after 5 years (further follow up at general practitioner)

g. Other causes specified

It became clear that it was not consistent whether a patient was set off study after 5, 10 or more years of follow up. From clinical experience at the out-patients´ clinic it was known that patients having dysplastic naevi and many naevi were offered lifelong follow up, further it was known that there was a tendency to follow the very thick lesions longer than the thinner lesions, as well as a tendency of longer follow up of nervous patients. Therefore the risk of selection bias probably should be expected when exceeding 5 years of follow up. As a consequence all patients were censored after 5 years of follow up in the recurrence-free survival analyses.

In the recurrence-free survival analyses information on recurrence was collected from the off study form. Event in the recurrence-free survival analyses was recurrence of any kind. Recurrence-free survival times were calculated from date of radical operation (re-excision) and were censored for patients who did not develop recurrence after 5 years of follow up as well as the causes outlined in appendix e (and above as paragraph a-g). The median time of follow up at the outpatient clinics were 4.95 years (range 0.08 – 11.63 years). The median time of follow up according to death of all causes by CPR-Registry or censoring date were 9.22 years, range 0.11 – 16.57 years.

	Mean Yrs	Median Yrs	Minimum Yrs	Maximum Yrs
Date of operation to date of off study or censoring	4.13	4.95	0.08	11.63
Date of operation to death or censoring	8.96	9.22	0.11	16.57

Table 7. Mean, median, minimum and maximum time of follow up (number of years between radical operation (re-excision) and off study or death of all causes assessed by the CPR-Registry or censoring date).

Cox proportional hazard with interaction

Initially a Cox proportional hazard model with interaction between type of primary biopsy and tumour thickness was calculated. The following variables were included in the model: Sex, age, level, tumour type, presence of ulceration, anatomical region, type of primary biopsy, tumour thickness, and length of surgical interval. The surgical interval was defined as number of days between date of primary biopsy and date of re-excision. All the implicated variables were categorical except for age which was continuous.

To investigate the proportional hazards a plot of Schoenfeld residuals was used (76, 77), and the following mathematical quotation was generated where the influence of the different descriptive variables was described through a series of parameters:

$$\beta(t) = \beta + \theta g(t)$$

$\beta(t)$ was the parameter to be investigated over time and $g(t)$ was a constant function specified in advance. When $g(t)$ was chosen it was relatively easy to test for $\theta = 0$; a test that specifies that the parameter was not dependent on time. If this function was constant it indicated that the assumption of proportional hazards was fulfilled. However, if it was not fulfilled the shape of the curve could indicate what was the problem.

In the overall survival analyses two variables showed to be problematic according to proportionality; tumour thickness and age. The curves of tumour thickness indicated that the effect of tumour thickness changed through the period. In the first approximately 5-7 years postoperatively the effect of tumour thickness seemed to be large, but then the effect totally disappeared.

More expected differences were found in the age curves. Of natural causes the 5-year overall survival and further on was decreased in the very old patients compared to the young patients.

To deal with the problem of lack of proportionality a model with stratification was chosen. The principle of stratification is to categorize the variable and then use a new baseline hazard of each category. Because of a large number of categories within the two variables (thickness: 5 and age: 7) stratification was only possible according to one variable (5*7 = 35 categories of stratification was considered problematic); tumour thickness was stratified. Age was modelled by a restricted cubic spline model with 5 knots and thereby fitted in the model (Fig. 4) (76).

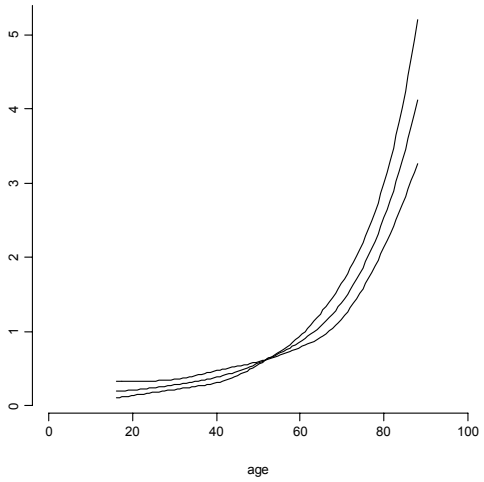

Fig. 4. Restricted cubic spline according to age.

In the recurrence-free survival analyses the age intervals fitted a linear model; tumour thickness was stratified. The log likelihood test was used to evaluate differences in outcome estimates.

After the first run of the analyses it was revealed that length of surgical interval was statistically insignificant. It was chosen to test out the variable, because exclusion would increase the number of cases in the model influentially (because the patients that were referred directly to a DMG-treatment centre, without a prior diagnostic procedure carried out elsewhere, were registered in the DMG-database without information on date of primary biopsy, and therefore had to be excluded).

Imputation

To implement an analysis with imputation an assumption of MAR (missing at random) had to be carried out to control that the missing values were missing at random and that they e.g. were not exclusively the highest or lowest values (78). In this case the mechanism was dependent on type of primary biopsy type, which was known in all cases; besides that it seemed to be coincidences that decided whether a value was missing or not in the selected variables for imputation. Four variables were chosen to be imputated: Level, tumour thickness, presence of ulceration and tumour type.

Because of a large data size and because the four variables to be imputated were categorical variables with only few levels (4 levels) a model with "hot-deck imputation" was chosen (78). A model with "hot-deck imputation" implies imputation of empirically distributed variables (Table 9).

Table 8 illustrates the pattern of missing values of the four variables included in the imputation model.

Type	Thickness	Level	Ulceration	Frequency
			+	35
		+		32
	+			82
	+		+	6
	+	+		86
	+	+	+	7
+				108
+			+	5
+		+		11
+		+	+	1
+	+			15
+	+		+	4
+	+	+		108
+	+	+	+	20

Table 8. Missing pattern of imputation variables (+ indicates that the information is missing).

Order of imputation was as follows:

1. *Imputation of tumour type*

If information on presence of ulceration was present the variables "Ulceration" and "Age" were used to predict the value of tumour type. If information on presence of ulceration was not present it was "Region" and "Age".

2. *Imputation of ulceration*

If information on tumour thickness was present the variables "Tumour Thickness" and "Age" were used to predict the value of ulceration. If information of tumour thickness was not present it was "Tumour Type" and "Age" (At this point all cases would have a value of tumour type due to the imputation carried out above).

3. *Imputation of level*

If information on tumour thickness was present the variables "Tumour Thickness" and "Ulceration" were used to predict the value of level. If information on tumour thickness was not present it was "Ulceration" and "Tumour Type".

4. Imputation of thickness

If information on Level was present "Level" and "Ulceration" were used to predict the value of tumour thickness. If information on Level was not present it was "Ulceration" and "Tumour Type".

Two variables were chosen for every one imputation. The reason for choosing two variables instead of more was to limit the number of distributions so that it matched the material size.
Order of imputation as well as picked variables for imputation was done partly due to background knowledge of the biology of the melanoma disease and partly due to the content of the data set.

(No ulceration)	0-50 yrs	>50-60 yrs	>60-70 yrs	>70-80 yrs	>80 yrs
SSM	0.88	0.86	0.79	0.75	0.60
NM	0.11	0.10	0.13	0.13	0.19
LMM	0.003	0.02	0.05	0.10	0.16
ALM	0.006	0.02	0.03	0.02	0.05

Table 9. Empiric imputation distribution of the variable tumour type when ulceration is not present according to age intervals used for assignation of values to replace missing values in the imputation model.

Hot-deck imputation implies random assignation of values of missing values according to probabilities in the distribution as the example scheduled in Table 9. The table was shown to illustrate how the variable "Tumour type" was imputated, in this example when presence of ulceration was known. Presence of ulceration and age was used to predict the assignment of tumour type (see page 30). The table shows that if a type unclassified tumour was not ulcerated the probability of assigning the tumour type as SSM in a patient 0-50 years was 88%, NM was 11%, LMM was 0.3%, and the probability of assigning it as ALM was 0.6%. If the patient was aged 80 or more the probability of assigning the tumour type as SSM was 60%, NM 19%, LMM 16%, and ALM was 5%, respectively, and further on.

The parameter estimates were calculated on basis of MI (multiple imputations), which means that the resultant parameter estimates were an average of parameter estimates of 10 different data sets (78). The confidence intervals were calculated on basis of a non-parametric bootstrap (75, 79). (The principle of bootstrapping is to construct new data sets by random selection of observation vectors (survival time with associated covariates)). In these analyses 1,000 bootstraps have been used, which comprise 10,000 imputations.
The outcome estimates were functions of the imputated actual numbers, which means that if the procedure were repeated, a different result would be expected. However, by choosing both bootstrapping and multiple imputation in the estimation, it somewhat has been taken into account

(because of the relative large number of imputations (10 imputations) together with a large number of bootstrapping (1,000 bootstraps)).
The confidence intervals were used to evaluate the results.

(If you wish to follow this subject, turn to page 50)

Unclassified malignant melanomas; problems related to TNM-classification

In the present study a melanoma was defined as an unclassified malignant melanoma if the tumour thickness was not measurable. Type unclassified, level unclassified, and ulceration unclassified melanomas also occurred, but when these terms were used, it was not defined whether the tumour thickness was measurable or not.
In the DMG protocol it was defined when a melanoma was categorized as unclassified within the different parameters. The definitions remained unchanged throughout the 2 protocol revisions. For the variables "Tumour Thickness", "Level" and "Presence of Ulceration" the term was used, when the value could not be assessed due to poor quality of the primary biopsy specimen, that is if the primary biopsy was insufficiently or incorrectly handled, or the melanoma was with pronounced regression or ulceration. For the variable "Tumour type" "unclassified" was used, both due to the above mentioned reasons, but also if the tumour type was categorized besides the predefined categories "Superficial spreading melanoma" (SSM), "Lentigo maligna melanoma" (LMM), "Nodular melanoma" (NM) or "Acral lentigo maligna" (ALM). In this material it was not possible to distinguish between the different causes, and the classification "unclassified" of the selected variables were a mix of all causes.
The definition of the different primary biopsy groups were the same as previously defined in "Materials and methods: Initial diagnostic biopsy procedure and survival analyses" (page 25).

In the previous parts of this study the event used in the survival analyses were death due to all causes (melanoma - and non-melanoma deaths). In the following (investigation of the thickness unclassified melanomas) the cause-specific death (which is death due to melanoma disease) was used as event in the survival analyses, because we wanted to compare the results with the survival rates calculated by AJCC, see page 11 (62). In the AJCC melanoma database the cause-specific death (death due to melanoma disease) was used as event in the survival analyses. Cause of death was procured from the Danish Cause of Death Registry and has been confirmed up to 31st of December 1998. The information procured from this registry was not optimal, because in Denmark

there is a tradition/tendency to register the death cause as death due to cancer if the patient had suffered from a cancer earlier in life, even though it was not obvious that the patient had died from this disease. Therefore an increase in incidence of cancer deaths could be expected. However, because a comparison of the cause-specific death was aimed, the data from the Danish Cause of Death Registry was considered as the most optimal choice. The median follow up time according to death of all causes by the Danish Cause of Death Registry or censoring date was 7.07 years, range 0.00 – 14.00 years.

	Mean Yrs	Median Yrs	Minimum Yrs	Maximum Yrs
Date of operation to death by CDR or censoring date	7.24	7.07	0	14.00

Tabel 10. Mean, median, minimum and maximum time of follow up (number of years between radical operation (re-excision) and melanoma death assessed by The Danish Cause of Death Registry or censoring date).

The following in- and exclusion criteria were used in the survival analyses:
Only the $T_xN_0M_0$ melanomas were included, because microstaging by sentinel node biopsy was not carried out at the time of the study. The number of metastatic nodes was not stated (counted by the pathologists), consistent information on radiological evaluation for metastases (x-rays of the chest), and information on level of serum-LDH was not present (because these factors were not included in the former Danish melanoma classification system). The extent of the disease (N_{0-1}) was determined only by clinical examination.

In all 461 melanomas were not measurable according to tumour thickness. Patients 90 years old and older were excluded (4 cases). Only patients in clinical stage I (Clinical stages defined by the DMG-protocol (42)) were included (49 cases excluded); if clinical stage was missing the cases were excluded (2 cases), as well as missing date of radical operation (3 cases). No cases of multiple melanomas were present. If less than 28 days were present between date of radical operation and recurrence the patient was considered as having recurrence at the date of operation and the case was excluded (2 cases). In all 402 thickness unclassified melanomas were included in the cause specific survival analyses. Cases with missing cause of off study or date of off study were excluded in the recurrence-free survival analyses, which were 14 cases. In all 388 cases were included in the recurrence-free survival analyses of the thickness unclassified melanomas.

For the univariate analyses and descriptive statistics the software programs SPSS and R were used. The univariate survival analyses were constructed using the method of Kaplan and Meier. The log rank test was used to evaluate differences in the survival distribution (80, 81).

There is no doubt that tumour thickness is the most important prognostic parameter, however when information on thickness is not present, other directions are to be sought. The variables level and ulceration were chosen; which are other important prognostic parameters (82, 83, 84, 85, 86, 87). According to level it is especially pronounced in thin melanomas (88).
Kaplan-Meier plots visualising survival according to level, stratified of presence of ulceration was calculated in order to perform a coarser categorization, because the number of cases within each separate level category were too small. In the light of these survival curves three categories were selected to describe the survival of other important prognostic parameters than the tumour thickness.

Categories
Level II ± ulceration
Level III ± ulceration and level IV – ulceration
Level IV +ulceration and level V ± ulceration

Tabel 11. Level - and ulceration categories selected to describe univariate survival of thickness unclassified melanomas.

The survival rates of level and ulceration categories were compared to the survival rates of TNM (Table 4) and according to matching survival rates the unclassified melanomas were emplaced in proper TNM-categories. Optimal treatment was determined due to the estimated thickness interval (Table 4).

(If you wish to follow this subject, turn to page 56)

Appendix a-e

Appendix a. DMG-83 registration form
Appendix b. DMG-89 registration form
Appendix c. DMG-92 registration form
Appendix d. Body chart
Appendix e. Off study form

Results

Validation of the database

In the period 1985-94 7362 persons with 7383 melanomas were registered in The Danish Cancer Registry (CR). In the same period at the time of the comparison in all 5268 persons with 5395 melanomas were registered in the DMG-database.

	CR		
DMG	Registered Cases	Non-registered Cases	
Registered cases	4993	275	5268
Non-registered cases	2369	130	2499
Total	7362	405	7767

Table 12. Estimation of completeness rate and the true population size

Completeness rate of data source 1 (DMG-database) = 4993/(4993+2369) = 0,678 = 67,8%

The Capture-Recapture analysis estimated that d=130 melanoma patients were lacking in both data sources, and therefore the true size of the Danish melanoma population in the period 1985-94 could be estimated to comprise 7767 melanoma patients.

The estimated lack in CR compared to the overall estimated melanoma population therefore was 405 (5.2%) melanomas, and in DMG it was estimated as 2499 (32.2%) melanomas.

The accuracy and degree of completeness of variables

The actual number of missing data within the different variables and the variable completeness measured in percent was presented in Table 13.

Variable:	Actual no. of Missing Values in Variables	Variable Completeness (%)
CPR	0	100%
Name	0	100%
Patient ID	0	100%
Project number	0	100%
Age	0	100%
Sex	0	100%
Anatomical site	3	99.9%
Type of primary biopsy	463	90.7%
Clinical stadium	13	99.7%
Date of operation	11	99.8%
Date of off study	241	95.2%
DMG treatment centre	0	100%
Melanoma type	2	99.9%
Level	6	99.9%
Tumour thickness	0	100%
Ulceration in tumour	21	99.6%

Table 13. Actual no. of missing values and the variable completeness (n=4984).

The variable completeness of the dataset varied between 90.7% and 100% (Table 13). In 25 cases date of operation was not stated. In 14 of the cases it was because the patient was not radically operated, in 11 it was not possible to procure the date of operation. In three cases anatomical site was not specified by a region number (region number according to DMG protocol/appendix d) and they were registered as missing values; however information on anatomical site was noted on the registration form and therefore they were included in the study even though the information was missing.

In 59.9% of the cases the primary examination of the melanoma sample was carried out by pathologists within DMG. In 40.1% melanomas were primary examined by pathologists outside DMG before they were sent and revised by pathologists within DMG.

Systematic errors

It was claimed that melanomas with a poorer prognosis were over-represented in the southern region, since a part of the trunk melanomas, the thick melanomas and the metastasized melanomas from the northern region were referred and treated in the southern region of Denmark (Fig. 2) giving a risk of systematic bias (poorer survival). However, it was found that the median tumour

thickness, the amount of trunk melanomas (Table 14) and the overall survival (Fig. 5) (Log rank: p=0.089) were not different in the three different regions of Denmark.

	Median tumour thickness (mean) mm(mm)	Trunk melanomas (%)
South	1.00 (2.12)	39.6
East	1.14 (2.04)	43.9
North	1.20 (2.16)	36.1

Table 14. Median tumour thickness and distribution of trunk melanomas within the different DMG regions.

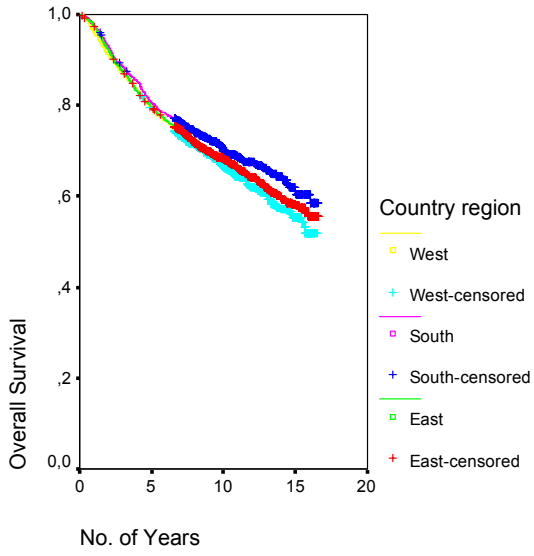

Fig. 5. Overall survival according to DMG region (n=4121) (Log rank: p= 0.089).

Test sample

After selection of 100 random cases the distribution of the different DMG treatment centres was as follows (distribution of all cases):

Rigshospitalet: 43 (36,1%)
Herlev/Gentofte: 23 (15,3%)
Odense: 10 (24,4%)
Århus: 24 (20,1%)

Of the 100 selected cases within the period 1985-94, 92 were available at the time of the study. One of the cases showed to be a local relapse and was therefore excluded.

The final number of cases therefore was 91 and distributed as follows.

Rigshospitalet: 39 (4 cases were not found)
Herlev/Gentofte: 20 (3 cases were not found)
Odense: 8 (2 cases were not found)
Århus: 24 (all cases were found)

Information from the DMG database and the patient files was compared in Table 15.

Variable	Present in DMG Actual no. (%)	Present in Pat. Files Actual no. (%)	No. Mistakes in DMG Actual no. (%)
CPR	91 (100)	91 (100)	0 (0)
DMG treatment center	91 (100)	91 (100)	0 (0)
Anatomical localisation	91 (100)	91 (100)	3 (3,3)
Melanoma type	91 (100)	91 (100)	2 (2,2)
Melanoma thickness	91 (100)	91 (100)	4 (4,4)
Date of operation	88 (96,7)	91 (100)	5 (5,7)
Cause of off study	44 (48,4)	91 (100)	9 (20,5)
Off study date	44 (48,4)	91 (100)	4 (9,1)

Table 15 Comparison on information in the DMG-database and in the patient files.

According to the variable "Date of operation" 5 cases were found defective. Three cases were wrong due to stated date of excision instead of date of re-excision. This gave a difference less than one month between the two dates. In one case the difference was more than two years; there was no explanation for this difference. One patient was not re-excised and the date stated therefore was the date of primary biopsy.

The off study dates were accepted as concurrent if the dates were within 2 months. This margin was accepted because more periods of natural causes could be stated as time of event. For example the date of relapse could be stated as date of histological diagnosis, as the date of operation for metastasis, as the date of the pathological answer, or it could be stated as the date in the patient file, where the patient was informed of the presence of metastases.

The information was procured before the database was updated and revised, which is the reason for a significant lack of information of some of the variables in the test sample. Only 44 cases of 91 possible were present with information on off study date. Of these 44 cases 9 cases had discrepancies in the dates of off study compared to the dates of the patient files, and 4 cases had concordant dates of off study but different causes of off study compared to the patient files. This represented a very large margin of error, and therefore a total up-date and a revision of these variables in the database was required.

Revision of the off study cards

Revising the off study cards revealed more recurrent mistakes in off study causes and in off study dates. Furthermore a substantial part of the material was lacking.

As an example of a recurrent mistake numerous cases had “new primary malignant melanoma” and “auto-treatment in 3 months” stated as cause of off study, but the causes showed to be others. In the above mentioned sample 3 patients were stated to have had “New primary malignant melanoma”, whereas in the patient file one patient was terminated after 5 years of control, one patient was terminated to further control outside DMG and one patient had developed metastases.

Due to this discovery, all the off study cards in the DMG office were compared to the content of the DMG database, and the mistakes in the database were corrected. Information on defective - and lacking off study cards were collected from the different DMG treatment centres and the DMG database updated.

(If you wish to follow this subject, turn to page 62)

Descriptive analysis of the Danish melanoma population

In all 2154 (43.2%) melanomas were distributed on 2104 (43.1%) males and 2830 (56.8%) melanomas were distributed on 2781 (56.9%) females (Table 16), which resulted in 98.2% patients presenting with one melanoma, and 1.8% patients presenting with two or more melanomas.

	Males No. (%)	Females No. (%)	Frequency No. (%)
Number of melanomas	2154 (43.2)	2830 (56.8)	4984
Number of patients:			
Females		2781 (56.9)	
Males	2104 (43.1)		
Total			4885
No. of melanomas:			
1 melanoma			4795 (98.2)
2 melanomas			83 (1.7)
3 melanomas			5 (0.1)
4 melanomas			2 (0.04)
Age:			
0-20	17 (0.8)	45 (1.6)	62 (1.2)
21-40	347 (16.1)	618 (21.8)	965 (19.4)
41-50	454 (21.1)	636 (22.5)	1090 (21.9)
51-60	414 (19.2)	448 (15.8)	862 (17.3)
61-70	480 (22.3)	485 (17.1)	965 (19.4)
>70	442 (20.5)	598 (21.1)	1040 (20.9)
Anatomical distribution:			
Trunk incl. lower back	1237 (57.4)	820 (29.0)	2057 (41.3)
Head and neck	336 (15.6)	291 (10.3)	627 (12.6)
Upper arm	125 (5.8)	310 (11.0)	435 (8.7)
Lower arm	86 (4.0)	173 (6.1)	259 (5.2)
Thigh	165 (7.7)	357 (12.6)	522 (10.5)
Lower leg	203 (9.4)	878 (31.0)	1081 (21.7)

Table 16. Clinical variables (values in parentheses are percentages) (n=4984).

The mean age of the total population was 55.0 years; the mean age of males (56.2 years) was significantly higher than the mean age of females (54.0 years) ($p<0.00001$). The incidence was evenly distributed between all age groups with the onset of the age of 21 years. Two patients were younger than 10 years of age (4 and 6 years); in both cases the malignant melanoma developed in giant congenital nevi. The oldest patient was 97 years.

The typical anatomical localisation was different in the two sexes. The most frequent anatomical site in males was the trunk, followed by head/neck, and then the lower leg. In females the most frequent anatomical site was the lower leg, followed by the trunk, and then the thigh (Table 16).

The distribution of the different anatomical sites in the three decades 1964-94 was examined. In the time periods prior to this study an increase in trunk melanomas was observed in males (20, 23); this increase continued through all time periods of this study, except the period 1973-82 where a small decrease was seen (Fig. 6). A decrease in the head/neck melanomas during the time periods 1964-94 was seen, except in the period 1973-82 where a small increase was seen. A steady state with minor fluctuations was seen according to melanomas on upper – and lower extremities in the former time periods as well as the time periods of this study.

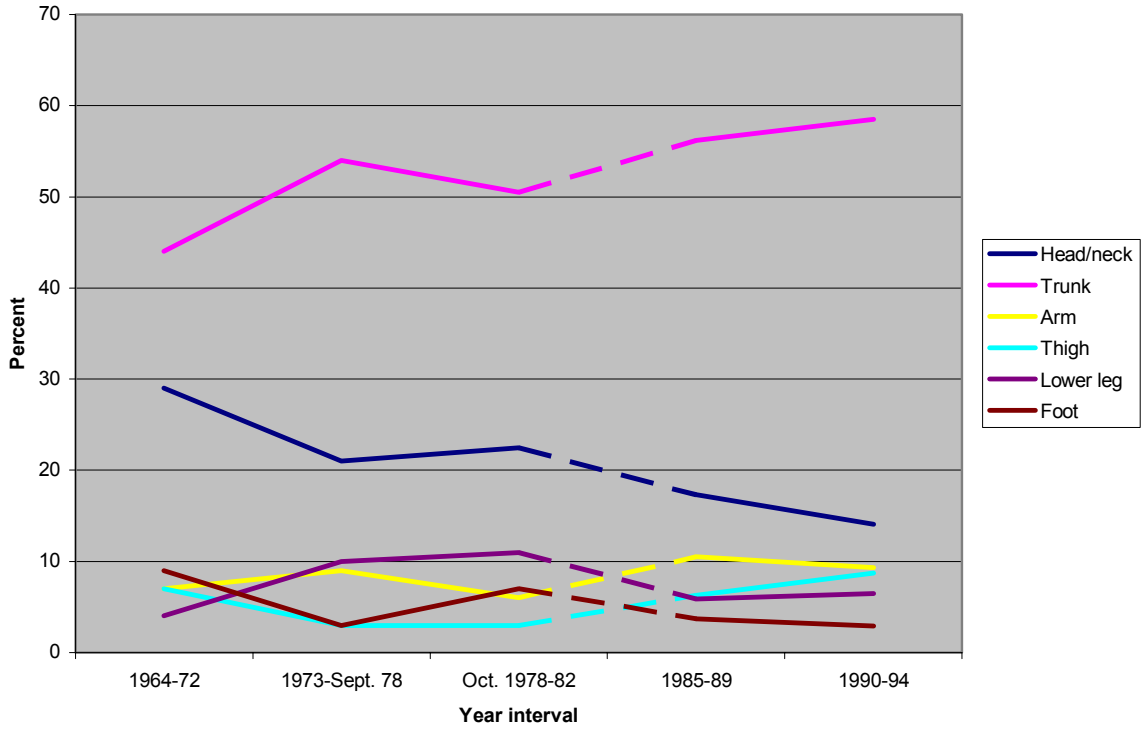

Fig. 6. Time trends in anatomical distribution in males 1964-94. Information on the periods 1964-82 was used with permission from Drzewiecki *et al* (23)

In females a great increase was seen in the occurrence of trunk melanomas both in the former time periods, and also through the time periods of this study compared to the other anatomical sites (20, 23). A significant decrease in occurrence was seen in lower leg melanomas and also in head and neck melanomas through all time periods 1964-82 (Fig. 7). In the time periods 1964-78 a significant increase was seen in melanomas of the thigh, then it levelled off and in the time periods from 1978-94 it was steady state.

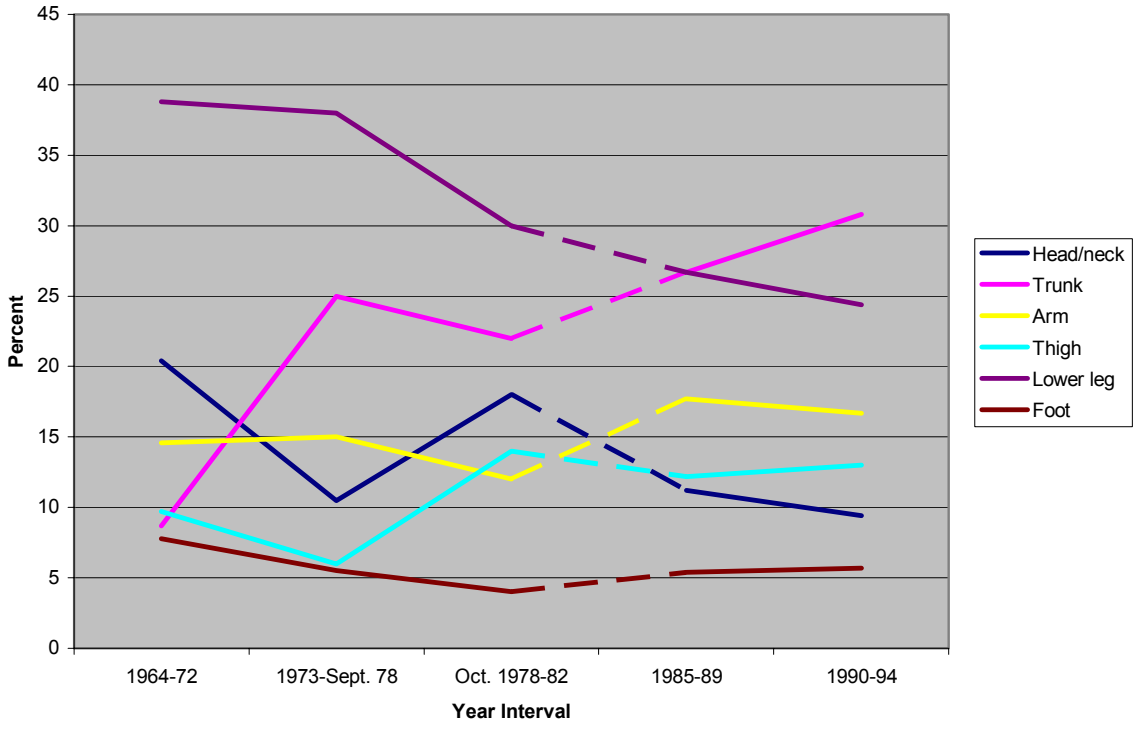

Fig. 7. Time trends in anatomical distribution in females 1964-94. Information on the periods 1964-82 was used with permission from Drzewiecki *et al* (23)

Pathology

The most frequent melanoma type was SSM (69.2%), followed by NM (18.8%), type unclassifiable melanomas (7.8%), LMM (2.7%), and ALM (1.4%). The distribution of melanoma types was different in the two sexes. In 72.4% of the cases in females the tumour type was SSM; in males this number was 65.0%. Males, on the other hand, had a higher frequency of NM on 22.0% compared to 16.4% in females; as well as a slightly higher frequency of type unclassified melanomas compared to females (9.1% compared to 6.9%, respectively).

	Males No. (%)	Females No. (%)	Frequency No. (%)
Melanoma Type:			
SSM	1401 (65.0)	2048 (72.4)	3449 (69.2)
LMM	59 (2.7)	76 (2.7)	135 (2.7)
NM	473 (22.0)	463 (16.4)	936 (18.8)
ALM	24 (1.1)	48 (1.7)	72 (1.4)
Unclassifiable	196 (9.1)	194 (6.9)	390 (7.8)
Tumour thickness in mm:			
<=1 mm	761 (35.3)	1360 (48.1)	2121 (42.6)
1,01-2 mm	448 (20.8)	572 (20.2)	1020 (20.5)
2,01-4 mm	434 (20.1)	409 (14.5)	843 (16.9)
>4 mm	298 (13.8)	241 (8.5)	539 (10.8)
Not measurable	213 (9.9)	248 (8.8)	461 (9.2)
Level:			
Level II	563 (26.1)	934 (33.0)	1497 (30.0)
Level III	666 (30.9)	856 (30.2)	1522 (30.5)
Level IV	653 (30.3)	744 (26.3)	1397 (28.0)
Level V	84 (3.9)	98 (3.5)	182 (3.7)
Unclassifiable	187 (8.7)	193 (6.8)	380 (7.6)
Ulceration in tumour:			
Yes	544 (25.3)	560 (19.8)	1104 (22.2)
No	1555 (72.2)	2211 (78.1)	3766 (75.6)
Unclassifiable	42 (1.9)	51 (1.8)	93 (1.9)

Table 17. Pathological variables (values in parentheses are percentages) (n=4984).

The overall median tumour thickness was 1.10 mm. The median tumour thickness was significantly thicker in males (1.40 mm, range 0.1-60 mm) compared to females (0.92 mm, range 0.03-40 mm) ($p<0.00001$). In both sexes the median tumour thickness increased with increasing age; the median tumour thickness increased from 0.90 mm at the age interval 0-20 years to 1.95 mm at the age interval >70 years.

In the time periods 1964-82 a great decrease from 3.73 mm to 2.14 mm in mean tumour thickness in males was seen; then the decrease levelled off and actually a small increase in mean tumour thickness was seen; in the period 1990-94 the mean tumour thickness was 2.21 mm (Fig. 8). In females a steady decrease in mean tumour thickness was seen through out all time periods. In 1964-72 the mean tumour thickness was 2.58 mm, in 1990-94 it was decreased to 1.63 mm (Fig. 8).

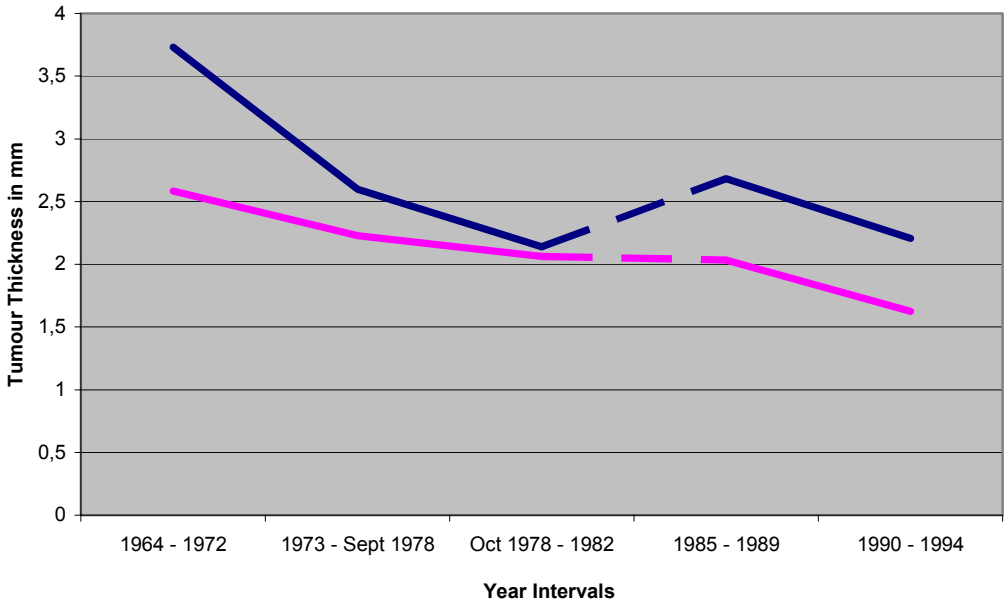

Fig. 8. Time trends in mean tumour thickness 1964-94 (— males) (— females). Information on the periods 1964-82 was used with permission from Drzewiecki *et al* (23)

A decrease in tumour thickness in both sexes was seen through the period of this study 1985-94; in the same period the amount of thin melanomas increased. It increased from 38.2% to comprise 44.9% of the malignant melanomas (Fig. 9).

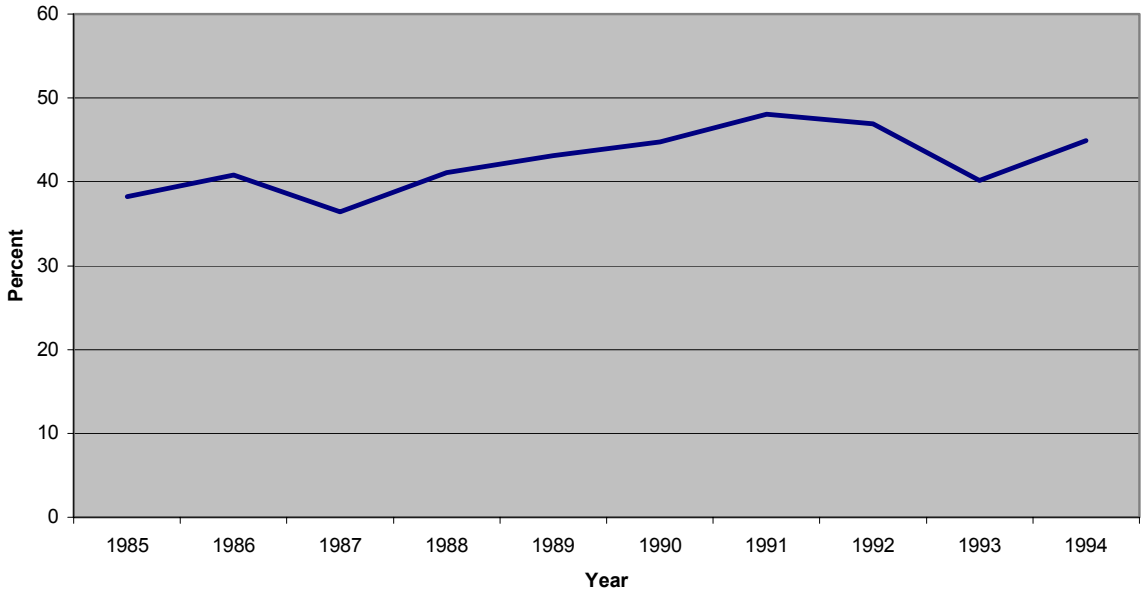

Fig. 9. Trends in occurrence of thin melanomas (< 1 mm) in the period 1985-94.

Five hundred forty four (25.3%) melanomas in males were diagnosed with ulceration. Ulceration occurred significantly less frequent ($p<0.0001$) in melanomas of the female population (19.8%). Through time periods between 1964 and 1994 the presence of ulceration in both sexes decreased. In 1964-72 the amount of melanomas diagnosed with ulceration in males was 54.3% and in females it was 40.8%. In the period 1990-94 the amount was decreased to 24.3% and 18.6% in males and females, respectively.

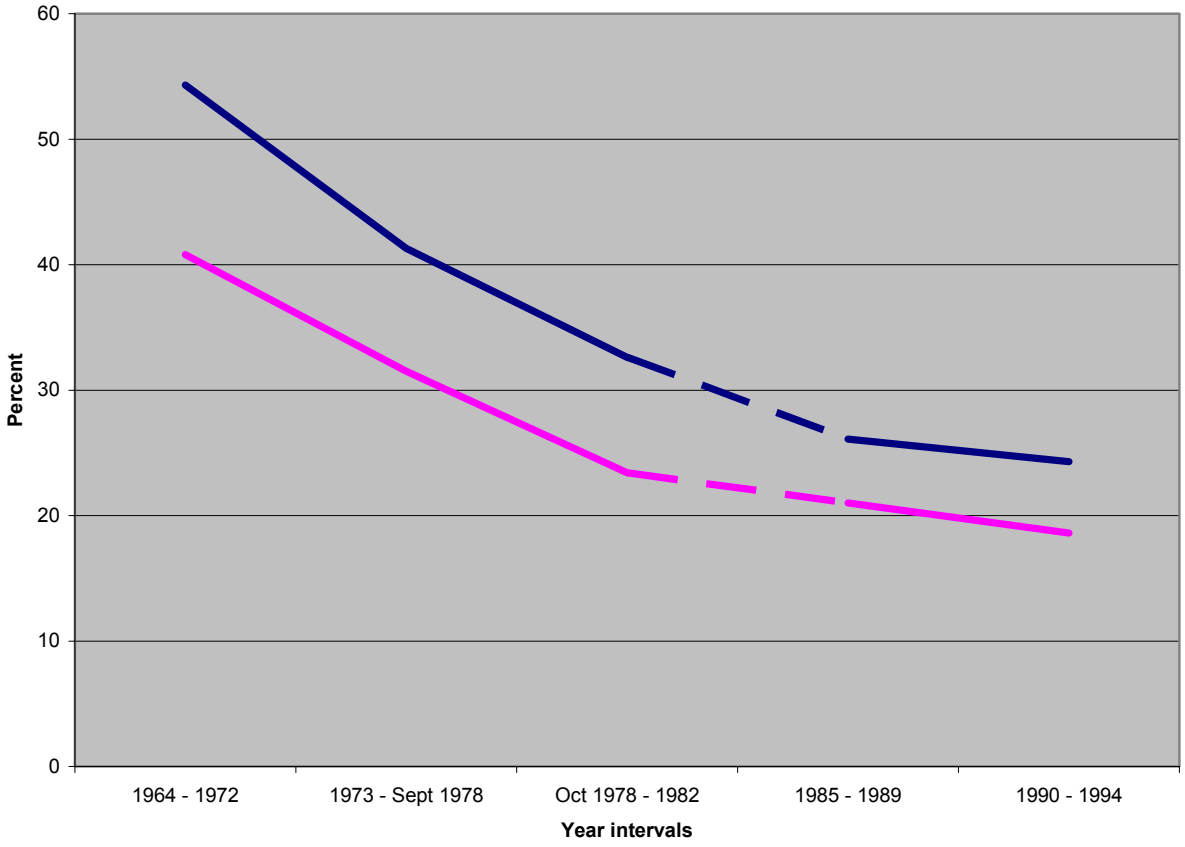

Fig. 10. Time trends in presence of ulceration 1964-94 (— males) (— females) Information on the periods 1964-82 was used with permission from Drzewiecki *et al* (23).

The melanoma levels were distributed equally between level II-IV with 1497 (30.0%) level II melanomas, 1522 (30.5%) level III melanomas and 1397 (28.0%) level IV melanomas. There were 182 (3.7%) level V melanomas and 380 (7.6%) were level unclassifiable melanomas (Table 17).

(If you wish to follow this subject, turn to page 64)

Survival analyses of the Danish melanoma population

Univariate Kaplan-Meier plots were carried out and the statistically significant prognostic parameters were selected for the multivariate survival analyses. The 5- and 10-year overall – and recurrence-free survival rates of the selected parameters were depicted in Table 18.

	Males 5-Year Survival %±SE	10-Year Survival %±SE	Females 5-Year Survival %±SE	10-Year Survival %±SE	Males 5-Year Rec. Surv. %±SE	Females 5-Year Rec. Surv. %±SE
Sex:	P<0.00001				P<0.00001	
Males	73.1±1.1	59.6±1.2	-	-	74.2±1.2	-
Females	-	-	84.6±0.7	74.8±0.9	-	84.9±0.8
Age:	P<0.00001				P<0.00001	
0-20	93.8±6.1	87.1±8.6	97.3±2.7	88.8±5.3	80.0±10.3	94.4±3.8
21-40	87.2±1.9	81.0±2.3	95.4±0.9	92.8±1.1	78.2±2.5	91.5±1.3
41-50	81.8±2.0	72.9±2.3	91.5±1.2	86.3±1.5	76.4±2.3	89.3±1.4
51-60	79.3±2.2	66.0±2.7	89.2±1.6	78.8±2.2	73.5±2.5	85.7±1.9
61-70	65.1±2.4	47.0±2.7	79.6±2.0	65.5±2.5	71.5±2.5	79.1±2.2
>70	50.5±2.8	29.2±2.7	60.0±2.4	39.1±2.5	70.4±3.3	69.2±2.9
Anatomical distribution:	P<0.00001				P<0.00001	
Trunk incl. lower back	72.1±1.4	59.5±1.6	84.5±1.4	77.1±1.7	72.6±1.5	84.5±1.5
Head and neck	64.6±3.0	47.7±3.3	75.0±3.0	56.9±3.5	76.5±3.1	84.7±2.7
Upper extremities	78.8±3.1	61.5±3.8	86.5±1.7	75.4±2.2	79.3±3.4	88.4±1.7
Lower extremities	80.2±2.3	68.9±2.8	85.9±1.1	76.7±1.4	74.8±2.7	84.0±1.2
Melanoma Type:	P<0.00001				P<0.00001	
SSM	79.4±1.2	67.1±1.4	88.9±0.8	80.8±1.0	81.6±1.2	90.0±0.8
LMM	60.9±7.2	37.7±7.6	77.4±5.8	53.5±7.0	75.1±7.9	85.7±6.1
NM	58.1±2.6	42.3±2.8	68.1±2.4	55.6±2.7	53.4±2.9	64.8±2.8
ALM	72.2±10.6	66.7±11.1	84.2±5.9	60.0±8.5	78.3±11.2	82.7±7.2
Unclassifiable	62.7±4.1	46.1±4.5	76.0±3.8	60.3±4.6	61.9±4.6	70.1±4.5
Tumour thickness in mm:	P<0.00001				P<0.00001	
<=1 mm	91.2±1.1	79.6±1.7	94.5±0.7	88.4±1.0	94.2±1.0	96.7±0.6
1,01-2 mm	77.7±2.1	64.5±2.6	84.5±1.7	73.5±2.1	79.2±2.3	85.1±1.8
2,01-4 mm	57.8±2.6	42.3±2.7	70.9±2.5	54.2±3.7	53.5±3.0	64.9±2.8
>4 mm	39.3±3.4	24.0±3.0	49.7±3.8	37.5±2.1	36.7±3.8	45.0±4.3
Not measurable	66.2±3.7	50.6±4.3	77.8±3.2	63.0±4.0	69.2±4.1	76.9±3.6
Level:	P<0.00001				P<0.00001	
Level II	92.2±1.2	81.6±1.9	94.5±0.8	89.3±1.1	95.6±1.0	97.3±0.6
Level III	76.5±1.8	60.7±2.2	88.5±1.2	79.4±1.6	75.2±2.0	87.5±1.3
Level IV	60.4±2.1	45.7±2.3	71.7±1.8	55.9±2.1	60.2±2.4	69.3±2.1
Level V	29.3±6.0	16.9±5.0	50.9±6.5	37.7±6.5	24.9±6.7	46.4±7.3
Unclassifiable	58.0±4.2	47.1±4.6	75.2±3.9	63.1±4.5	62.3±4.7	77.6±4.3
Ulceration in tumour:	P<0.00001				P<0.00001	
No	80.0±1.1	67.3±1.4	89.8±0.7	81.4±0.9	81.5±1.2	91.1±0.7
Yes	51.8±2.5	36.0±2.5	64.1±2.3	48.2±2.5	50.4±2.8	58.0±2.6
Unclassifiable	63.3±8.8	44.8±9.4	60.6±8.5	53.7±8.8	60.7±9.8	67.9±8.5

Table 18. Univariate survival rates of prognostic variables (log rank test was used to evaluate differences)

The univariate survival analyses of localised melanoma disease revealed significantly decreased overall – and recurrence-free survival in males compared to females (Log Rank<0.00001). The cumulative 5- and 10-year overall survival for the period 1985-94 in males was 73.1% and 59.6%,

in females it was 84.6% and 74.8%, respectively; the 5-year recurrence-free survival in males was 74.2%; in females it was 84.9%.

Not surprisingly the overall survival decreased with increasing age in both sexes (Log Rank<0.00001). A decrease in recurrence-free survival according to increasing age was also present; however it was not as pronounced.

A significant difference in overall survival was found according to anatomical site. The lowest survival rates in both sexes were found to be head and neck melanomas, where the 5- and 10-year survival in males was 64.6% and 47.7%; it was 75.0% and 56.9% in females, respectively. It was followed by trunk melanomas. The highest survival rates were found in melanomas on upper – and lower extremities. The lowest 5-year recurrence-free survival was seen for trunk melanomas in males (72.6%), and melanomas on the lower leg in females (84.0%). The highest 5-year recurrence-free rate was found for melanomas on upper arms in both sexes (males: 79.3%, females: 88.4%).

Differences were found in the survival of the two sexes according to the type of melanoma. In males the 5-year survival rate was poorest for NM (58.1%), followed by LMM (60.9%), type unclassifiable melanomas (62.7%), and ALM (72.2%). The highest survival rate was found in SSM (79.4%). At 10 years following date of operation the survival of LMM (37.7%) turned to be poorer than that of NM (42.3%). The poorest 5-year survival rate in females was as in males for NM (68.1%); however, the survival was better compared to males. It was followed by the type unclassified melanomas (76.0%), LMM (77.4%), and ALM (84.2%). As in males the highest survival rate was seen in SSM (88.9%). At 10 years following date of re-excision the same pattern of survival rates according to tumour type was seen in females as in males; however, the rates were higher. Recurrence was most likely to happen in NM (5-year recurrence-free survival in males 53.4%; in females 64.8%), followed by type unclassifiable melanomas (males: 61.9%; females: 70.1%). The recurrence following LMM (males: 75.1%; females 85.7%) resembled that of ALM (males: 78.3%; females: 82.7%). Recurrence was less likely to occur following SSM in both sexes (males: 81.6%: females: 90.0%).

Both overall - and recurrence-free survival decreased with increasing tumour thickness. The 5- and 10-year survival rates in thin melanomas (<1mm) in males were 91.2% and 79.6%; in females it was 94.5% and 88.4%. In thick melanomas (>4 mm) the 5- and 10-year survival in males was decreased to 39.3% and 24.0%; in females it was 49.7% and 37.5%, respectively. The 5-year recurrence-free survival following a thin melanoma was 94.2% in males and 96.7% in females. Following thick melanomas it was decreased to 36.7% in males and 45.0% in females, respectively.

The same pattern as in tumour thickness was seen in survival according to level; the overall – and recurrence-free survival decreased with increasing level.

Presence of ulceration was a strong determinant of decreased univariate survival. The 5- and 10-year survival rates in males were 80.0% and 67.3%, in females it was 89.8% and 81.4% when ulceration was not present. It decreased to 51.8% and 36.0%in males and 64.1% and 48.2% in females when ulceration was present. The recurrence-free survival decreased from 81.5% to 50.4% in males and from 91.1% to 58.0% in females when ulceration was present.

(If you wish to follow this subject, turn to page 65)

Initial diagnostic biopsy procedure and survival analyses

Excision biopsy was carried out in 72.3% of the cases, incision biopsy in 13.0%, curettage in 4.9%, and other kinds of biopsies in 0.5% of the cases; type of primary biopsy was not stated in 9.3% of the cases.

A surgical interval less than two weeks was seen in 8.6% of the cases, 27.4% was between 15-28 days, 13.8% was between 29-42 days, 3.2% was between 43-56 days, and 2.1% had a surgical interval exceeding 56 days (Table 19). The surgical interval was defined as the time between primary biopsy procedure and definitive surgical procedure.

	Males No. (%)	Females No. (%)	Total No. (%)
Type of primary biopsy:			
Excision biopsy	1515 (70.3)	2088 (73.8)	3603 (72.3)
Incision biopsy	285 (13.2)	363 (12.8)	648 (13.0)
Curettage	105 (4.9)	138 (4.9)	243 (4.9)
Other biopsy types	12 (0.6)	15 (0.5)	27 (0.5)
Surgical interval:			
0-14 days	175 (8.1)	256 (9.0)	431 (8.6)
15-28 days	555 (25.8)	811 (28.7)	1366 (27.4)
29-42 days	291 (13.5)	398 (14.1)	689 (13.8)
43-56 days	65 (3.0)	96 (3.4)	161 (3.2)
>56 days	47 (2.2)	58 (2.0)	105 (2.1)

Table 19. Distribution of type of primary biopsy and length of surgical interval.

According to both sexes (not shown) decreased overall - and recurrence-free survival was found when the primary biopsy was incision biopsy compared to excision biopsy (Log Rank<0.00001). When the primary biopsy was curettage compared to excision biopsy a highly significant decreased overall survival was found (Log Rank = 0.0011); the recurrence-free survival was only marginally decreased (Log Rank= 0.0434). No difference in both overall - (Log Rank= 0.2456) and recurrence-

free survival (Log Rank= 0.5196) was found when the primary biopsy was curettage compared to incision biopsy.

	Males 5-Year Survival %±SE	10-Year Survival %±SE	Females 5-Year Survival %±SE	10-Year Survival %±SE	Males 5-Year Rec. Surv. %±SE	Females 5-Year Rec. Surv. %±SE
Initial diagnostic biopsy:	P<0.00001				P<0.00001	
Excision biopsy	75.4±1.2	62.0±1.4	86.4±0.8	77.1±1.0	75.8±1.3	86.3±0.9
Incision biopsy	63.5±3.0	49.4±3.3	74.1±2.5	63.4±2.8	68.0±3.3	77.0±2.6
Curettage	64.4±5.0	51.3±5.3	83.2±3.4	67.9±4.6	66.6±5.6	82.2±4.0

Table 20. Univariate survival rates of overall – and recurrence-free survival according to type of initial diagnostic procedure.

The hazard ratios (exp ß) of overall - and recurrence-free survival were presented in Table 21.

	Overall Survival Exp (ß) [95% Conf. Int]	Recurrence-Free Survival Exp (ß) [95% Conf. Int]
Sex:	P<0.00001	P<0.000077
Females	1.00	1.00
Males	1.43 [1.27-1.61]	1.30 [1.10-1.54]
Age:	P<0.00001	P=0.57
Age	*	1.00 [1.00-1.01]
Anatomical distribution:	p=0.00009	P<0.000013
Trunk incl. lower back	1.00	1.00
Head and neck	0.88 [0.75-1.05]	0.61 [0.46-0.81]
Upper extremities	0.69 [0.58-0.83]	0.64 [0.49-0.83]
Lower extremities	0.79 [0.68-0.91]	0.85 [0.70-1.03]
Melanoma type:	P=0.36	P=0.011
SSM	1.00	1.00
LLM	1.36 [1.01-1.84]	2.09 [1.15-3.82]
NM	1.02 [0.89-1.18]	1.24 [1.03-1.48]
ALM	0.90 [0.59-1.37]	0.85 [0.42-1.74]
Unclassifiable	0.99 [0.79-1.23]	1.28 [0.96-1.71]
Level:	P=0.0010	P<0.00001
Level II	1.00	1.00
Level III	1.39 [1.14-1.69]	2.65 [1.79-3.93]
Level IV	1.42 [1.14-1.77]	2.55 [1.68-3.86]
Level V	1.89 [1.38-2.60]	4.06 [2.46-6.70]
Unclassifiable	1.62 [1.14-2.31]	2.38 [1.36-4.18]
Ulceration in tumour:	P<0.00001	P<0.00001
No	1.00	1.00
Yes	1.45 [1.28-1.65]	1.74 [1.47-2.06]
Unclassifiable	1.15 [0.81-1.62]	1.32 [0.83-2.10]
Likelihood-ratio:		
Type of primary biopsy	P=0.39	P=0.011
Excision biopsy	1.00	1.00
Incision biopsy	1.16 [0.99-1.35]	1.40 [1.12-1.74]
Curettage	1.14 [0.81-1.61]	0.82 [0.43-1.54]
Type of prim. biopsy when unclass.:		
Excision biopsy	1.00	1.00
Incision biopsy	1.47 [0.94-2.32]	1.63 [0.84-3.15]
Curettage	0.99 [0.61-1.60]	2.03 [1.04-3.95]

Table 21. Cox proportional hazard analysis of overall and recurrence-free survival. Log likelihood test was used to evaluate differences. * Hazard ratio of age should be read according to restricted cubic spline (graph).

Cox proportional hazard analysis with imputation:

The Cox proportional hazard analyses with imputation were presented as the quantiles from 1-99%, in that way the spectrum of uncertainty of the estimate was visualised. The 50% quantile represented the estimate (hazard ratio); the 2.5% and 97.5% quantiles represented the 95% confidence interval (Table 24, Table 25). The baseline parameters were female sex, trunk melanomas, SSM, ulceration not present, level II, age 60, and excision biopsy.

	1%	5%	10%	15%	25%	40%	50%	60%	75%	85%	90%	95%	99%
Sex:													
Male	1.254	1.312	1.340	1.357	1.388	1.424	1.447	1.477	1.512	1.548	1.571	1.601	1.652
Anatomical region:													
Upper extremities	0.575	0.606	0.624	0.636	0.660	0.685	0.702	0.717	0.743	0.770	0.783	0.803	0.843
Lower extremities	0.672	0.706	0.724	0.736	0.759	0.781	0.794	0.808	0.832	0.852	0.865	0.885	0.922
Head and neck	0.715	0.760	0.789	0.805	0.832	0.864	0.886	0.908	0.940	0.969	0.991	1.022	1.090
Tumour type:													
NM	0.892	0.932	0.954	0.972	0.996	1.027	1.042	1.061	1.089	1.119	1.138	1.169	1.211
LMM	0.924	1.080	1.140	1.186	1.258	1.336	1.385	1.436	1.524	1.607	1.652	1.732	1.900
ALM	0.568	0.658	0.709	0.750	0.803	0.873	0.917	0.963	1.059	1.135	1.182	1.263	1.460
Ulceration:													
Yes	1.191	1.247	1.281	1.304	1.334	1.372	1.396	1.420	1.461	1.499	1.520	1.556	1.634
Level:													
Level III	1.065	1.129	1.161	1.189	1.221	1.271	1.301	1.336	1.388	1.435	1.467	1.518	1.607
Level IV	1.043	1.119	1.156	1.186	1.233	1.283	1.319	1.356	1.423	1.483	1.513	1.564	1.687
Level V	1.097	1.206	1.295	1.340	1.400	1.494	1.543	1.606	1.711	1.814	1.878	1.983	2.174
Age interval*:													
1	0.991	1.001	1.007	1.011	1.017	1.024	1.029	1.033	1.040	1.046	1.050	1.057	1.071
2	0.888	0.933	0.959	0.973	0.995	1.023	1.040	1.062	1.090	1.120	1.134	1.171	1.232
3	0.437	0.533	0.592	0.642	0.713	0.799	0.848	0.931	1.031	1.136	1.209	1.364	1.626
4	0.545	0.701	0.813	0.883	1.000	1.158	1.270	1.388	1.609	1.817	2.011	2.327	2.824
Primary biopsy type:													
Incision biopsy	1.002	1.053	1.077	1.096	1.126	1.164	1.186	1.211	1.250	1.285	1.306	1.339	1.415
Curettage	0.755	0.813	0.847	0.872	0.911	0.960	0.989	1.015	1.067	1.113	1.136	1.182	1.272

Table 22. 1%-99% quantiles of overall survival calculated by imputation. Age is modelled with a cubic spline with 5 degrees of freedom; all influences of factors are included additively. The 50% quantile is used as the estimate. * The estimates of the age intervals must be interpreted in accordance with the restricted cubic spline graph (Fig. 4).

	1%	5%	10%	15%	25%	40%	50%	60%	75%	85%	90%	95%	99%
Sex:													
Male	1.059	1.114	1.157	1.181	1.220	1.268	1.295	1.321	1.369	1.415	1.447	1.495	1.584
Anatomical region:													
Upper extremities	0.448	0.501	0.526	0.544	0.576	0.610	0.635	0.661	0.697	0.732	0.757	0.785	0.856
Lower extremities	0.694	0.737	0.760	0.779	0.813	0.845	0.867	0.890	0.928	0.959	0.980	1.013	1.074
Head and neck	0.462	0.504	0.535	0.556	0.582	0.616	0.641	0.667	0.715	0.756	0.778	0.821	0.899
Tumour type:													
NM	1.000	1.060	1.091	1.117	1.153	1.194	1.223	1.247	1.295	1.332	1.358	1.389	1.454
LMM	0. 829	1.259	1.535	1.730	1. 859	1.996	1.859	1.996	2.250	2.458	2.654	2.902	3.448
ALM	0.293	0.525	0.660	0.776	0. 848	0. 911	0.848	0.911	1.030	1.151	1.235	1.399	1.652
Ulceration:													
Yes	1.329	1.404	1.449	1.480	1.529	1.587	1.623	1.661	1.720	1.774	1.818	1.883	2.038
Level:													
Level III	1.280	1.499	1.588	1.661	1.771	1.903	1.981	2.052	2.196	2.364	2.490	2.636	3.042
Level IV	1.256	1.429	1.528	1.595	1.693	1.838	1.918	1.999	2.172	2.333	2.436	2.600	2.962
Level V	1.562	1.814	1.980	2.072	2.229	2.465	2.612	2.805	3.044	3.278	3.416	3.737	4.482
Age:													
Age	0.999	1.001	1.002	1.002	1.003	1.004	1.005	1.006	1.007	1.008	1.009	1.010	1.012
Primary biopsy type:													
Incision biopsy	1.042	1.108	1.162	1.198	1.244	1.298	1.343	1.379	1.449	1.503	1.531	1.574	1.688
Curettage	0.803	0.909	0.986	1.034	1.098	1.175	1.231	1.279	1.363	1.439	1.492	1.548	1.670

Table 23. 1%-99% quantiles of recurrence-free survival calculated by imputation. The 50% quantile is used as the estimate.

Comparison of "conventional" Cox proportional hazards model and model with imputation:

		Imputation:			Conventional:	
	2.5%	Estimate	97.5%	2.5%	Estimate	97.5%
Sex:						
Male	1.287	1.447	1.628	1.274	1.431	1.607
Anatomical region:						
Upper extremities	0.591	0.702	0.827	0.582	0.693	0.826
Lower extremities	0.688	0.794	0.900	0.683	0.786	0.906
Head and neck	0.741	0.886	1.054	0.745	0.883	1.048
Tumour type:						
NM	0.917	1.042	1.190	0.890	1.024	1.177
LMM	1.033	1.385	1.789	1.012	1.364	1.839
ALM	0.613	0.917	1.365	0.593	0.901	1.368
Presence of ulceration:						
Yes	1.227	1.396	1.588	1.278	1.450	1.645
Level:						
Level III	1.096	1.301	1.560	1.143	1.392	1.694
Level IV	1.083	1.319	1.608	1.138	1.420	1.771
Level V	1.145	1.543	2.065	1.377	1.893	2.603
Age interval*:						
1	0.996	1.029	1.063	0.997	1.028	1.059
2	0.912	1.040	1.199	0.913	1.041	1.188
3	0.485	0.848	1.461	0.498	0.867	1.507
4	0.634	1.270	2.579	0.614	1.218	2.417
Primary biopsy type:						
Incision biopsy	1.032	1.186	1.377	0.994	1.160	1.353
Curettage	0.781	0.989	1.227	0.807	1.139	1.607

Table 24. Cox proportional hazard analysis with imputation compared with "conventional" model for overall survival. The lower value of the 95% confidence interval should be read from the left column, and the high value from the right. The estimate is in the middle. * The estimates of the age intervals must be interpreted in accordance with the restricted cubic spline graph (Fig. 4).

The overall risk of dying was increased by 43-45% in males compared to females when adjusted for anatomical region, tumour type, tumour thickness, level, ulceration, age, and type of primary biopsy. The increase was statistically significant. The overall survival was decreased 30-31% in

patients with trunk melanomas compared to melanomas on upper extremities, which was found to have the best prognosis. Intermediate overall survival was found in melanomas on the head/neck followed by melanomas on the legs. The differences in survival were statistically significant. LMM was found with decreased survival compared with the other melanoma types; in the "imputation" analysis it was by 38%, in the "conventional" analysis it was by 36%. Presence of ulceration decreased overall survival by 40-45%; the variable was imputated but no significant difference in importance was seen whether the unclassified cases were included or not in the analyses. Also the variable "Level" was imputated. The importance of including the level unclassified melanomas in the model (imputation) was a decrease in importance of level on overall survival. According to level III melanomas the overall survival was decreased by 39% compared to the survival following level II melanomas (which were baseline) in the conventional analysis; in the "imputation" analysis the importance decreased to 30%. In level IV melanomas a decrease from 42% to 31% in overall survival (compared to level II) was seen; in level V melanomas a markedly decrease from 89% to 54% was seen. The importance of level and ulceration on overall survival was statistically significant.

The overall survival was decreased by 16% when the primary biopsy was incision biopsy compared to excision biopsy; the decrease in survival became more pronounced when the unclassified melanomas was included in the analysis (the "imputation" analysis), the survival decreased by 19%. Overall survival was decreased by 14% when the primary biopsy type was curettage compared to excision biopsy in the conventional analysis; this decrease disappeared in the analysis with imputation.

	Imputation:			Conventional:		
	2.5%	Estimate	97.5%	2.5%	Estimate	97.5%
Sex:						
Male	1.076	1.295	1.529	1.103	1.301	1.535
Anatomical region:						
Upper extremities	0.481	0.635	0.819	0.489	0.635	0.826
Lower extremities	0.714	0.867	1.056	0.704	0.850	1.026
Head and neck	0.485	0.641	0.864	0.463	0.612	0.809
Tumour type:						
NM	1.032	1.223	1.411	1.034	1.237	1.480
LMM	0.990	1.859	3.173	1.148	2.094	3.818
ALM	0.385	0.848	1.484	0.418	0.854	1.743
Presence of ulceration:						
Yes	1.362	1.623	1.960	1.467	1.738	2.059
Level:						
Level III	1.410	1.981	2.842	1.786	2.649	3.930
Level IV	1.304	1.918	2.746	1.681	2.546	3.856
Level V	1.676	2.612	4.161	2.464	4.064	6.704
Age:						
Age	1.000	1.005	1.011	0.999	1.004	1.010
Primary biopsy type:						
Incision biopsy	1.077	1.343	1.627	1.120	1.397	1.742
Curettage	0.858	1.231	1.625	0.432	0.815	1.535

Table 25. Cox proportional hazard analysis with imputation compared with "conventional" model for recurrence-free survival. The lower value of the 95% confidence interval should be read from the left column, and the high value from the right. The estimate is in the middle.

The risk of developing recurrence was 30% increased in males compared to females, which was statistically significant. The risk of developing metastases following a trunk melanoma was increased by 36% compared to the risk of developing recurrence following melanomas on the upper extremities, which was statistically significant. Intermediately were the legs and the head/neck. The risk of developing metastasis was highest following a LMM melanoma in both types of analyses, even though a decrease was seen in the "imputation" analysis compared to the "conventional". After LMM followed NM and SSM; the most decreased risk of developing recurrence was seen following ALM. The risk of developing metastases increased with increasing level. The importance of level on recurrence decreased when the level unclassified cases were included (imputation analyses). Both tumour type and level were statistically significant important factors in the recurrence-free survival. Age was of no importance according to the risk of developing metastases, either in the "conventional" - or in the analyses with imputation. Effect of initial diagnostic procedure on recurrence-free survival revealed a 40% increased likelihood of developing metastases if the initial diagnostic procedure was incision biopsy compared to excision biopsy, this increase was statistically significant at a 95% significance level (p=0.011). In the imputation analyses it was increased by 34%.

In the initial analyses the surgical interval was included, the results within this variable of the two multivariate types of analysis were presented in Table 26. The surgical interval 15-28 days was used as baseline. No differences in overall – or recurrence-free survival were found according to length of surgical interval.

		Imputation:			Conventional:	
Overall survival	2.5%	Estimate	97.5%	2.5%	Estimate	97.5%
Surgical interval	P=0.28					
0-14 days	0.923	1.125	1.373	0.931	1.143	1.400
29-42 days	0.779	0.935	1.116	0.784	0.933	1.111
43-56 days	0.753	1.015	1.393	0.781	1.038	1.379
>56 days	0.492	0.793	1.252	0.550	0.838	1.277
Recurrence-free						
Surgical interval	P=0.18					
0-14 days	0.849	1.120	1.450	0.903	1.168	1.510
29-42 days	0.653	0.838	1.070	0.642	0.815	1.034
43-56 days	0.497	0.824	1.287	0.505	0.793	1.244
>56 days	0.659	1.244	2.102	0.771	1.295	2.173

Table 26. Estimates and confidence intervals of the surgical interval according to overall – and recurrence-free survival. The log likelihood test was used to evaluate differences.

(If you wish to follow this subject, turn to page 65)

Unclassified malignant melanomas; problems related to TNM-classification

In all 461 (9.2%) of 4984 malignant melanomas were unclassified due to one or more parameters including measured tumour thickness.

Level could be classified in 137 (29.7%) cases even though the tumour thickness could not be assessed, presence of ulceration could be assessed in 395 (85.7%) cases, and the melanoma type could be assessed in 239 (51.8%) cases.

In 101 (21.9%) cases it was possible to assess level, presence of ulceration, and tumour type, when tumour thickness was not assessable, in 122 (26,5%) cases level and ulceration could be assessed, and in 35 (7.6%) cases all 4 parameters were unclassified.

An increased occurrence of incision biopsies and curettage as primary biopsy was seen among the unclassified malignant melanomas; 25.2% of the biopsies were incision biopsies compared to 13.0% in the overall melanoma population and 29.9% of the primary biopsies were curettage compared to 4.9% in the overall melanoma population (Table 27). Other treatments were ointment treatments and massage among others. Eighty (17.4%) cases of the thickness unclassified melanomas were without information on type of primary biopsy.

	Unclassifiable Melanomas No (%)	Total Melanoma Population No (%)
Excision biopsy	122 (26.5)	3603 (72.3)
Incision biopsy	116 (25.2)	648 (13.0)
Curettage	138 (29.9)	243 (4.9)
Others	5 (1.1)	27 (8.0)

Table 27. Distribution of thickness unclassified melanomas according to type of primary biopsy.

The unclassified melanomas were more frequently situated on the head and neck region compared to the melanomas of the overall melanoma population (22.8% and 12.6%, respectively); they were less frequently located on the legs (25.4% compared to 32.2% in the overall melanoma population).

Fig. 11 visualises the overall survival according to tumour thickness of the total melanoma population. The survival curve of the patients with melanomas not measurable for tumour thickness was situated in the middle of all the survival curves suggesting this group being a mix of all tumour thicknesses.

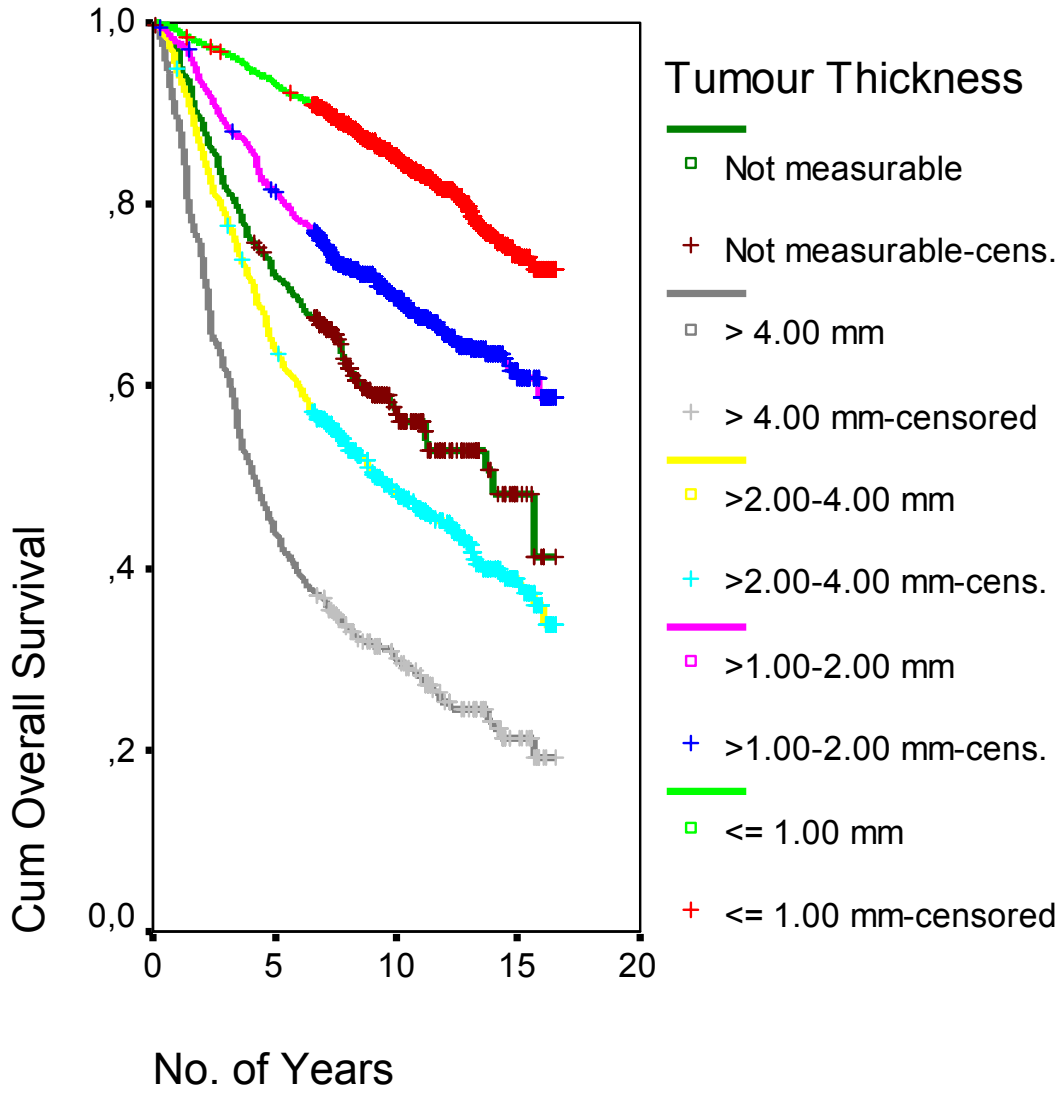

Fig. 11. Kaplan-Meier plot of overall survival rates according to tumour thickness of total melanoma population (Log rank: p<0.00001).

The median follow-up time of the unclassified malignant melanomas was 6.1 years.

	Presence of Ulceration	No of Pts.	5-Year Survival %±SE	10-Year Survival %±SE
Level II:	-	35	100.0	100.0
	+	4	100.0	100.0
Level III:	-	21	85.0±8.0	76.5±10.8
	+	14	78.6±11.0	39.3±28.3
Level IV:	-	14	92.9±6.9	74.3±17.5
	+	15	60.0±12.7	60.0±12.7
Level V:	-	3	50.0±35.4	50.0±35.4
	+	5	60.0±21.9	60.0±21.9

Table 28. Univariate cumulative survival rates of level stratified of ulceration (when classifiable) according to cause specific survival (log rank: p= 0.038).

Table 28 illustrated the 5- and 10-year cause-specific survival of level and ulceration. The number of cases in the different categories was small, and because of that the 95%-conf. intervals were extremely wide (below 0 and above 100%). However, a closer look at the distribution of the 5- and 10-year estimates (Table 28) as well as the Kaplan-Meier plots (not shown) revealed that a coarser categorization was possible. Three suitable categories naturally appeared when the survival rates were compared, and the subpopulation was divided in 1. level II ±ulceration, 2. level III ±ulceration and level IV –ulceration, and 3. level IV +ulceration and level V ±ulceration (Fig. 12).

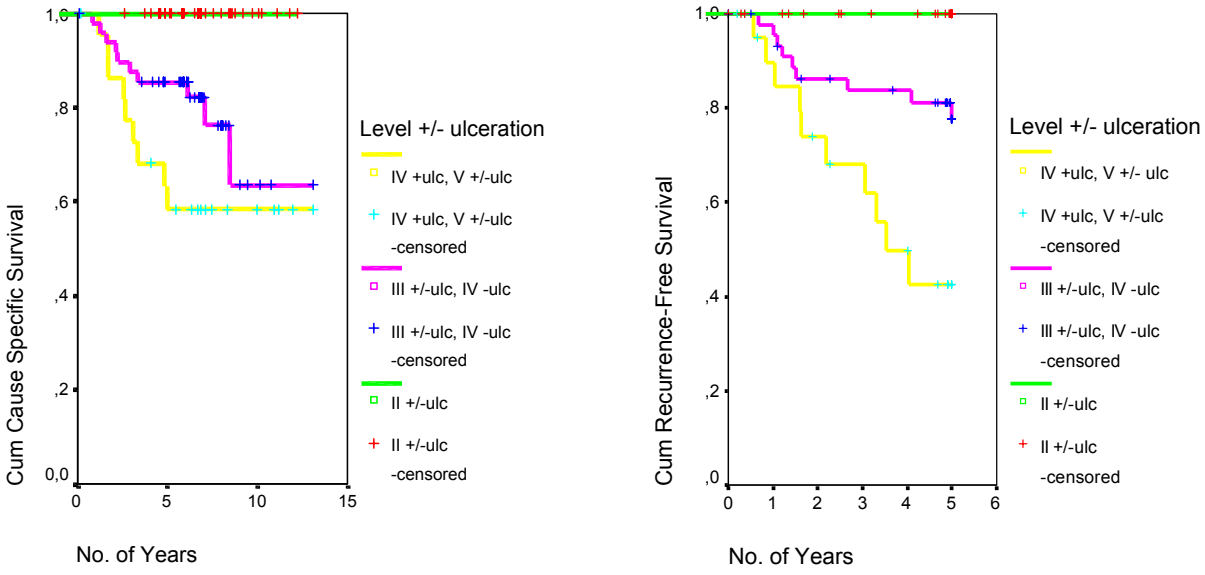

Fig. 12. Kaplan-Meier plots of the 5- and 10-year cause-specific survival (Log rank: p<0.0003) and 5-year recurrence-free survival (Log rank: p<0.00001) of patients with thickness unclassified melanomas according to level categories.

Cause-specific survival according to the three categories of level and ulceration was calculated (Table 29). The 5- and 10-year cause-specific survival of a level II melanoma with or without ulceration was, as well as the 5-year recurrence-free survival rate, 100%. To get an impression whether the survival of patients with level II melanomas was equal when ulceration was present or not, the cause specific survival of patients with level II melanomas of the overall melanoma population was calculated. The 5-year survival of patients with non-ulcerated level II melanomas were 94.4% (n=1262), the 10-year survival were 87.3%. The 5-year survival of patients with ulcerated level II melanomas were 76.1% (n=51), the 10-year survival was 62.9% (log rank: $p<0.00001$).

A level III melanoma ±ulceration categorised with level IV melanomas without ulceration revealed a 5- and 10-year cause-specific survival of 85.4% and 63.6%, respectively. The 5-year recurrence rate was 81.2%. A level IV melanoma without ulceration categorised with level V melanomas ±ulceration revealed a 5- and 10-year cause-specific survival rate of 58.4% and 58.4%, respectively. The 5-year recurrence rate was 42.5%.

	No.	5-y Survival (%±SE)	10-y Survival (%±SE)	No.	5-y Rec.Survival (%±SE)	TNM	Optimal Treatment	SN
Level classified:								
Level II +/– ulceration	39	100.0	100.0	37	100.0			
Level II – ulceration						T1a	Narrow excision (1 cm)	-
Level II + ulceration						T1b	Narrow excision (1 cm)	+
Level III +/- ulc., Level IV – ulc	49	85.4±5.9	63.6±13.3	47	81.2±6.0	T2a+b	Intermediate excision (2 cm)	+
Level IV + ulc., Level V +/- ulc	23	58.4±10.6	58.4±10.6	23	42.5±12.2	T4a+b	Wide excision (2-4 cm)	+
Level unclassified:								
Level unclassified – ulceration	163	85.9±2.9	71.2±5.2	156	76.8±4.2	(T2b+T3a)	.	.
Level unclassified + ulceration	73	66.9±5.8	64.7±6.0	72	43.9±6.9	T4a	Wide excision (2-4 cm)	+
Level unclass., ulc. unclass.	31	90.2	90.2	29	87.0±7.0	(T1b+T2a)	.	.

Table 29. Thickness unclassified melanomas categorized according to level and ulceration. The 5- and 10-year survival estimates and 5-year recurrence-free survival with standard error. Proper emplacement in TNM, optimal treatment, and indication of sentinel node biopsy (SN).

Level unclassified melanomas: Level was not assessable in 310 (67.2%) of 461 cases of thickness unclassified melanomas; in 269 (86.8%) of these cases presence of ulceration could be assessed. Ulceration was present in 86 (27.7%) of these cases, 183 (59.0%) were not ulcerated and 41 (13.2%) were ulceration unclassified. The 5-year cause-specific survival rate of a non-ulcerated, thickness - and level unclassified melanoma was 85.9%, the 10-year survival was 71.2% (n=163). When the thickness - and level unclassified melanoma was ulcerated the 5-year cause-specific survival was 66.9%, the 10-year survival was 64.7% (n=73) (Table 28). When thickness, level and ulceration were unclassified the 5-year survival was 90.2%, the 10-year survival was 90.2% (n=31).

A statistically significant difference in survival was found if ulceration was present, unclassified or not present (log rank: p=0.004).

Emplacement in proper TNM category as well as settlement of optimal treatment and indication of sentinel node biopsy was carried out accordingly and the results were presented in Table 29. By this procedure, optimal treatment was settled for 45.8% of the thickness unclassified melanomas.

(If you wish to follow this subject, turn to page 68)

Discussion

Validation of the database

The Capture-Recapture analyses calculated the completeness of the DMG-database to be 67.8% of the total estimated Danish melanoma population. Therefore the database is not optimal to describe national conditions within the melanoma disease.

The completeness of the data within the different variables in the database varied between 90.7% and 100% and revealed a database of very high completeness. The test sample revealed different systematic errors on off study causes as well as a significant lack of information on both off study cause and date. Therefore the database was meticulously revised and after that the failure rate was estimated to be diminished to 0-6%, and the DMG database was considered of very high correctness.

Because of a very high completeness within the different variables and a high correctness the DMG-database is considered very sufficient for describing a large number of clinical and pathological variables collected on the Danish melanoma population.

The comparison between the Danish Cancer Registry and the DMG-database gave unique possibilities by the Capture-Recapture analyses to estimate the true Danish melanoma population. The outcome estimate on 7767 melanomas as true size of the Danish melanoma population in the period 1985-94 is considered a very qualified estimate; partly because of the high completeness rate on 95-98% of the Danish Cancer Registry (73), but also because of a high regional completeness rate of the DMG-database.

The comparison of CR and DMG revealed that 21 cases were registered as multiple melanomas in CR whereas it was 126 cases in the DMG database. It should be questioned what was the cause of this difference. Was it an insufficient registration in CR of multiple melanomas, or was double registration of the same melanoma (and the patient in reality only had one melanoma) in the DMG-database the cause. A uniquely pathological identification number was distributed to all melanoma cases by the pathological departments, and during the validation of the database it had been investigated that the same identification number did not occur twice. Therefore suspicion was aimed at insufficient registration at CR.

At the time when the comparison of the two registers was carried out, accurate information on criteria of registration was obtained, especially according to the registration of level I melanomas that are non-invasive lesions and therefore there are no obligations to report these cases to the registry. A telephone call to the staff of CR revealed an inconsistency in the registration of level I

melanomas; because a significant number of the reports received on level I melanomas were registered in CR.

In 20% of cases with multiple malignant melanomas one of the melanomas was a level 1 melanoma; insufficient registration of the multiple melanomas in CR could be explained by inconsistent registration of level I melanomas. However, due to the finding of the registration of level I melanomas, it was revealed that optimal information on this type of melanomas should be obtained from the DMG-database and not from CR.

A potential systematic bias was investigated. A non-specified number of the trunk melanomas, the thick melanomas and the metastasized melanomas from the northern region of Denmark were referred and treated in the southern region. If the influence of an eventual bias was significant, it would be expected that the median tumour thickness would increase, and an increased amount of trunk melanomas and disseminated disease would be present, and because of that a decreased overall survival would be expected in the southern region of Denmark compared to the other regions. However, the median tumour thickness, the amount of trunk melanomas (Table 14) and the overall survival (Fig. 5) (Log rank: p=0.089) was not different in this region compared to the others, so the issue was considered unimportant. It should be mentioned that the importance of this bias was mostly pronounced if an examination of the quality of treatment between the different regions of Denmark was to be carried out; however, this was not an issue in this study.

The organization of the off study part of the DMG-database revealed more inexpedient limitations in using the generally very valuable data.

The patients were registered as off study according to the DMG protocol due to a number of causes (42). If the patient died, if the patient did not want follow up, if another malignant disease developed, at recurrence, and when follow up was terminated either after 5 - or 10 years.

If a patient e.g. was put off study due to development of another malignant disease, no information on an eventual later recurrence was obtained. Due to this organisation of the DMG database, information on development of recurrence was not available on all patients; and the amount and thereby completeness of the very interesting descriptive data was significantly limited. In that way, it was not possible to calculate incidence rates of recurrences, calculations on distribution of type of recurrence as well as the anatomical site of recurrence (which was rather accurately stated, see appendix e). However, the organization of the database at that time was not within the influence of this study. In the recurrence-free survival analyses the patients registered as off study of other causes than recurrence were censored.

Descriptive analysis of the Danish melanoma population

It is worldwide confirmed, that there are differences in presentation of the melanoma disease in the two sexes. A higher incidence of melanomas in females is seen in the Northern - (except Sweden) and Central part of Europe (89, 90), whereas in USA, Australia, Sweden, and also New Zealand since the beginning of the 90s, the incidence is higher in males (90, 91, 92). In the Danish melanoma population significantly more females than males had developed malignant melanoma, 58.8% compared to 43.2%.

In the present study the mean age was 55 years: 54.0 years in females compared to 56.2 years in males ($p<0.00001$) (Table 16). In the period 1958-82 previous studies of the Danish population found the mean age to be between 52-54 years. In that way a tendency towards increasing age, especially among males in the following time period 1985-94 was revealed.

In 22.2% of the melanomas in males ulceration was present compared to 19.8% in females in the period 1985-94 ($p<0.0001$). In the period 1964-72 the amount of melanomas diagnosed with ulceration was 54.3% in males and 40.8% in females; during these periods a marked decrease took place in the occurrence of this prognostic important variable. However, through the studied time periods the occurrence of ulceration was always higher in males compared to females. The same phenomenon was seen in the case of tumour thickness. A marked decrease in both median and mean tumour thickness was seen in the period 1964-94. In the period 1964-72 the mean tumour thickness in males was 3.73 mm, in females it was 2.58 mm. In the period 1985-94 it decreased to 2.44 mm in males and 1.82 mm in females, respectively (Fig. 8). Also the mean tumour thickness was significantly thicker in males compared to females through the studied periods. A decrease in mean and median tumour thickness is also seen in other countries (90).

Also in the literature the mean age is found to be lower in females (90), presence of ulceration is less frequent (90), and the median tumour thickness is thinner (89, 90); all leading to a better survival in females compared to males (93).

Worldwide the anatomical distribution has been found to be different in the two sexes; the most frequent anatomical site in males was the trunk, whereas it was the lower leg in females (89, 90, 92). The same was seen in the Danish melanoma population, where 57.4% of the melanomas in males were trunk melanomas and 43.6% of the melanomas in females were melanomas on the lower leg (Table 16). In previous studies of the Danish melanoma population Østerlind (20) found that melanomas on the lower leg were more frequent than head/neck melanomas in males; whereas Drzewiecki *et al* (22, 23) found the opposite. This study revealed that melanomas on the head/neck

were more frequent than melanomas on the lower leg in males, and it supports the finding of Drzewiecki *et al.* The increase in trunk melanomas for both sexes was especially pronounced for SSM melanomas.

A trend towards an increasing incidence of malignant melanoma with predominantly thin lesions is confirmed worldwide (89, 90, 94, 95, 96, 97). This is confirmed in the Danish melanoma population (Fig. 9).

Alterations in anatomical site with a trend towards increasing number of trunk melanomas have been confirmed in earlier studies of the Danish melanoma population (23, 24, 98). This trend continued through the period of this study; the increase was especially pronounced in females.

Survival analyses of the Danish melanoma population

Carstensen *et al* and Østerlind and Kjems (4, 5) investigated the survival of Danish melanoma patients in the period 1943-87 on basis of the Danish Cancer Registry. They found a markedly increase in survival during the period. In males the 5-year overall survival increased from 34.4% in the period 1943-47 to 61.6% in the period 1983-87. In females the increase was from 49.4% to 77.7% in the same time periods. Even though the results could not be compared directly, in this study it seems as if a further increase in survival was seen of the following periods. In the period 1988-92 the 5-year survival was found to be 72.6% in males and 85.7% in females. In the time period 1993-94 it was found to be 76.6% in males and 86.7% in females, respectively. These findings are in good correlating with the findings that the mean and median tumour thickness decreased during the period 1943-94 (Fig. 8), as well as the presence of ulceration; and an increase in the amount of thin melanomas was seen (Fig. 9).

Initial diagnostic biopsy procedure and survival analyses

The rate of incision biopsy in this study was 13.0% and the rate of curettage was 4.9%. In the literature the rate of incision biopsy varies between 5.6%-30.2% (48, 49, 52, 53, 55, 99, 100), the wide variation is due to different definitions of "incision biopsy".

Seventeen percent of the cases of incision biopsy and 56.8% of the cases of curettage were not measurable for tumour thickness. In the literature the rate of incision biopsies not measurable for tumour thickness varies from 8.3% to 39.6% (52, 53, 99). The rate of curettage not measurable for tumour thickness as well as the survival according to curettage as initial diagnostic procedure has not previously been addressed. Surprisingly as much as 43.2% of the primary biopsies taken by curettage were measurable for the tumour thicknesses; a significantly lower number was expected.

An explanation of this phenomenon could be the fact, that melanomas that are biopsied by curettage are likely to be thinner than melanomas biopsied as excision biopsies, and therefore they could have been removed *in toto* at the curettage. The decision whether the tumour thickness could be measured or not was decided when the re-excision specimen was revised, and probably in some cases it was possible to assess the tumour thickness even though the primary biopsy and re-excision specimen was examined separately.

The estimates of the non-imputated variables, in the two types of multivariate survival analyses ("conventional" and "imputation") were identical; therefore the analyses with imputation were considered as correctly constructed as well as without miscalculations.

In the estimates of the imputated variables of the overall survival analyses no differences in the estimate values of tumour type were found. The importance of level and ulceration decreased in the analyses with imputation; however they were still significant factors. The results of both types of the multivariate analyses of overall survival revealed no difference in survival whether the initial diagnostic procedure was excision biopsy, incision biopsy or curettage (likelihood-ratio: $p=0.39$), which was different from the univariate analyses that strongly indicated differences in survival; however, when adjusted for other prognostic variables these differences disappeared. Important prognostic factors in both the "conventional" and "imputation" analyses were sex ($p<0.00001$), anatomical region ($p=0.00009$), level ($p=0.0010$), presence of ulceration ($p<0.00001$) and age ($p<0.00001$). Tumour thickness was stratified and therefore was incorporated in the model. In the initial analysis the surgical interval was incorporated in the model. No difference was found in overall survival between the different time intervals, suggesting that the length of the time interval between initial primary biopsy and re-excision procedure was without importance. However, the number of cases in the time intervals 43-56 days and >56 days was very small, and a statement exceeding 42 days (6 weeks) was uncertain. The study therefore indicates that an interval up to 6 weeks between initial diagnostic procedure and re-excision procedure does not affect survival of the patients.

In the world literature as well as in earlier studies of the Danish melanoma population LMM have been found to have better survival compared with the other melanoma types (23, 24, 39). Surprisingly it was found that the prognosis of LMM was worse compared to the other tumour types, which was the case in both multivariate analysis types. Patients with LMM are generally older than patients with other tumour types (SSM, NM, ALM), and an insufficient stratification according to age in the chosen model could be an explanation of the phenomenon. If this was

entirely the case it would be expected that the rate of recurrence following LMM would decrease considerably in the recurrence-free survival (not disappearing because some effect of age probably would influence the univariate recurrence-free rate); however only a small decrease in the parameter estimate of LMM was seen, and an insufficiently stratification according to age therefore was not the entire explanation of the decreased survival of LMM. Some of the deviation from the expected outcome probably also could be explained by analysis result coincidences. However, the importance of this phenomenon should be seen in the light of all the other outcome estimates turning out as expected.

The overall survival was used as event in this part of the study. If the survival of other primary malignancies in patients with malignant melanoma was markedly decreased, then a bias towards a decreased survival of the Danish melanoma population would be expected. Increased occurrence of few selected malignancies as non-melanoma skin cancers, oropharyngeal cancer among others have been found by Swerdlow *et al* (29); however, the increased incidence of these malignancies did not affect the overall likelihood of developing all non-skin malignancies. Also Østerlind *et al* (26) concluded that patients diagnosed with malignant melanoma of the skin were at no greater risk of developing a new cancer than were individuals in the general population. The finding of Østerlind incentive not to exclude patients with other malignant diseases in the off study part of the DMG-database; however, the structure of the DMG database at that time was beyond decision of this present study.

Also in the recurrence-free survival analyses the estimated values of the non-imputated variables, in the two types of multivariate analyses ("conventional" and "imputation") were identical. The importance of LMM according to recurrence decreased in the analyses with imputation compared to the other melanoma types. According to the 95%-confidence interval it changed towards insignificance in the "imputation" analysis (exceeding below 0); however, it was mostly due to a large increase in the range of the interval. As seen in the analyses of overall survival the importance of level decreased in the analyses with imputation; this time more pronounced.

Important prognostic factors in both types of analyses of recurrence-free survival were sex ($p<0.0017$), anatomical region ($p=0.00013$), level ($p<0.0001$), presence of ulceration ($p<0.0001$) and at a less degree tumour type ($p=0.028$). The importance of age disappeared ($p=0.109$). Also in the recurrence-free survival analyses the tumour thickness was stratified and therefore was incorporated in the model.

Effect of initial diagnostic procedure on recurrence-free survival revealed a 40% increased likelihood of developing metastases if the initial diagnostic procedure was incision biopsy compared to excision biopsy. In the imputation analyses it was increased by 34%. Surprisingly a decreased risk of developing metastases on 18% was seen if initial diagnostic procedure was curettage compared to excision biopsy. However, the "protecting" effect of curettage as initial diagnostic procedure disappeared in the imputation analyses, and an increase in risk of developing metastases on 23% was found compared to excision biopsy. The log likelihood test in the "conventional" analysis was significant on a 95%-significance level (p=0.011), however the parameter estimate of the imputation analyses was inferior and the level of significance was expected to be situated around a 95%-significance level. In that way an influence was found of type of biopsy on recurrence-free survival, however, the finding was not convincing. On the other hand, the conclusion that recurrence-free survival is independent of type of initial diagnostic procedure can not be accomplished.

Unclassified malignant melanomas; problems related to TNM-classification

It is recommended to perform an excision biopsy with a 2-5 mm free resection margin as primary biopsy of pigmented lesions (39, 42, 43, 44, 45, 46). However, when the clinician is uncertain on the melanoma diagnosis incision biopsies, curettage, or other kinds of biopsy procedures are carried out. If the primary biopsy is insufficient the pathological classification of the melanoma is likely to be impaired. When a melanoma is removed by curettage the thickness of the melanoma is often not assessable because the deep resection margin is not free (44, 45, 46). If the primary biopsy is incision biopsy the specimen is not complete. Therefore it is not certain if the thickest part of the tumour is included in the specimen for the pathology, and the measurement of the tumour thickness could become inaccurate (44, 45, 46). Pronounced regression and inappropriate handling of the specimen could also be causes of impaired classification.

In the literature a few authors dealt with the problem of thickness unclassified melanomas, which accounted for 4.5 – 27.6% in the investigated melanoma populations (20, 52, 53, 83, 99,). Wagner *et al* (101) found in a study of 235 patients 25 (11%) thickness unclassified tumours, 3 (12%) of them developed recurrence; 1 patient died from systemic metastases, 2 patients remained disease-free following re-excision surgery.

In the literature 12.7%-16.4% of the melanomas are reported unclassified according to the type of melanoma (20, 53, 83, 102), compared to 7.8% in this study. The number of level unclassified melanomas in the literature varies between 6.3%-8.5% (20, 53); in the present study it was 7.6%.

The total number of thickness unclassified melanomas in the Danish melanoma population was 9.2%, and until now this group of melanomas have received little attention.

In many countries guidelines for optimal treatment of melanoma have been developed. However, Danish guidelines of melanoma treatment (42, 63, 64) as well as guidelines from many other countries do not give the recommendations regarding treatment of the unclassified melanomas (39, 43, 65, 66, 67, 68, 69).

It was not possible to obtain information on how the unclassified melanomas are treated in other countries. In Denmark the tradition has been to treat the unclassified melanomas as "worst case" (tumour thickness > 4 mm), independent of the other prognostic parameters. This tradition is empirical. It has not been investigated, whether this is the optimal treatment in all cases. Sentinel node biopsy is carried out in all patients with unclassified melanomas as well.

In this study the survival of the patients with thickness unclassified melanomas decreased with increasing level and presence of ulceration, however the number of cases within the different categories was small, which was reflected in the very large confidence intervals (Table 28). To obtain statistically more suitable groupings three sub groups was defined as described in Table 29.

The survival rates of the three level and ulceration sub groupings was calculated and revealed that an unclassified melanoma categorised as level II with or without ulceration had both 5- and 10-year cause-specific survival of 100%, which is comparable to the survival of a T1a melanoma (TNM-classification) (Table 4).

As it can be recalled from the TNM-classification system (Table 2) the T1a melanoma is a thin (<1 mm) non-ulcerated melanoma; sentinel node biopsy is not indicated (61, 62, 103). If ulceration is present in a thin melanoma (categorized as T1b) sentinel node biopsy is suggested.

The results of this study indicated that level II unclassified melanomas with or without ulceration could be treated as T1a melanomas (narrow excision without sentinel node biopsy). However univariate analysis of the survival of level II melanomas stratified by ulceration of the total Danish melanoma population revealed a significant difference in survival if ulceration was present (non-ulcerated (n=1262): 5-year survival: 94.4%±2.3 10-year survival: 87.3%±1.9, ulcerated (n=51): 5-year survival: 76.1%±11.8 10-year survival: 62.9%±13.8. Log rank: $p<0.00001$). When ulceration was present the survival of level II melanomas was significantly decreased; there is no reason to believe that the thickness unclassified level II melanomas behave differently. The difference in survival was not detected, probably due to the small population size. It is therefore suggested that

patients with level II, ulcerated and thickness unclassified melanomas are offered narrow excision and sentinel node biopsy. Narrow excision only is sufficient for non-ulcerated tumours.

In this study the level was found to be a statistically significant prognostic factor for the overall survival, therefore it was used together with ulceration to prognosticate thickness unclassifiable melanomas. A group of thickness unclassified melanomas, level III with and without ulceration and level IV melanomas without ulceration had 5-year survival of 85.4%, and 10-year survival of 63.6%. The survival of this group was comparable to the 5-year survival of a T2a melanoma and the 10-year survival of T2b melanomas (TNM-classification). T2a and T2b are intermediate thickness melanomas with and without ulceration. In Denmark T2a and T2b tumours are treated with an intermediate margin of excision of 2 cm. A diagnostic sentinel node biopsy is routinely performed in these patients. It is therefore suggested that the thickness unclassified melanomas level III with or without ulceration and level IV without ulceration are treated as above mentioned intermediate thickness melanoma (1.01-2.00 mm).

The group of thickness unclassified melanomas level IV with ulceration and level V with and without ulceration had 5-year survival of 58.4%, and 10-year survival of 58.4%. Survival of this group is comparable to T4a and T4b melanomas (TNM-classification). These are thick melanomas with and without ulceration. In Denmark T4a and T4b melanomas are treated with a wide margin of excision, which is 2 or 4 cm depending on anatomical site (4 cm: Trunk, upper arm, thigh; 2 cm: Head/neck, lower arm, hand, lower leg, and foot). Furthermore sentinel node biopsy is carried out. It is therefore suggested that the thickness unclassified melanomas level IV with ulceration and level V with or without ulceration are treated as above mentioned thick melanomas (>4.00 mm).

Increased morbidity should be taken into considerations when treating all unclassified melanomas as if they were thick melanomas. It also becomes inexpedient, when the patient wants to take out insurances, when they are registered and diagnosed as having an aggressive invasive cancer, which this study shows, they do not necessarily have. Furthermore, inexpedient situations could arise when patients with unclassified melanomas want to apply for jobs. Some job types as air craft pilots can not be applied for, when the applicant suffers from a potentially serious disease. Also cases of child adoption could be impaired.

Level was not assessable in 310 (67.2%) cases of the thickness unclassified melanomas; in 269 (86.8%) of these cases presence of ulceration could be assessed. Ulceration was present in 86 (27.7%) cases, 183 (59.0%) were not ulcerated and 41 (13.2%) were unclassified for ulceration.

Ulceration occurred more frequently compared to the overall melanoma population (27.7% and 22.2%, respectively).

The 5- and 10-year survival of non-ulcerated level - and thickness unclassified melanomas (melanomas classifiable with only one parameter) were 85.9% and 71.2%, which resembled the survival of T2b and T3a melanomas (TNM-classification). The 5- and 10-year survival of ulceration unclassified melanomas were 90.2% and 90.2%, respectively, which resembled the survival of T1b and T2a melanomas (TNM-classification). The parameter ulceration seems to be suitable for prognostication of thickness unclassified melanomas, because 85.7% of the cases in this material could be classified, and because of the high prognostic value. However, the use of only one parameter in prognostication of the thickness - and level unclassified melanomas was considered insufficient. It could not be distinguished whether the survival rate of this group was influenced by presence of intermediate thickness melanomas only (which would be the ideal situation) or it was an expression of an inhomogeneous group of melanomas containing both thin and thick tumours, whose average ended up as an intermediate survival group. Therefore the role of other parameters as age, localisation, and gender for better forecast of prognosis for this group of patients should be looked upon. Thickness - and level unclassified melanomas account for 49% of the thickness unclassified melanomas.

The 5- and 10-year survival rates of the ulcerated thickness - and level unclassified melanomas were 66.9% and 64.7%, respectively, which resembled the survival of T4a melanomas (TNM-classification). The use of only one parameter to describe prognostication of the thickness - and level unclassified melanomas was considered insufficient as described above; however, the issue was less important, because the recommended treatment is wide excision and sentinel node biopsy.

Recent TNM-classification is based on a very large multi-institutional analysis (39, 62, 88). However, thickness unclassified melanomas were apparently not analysed. The thickness unclassified melanomas are not implemented in the stage groupings of the TNM-classification system even though they comprise around 10% of a melanoma population. This study is believed to provide some evidence for inhomogenity of the group thickness unclassified melanomas and a tool to solve some of the classification problems.

Danish summary

Ph.d.-afhandlingen omfatter validering, deskriptiv analyse og overlevelsesanalyser af den danske melanom population behandlet i perioden 1985-94, baseret på data fra den kliniske DMG-database. Indflydelsen af biopsitype, og tiden mellem diagnose og radikal behandling, på overlevelsen er ligeledes blevet undersøgt. Endelig er detaljerede overlevelsesanalyser indenfor gruppen tykkelsesuklassificerbare melanomer (TUM) blevet gennemført med henblik på anvendelse af TNM-klassifikationen (TNM) for disse tumorer, som udgør op til 10% af melanom populationen.

Hverken biopsitype eller tiden til radikal behandling havde indflydelse på overlevelse, såfremt radikal behandling skete inden for 6 uger. Såvel curettage som incisionsbiopsier resulterede dog i flere recidiver sammenlignet med excisionsbiopsier.

TUM er en signifikant del af en melanompopulation. Det er en overset gruppe. I danske og internationale melanomguidelines forefindes ingen rekommandationer for behandling af disse tumorer. De har ikke fundet plads i den kliniske eller patologiske stadieinddeling i TNM. I denne afhandling er andre prognostiske faktorer som level og ulceration blevet undersøgt for TUM med henblik indplacering i TNM. Det er blevet fundet at TUM er en inhomogen gruppe, samt at en betragtelig del af disse patienter kan TNM-klassificeres ved anvendelse af en kombination af andre prognostiske parametre end tykkelsen af tumor.

Abstract

Objective of this PhD study was to validate a clinical database run by the Danish Melanoma Group, and to make a descriptive analysis and survival analyses of the Danish melanoma population in the period 1985-94. The influence of type of primary biopsy and the time between primary biopsy and radical treatment on survival was investigated as well. Finally detailed survival analyses of the group thickness unclassified melanomas (TUM) were carried out in order to apply the TNM-classification system (TNM) on these tumours that comprise up to 10% of a melanoma population.

Neither the type of primary biopsy, nor the time to radical treatment influenced the survival, if radical treatment was carried out within 6 weeks. However, both curettage and incision biopsies revealed more recurrences compared to excision biopsies.

TUM is a significant part of a melanoma population. They are disregarded. Danish and international melanoma guidelines do not give recommendations regarding treatment of these tumours. They are not implemented in the clinical and pathological stage groupings in TNM. In this treatise other prognostic parameters as level and ulceration has been investigated for TUM with purpose to implement these tumours in TNM. It was found that TUM are an inhomogeneous group and that a substantial part of these tumours could be implemented in TNM by using a combination of other prognostic parameters than tumour thickness.

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