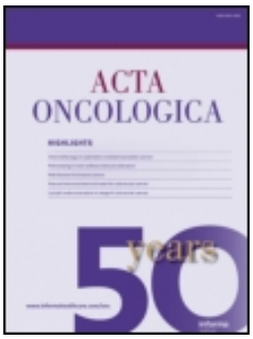

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C. Lindholm, P.-Å. Hofer & H. Jonsson

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FROM THE DEPARTMENTS OF ONCOLOGY AND PATHOLOGY AND THE CENTRE OF ONCOLOGY, UNIVERSITY OF UMEÅ, S-901 87 UMEÅ, SWEDEN.

KARYOMETRIC FINDINGS AND PROGNOSIS OF STAGE I CUTANEOUS MALIGNANT MELANOMAS

C. LINDHOLM, P.-Å. HOFER and H. JONSSON

Abstract

A material consisting of 82 stage I cutaneous melanomas was analysed clinically, histopathologically and karyometrically. High age, deep Clark level of invasion and thick melanomas were associated with a negative prognosis. There was a good correlation between the nuclear area and the melanoma thickness. By applying Cox's proportional hazard method to clinical, histopathological and karyometric data, it was demonstrated that karyometry provided both prognostic and biological information. Both a large variation (percentile 90–percentile 50) in nuclear area and a large standard deviation of form factor was related to a negative prognosis ($p < 0.0003$ and $p < 0.04$ respectively).

Key words: Skin neoplasms; malignant melanoma, prognostic factors, karyometric data.

In cutaneous malignant melanomas, clinical variables, such as age, sex, anatomical location (2, 7, 9, 12, 21, 38, 40, 41), and histopathological variables, such as thickness, level of invasion, occurrence of ulceration and mitotic frequency all have prognostic value (3, 8, 10, 14–16, 18–20, 24, 27, 30, 39). Differences of cell type are, on the other hand, of little prognostic value in cutaneous melanomas (13, 17, 22, 31, 35–37). In uveal melanomas, however, cell type and size of nuclei, nucleoli and their standard deviations can be used to assess the prognosis (11, 28, 29).

The aim of the present study was to examine if karyometric findings provide prognostic information for clinical stage I cutaneous malignant melanomas.

Material and Methods

Patient data. Between 1st January, 1972 and 31st December, 1974, 114 cutaneous malignant melanomas were entered in the cancer registry of the 3 northern counties (Västerbotten, Västernorrland and Norrbotten) of Sweden. From this material, 32 cases were excluded since the tumours registered (1972–1974) represented metastases from earlier diagnosed melanomas (7 cases) or from not detected primary melanomas (4 cases), the diagnosis derived from autopsy (one case), they were clinical stage II and III melanomas (9 and 4 cases respectively), it was a Spitz naevus (3 cases) or benign acquired compound naevus (one case), and since there was no or insufficient histopathological material (3 cases). Thus 82 malignant melanomas, all in clinical stage I, were included in the present study.

Primary therapy consisted of wide excision with primary closure in 22 cases, primary excision followed by secondary wide excision and skin transplant in 55 cases and amputation or cautery in 5 cases. In 9 cases, elective lymphadenectomy was done. Secondary treatment, if any, consisted of surgery, radiotherapy or chemotherapy. The minimal follow-up for all patients was 10 years.

Histopathological investigation. The malignant melanomas were reexamined and histologically typed as superficial spreading malignant melanoma (SSM), nodular malignant melanoma (NM), lentiginous malignant melanoma (LMM), acral lentiginous melanoma (ALM) and malignant melanoma unclassifiable (MMU) (16).

The Clark level of invasion (16) and the thickness measured according to Breslow (10), was estimated separately by both authors and in cases where there was controversy, the specimen was reevaluated after discussion and reexamination.

Karyometry. New 5-μm-thick sections were cut from available formalin-fixed and paraffin-embedded speci-

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mens. The original sections were used if paraffin blocks were missing (12 cases). The sections were stained with haematoxylin-eosin and according to Herovici's variant of van Gieson's method (33). The diagnosis was confirmed by one of the authors (P-Å H) and the slides were coded. All specimens were photographed using a 40× objective (Zeiss Planapo 40/0.95). A 10 micron step stage micrometer was used to assess the exact final magnification of each series of photomicrographs. The areas photographed were selected using a 4× objective. Care was taken to make sure that the areas were evenly distributed over the section. Areas of necrosis or ulceration were rejected. The final magnification of the photomicrographs was close to ×1 100. For each case, at least 150 nuclei were selected from the photomicrographs. If there was a large number of nuclei in the photographs, nuclei were selected evenly distributed over the photocopies. The nuclear profiles were measured by one of the authors (CL) who had no prior knowledge of the clinical data, using a semi-automatic image analysis system, Leitz A.S.M.

As an earlier test had demonstrated considerable inter-individual differences, all karyometric measurements were made by the same person. The individual error, according to the method described by Eränkö (26), was 3.8% for 31 double measurements.

Mean values and standard deviation of the nuclear profile area, maximal nuclear diameter and form factor (F.F. = 4π area/perimeter^2) were determined. The form factor for a perfect circle is 1.0 and irregular or elliptical structures deviate from unity towards zero, as their circularity becomes less perfect. As we were particularly interested in the influence of large nuclei, the percentages of nuclear profile areas larger than 60 μm^2 (P60), 80 μm^2 (P80), 100 μm^2 (P100), 120 μm^2 (P120) and the 90th percentile of nuclear profile area minus the 50th percentile (Pe90-Pe50) were estimated. The last mentioned variable is probably a better estimation of nuclear profile area variation than the standard deviation of the mean since small profiles due to sectioning 'artefacts' and the few extremely large profiles are not included. Examples of melanomas photographed and their nuclear area histograms and parameters measured are presented in Figs 1 and 2.

Statistical methods. For sex, age of patient and location of melanoma the relative survival rate was estimated according to the method of Hakulinen & Abeywickrama (32). For the different Clark levels of invasion, the different thicknesses of the melanomas and the measured karyometric variables, the crude survival rate was estimated according to Kaplan-Meier and the differences of survival were tested by the log rank test (1). To determine if there was a relationship between the karyometric findings and the numerical variables of age and melanoma thickness, linear regression coefficients were determined. The influence of clinical, histopathological and karyometric findings on survival were analyzed by Cox's proportional hazard method (34).

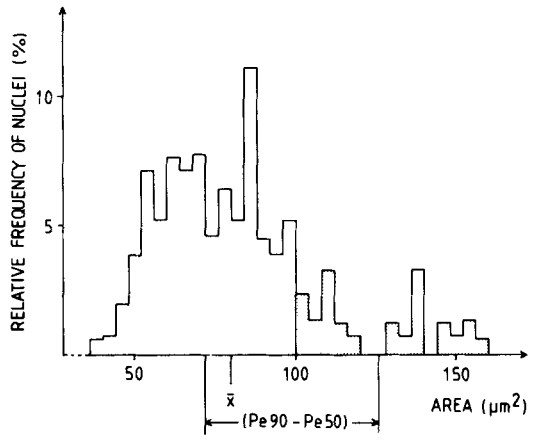

Fig. 1. Examples of karyometric parameters measured. x̄=mean nuclear area (μm^2). Shadowed area represents fraction of nuclei larger than 100 μm^2. Pe 90–Pe 50 = nuclear area of the 90th percentile – the 50th percentile (μm^2).

Table 1

Relative survival rates of stage I cutaneous melanomas ±2 SE

	n	5 years (%)	10 years (%)
Total	82	76±12	70±15
Males	36	74±19	71±22
Females	46	79±15	70±19
Age 30–59 years	34	84±13	78±16
Age ≥60 years	40	68±20	57±27
Trunk	30	74±18	77±20
Extremities	38	76±18	67±27

Results

Clinical data and survival. The median age for all patients was 58 years (range 20–92), for the 36 males it was 51 years (range 28–90) and for the 46 females it was 61 years (range 20–92). Fourteen melanomas were located to the head and neck region, 30 to the trunk and 38 to the extremities.

The relative 5- and 10-year survival rates in the total material were 76 and 70% respectively (Fig. 3). The relative survival rates for different sex, age groups and melanoma locations are presented in Table 1.

Fifty-two melanomas were of SSM type, 23 of NM type and the remaining were of LMM, ALM or MMU types. The histopathological melanoma types were included in the Cox's proportional hazard analysis but no separate analysis was made since other investigators have shown that survival difference between SSM and NM melanomas becomes negligible if correction for melanoma thickness is made (4).

The melanomas were distributed in Clark levels: I: 3; II: 17; III: 37; IV: 21 and V: 4. The 5- and 10-year crude survival rates for level I and II were 95 and 79%, for level

Table 2

Relation of sex, age and location to karyometric data (median values and confidence intervals)

	n	Median of mean nuclear area μm^2	Median of mean max. nuclear diameter μm	Median of P 120 %	Median of Pe90–Pe50 μm^2
Males	36	59.4	11.0	1.3	26
c.i. 97%		(54.9–66.1)	(10.4–12)	(0–3.7)	(24–34)
Females	46	59.4	11.3	1.0	30
c.i. 95%		(55.9–68.2)	(10.8–11.8)	(0.6–1.9)	(24–32)
<50 years	27	59.2	10.9	0.7	24
c.i. 95%		(53.4–65.4)	(10.4–11.5)	(0.0–3.1)	(22–34)
≥50 years	55	59.4	11.2	1.2	28
c.i. 94%		(57.7–66.5)	(10.9–11.8)	(0.6–2.0)	(26–32)
Head and neck	14	55.9	11.0	0.3	26
c.i. 94%		(52.7–74.8)	(10.2–12.0)	(0–4.0)	(20–34)
Trunk	30	59.2	10.8	1.25	26
c.i. 96%		(53.5–64.8)	(10.6–11.4)	(0–3.1)	(23–32)
Extremities	38	63.8	11.5	1.5	30
c.i. 97%		(56.4–69.5)	(11.2–12)	(0.6–2.6)	(24–34)

Table 3

Relation of Clark level of invasion and melanoma thickness to karyometric data (median values and confidence intervals)

	n	Median of mean nuclear area μm^2	Median of mean max. nuclear diameter μm	Median of P 120 %	Median of Pe90–Pe50 μm^2
Clark II	17	58	10.9	1.3	26
c.i. 95%		(53.5–59.7)	(10.8–11.5)	(0–3)	(24–32)
Clark III	37	64.5	11.3	1.2	30
c.i. 95%		(57.7–76.5)	(10.6–12.1)	(0.5–7.2)	(24–34)
Clark IV	21	62.4	11.4	1.7	28
c.i. 97%		(55.9–70.2)	(10.7–12)	(0–3.8)	(22–34)
<2.0 mm	42	57.9	10.9	0.6	26
c.i. 96%		(53.6–59.4)	(10.6–11.3)	(0–1.3)	(24–30)
≥2.0 mm	40	65.7	11.7	1.9	26
c.i. 96%		(59–75.7)	(11–12.3)	(0.7–8.8)	(26–36)

III they were 65 and 57% and for level IV and V 48 and 28% respectively (Fig. 4).

The melanoma thickness was: 0–0.79 mm in 22 cases; 0.8–1.99 mm in 20 cases; 2–3.49 mm in 16 cases and ≥3.5 mm in 24 cases. The 5- and 10-year crude survival rates for thickness 0–0.79 mm were 95% and 86%, for thickness 0.8–3.49 mm 72% and 53% and for thickness ≥3.5 mm 33% and 24% respectively (Fig. 5).

As expected, log rank tests of both Clark level of invasion and melanoma thickness demonstrated a significant influence on survival (Clark levels I–II versus IV–V respectively melanoma <0.8 mm versus ≥3.5 mm) ($p<0.00001$ for each factor).

Karyometric variables and survival. The median values and their nonparametric confidence intervals for the measured karyometric variables are presented in Tables 2 and 3. There were no distinct differences in the karyometric data between sex, age of patient, or anatomical location of the melanomas.

The median value of the mean nuclear area was about 10% higher for melanomas of Clark levels III and IV than for melanomas of level II and the same difference was found between melanomas of ≥2 mm of thickness and thinner melanomas. We could thus not exclude an association between melanoma thickness and mean nuclear area. The linear regression coefficient was significantly positive ($p<0.005$). No obvious association was found between patient age and mean nuclear area according to a similar analysis ($p<0.2$).

The crude survival rates for the measured karyometric

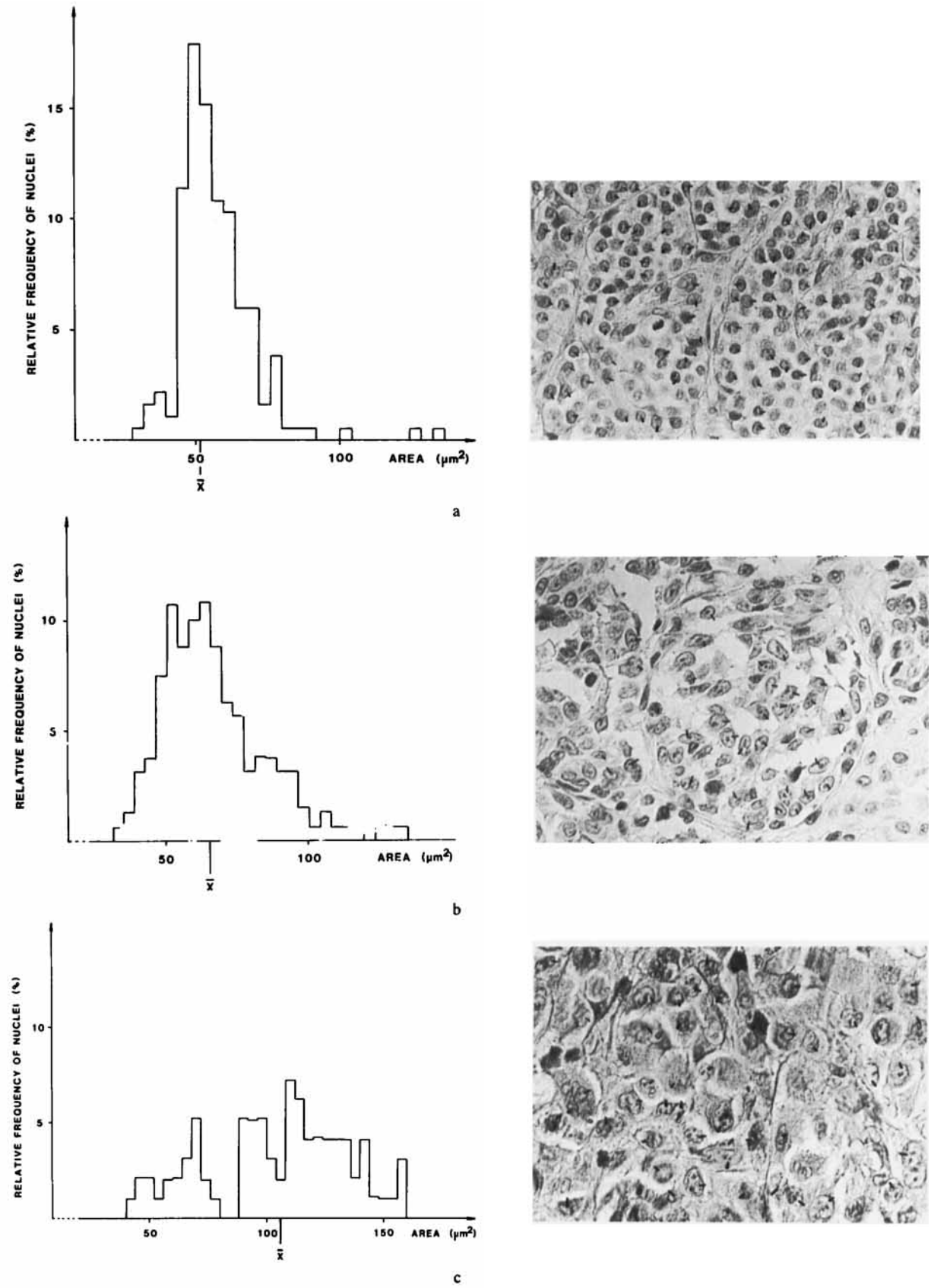

Fig. 2. Examples of nuclear area histograms and microphotographs. a) Narrow histogram with corresponding small nuclei, b) broad histogram with large oval nuclei and c) extremely broad histogram with occurrence of both small and large nuclei.

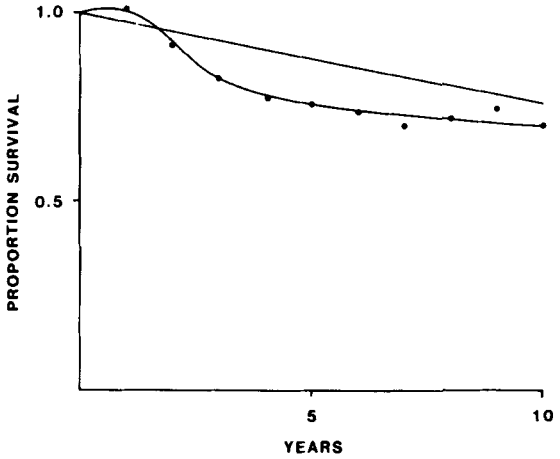

Fig. 3. Expected (——) and relative (–·–·–) survival rates of stage I cutaneous melanomas.

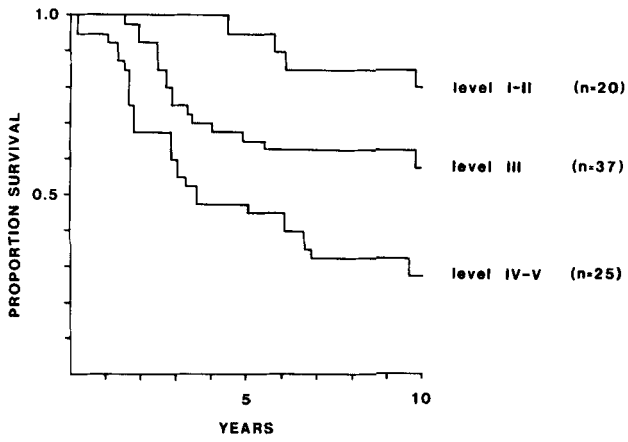

Fig. 4. Clark level of invasion related to crude survival rate.

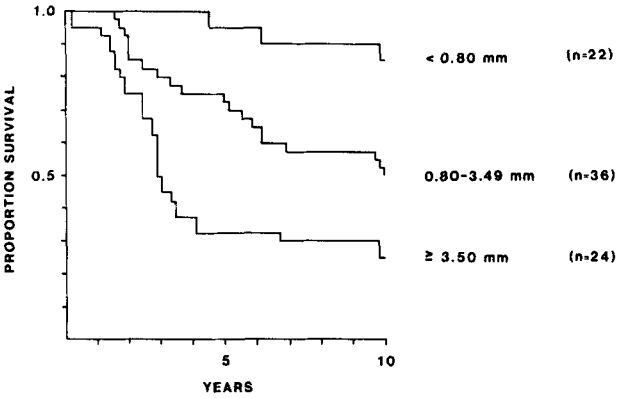

Fig. 5. Thickness of melanomas related to crude survival rate.

Table 4

Statistically significant prognostic factors obtained with Cox's proportional hazard test applied to clinical, histopathological and karyometric findings

Variable	Regression coefficient	p-value
Patient age ≥60 years	1.76	0.002
Melanoma thickness 0.8–3.4 mm	1.11	0.02
Melanoma thickness ≥3.5 mm	1.94	0.0001
Mean of max. nuclear diameter	−0.417	0.01
Pe90-Pe50	0.080	0.0003
Standard deviation of form factor	0.0249	0.04

variables were estimated according to Kaplan-Meier and differences were tested with the log rank test. For each factor the melanomas were subdivided into 3 equally large groups and the survival rates in the groups with the highest and the lowest values were compared. The only significant differences were found for P 100 ($p<0.01$), P 120 ($p<0.02$) and Pe 90-Pe 50 ($p<0.02$).

The Cox's proportional hazard method was used to determine if age, sex, anatomical location, histological type, Clark level of invasion, melanoma thickness and the measured karyometric variables, were related to survival. In our model, the following factors were significantly associated with survival: patient age ($p<0.002$), melanoma thickness ≥3.5 mm ($p<0.0001$), Pe90–Pe50 ($p<0.0003$), mean maximal nuclear diameter ($p<0.01$) and standard deviation of form factor ($p<0.04$) (Table 4). Similar results were obtained if the Clark level of invasion replaced the melanoma thickness. Since a preliminary single factor analysis demonstrated influence of age and melanoma thickness on survival we also tested a model with these 2 factors as stratification variables and again similar results were obtained for the other factors.

Discussion

The present clinical and histopathological observations have been compared with some previously reported materials from the Scandinavian countries. The median age of 58 years in our material was slightly higher than that in a study from southern Sweden (Gothenburg) and from Denmark (55 and 53 years respectively) (23, 25). The age distribution of males (median age 51 years) and of females (median age 63 years) in the present study differed from a Norwegian material in which an equal age distribution of males and females was found (35). Age had unfavourable influence on the prognosis in our series; this may be accounted by the inclusion of patients dying from intercurrent diseases and also since elderly patients tended to have thicker melanomas. The latter finding fits well with the results of Balch et al. (6) who demonstrated that high

age is a negative prognostic factor and is correlated to melanoma thickness.

The frequency (25%) of melanomas of Clark level IV found in our study was lower than those in the Swedish and Danish studies (32 and 35%); which might be due to differences in the subjective assessment of the border between level III and IV. The frequency of melanomas of Clark level V (5%) in our material was, however, similar to those observed in the other studies (5–8%). The melanomas in the present study were thicker than 4 mm in 27% of the cases which was more than that found in the studies from southern Sweden (Gothenburg) (13%) or Denmark (19%) (23, 25).

It is possible that these major differences in age and thickness distribution between the present results and the other cited series (23, 25) can be accounted by the fact that these studies included patients with melanomas diagnosed in the late seventies, a period during which melanomas tended to be thinner at diagnosis, probably due to better public and medical education (5). Since the melanoma incidence in the northern part of Sweden is relatively low, patients may consult late for their disease and doctors may have a longer delay in diagnosis and treatment.

Regarding survival rates, we found in agreement with the other studies (3, 8, 10, 14–16, 20, 24, 27, 30, 40) that a deep level of invasion and a large melanoma thickness was associated with a poor prognosis.

As far as cutaneous melanomas are concerned, routine histopathologic grading of atypia is generally considered to be meaningless. The findings of McGovern et al. (30) and Søndergaard & Schou (42), however, indicate that a high grade of nuclear pleomorphism is a negative prognostic sign. Our analysis suggests that the factors Pe90–Pe50, mean maximal nuclear diameter, and mean standard deviation of form factor do influence prognosis and are in line with the similar findings in uveal melanomas for which nuclear features, such as area, length, width, circumference and circumference/area have been found to be correlated to prognosis (29). In that study (29) these different nuclear factors were also found to be correlated to each other and if one new nuclear factor was introduced in a multivariate analysis the value of other nuclear factors was reduced.

Our present karyometric data concerning nuclear area variables partially quantitate nuclear atypia. Our results suggest that large variation in nuclear area (Pe90–Pe50) and large standard deviation of nuclear form factor both indicate growth and nuclear heterogeneity of melanomas with bad prognosis. We thus found that karyometry added important biological and prognostic information about cutaneous melanomas.

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Request for reprints: Dr C. Lindholm, Department of Oncology, University of Umeå, S-901 87 Umeå, Sweden.

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