

A Prospective Population-Based Study of Cutaneous Malignant Melanoma of the Head and Neck

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Objectives/Hypothesis: For cutaneous malignant melanoma (CMM) of the head and neck, neither prognostic factors in population-based groups, nor outcome with respect to surgical resection margins is clear. Therefore, we analyzed data in a regional registry to align treatment results for CMM of the head and neck with prognosis and survival times. **Study Design:** Patient material collected prospectively for an 18-year period in a Swedish cancer registry underwent statistical analyses to establish the most reliable prognostic factors and the influence of surgical treatment on the survival of patients with CMM of the head and neck. **Methods:** Data originated from the CMM database of the Stockholm-Gotland area of Sweden. Tumor thickness or invasiveness (Breslow or Clark's levels), extent of surgical margin, sex, histogenetic type, anatomic site, and ulceration were compared statistically for 469 patients. **Results:** Male patients with head and neck CMM had a 68% 10-year survival rate; the 10-year survival rate for female patients was 87%. The corresponding figures for CMM at other sites were 83% and 90%, respectively. Tumor thickness (or Clark level of invasion) was the only statistically significant prognostic factor in a multivariate analysis ($P < .001$). The surgical resection margin seemed to be of no importance to outcome. **Conclusions:** Long-term survival after treatment for CMM of the head and neck is better than reported in most earlier publications, presumably because our evaluation used population-based materials, an important factor in accurate reporting of this kind. Tumor thickness is the main prognostic factor in estimating outcome. **Key Words:** Melanoma, head and neck neoplasms, epidemiology, treatment outcome, prognostic factors.

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INTRODUCTION

Cutaneous malignant melanoma (CMM) is a heterogeneous group of tumors with a broad biological variability.¹ In the head and neck area, the characteristics of CMM differ from those of CMM occurring at other anatomic sites.^{1–3} In addition, the clinical problems related to treating CMM of the head and neck are specialized because of the difficulty in performing surgery with adequate margins and the complications stemming from these patients' generally more advanced age.^{1,3,4}

The literature on CMM of the head and neck shows great diversity regarding treatment results, and with a few exceptions,^{4–6} publications on CMM of the head and neck have not described population-based patient materials. Only a few papers (non-population-based) have compared outcome related to the size of margins around surgically resected primary tumors.^{7,8} In contrast, many authors have debated the advisability of elective lymph node dissection (ELND).^{1,9–19} Opinions about prognostic factors vary greatly^{4,13,18–20} and survival rates for patients with CMM of the head and neck versus those of the skin as a whole have not, apparently, been compared.

This study focuses on establishing the best prognostic factors and suggests beneficial treatment results for patients with CMM of the head and neck. For that purpose, we used prospectively collected patient materials registered in the database of the Stockholm-Gotland area of Sweden from 1976 through 1994 and identified 496 patients with invasive CMM of the head and neck.

MATERIALS AND METHODS

The Swedish National Cancer Registry

Every citizen in Sweden holds a unique national registration number (NRN) based on the date of birth and four additional digits. The registers of malignant disease and causes of death are based on the NRN. Clinicians and pathologists are obliged to file independent reports on every new diagnosis of malignant disease in Sweden to the Swedish National Cancer Registry (SNCR). In 95% of new malignancies SNCR receives a report from both the clinician and the pathologist or cytologist. Thus almost all malignant tumor diseases in Sweden are registered. For example,

we know that in 1978 only 0.7% of skin cancers were not registered.²¹

The Stockholm-Gotland Patient Database

The patients we included were located in the Stockholm-Gotland area of Sweden, mainly an urban population. The mean population per year during the study period was 1,640,000.

In a care program for patients with CMM initiated in 1976, all new cases of CMM have been prospectively registered in the Regional Cancer Registry. Between January 1976 and December 1994, 5136 tumors (invasive CMM, 4221 [82%], and melanoma in situ, 915 [18%]) from 4964 patients were registered. Of these, 771 tumors from 756 patients occurred in the head neck: 496 (66%) were invasive CMM and 260 (34%) were melanoma in situ.

The database entries include patients' age at diagnosis, sex, and tumor site. The tumor sites were classed separately as face or eyelid and corner of the eye; scalp; auricle or external ear canal, or neck. Also included were clinical stage at diagnosis, resection margins, and performance of ELND, if done. For clinical staging, the three-stage system for classification of CMM was used.²² Stage I denotes primary lesion alone with or without satellites within 5 cm of the primary lesion and no other demonstrable disease; stage II denotes regional nodal or in transit metastases; and stage III denotes disseminated disease. Extensive radiological evaluations for patients with primary melanoma are not indicated in asymptomatic patients.²³ Accordingly, our care program recommends no routine work-up in search of metastases at time of diagnosis. Clinical staging is based on clinical examination.

Histogenetic types of CMM were classified according to Clark²⁴: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), and nodular melanoma (NM). Further data include ulceration (as seen by microscopic examination), tumor thickness according to Breslow,²⁵ level of invasion using the Clark microstaging criteria,²⁴ and maximum tumor width. All histopathological slides were re-evaluated by an experienced pathologist.

Patients excluded from this study were those with clinical stage II disease or higher at diagnosis, a diagnosis of CMM before 1976 (from 1958, when the SNCR was introduced), or two or more invasive CMMs on any part of the skin during the study period. These criteria excluded 27 patients, leaving 469 patients for our evaluation.

Causes of Death

Physicians in Sweden report every death to The National Board of Health and Welfare with the cause as stated on the death certificate, in some cases based on an autopsy. (The overall annual mean autopsy rate during the study period was 48% of the diseased patients in Stockholm and 18% of patients in Gotland.²⁶) In 1994 the dropout rate (i.e., missing death diagnoses) was 0.45% and there is no more than a 2-year delay in the national registration.²⁶ The study endpoint was melanoma-specific survival after treatment for CMM.

Patients' deaths were recorded as stemming from CMM only when that was the underlying cause of death according to the general rules of the World Health Organization (WHO).²⁷ Swedish official statistics uses the WHO medical certificate of cause of death.²⁶ When the official statistics for deaths from breast cancer in Sweden in 1995 underwent validation by a committee reviewing blinded samples, in only 6.9% of cases was there disagreement as to whether breast cancer was actually the underlying cause of death.²⁸ Subsequent comparison of the intercurrent mortality in the patients studied here with the expected mortality rate in the Stockholm region, given the demographic figures from our database, determined that 121 patients died from an inter-

current cause, in accord with the expected number, which was 121.5. To confirm causes of death, we followed patients through the end of December 1995.

Surgical Treatment

Traditional guidelines for the wide excision of the primary CMM are often impossible to follow when treating the head or neck because of the limited space. For such patients, our care program recommends a 1-cm surgical resection margin for CMMs less than 0.8-mm thick and for thicker tumors a margin of at least 2 cm, when possible. Here, the median excision margin for all head and neck subsites was 10 mm, ranging from 1 mm to 70 mm. The database holds information about the resection margin at the primary excision and (if it was required) margins at the secondary enlarged excision. The figure noted is always the minimum surgical margin, from the end of the tumor to the end of the surgical skin specimen. In cases of surgery with enlarged excisions the margins at both operations are summarized. When no resection margin was noted in the database, patient records were reviewed again, and the database was updated if possible.

Because of controversy as to whether ELND contributes to a favorable outcome for patients with clinical stage I CMM of the head and neck and because no prospective randomized trials have yet evaluated ELND for the head and neck region, we added yet another retrospective dimension to our analysis. Forty-four ELNDs were performed among the 469 patients evaluated here, the last one in 1988. The study period coincides with a transitional period regarding the indications for an ELND: therefore, the choice of this management option was based on subjective clinical judgment.

Statistical Analysis

All patients whose disease was diagnosed from 1976 to 1994 were followed until December 1995. The median follow-up was 10 years (range, 1–20). Survival times were calculated from the day of diagnosis to the day of death, or end of follow-up. Overall survival and melanoma-specific survival rates were estimated using the method of Kaplan and Meier.²⁹ In the analysis of the melanoma-specific survival rate, deaths due to causes other than melanoma were treated as censored observations. Distribution comparisons were made using the two-tailed log-rank test.³⁰ The Cox's proportional hazard regression model³¹ was used to access the independent prognostic contribution of clinical variables, either alone, or after adjustment for other clinical variables. In the

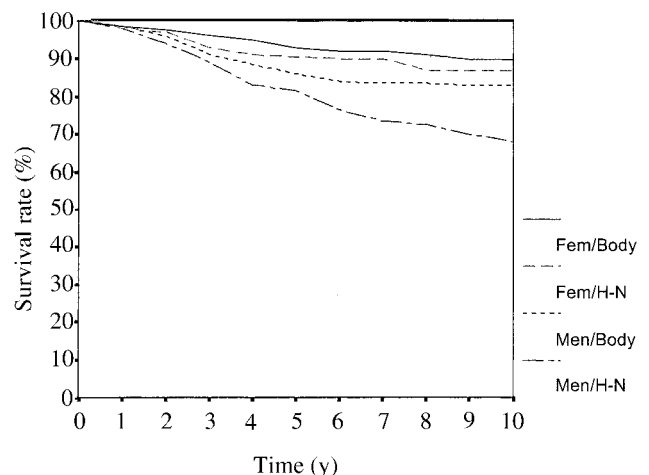


Fig. 1. Survival rates grouped according to sex and site. H-N = head and neck; Body = all other sites.

TABLE I.
Five-Year Survival Rate and Descriptive Data for Subgroups of 469 Patients With Invasive Cutaneous Malignant Melanoma of the Head and Neck.

Subgroups		No. (M/F)	5-Year Survival Rate (%)*
Sex	M	229	81
	F	240	89
Histogenetic type	SSM	221 (117/104)	88
	LMM	102 (30/72)	98
	NM	73 (44/29)	68
	Unclassifiable	73 (38/35)	77
Clark's level of invasion	II	188 (78/110)	98
	III	112 (63/49)	84
	IV	105 (65/40)	77
	V	33 (11/22)	53
	Unclassifiable	31 (12/19)	67
Anatomic site	Face or eye†	316 (121/195)	87
	Ear‡	49 (39/10)	85
	Neck	83 (56/27)	79
	Scalp	21 (13/8)	81
Ulceration	Y	115 (66/49)	72
	N	343 (157/186)	90
	Data missing	11 (6/5)	—
Tumor thickness (mm)	≤1.5	275 (120/155)	94
	1.6–3.0	78 (49/29)	76
	≥3.1	99 (53/46)	73
	Data missing	17 (7/10)	—
Resection margins	1–10 mm	204 (80/124)	90
	11–70 mm	167 (98/69)	83
	Data missing	98 (51/47)	77
Tumor width (mm)	1–10	194 (98/96)	85
	11–120	124 (58/66)	82
	Data missing	151 (73/78)	—
All patients		469	85

*Only melanoma deaths defined as event.

†Eyelid and corner of the eye.

‡Auricle and external ear canal.

SSM = superficial spreading melanoma; LMM = lentigo maligna melanoma; NM = nodular melanoma.

multivariate analysis, tumor thickness was the prognostic variable used instead of Clark's level of invasion. The prognostic effects of clinical variables were expressed as hazard rate ratios with 95% confidence intervals.

The expected number of deaths was calculated by the "person-years" method.³² Death rates in the reference population were based on information derived from national mortality data for Sweden for the period 1970–1995,³³ adjusted with demographic data from the Stockholm region.³⁴ Data were processed using SPSS (SPSS Inc., Chicago, IL) statistical software.

RESULTS

In evaluating invasive CMM, our study population of 469 patients with head and neck melanoma accounted for 12% of all CMM. At the time of diagnosis 464 of these patients with invasive CMM had a primary tumor only, five also had satellites (within 5 cm of the primary tumor). Five patients' disease was in clinical stage II, none was in stage III.

The mean age at diagnosis was 66 years. For men ($n = 229$, 49%) it was 63 years, for women ($n = 240$, 51%) it was 68 years. The overall estimated 5-year and 10-year CMM-specific survival rates were 85% and 77%, respectively. Computation of survival according to sex (Fig. 1) disclosed a 10-year 87% survival rate for women and a 68% survival rate for men ($P < .001$). The corresponding figures for patients with CMM on all other sites, head and neck excluded, yielded a 90% survival rate for women and an 83% survival rate for men.

Table I lists descriptive data for the patient population. In the head and neck area, men compared with women had a higher count of ulcerated primary tumors (66 in 49 patients [57%]), nodular melanomas (44 in 29 patients [60%]), and tumors located within the scalp (13 in eight patients [62%]) and ear (39 in 10 patients [80%]). The median tumor thickness for men was 1.4 mm and for women 0.8 mm (mean, 2.1 mm and 1.8 mm).

TABLE II.
Relative Hazard for Disease-Specific Death for 469 Patients With Invasive Cutaneous Malignant Melanoma of the Head and Neck.*

Factor	Patients (n)	Events (n)	Relative Hazard (95% CI)			
			Unadjusted	P Value	Adjusted†	P Value
Sex						
M	229	50	1.0	.002	1.0	.17
F	240	27	0.5 (0.3–0.8)		0.7 (0.4–1.2)	
Age						
≤65 y	192	37	1.0	.84	1.0	.55
>65 y	277	40	1.0 (0.7–1.6)		1.2 (0.7–2.0)	
Histogenetic type						
SSM	221	36	1.0	<.001	1.0	.29
LLM	102	4	0.3 (0.1–0.8)		0.3 (0.1–1.0)	
NM	73	21	2.2 (1.3–3.8)		0.9 (0.5–1.6)	
Unclassifiable	73	16	1.6 (0.9–2.9)		0.8 (0.5–2.0)	
Clark's level of invasion						
II	188	6	1.0	<.001		
III	112	21	6.7 (2.7–16.6)			
IV	105	29	10.2 (4.2–24.7)			
V	33	13	23.7 (9.0–62.7)			
Unclassifiable	31	8	10.5 (3.6–30.2)			
Anatomic site						
Face or eye‡	316	41	1.0	.02	1.0	.55
Ear§	49	7	1.2 (0.6–2.8)		0.8 (0.3–1.9)	
Neck	83	23	2.1 (1.3–3.5)		1.4 (0.8–2.5)	
Scalp	21	6	2.4 (1.0–5.7)		1.4 (0.5–3.9)	
Ulceration¶						
No	343	45	1.0	<.001	1.0	.26
Yes	115	30	2.7 (1.7–4.3)		1.4 (0.8–2.3)	
Tumor thickness (mm)						
≤1.5	275	21	1.0	<.001	1.0	<.001
1.6–3.0	78	20	3.9 (2.1–7.1)		3.2 (1.6–6.1)	
≥3.1	99	30	5.9 (3.4–10.3)		4.3 (2.2–8.6)	

*All data were available for 447 patients in the adjusted analyses.

†Adjusted for the other factors listed (except Clark's level of invasion).

‡Eyelid and corner of the eye.

§Auricle and external ear canal.

¶Data missing for 11 patients.

||Data missing for 17 patients.

Table II lists univariate and multivariate analyses of prognostic factors for patients with invasive CMM of the head and neck. Sex, histogenetic type, level of invasion according to Clark, tumor thickness according to Breslow, anatomic site, and ulceration of the primary tumor were all significant prognostic factors in the unadjusted analysis. However, on adjusted analysis, tumor thickness remained the only significant prognostic factor ($P < .001$). Moreover, the level of invasion according to Clark showed prognostic power equal to that of tumor thickness when the other prognostic factors remained the same ($P < .001$). Sex, ulceration of the primary tumor, histogenetic type, and anatomic site had no statistically significant prognostic value in the adjusted analysis. Surgical treatment results are presented in Table III. However, the size of the

resection seemed to be of no importance in the adjusted analysis ($P = .8$).

When histopathological and clinical findings in the 44 patients treated with ELND were evaluated (Table IV), metastatic disease was found in 7 patients. We then compared the patients with positive nodes ($n = 7$) with the patients with negative findings ($n = 37$). In the group with nodes positive for disease men were overrepresented—86% versus 54%. The mean tumor thickness was 5.4 mm versus the 2.8-mm mean tumor thickness of the group with nodes negative for disease. Seventy one percent (five of seven) died of CMM before the end of follow-up in the group with positive histological findings compared with 30% (11 of 37) in the group with negative findings. No survival benefit was shown for the 44 patients who under-

TABLE III.
Relative Hazard for Disease-Specific Death for 359 Patients With Invasive Cutaneous Malignant Melanoma of the Head and Neck Related to Resection Margins.

Factor	Patients (n)	Events (n)	Relative Hazard (95% CI)			
			Unadjusted	P Value	Adjusted*	P Value
Resection margin (mm)						
1–10	195	20	1.0	0.01	1.0	0.8
11–70	164	38	2.0 (1.2–3.4)		0.9 (0.5–1.8)	

*Adjusted for the factors listed in Table II; 359 patients in the analyses because of missing data.

went an elective ELND compared with the rest of the patients (in a Cox analysis, adjusted for tumor thickness, $P = .5$).

DISCUSSION

We report here a comprehensive review of 496 patients with CMM of the head and neck and establish that the only reliable prognostic factor was tumor thickness. The fact that these patients' long-term survival period after treatment for CMM of the head and neck exceeded that in previous reports^{7,18–20,35} indicates that analysis of patients in a population-based registry (with a prospective data collection) provides more accurate patient selection than other samplings and emphasizes the value of using such materials for scientific reports. Few population-based and quality-controlled patient materials on prognosis after treatment for CMM of the head and neck have been published.^{4–6} Instead, most publications documenting clinical characteristics, prognosis, and treatment results originate from databases of hospitals or multiple institutions.^{1,7,8,12,13,15,18–20,36–40} Selection bias leading to less favorable estimations of prognosis may hamper the latter studies. Furthermore, some results may be skewed because authors include patients in clinical stages other than I^{5,12,19,20,38,40,41} or do not exclude melanoma in situ, in their analyses,^{38,42} as we did.

The only significant prognostic variable we found in a multivariate analysis of patients with CMM of the head and neck was tumor thickness. Previously, one multivariate analysis attributed independent prognostic power to thickness, site, and sex⁴; another to age, site, histogenetic type, and ulceration²⁰; and still others to site, ulceration, and thickness¹³; or site, level of invasion, thickness, and ulceration.¹⁸ In the report by Cox et al.⁵ tumor thickness was the dominant prognostic variable, but a stepwise proportional hazard analysis asserted that sex, ulceration, and level of invasion also showed significant prognostic power after controlling for thickness. We conclude that tumor thickness is the most important prognostic factor for these patients' outcomes, although Clark's level of invasion showed the same prognostic power when used instead of tumor thickness in the statistical multivariate model.

Several reports in the literature claim that patients with CMM of the head and neck have a unfavorable prognosis as compared with CMM originating on extremities or the trunk.^{43–45} In our comparison of 10-year survival rates from CMM of the head and neck versus all other

sites, the figures showed small differences in women (87 vs. 90%, respectively), whereas men with head and neck CMM fared less well than did those whose CMM originated elsewhere on the skin: 68% versus 83% (Fig. 1). In a previous Swedish report on 12,353 patients³⁵ (all stages included), the 10-year survival rate was 75% for women and 62% for men. Furthermore our head and neck patient group as a whole did better (77% overall 10-year survival) than patients in other studies of head and neck CMM; 55%¹⁸ (only stage I patients), 75%⁷ (only stage I patients), 66%,²⁰ and 45%.¹⁹ Nevertheless, men with CMM of the head and neck carry a poorer prognosis than do women and men with such tumors at other sites. The probable causes are a high median tumor thickness in men and possibly the cumulative effect of other unfavorable, although not independently statistically significant, prognostic factors.

Among the foregoing reports, the proportion of patients in clinical stage I at the time of diagnosis varied from 54% to 85%.^{4,9,11,12,15,18,19} Analysis of our database portrays a more favorable clinical stage at time of diagnosis.

TABLE IV.
Histopathological and Clinical Findings in 44 Patients Who Underwent Elective Lymph Node Dissection.

	Lymph Node Status	
	Positive (n = 7)	Negative (n = 37)
Sex		
M	6	20
F	1	17
Mean tumor thickness (mm)	5.4	2.8
Histogenetic type		
SSM	2	17
LMM	—	3
NM	3	15
Unclassifiable	2	2
Ulceration		
N	3	27
Y	3	10
Missing data	1	—
Mean age at diagnoses (y)	55	57
Dead of CMM before endpoint (951231)	5	11

CMM = cutaneous malignant melanoma.

sis, because 99% were in clinical stage I. In seven patients, however, positive nodes were found after ELND, placing them in pathological stage II. This is still a very favorable figure compared with the reports cited above. Our lower-than-expected finding probably resulted from recently increased public awareness, leading to earlier diagnosis. Again we consider population-based patient materials an important factor and necessary for accurate conclusions.

In retrospective studies, some authors have found that ELND increased survival time,^{9–12} but others agree only when the tumors are of intermediate thickness.^{13,14} Still others failed to see any such improvement.^{1,15–19} In prospective randomized trials of patients with CMM outside the head and neck region, no improved survival has been linked with ELND.^{46,47} Similarly, for patients with CMM of the head and neck, we found no support for the usefulness of ELND.

Prior assertions that head and neck CMM have a more favorable prognosis in women than men^{4,6,9,40,48,49} are supported by our study (except in the adjusted Cox analyses). In contrast to an earlier Swedish report³⁵ (CMM at all sites), our 10-year survival curve (Fig. 1) shows a steady decline in cumulative survival for men over time, whereas a plateau is seen for women after only 5 years. This might indicate yet another biological singularity of CMM of the head and neck.

No prospective randomized trials have compared resection margins in patients treated surgically for head and neck CMM. The few retrospective studies done show that the resection margin's size at the primary tumor site has no effect on local recurrence.^{7,8} In accord, we found no differences in survival rate between two groups of patients, one with resection margins of 1 to 10 mm and the other of 11 to 70 mm. With respect to mean tumor thickness, the measurement was 1.9 mm for patients whose resection margins were known in the present study compared with 2.3 mm for those without data on resection margins. In our opinion, however, a prospective randomized trial would probably be the best way to establish optimal resection margins.

Unexpectedly, ulceration of the primary tumor was not an independent prognostic factor here, although it was in some studies,^{13,18,20} but not in all.^{7,19,36} Whether these differing results reflect methodological or histological variation remains to be elucidated.

To obtain correct information about treatment results, data input must come from population-based materials. Patient prognosis after treatment for CMM of the head and neck was more favorable than formerly reported, presumably owing to early diagnosis of the disease. Studies of the Stockholm-Gotland database certify such improvement successively over the past decades (Månsson-Brahme, Unpublished observations, April 1999), demonstrating the usefulness of such databases, the improvement in outcome after early diagnosis, and the importance of prognostic criteria.

CONCLUSION

In evaluating survival after surgery and the impact of prognostic factors for CMM, the use of population-based patient material is essential. In doing so we found a longer survival time for our patients with CMM of the head and

neck than previously reported. Tumor thickness (or Clarks level of invasion when used instead) was the most important, and only statistically significant, prognostic factor in a multivariate model. A retrospective analysis of the effect of surgical margins showed no difference when two groups (greater vs. smaller than 10 mm) were compared. Moreover, the use of ELND seemed to be of no importance to patient outcome.

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