Epidemiological Features and Prognostic Factors of Cutaneous Head and Neck Melanoma

A Population-Based Study

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Objectives: To describe the epidemiological features of cutaneous head and neck melanoma (CHNM) and to identify factors associated with mortality from this disease.

Design: A population-based cohort study.

Setting: Patients treated for CHNM in Ontario between January 1, 1994, and December 31, 2002, were identified through the provincial Cancer Registry. A Cox proportional hazards regression model was used to analyze the data.

Patients: A total of 2218 patients with CHNM were identified, comprising 15.8% of all melanomas in Ontario. The mean age of the cohort was 66 years (SD, 16 years); 1363 patients (61.5%) were males.

Main Outcome Measure: Patients' vital status (dead or alive).

Results: The incidence of CHNM increased from 2.0 per 100,000 in 1996 to 2.7 per 100,000 in 2001, while mortality remained stable. The Cox proportional hazards regression model showed that increased age (hazard ratio [HR], 1.06; 95% confidence interval [CI], 1.04-1.06) and male sex (HR, 1.31; 95% CI, 1.03-1.66) had a significantly higher risk of death. Patients with lesions of the scalp and neck had a 53% higher risk of death than those with lesions of the face. Nodular melanoma (HR, 1.61; 95% CI, 1.17-2.24) had the worst prognosis compared with other morphological types. Increased tumor thickness (HR, 1.05; 95% CI, 1.03-1.07), ulceration (HR, 1.53; 95% CI, 1.08-2.07), and Clark level V (HR, 1.52; 95% CI, 1.01-2.22) were significantly associated with increased mortality.

Conclusions: Our study demonstrated an increase in the incidence of CHNM. Advanced age, male sex, nodular morphological features, tumor thickness, ulceration, and Clark level V carried a significant risk of death, whereas facial melanomas had a favorable prognosis.

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Melanoma is a potentially fatal cancer derived from abnormally proliferating melanocytes. Because of anatomical distributions of melanocytes, melanoma usually originates in the skin and less frequently in the mucosa of other organs. Although the epidemiological features of melanoma have been previously described, factors that affect mortality in head and neck melanoma are poorly understood. Previous reports demonstrated that anatomical locations of a primary tumor bear prognostic significance, such that the patients with tumors of the extremities have a significantly more favorable prognosis than those with tumors of the axial body (trunk, head, and neck).1 However, many clinicians suspect that melanomas arising from the head and neck region have a worse prognosis and require better understanding of the factors that play a role in the disease. By identifying the factors that affect survival of patients with head and neck melanoma, we can devise therapies and preventative strategies that will alter the mortality from this disease.

The aims of this study were to describe the epidemiological features of cutaneous head and neck melanoma (CHNM) in the population of Ontario and to identify the factors affecting mortality from this disease.

Methods

This is a population-based cohort study. The records of patients diagnosed as having or treated for melanoma between January 1, 1994, and December 31, 2002, were obtained from the prospectively generated registry established in 1979 by Cancer Care Ontario. The Ontario Cancer Registry is a computerized database of information on all Ontario residents who have been newly diagnosed as having cancer or who have died of cancer. The Cancer Act provides a legal mandate for Cancer Care Ontario to establish and maintain a cancer registry. Under the Cancer Act, any information...
about a registered case must be kept confidential and not be
used or disclosed for any purpose other than medical or epi-
demiological research. The Ontario Cancer Registry relies on
4 major data sources for completion of its records: (a) hospital
discharge and surgical summaries; (b) pathological reports; (c)
records of patients referred to 8 Regional Cancer Centers and
the Princess Margaret Hospital, which specializes in treating
patients with cancer in Ontario; and (d) death certificate with
cancer recorded as the underlying cause of death. Pathologi-
cal reports are sent to the Ontario Cancer Registry by the hos-
pitals and private pathology laboratories. The diagnoses are
coded according to the World Health Organization’s Interna-
tional Classification of Diseases, Ninth Revision (ICD-9).1

In this study, every patient was identified using the Interna-
tional Classification of Diseases, Ninth Revision (ICD-9) code
for cutaneous melanoma and then coded in our database with
a unique identifier for security. The data were limited to the
head and neck region or any site above the clavicles. Ocular
and mucosal melanomas were excluded. The data included pa-

tient’s demographics, date of diagnosis, anatomical site, coex-
xisting malignancies, first treatment, and vital status (dead or
alive). The pathological data included tumor morphological fea-
tures and thickness, Clark level of invasion, presence of ulcer-
ation, and lymphovascular and perineural invasion. The study
also examined whether reported positive or negative margins
of resection had prognostic significance.

Study design and analysis were performed with the assist-
tance of the Institute for Clinical Evaluative Sciences at Sun-
nysbrook Health Sciences Centre, Toronto. Descriptive statis-
tics were calculated for all variables of interest. Continuous
measures, such as age, were summarized using means and stan-
dard deviations, whereas categorical measures were summa-
rized using counts and percentages.

The primary analysis was carried out by a Cox propor-
tional hazards regression model, which assessed the impact of
variables of interest on time to death. Kaplan-Meier survival
curves were produced to illustrate the survival differences for
the different levels of each categorical variable found signifi-
cant in the regression model.

All analyses were carried out using SAS statistical software,

RESULTS

DEMOGRAPHICS

There were 2218 patients diagnosed as having and treated
for CHNM in Ontario between 1994 and 2002, comprising
15.8% of all melanoma cases in the province. After
adjusting for population growth, the number of new cases
of CHNM increased from 2.0 per 100,000 in 1996 to 2.7
per 100,000 in 2001 (Figure 1). Although 725 (32.7%)
of the patients died, overall mortality remained stable dur-
ing the study period.

The mean age of the cohort was 66 years (SD, 16 years).
Older patients were more likely to die from this disease,
with an estimated 5.7% risk of death for every year in-
crease in age. Male patients were most of the cohort, at
61.5% (n=1363), with 36.8% (502/1363) of deaths among
males compared with 26.1% (223/855) among females.
Males were significantly more likely to die (hazard ra-
tio, 1.31; 95% confidence interval, 1.03-1.66) (Figure 2).

Ontario was subdivided into 4 major regions based on
the Canada Post mapping: central, eastern, northern, and
southwestern (Table 1). Central Ontario contributed

PATHOLOGICAL FEATURES

Superficial spreading melanoma was the most common his-
tological feature (Table 2), and was diagnosed in 27.6% of
the 2218 patients. Lentigo maligna melanoma was the
second most common histological subtype, with 25.6% of
cases, followed by 13.3% for nodular melanoma. The most
rare type was desmoplastic melanoma, diagnosed in 2.8%
of cases. Of all morphological features, nodular melano-
ma carried the significantly worst prognosis, with 52.7% (156/296)
mortality (Figure 4), and was associated with increased death from the disease (hazard ratio, 1.61; 95% confidence interval, 1.17-2.24).

Tumor thickness was significantly (P=0.01) associated with patient’s prognosis. For every 0.1-mm in-
crease in tumor thickness, there was a 2.2% increase in
hazard of death. Also, tumors with ulceration had an un-
favorable prognosis (Figure 5). Of patients with re-
ported ulceration on the pathological examination, 58.9%
(124/212) did not survive, compared with 25.8% (323/
1254) of patients with nonulcerated tumors. The risk of

Figure 1. Number of new cases of cutaneous head and neck melanoma from January 1, 1994, to December 31, 2001.

Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>855</td>
</tr>
<tr>
<td>Eastern</td>
<td>726</td>
</tr>
<tr>
<td>Northern</td>
<td>337</td>
</tr>
<tr>
<td>Southwestern</td>
<td>290</td>
</tr>
</tbody>
</table>

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dying was 54% higher in the ulcerated lesion group (hazard ratio, 1.53; 95% confidence interval, 1.08-2.07).

Clark level of invasion V had the highest mortality (58.8%), and it decreased with a lesser level of invasion (Clark level of invasion IV, 35.8%; Clark level of invasion III, 27.7%; and Clark level of invasion I/II, 15.6%). Clark level of invasion V was also associated with increased mortality when compared with other levels of invasion (hazard ratio, 1.52; 95% confidence interval, 1.01-2.22) (Figure 6).

Other factors, such as vascular (P = .08) or neural (P = .07) invasion, were not significant. Of patients with positive tumor margins following the resection, 29.1% (178/612) did not survive, compared with 32.0% (261/815) of patients with negative tumor margins. Tumor margins were not associated with patient's prognosis. Patients with positive tumor margins did not seem to have a worse outcome.

**COMMENT**

The National Cancer Institute Surveillance, Epidemiology, and End Results database reports that, from 1950 until 2000, there has been a 619% increase in annual diagnoses of cutaneous melanoma and a 165% increase in annual mortality. There were 3719 new melanoma cases diagnosed in Canada in 2000, with 709 patients dying of the disease. Ontario led the other provinces, with 1680 new cases and 330 deaths in 2000. To our knowledge, the epidemiological features and incidence of CHNM have not been reported in North America. This study found a sizable increase in new cases of CHNM in a relatively short period (1996-2001). Similar to a population-based study from Sweden, which reported 17.3% of all cutaneous melanomas in the head and neck, and a Scottish Melanoma Group database reporting 21% of cutaneous melanoma arising from the head and neck, this study found that, in Ontario, 15.8% of all cutaneous melanoma cases were diagnosed on the head and neck. Cutaneous melanoma of the head and neck constitutes a unique biological subset of melanomas. The authorities in the field of melanoma claim that head and neck melanomas carry the worst prognosis when compared with other anatomical sites. In fact, several researchers have supported this claim in their
reports. Whether this is because of thinner skin, long-term sun exposure, or vast lymphatic and blood supply that allows for higher metastatic potential remains unknown. At the same time, there are other established differences. Cutaneous head and neck melanoma tends to have a higher preponderance in older patients, and its histogenetic type differs from other anatomical sites, with predominance of the lentigo maligna type. Knowing these histogenetic differences of CHNM from other sites, several studies have attempted to demonstrate its prognostic value. One study showed that lentigo maligna melanoma had a higher (89%) survival rate, followed by the superficial spreading (77%) and nodular (63%) types. However, the same study also noted that the lentigo maligna type was found significantly higher \((P < 0.001)\) in female than in male patients, which could explain such results. In fact, other researchers also demonstrated a better survival rate with the lentigo maligna subtype when compared with other types in isolation; however, when a stepwise Cox proportional hazards regression model was used, the histogenetic subtype did not remain an independent prognostic factor. In this study, the superficial spreading type was diagnosed more often (27.6%), but came close to the lentigo maligna subtype (25.6%). Contrary to previous reports, we found that nodular melanomas carried prognostic significance and were associated with increased mortality. Although the nodular type is not included in the current staging system, future reexamination of its role in determining the prognosis of patients with CHNM may be warranted.

Patients’ age has also been implicated to play a role in survival from melanoma, such that older patients have a poorer prognosis. This study also found age to be an independent prognostic factor. We found that older patients had significantly poorer prognosis, even when accounting for other factors. In discordance, Ringborg et al estimated corrected survival in different age groups of patients and found no difference between the age groups. Similar to the latter report, other researchers found age not to be a significant prognostic indicator for survival.

Most of the studies reported male predominance in their cohorts. We also found a higher male-female ratio.

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**Table 2. Frequency of the Most Common Morphological Subtypes of Melanoma**

<table>
<thead>
<tr>
<th>Vital Status</th>
<th>Superficial Spreading</th>
<th>Lentigo Maligna</th>
<th>Nodular</th>
<th>Desmoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>476</td>
<td>418</td>
<td>140</td>
<td>37</td>
</tr>
<tr>
<td>Dead</td>
<td>137</td>
<td>150</td>
<td>156</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>613</td>
<td>568</td>
<td>296</td>
<td>61</td>
</tr>
</tbody>
</table>

*The mortality for each subtype was as follows: superficial spreading, 22.3%; lentigo maligna, 26.4%; nodular, 52.7%; and desmoplastic, 39.3%.*

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**Figure 3.** The risk of mortality was significantly increased with cutaneous melanomas of the scalp or neck compared with facial melanomas.
At the same time, other studies noted the reversal of the trend. Male sex has been postulated to be a prognostic indicator and to bear the worst prognosis. Our study also found sex to be an independent predictor of survival, with males at a higher risk of mortality than females.

There is notable disagreement in the literature with regard to the prognostic value of the anatomical location of the primary lesion within the head and neck. Several reports concluded that location of the primary tumor was strongly associated with patients' prognosis. Our study also found sex to be an independent predictor of survival, with males at a higher risk of mortality than females.

Various histopathologic features of the primary tumor have also been analyzed in order to link the microscopic features of the lesion with patient's prognosis. Pathological reports include extensive details of tumor characteristics, including Breslow thickness, Clark level of invasion, epidermal ulceration, cell type, adnexal or vascular invasion, tumor regression, and high field mitotic count. However, only tumor thickness and ulceration are used for primary melanoma staging in the absence of lymphatic or distant metastasis. Despite the many histopathologic variables and the many attempts to define their association with patients' outcome, only tumor thickness (Breslow score) has been consistently found to correlate with patients' prognosis. In agreement with other reports, we found that tumor thickness, ulceration, and Clark level V were associated with patients' vital status. This study again confirmed that Clark level of invasion is an important component of pathological reporting. None of the other pathological features were impacting patients' survival.

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Author Contributions: Drs Golger and Neligan and Ms Young had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Golger, Ghazarian, and Neligan. Acquisition of data: Golger and Young. Analysis and interpretation of data: Golger. Drafting of the manuscript: Golger. Critical revision of the manuscript for important intellectual content: Young, Ghazarian, and Neligan. Statistical analysis: Golger. Obtained funding: Golger. Administrative, technical, and material support: Young. Study supervision: Ghazarian and Neligan. Financial Disclosure: None reported. Funding/Support: This study was supported by Physician’s Services Incorporated Foundation. Role of the Sponsor: The funding body had no role in data extraction and analyses, in the writing of the manuscript, or in the decision to submit the manuscript for publication. Previous Presentation: This study was presented at the American Head and Neck Society 2006 Annual Meeting and Research Workshop on the Biology, Prevention, and Treatment of Head and Neck Cancer; August 19, 2006; Chicago, Ill. Acknowledgment: We thank Alexander Kiss, PhD, Department of Research Design and Biostatistics, Sunnybrook Health Sciences Centre, for his assistance in study design and data analysis.

REFERENCES