Clinical Study

Malignant Melanoma, with emphasis on first relapse cases

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Abstract

Objectives: Malignant melanoma is the eighth most commonly diagnosed malignancy in Nova Scotia, Canada. The incidence of and death from malignant melanoma are increasing, despite surgical resection of lesions. The risk for local recurrence after treatment is 3.2%. Our aim was to determine the characteristics of malignant melanoma and the risk for relapse in an industrial region of Nova Scotia.

Methods: We performed a retrospective analysis of the records of 90% of all melanoma patients in 1999–2010 in Cape Breton, Nova Scotia (N = 100). Data were derived from the patients’ medical records kept at the Cape Breton District Health Authority.

Results: Of the 100 cases of malignant melanoma, 57 were in men and 43 were in women. Treatment consisted of local excision for 91 patients, therapeutic lymph node dissection for 5 and no treatment for 2. Relapses occurred in 16 patients (10 men, 6 women) between 2003 and 2010. Eleven of the 16 patients with relapses (69%) were alive at 1 year, four (25%) at 2 years and three (19%) at 5 years. The majority, 80/100, of patients are still alive without malignant melanoma, while two patients are alive but with malignant melanoma. Of the 18 patients who died, eight died from malignant melanoma.

Conclusions: We obtained a better 5-year survival rate (82%) than that reported in the literature (73%). In Cape Breton, more men than women have malignant melanoma and are more likely to have local recurrence. The long-term survival rate after relapse was poor.

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Introduction

The incidence of malignant melanoma is increasing dramatically among people with light-coloured skin in all parts of the world, and the incidence is increasing faster than that of any other cancer.1 The rate of death from melanoma is also increasing, despite the improved survival associated with early surgical removal of lesions. In 1935, for example, one in 1500 Americans developed malignant melanoma; melanoma now occurs in one of every 50 Americans, particularly among males aged 15–35, for whom it is among the leading causes of death from cancer.2 Worldwide, the incidence varies from a high of 28.4 per 100000 in Australia to 0.2 per 100000 in Japan.3

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The risk for local recurrence of malignant melanoma after treatment is 3.2%, and the risk for systemic recurrence depends on the depth of penetration.

Malignant melanoma is the eighth most commonly diagnosed malignancy in Nova Scotia, Canada, accounting for 3% of all cancers. Despite awareness of the high incidence rates of various cancers among people in Cape Breton, there are no published data on either the occurrence or the recurrence of malignant melanoma. The purpose of our study was to assess the Cape Breton experience of malignant melanoma with an emphasis on first relapse cases.

Materials and Methods

We conducted a retrospective analysis of cases of malignant melanoma between January 1999 and October 2010. All data were derived from hospital charts from the Department of Medical Records, which contains data on 100 of all 113 patients with malignant melanoma in the four hospitals in industrial Cape Breton, in Sydney, North Sydney, Glace Bay and New Waterford. These hospitals are the main referral hospitals for rural Cape Breton.

The 113 patients identified from the Nova Scotia Cancer Registry database for Cape Breton had one of the five forms of malignant melanoma: radial (superficial) spreading, lentigo maligna, nodular, acral lentiginous or unclassified melanoma. Thirteen patients (10%) were excluded because the reports were inconsistent, incomplete or unreadable, leaving 100 patients for analysis. Demographic data were obtained.

As comorbidity significantly influences the survival of patients with melanoma, the effect of coexisting conditions was examined by consulting outpatient records and discharge summaries. The comorbid conditions were naevus, non-melanoma skin malignancy, other malignancy and non-melanoma causes such as cardiac conditions, peripheral vascular disease, cerebrovascular ischaemia, chronic obstructive pulmonary disease, gastrointestinal disease and liver disease.

The location of the tumour was determined, as it can affect survival and recurrence rate. Clark’s method of microstaging malignant melanoma, which is based on a qualitative description of increasing levels of penetration through the dermis to the subcutaneous fat, was used. We also used the Breslow microstaging method, in which an ocular micrometer is used to quantify the vertical depth of invasion (in mm) from the granular layer of the epidermis (or the base of an ulcer) to the deepest identifiable contiguous melanoma cell.

Sixteen patients were found to have relapsed over the 7-year period 2003–2010. We examined the relapse characteristics and comorbid conditions of these 16 patients.

Survival time was calculated from the date of first relapse to the date on which the data were censored or the date of death from melanoma or from any cause. Data were censored if a patient underwent therapy, was still alive at the end of the study or was lost to follow-up. Survival analysis was performed for patients who relapsed, died or survived.

Results

One hundred patients with malignant melanoma were followed up for 11 years. Of these, 57 were men and 43 were women, with a mean age of 60.3 years (range, 17–92 years) They were all white. Within the Cape Breton area, 79 patients were from Sydney, 10 from North Sydney, 9 from Glace Bay and 2 from New Waterford.

Ten patients had a pre-existing naevus in the same location, and 15 had had other skin malignancies (basal cell or squamous cell carcinoma) at various locations.

Tumour characteristics

The location of malignant melanoma was on the extremities in 39 cases, the trunk in 34 cases, the head and neck region in 22 cases and lymph nodes in 5 cases. Primary malignant melanoma was diagnosed in 95 cases, and 5 cases were metastatic. Figure 1 shows the tumour staging according to Clark’s level of penetration: 29 patients had stage I tumours above intact basal lamina, 22 had stage II tumours reaching the papillary-reticular dermis interface, 18 had stage III tumours invading the papillary dermis, 13 had stage IV tumours invading the reticular dermis, and 3 patients had stage V tumours invading the subcutaneous fat. The remaining 15 patients had tumours of unknown depth.

Figure 1: Patients’ rate as per Clark’s staging.

Figure 2: Patients’ rate as per Breslow’s staging.

Figure 3: Types of treatment for all patients.
of unknown stage, because of mixed cell type, metastasis favouring malignant melanoma, primary tumour in a lymph node or no specific staging report.

Figure 2 shows the tumour staging according to Breslow depth of invasion. In 26 patients, the tumour was classified as 0 (granular layer of epidermis), 25 patients had tumours >0 but <0.76 mm, 17 tumours were >0.76 mm but <0.50 mm, 10 were >1.51 mm but <4 mm, 2 were >4 mm, and the remaining 20 patients were classified as ‘unknown’.

**Treatment**

Figure 3 summarizes the therapeutic approach, which varied considerably, depending on the location and depth of the primary lesion. Local excision was used for 91 patients, therapeutic lymph node dissection for 5 patients, chemotherapy for 2 patients, and 2 patients received no treatment. Further therapeutic interventions were carried out for 78 of the 91 patients who underwent local excision: wide re-excision was required for 70 patients, additional prophylactic lymph node dissection for 3 patients, further therapeutic lymph node dissection for 2 patients and chemotherapy for 3 patients.

**Outcomes**

Figure 4 shows the outcomes: 16 cases of relapse and 84 cases of non-relapse. Of the patients who relapsed, 10 were men and 6 were women aged 29–79 years. Figure 5 shows the age distribution of these first-relapse cases. Two patients had a pre-existing naevoid in the same location, and three had had a basal cell or squamous cell carcinoma at various locations. Figure 6 shows the timing of the relapses. Two occurred within <1 year, six occurred within 1 year, four within 2 years, two within 3 years and 1 within 5 years.

Figure 7 shows the tumour staging of the relapses according to Clark’s level of penetration. Seven were classified as ‘unknown’; two were stage II, four were stage III, two were stage IV, and one was stage V. Figure 8 shows the tumour staging according to Breslow depth of invasion. Eight were classified as ‘unknown’, one was <0.76 mm, two were 0.76–1.50 mm, and five were 1.51–4 mm.

The treatment given, according to the site of relapse, is shown in Figure 9. All six patients with local relapses underwent local wide excision; four of the six patients with regional relapses were treated by node dissection only and two by node dissection and chemotherapy. Three of four patients with distant relapses were treated with chemotherapy, and the other received palliative care.
Eleven of the 16 patients with relapses (69%) were alive at 1 year, four (25%) were alive at 2 years, and three (19%) were alive at 5 years.

The majority, 80/100, patients are still alive without malignant melanoma, while two patients are alive but with malignant melanoma. Of the 18 patients who died, eight died from malignant melanoma.

Discussion

Of the 100 patients with malignant melanoma between 1999 and 2010, 16 developed local, regional or distal recurrence. Of these, 11 survived for 1 year and four for 2 years. The local recurrence rate was very high, 6%, whereas reports from other countries such as the United States give a rate of only 3.2%.5 The rate may be increased by thickness >4 mm (13%),8 ulceration (11.5%),4 and face, scalp, hand or foot location (5–12%).9 Older patients tend to have a worse prognosis,10,11 and we found that 13/16 relapses were in patients ≥50 years of age. It is unclear, however, why our local recurrence rate was so high. The American Physicians Data Query Cancer Information File (an online database) shows that local recurrence and subsequent metastasis largely depend on tumour thickness. Although the risk for systemic (lymph node and distant) recurrence depends on the depth of penetration by Breslow staging, we were unable to estimate the risk accurately because of the large number of 'unknowns': in 20% and 50% of primary and relapse cases, respectively. Furthermore, 13 patients with malignant melanoma were excluded because of inconsistent, incomplete or unreadable records.

There appears to be an association between certain pre-existing pigmented skin lesions and cutaneous melanoma. The National Institutes of Health Conference concluded that melanoma may arise de novo13 or in association with pre-existing melanocytic naevi.1,13 The pre-existing lesions include dysplastic naevi, congenital naevi and common acquired naevi. The lifetime risk of melanoma may approach 100% for people with dysplastic naevi who are from melanoma-prone families,14,15 and the lifetime risk for melanoma in patients with large congenital naevi has been estimated at 5–20%.16 The extent to which melanoma develops in smaller congenital naevi is unclear,17 the incidence has been reported to be increased,18 but the magnitude of that increase is not well established. In our series, pre-existing melanocytic naevi were found in 10% of all patients and two of 16 who had relapses; and 15% of all patients and 3/16 relapse cases had had basal cell or squamous cell carcinoma at some time previously. It is unclear whether there is an association between other skin malignancies and melanoma; however, most of the risk factors (older age, sex, race) are the same.19

Although our study suggests that melanoma can develop in people of all ages and both sexes, all the patients were white, as very few people of other races live in Cape Breton. It has been reported that melanoma affects all races, although the risk of whites is 17 times greater than that for blacks,20 for example.

The only effective therapy for melanoma is surgical resection;21,22 however, several European reports suggest that superficial contact X-ray therapy at extremely high doses (>10000 cGy) with rapid fall-off (over 50% at 1 mm) may be indicated for large, superficial lesions in critical cases23 (e.g. lentigo maligna melanoma of the head and neck). Other reports suggested that both radiotherapy and regional hyperthermic limb perfusion can be used for palliative treatment of metastases24,25 (e.g. cerebral, bone) and for local recurrences of melanoma of the lower extremities.26,27 In our study, none of the patients with primary malignant melanoma or relapse received any form of radiotherapy or hyperthermic limb perfusion. In fact, according to the Nova Scotia Cancer Registry electronic database, only 5% (23/463) of new melanoma patients diagnosed in Nova Scotia between 2006 and 2009 received radiotherapy for this disease. The rates of radiotherapy use in other Canadian provinces are much lower than the accepted national and international targets and lower than rates reported from other jurisdictions.28 The highest rates were recorded in communities close to radiotherapy centres.28 This, in addition to the very low rates of radiotherapy use in Nova Scotia, may explain why radiotherapy is rarely used for malignant melanoma in Cape Breton.

According to the Canadian Cancer Statistics,7 the incidence rate of malignant melanoma in women has been decreasing since the 1970s but increasing in men during the same period. The estimated average annual percentage change for 1999–2009 was 0.9% among men and –0.3% among women. The corresponding values for Nova Scotia were 2.2% for men and –0.4% for women. Neither trend was statistically significant. For Cape Breton county, the average annual percentage change for women was 1.8% (not decreasing but not significantly different from zero) and that for men was 7.3%, which
was of borderline significance ($p = 0.086$) but with annual variation because of the small number of cases seen. Nova Scotia has higher rates of melanoma than Canada and has had for some time (currently about 30% higher). Although there may have been a decrease in the 1970s and early 1980s in the incidence of melanoma in women, the evidence for a recent decrease in women is weak in Canada and weak or nonexistent in Nova Scotia. There is somewhat more evidence of an upward trend in the incidence among men in recent years (in both Canada and Nova Scotia), but the evidence can be described as ‘weak’ at best.

Our study explains neither the high incidence nor the high local recurrence rate of malignant melanoma in Cape Breton. We found that, despite the high incidence of malignant melanoma and irrespective of the level or depth of the primary lesion, the 5-year survival rate was 82% for patients with pathologically negative lymph nodes. A 5-year survival rate of 73% has been reported. The higher rate in our study can be ascribed to early detection and surgical excision of early primary lesions.

**Conclusion**

We conclude that people (men more than women) in Cape Breton have a high incidence of malignant melanoma, a high local recurrence rate and poor long-term survival after relapse. Our findings indicate the need for a clinical practice guideline and more aggressive strategies for the prevention, treatment and follow-up of patients with malignant melanoma and those with precancerous pigmented lesions.

**Authors’ contributions**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors’. We declare that we have no conflict of interest.

Dr. Hafez: principal author. Responsibilities included: literature search, figures, study design, data collection, data analysis, data interpretation, writing all sections.

Dr. MacCormick: second author. Responsibilities included: Study design, data interpretation, review figures and manuscripts.

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**References**

