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Female Sex is a Risk Factor for Satellite and in-transit Recurrences from Cutaneous Melanoma

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Abstract—*The presence of satellite and in-transit (SIT) metastases was investigated in 388 patients with cutaneous melanoma of the extremities, registered between 1956 and 1980. Out of 99 males 20 showed evidence of SIT lesions at the time of diagnosis or during follow-up, compared with 78 out of 289 females ($P<0.05$, allowed for clinical stage). The difference is even more striking if we consider that female patients had more favourable prognostic tumour characteristics than males.*

INTRODUCTION

REGIONAL isolated perfusion therapy has been practised for almost 30 yr in combatting loco-regional recurrences of cutaneous melanoma of the extremities [1, 2]. In this context the designation *regional* refers to the skin and subcutaneous tissues of the extremity involved and not to the regional lymph nodes. Tumour deposits in the regional area are usually designated as satellites (≤5 cm from the primary) and in-transit lesions (>5 cm from the primary). They are considered as being of lymphogenic origin. Little is known about the factors that predispose to satellite or in-transit (SIT) metastases. It has been shown that thick melanomas favour local recurrences [3, 4] as well as satellite lesions [5, 6]. Other risk factors have never been properly investigated.

It has been demonstrated that first evidence of metastatic disease occurs predominantly at visceral (haematogenic) sites in males, compared with a female preference for lymphogenic metastases [7, 8]. It is tempting to speculate, therefore, that females are more likely to develop SIT lesions than males. We report herein our findings on the incidence of SIT metastases in male and female patients with extremity melanomas.

MATERIALS AND METHODS

Between 1956 and 1980, 814 patients were referred to the Rotterdamsch Radiotherapeutisch Instituut (RRTI) with cutaneous melanoma. Of these, 20 were excluded because of insufficient data. Of the remaining patients, 388 had extremity melanomas: 99 were males and 289 were females. Non-invasive melanomas (Clark level I) and occult primary melanomas were not considered.

All cases were scrutinized for the presence of SIT lesions. No distinction was made between patients who exhibited SIT metastases at the time of diagnosis and those who developed SIT lesions later during the course of disease. The occurrence of SIT lesions was correlated with the clinical stage of the disease at diagnosis (stage I = primary tumour only; stage II = regional lymph node metastases; stage III = distant metastases) and, as far as stage I melanoma is concerned, with the maximum diameter of the lesion, the level of invasion and the tumour thickness. Since recording of the Clark–Breslow microstages became the vogue in the seventies, information on these minutiae has not always been available.

RESULTS

Out of 289 females, 78 showed SIT lesions at the time of diagnosis or during follow-up (27.0%). In the male group 20 out of 99 cases developed SIT lesions (20.2%). The difference is statistically significant if clinical stage is taken into account (Mantel–Haenzel test; $\chi^2 = 4.10$; $P<0.05$). Females had a more favourable clinical stage at the time of diagnosis than males; only 23 females exhibited metastatic disease (8.0%) as opposed to 33 males (33.3%). Stage by stage females showed a preference for developing SIT metastases (Table 1). This was most conspicuous in stage I melanoma (25.6 vs 13.6%; $\chi^2 = 4.22$; $P<0.05$).

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Table 1. Occurrence of SIT lesions in male and female patients according to (micro)stage of the disease

Stage	SIT lesions* Males		Females	
Stage I (total)	9/66	(13.6)	66/266	(25.6)
(a) Tumour diameter (246)†				
≤10 mm	1/12	(8.3)	11/81	(13.6)
11–20 mm	2/24	(8.3)	25/83	(30.1)
>20 mm	1/11	(9.1)	14/35	(40.0)
(b) Level of invasion (206)				
Clark II–III	2/12	(16.7)	13/74	(17.6)
Clark IV–V	2/23	(8.7)	22/97	(22.7)
(c) Tumour thickness (111)				
≤2 mm	1/9	(11.1)	9/58	(15.5)
>2 mm	0/10	(-)	9/34	(26.5)
Stage II–III	11/33	(33.3)	10/23	(43.5)

*Number/cases at risk; percentages in parentheses.
†Number of evaluable cases.

The details on tumour (micro)stage and the occurrence of SIT lesions are also shown in Table 1. Females with stage I melanoma had smaller lesions than males; tumour diameter was 10 mm or less in 41% of women and in 26% of men. Superficially invasive tumours (Clark level II–III) were more common in females: 42 vs 34%. Similarly, tumour thickness was less pronounced in females: 63% had melanomas ≤2 mm thick as compared with 47% of males. Despite these favourable prognostic determinants, female patients with stage I melanoma exhibited a higher incidence of SIT metastases than their male counterparts. In all subsets of patients identified on the basis of maximum lesion diameter, level of invasion and tumour thickness, females showed a clear preference for developing SIT lesions. With regard to tumour diameter, the difference is statistically significant (Mantel–Haenzel test; $\chi^2 = 6.74$; $P < 0.05$). As to the Clark–Breslow subsets, the trends noticed did not reach statistical significance, mainly because of small group sizes. The female preponderance with respect to the development of SIT lesions was most marked in the poor prognosis categories (diameter >10 mm, Clark level IV–V and Breslow thickness >2 mm). In these groups males showed evidence of SIT metastases in less than 10% of cases, as opposed to a 20–40% incidence in females.

DISCUSSION

Few data exist on the predictive value of tumour and host characteristics with regard to the development of SIT metastases in cutaneous melanoma. The only accounts on this subject to be found in the literature are the studies of Day *et al.* [5] and Elder *et al.* [6], who correlated the presence of satellitosis with 'thick' melanomas only. This would indicate that tumour thickness is a justifiable criterion for the selection of melanoma patients for elective regional isolated perfusion therapy. Attention should be addressed to the delineation of other risk factors which predispose to SIT lesions.

The present report is the first to demonstrate that female sex is correlated with an increased incidence of SIT metastases when compared with males of similar (micro)stage. Our findings are in agreement with previous observations indicating that females are more inclined to have lymphogenic tumour spread, whereas males more frequently display metastasization via the haematogenic route [7, 8]. These studies, however, focused on nodal and visceral metastases but not on the incidence of SIT recurrences.

Our data provide evidence that SIT lesions are more predominant in females than in males. Elective regional perfusion therapy aims at the sterilization of microscopic residual locoregional tumour deposits in patients at risk. Apart from lesion thickness female sex appears to be a second independent risk factor with regard to regional lymphogenic (cutaneous) metastases. It is anticipated, therefore, that the ideal break point of tumour thickness in high-risk patients, eligible for perfusion therapy, might be different in males and females. In other words, our findings suggest that perfusion therapy should be instituted as from a smaller thickness in females than in males. These subtleties, however, await further scrutiny.

Isolation perfusion of the limbs is not a very hazardous procedure. Yet its efficacy as a prophylactic measure in high-risk patients remains unproven. Perfusionists have for too long advocated their method without having ratified its value by means of a randomized study.

Moreover, the patient group at risk has never been properly delineated. This study may contribute to the resolution of this complex matter. Further reports from other institutions are most necessary in order to arrive at a well-founded perfusion therapy.

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