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Sentinel lymph node biopsy in elderly irish patients with malignant melanoma.

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Sentinel Lymph Node Biopsy In Elderly Irish Patients with Malignant Melanoma

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Abstract

In patients with malignant melanoma, Breslow depth increases with age. However, studies suggest that the frequency of sentinel lymph node metastases in malignant melanoma decreases with age. We investigated whether this applied to the cohort of patients undergoing sentinel lymph node biopsy (SLNB) in our institution. In a prospectively accrued database we identified 149 patients undergoing SLNB from 1997 to 2005. Tumour thickness as measured by Breslow depth was assessed in stratified age groups. We assessed the relationship between SLNB positivity and age using the Chi-square for trend. We directly examined the relationship between SLNB positivity in patients aged less than 65 and aged 65 years of age and over. Disease-free and overall survival in patients aged less than 65 and aged 65 years of age and over were also assessed. Comparing the age groups, there was no significant difference identified in Breslow depth (<65 years, median Breslow=1.2mm (range 0.2-9.7); =65 years, median Breslow=1.4mm (range 0.12-8.5); p=0.06, Mann-Whitney U). Chi-square for trend identified no significant relationship between SLNB positivity and age. We found n=120 patients <65 had SLNB, of which 26 (21.7%) were positive. In patients =65, n=29 had SLNB of which 3 (10.3%) were positive. These differences were not statistically significant (Fisher's exact test, p=0.2). There was no difference in disease-free or overall survival between patients aged <65 or =65 who had SLNB (median follow-up 37.5 months (range 5 – 70); disease-free survival, p=0.08; overall survival, p=0.3, Logrank test). We did not find that elderly patients with malignant melanoma had a demonstrable difference in tumour thickness when compared to younger patients. In those patients who underwent SLNB there was no significant difference in node positivity between the age groups. Disease-free and overall survival were not significantly different between the age groups. Further study and longer follow-up will help establish the relationship between age and SLNB positivity.

Introduction

Malignant melanoma is the leading cause of death from skin cancer in Ireland, accounting for two percent of all invasive cancers, and has a mortality rate of one percent.[1] The most important adverse prognostic factors in patients with malignant melanoma are Breslow depth and lymph node metastasis.[2] Sentinel lymph node biopsy (SLNB) is often employed to evaluate the regional lymph node status in order to avoid regional lymph node dissection. Moreover, it has recently been shown that disease-free survival is higher in those patients with a diagnosis of primary cutaneous melanoma with subclinical sentinel-node metastases who undergo SLNB and immediate lymphadenectomy as compared with delayed lymphadenectomy for clinically detected nodal relapse.[3] The probability of a positive sentinel lymph node increases with increased Breslow depth.[4,5,6] Previous studies have suggested that Breslow depth increases with age.[7,8] In the prospective randomized clinical trial by Chao et al, the mean tumour thickness in patients aged 18-30 was 1.96mm, whereas in those aged greater than 60 years, the mean thickness was 2.49mm ($p<0.001$).[7]Cohen et al found that mean Breslow depth steadily increased with age, from 1.76mm in the 11-20 age group to 4.70mm in the group over 90 years of age.[8] However, the frequency of sentinel lymph node metastasis appears to decrease with age.[6,7,9,10] In this study we aim to determine the relationship between patient age and sentinel lymph node status in our cohort of patients at St Vincent's University Hospital.

Patients and Methods

From January 1997 to July 2005, a prospective database was collated which incorporated all malignant melanoma patients treated at St Vincent's University Hospital (n=363; female n=218). The database contained information on patient's age at time of surgery, gender, primary tumour location, and histopathological parameters (histological subtype, Breslow depth, Clark's level, presence or absence of ulceration). For analysis, we stratified these patients into seven age groups (18-30, 31-40, 41-50, 51-60, 61-70, 71-80 and 81-97 years of age). We also directly compared patients aged less than sixty-five to those aged sixty-five and over.

Those patients with a melanoma of Breslow depth >1mm were offered sentinel lymph node biopsy, providing they did not have clinically palpable lymph nodes or evidence of distant metastases. However, there were 32 patients with a Breslow depth <1mm who specifically requested to have SLNB performed and these patients were included in the study. From the 363 patients in the database, we identified 149 patients undergoing SLNB.

SLNB Technique

Our approach to sentinel lymph node biopsy has been previously described.11 Briefly, preoperative lymphoscintigraphy was performed which involved injection of 2ml of 20 MBq technetium labelled human albumin colloid (Nanocoll®, Amersham Health, UK) intradermally immediately adjacent to the tumour or biopsy site. Dynamic imaging was then performed until the sentinel lymph node was identified. The location of the putative sentinel node was identified on the skin using an indelible marker. A handheld gamma probe (neo2000® Gamma Detection Systems, Battelle Healthcare Products, OH, USA) was used intraoperatively to confirm the site of the sentinel node. One millilitre of 1% isosulfan blue (Lymphazurin™, US Surgical, CT, USA) was also injected in all cases except those involving the face, so as to avoid cosmetically unacceptable tattooing.

Histopathological Analysis

Sentinel lymph nodes were fixed in formalin and paraffin-embedded. Each node was sectioned at three levels and stained with haematoxylin and eosin (H&E). If no metastasis was detected in the H&E-stained slides, immunohistochemical staining with antibodies to melanoma markers (S-100 protein, HMB-45, tyrosinase) was performed on additional sections prepared at the middle level.

Statistics

After stratifying the patients in our database into seven age groups, the relationship between tumour thickness as measured by Breslow depth and age was assessed using the Kruskal-Wallis test. Using the database, we separated the patients into two groups: those less than sixty-five years and those aged sixty five and over. The Kolmogorov-Smirnov test determined our data were not normally distributed. The Mann-Whitney U test was used to examine for significant difference in Breslow depth between these two groups. From the 363 patients in the database, we identified 149 patients undergoing SLNB. We assessed the relationship between SLNB positivity and increasing age using the Chi-square for trend on groups described earlier. Fisher's exact test was used to determine whether there was any difference in SLNB positivity in those aged sixty-five years and those aged sixty five and over. The Logrank test was used to examine for any difference in disease-free survival or overall survival in those aged sixty-five years and those aged sixty five and over who underwent SLNB. Data were analysed with InStat 3.0 and GraphPad Prism V4.0 (GraphPad, SD, USA).

Results

There were 363 consecutive patients identified in the database. The clinicopathological characteristics of our patient population are listed in Table 1. Comparing the 7 age groups, there was no significant difference identified in Breslow depth (Table 2) (p=1.602, Kruskal-Wallis). The median Breslow depth in those aged <60 years and those ≥65 years did not differ significantly (Table 3) (p=0.0646, Mann-Whitney U). Chi-square for trend identified no significant relationship between SLNB positivity and age (Table 4) (p=0.5759). One hundred and twenty patients aged <65 years underwent SLNB, of which 26 (21.7%) were positive. Of the 29 patients aged =65 years, three (10.3%) were found to have positive sentinel lymph nodes. This difference was not statistically significant (Table 5) (p=0.2006, Fisher's exact test). From the 149 patients who underwent SLNB, there were 4 deaths and 7 recurrences. The median follow-up period was 37.5 months (range 5 – 70). Survival analyses were performed to determine if there was any difference in disease-free survival and overall survival between patients aged <65 years and =65 years who underwent SLNB. Kaplan-Meier curves were plotted (data not shown). Using the Logrank test there was no significant difference in either disease-free (p=0.0833) or overall (p=0.3173) survival. The number of patients in whom SLNB was performed but in which the sentinel node could not be identified was 12. This gave an overall failure rate for SLNB in our study of 7.4% (12/161).

Discussion

The 2002 national census estimated that Irish males have a life expectancy of 75.1 years while females have a life expectancy of 80.3 years. Eleven percent of the Irish population in 2002 were aged 65 years and over. This percentage is likely to continue to increase with the continuing improvements in healthcare and living standards of the Irish population. This may predict an increase in the number of elderly patients with malignant melanoma in the future.

The prospective randomized clinical trial by Chao et al demonstrated that Breslow depth increases with age.[7] In this trial, in patients aged 18-30, the mean tumour thickness was 1.96mm, whereas in those aged greater than 60 years, the mean thickness was 2.49mm (p<0.001). Cohen et al found that mean Breslow depth steadily increased with age, from 1.76mm in the 11-20 age group to 4.70mm in the group over 90 years of age.[8] The reason for this remains unclear. Skin thickness has previously been shown to decrease gradually with age.[12] Levine et al hypothesised that decreased skin thickness in elderly persons permits a deeper level of invasion for lesions of similar thickness.[13] However, this theory was refuted by Loggie et al, who were unable to correlate increased level of invasion with a given skin thickness.[14] Other possible reasons for the increase in Breslow depth with age include a delay in diagnosis or immunological defects which occur with age.[13]

Previous studies have highlighted an apparent decreased risk of sentinel lymph node metastasis in older patients with malignant melanoma.6,7,9,10 McMasters et al found that patients aged greater than 60 years had a 48% decreased risk of sentinel lymph node metastasis in comparison with those aged 60 years and under (odds ratio 0.520, p=0.008).6 In a cohort study of 263 patients, Statius Muller et al noted a decreased SLNB positivity rate in older patients. The rate decreased from 37% in the 18-30 age group to 17% in the 71-84 age group.[9]

In our study we examined for gross difference between increasing age and SLNB positivity using two approaches: by looking for variation in SLNB positivity in stratified age groups and, then, specifically comparing SLNB positivity in those aged less than sixty-five and those aged sixty-five and over. Although in our study there appeared to be a difference in SLNB positivity between those aged less than sixty-five and those aged sixty-five and over

(21.7% versus 10.3%), this difference was not significant (p=0.2006). Breslow's depth is the most important determinant of sentinel lymph node positivity.[4,5,6] We found no variation in Breslow's depth in different age groups, therefore we could exclude it as a cause of differing SLNB positivity. Although there was no statistically significant difference found in the Breslow depth between our groups, it is possible that this is due to the small patient numbers in our cohort (patients greater than 70, n=73).

In our cohort there were no significant differences in sentinel lymph node status between the age groups. However, it has been suggested that the decrease in frequency of sentinel lymph node metastasis in older patients, highlighted in previous studies, may represent a decreased sensitivity of the SLNB procedure in older patients leading to a higher false-negative rate, or that malignant melanomas in elderly persons may have a different biological behaviour, spreading haematogenously rather than via the lymphatics.[7] The failure rate for SLNB in our study was 7.4%. This is comparable to that of the international multicentre trial by Morton et al in which the failure rate was 4.7%.[15]

A recent study from Australia suggests that there is increased awareness amongst the general public regarding signs and symptoms of melanoma.[16] It is therefore possible that patients with malignant melanoma are presenting at an earlier stage. Sun-exposed and non-sun-exposed melanomas have different underlying mutations and molecular mechanisms of carcinogenesis.[17] This may be the biggest determinant of biological behaviour as opposed to age. Bittner et al have also demonstrated different molecular subtypes in melanomas with distinct gene expression.[18] A specific age-dependent gene expression was not identified. Therefore, the underlying genotypic variations, as opposed to increasing age, may determine melanoma biology.

Disease-free survival and overall survival in those aged sixty-five years and those aged sixty five and over who underwent SLNB was found in our study not to be significantly different. This is probably due to the small number of recurrences (n=7) and deaths (n=4) in the group who underwent SLNB.

In conclusion, we did not find that elderly patients with malignant melanoma had a demonstrable difference in tumour thickness when compared to younger patients. There was no difference in SLNB positivity between the age groups. There was also no difference in disease-free or overall survival between the age groups. This may suggest that the elderly population of Ireland are presenting earlier and their disease is consequently at an earlier stage of invasion. Further study and longer follow-up will help establish the relationship between age and SLNB positivity.

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