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HEDS Discussion Paper

No. 12/14

Incidence of advanced cutaneous malignant melanoma in the UK: a systematic review.

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Abstract

Objectives: Cutaneous melanoma (CM) is one of the most aggressive forms of skin cancer. In 2008, CM was found to be the sixth most common cancer in the UK. The aim of this review was to systematically identify patients with advanced CM, limited to stage IIIc and stage IV disease.

Methods: Literature searches were undertaken in the Cochrane Library, MEDLINE, CINAHL and EMBASE between December 2010 and March 2011. Webpages of the Office of National Statistics, Cancer Research UK and the Welsh Cancer Intelligence and Surveillance Unit were also scanned. A narrative synthesis was undertaken due to the heterogeneity of included studies.

Results: Three observational studies were identified. One study was in East Anglia, England while the remaining two were in Scotland. Both studies in Scotland estimated that 2% of all melanoma patients had advanced CM at the time of diagnosis. It was also noted that, in East Anglia, the incidence of stage IV CM decreased from 0.42 to 0.13 per 100,000 population per year between 1991 and 2004. The review highlighted the challenges in identifying patients with advanced CM from available data.

Conclusions: This review highlighted the lack of, and the need for primary studies to estimate the incidence of advanced CM in the UK. Defining this subgroup of patients is important for identifying patients for targeted treatment. We suggest that researchers must clearly define this population of patients in future studies.

Keywords: advanced, cutaneous melanoma, incidence, review, UK

Introduction

Cutaneous melanoma (CM), one of the most aggressive forms of skin cancer, results from the malignant transformation of the melanin-producing cells (melanocytes). In 2008, CM was the sixth most common cancer in the UK and the second most common cancer in those aged between 15 and 34 years.[1] Projected trends suggest that the incidence of CM will continue to increase for the next decade.[1-3] Increased incidence of melanoma has been linked with a greater exposure to ultra-violet (UV) radiation.[4] However, there is uncertainty regarding the precise role of UV light in the development of CM.[4-6] Data on the current trends of advanced CM will provide information for preventive measures.

The presentation of CM is varied; lesions are often described on the basis of clinical features and pathology. Occasionally, some patients may present with disseminated disease without an identifiable primary lesion - metastatic melanoma of unknown primary origin (MUP). The formation of new blood vessels and/or lymphatic vessels, invasion of local tissues and the widespread circulation of melanoma cells through the lymphatic or vascular systems results in CM progression.[7] The extent of CM spread is determined by clinical examination, pathologic diagnosis and microscopic staging. Current staging methods described in the 7th edition of the American Joint Committee on Cancer (AJCC) staging criteria is based on the tumour-node-metastasis (TNM) system.[8] Accordingly, CM may be classified as one of five stages: stage 0, stage I, stage II, stage III and stage IV. Stage 0 denotes melanoma in situ or non-invasive melanoma, which is characterised by tumour cells confined to the epidermis. Stages I and II refer to the early stages of the invasive CM, while stage III and stage IV represent late stages. Local spread via the lymphatic system to the skin, subcutaneous tissue or regional lymph nodes constitutes stage III disease (regional spread). Within this category, patients may present with satellite or in-transit metastases (non-nodal spread).[9] Satellite lesions constitute tumour deposits within 5cm of the primary melanoma whereas in-transit metastases are subcutaneous or cutaneous tumour cells between the primary lesion and regional lymph nodes. Disseminated

disease through the blood circulation to distal parts of the body results in stage IV CM (distant spread).[8] It is estimated that approximately 15% to 25% of patients develop metastases.[10]

In the early stages of the disease, surgical resection of the primary tumour may provide a cure. However, advanced CM is more refractory to current treatments including chemotherapy and immunotherapy.[7] The need to develop newer and more effective therapies is essential. For this reason, information on the proportion of patients with advanced CM is crucial to assess the impact of these emerging technologies. Additionally, the revised UK guidelines[11] for managing CM recommend the recruitment of stage IV patients in clinical trials of new treatments.

The aim of the review was to systematically summarise the incidence and prevalence of advanced CM in the UK from available data. Definition of advanced CM was restricted to patients with stage IIIc (unresectable stage III) or stage IV melanoma based on the 7th edition of the AJCC staging recommendations.[8] For UK-specific information, data from a representative population of patients in England, Northern Ireland, Scotland and Wales were assessed.

Materials and Methods

Data sources and search strategies

Literature searches were conducted in the Cochrane Library, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica (EMBASE) and Science Citation Index (via Web of Science) between December 2010 and March 2011. Examination of proceedings, abstracts and posters of conferences of dermatological societies (British Association of Dermatologists and British Society of Investigative Dermatology) was undertaken. Reference lists of reviews and included papers were also examined. Supplementary searching included hand-searching of relevant journals and scanning of web-pages of the Office of National Statistics[12], Cancer Research UK[1] and the Welsh Cancer Intelligence and Surveillance Unit.[13]

Free text and medical subject heading terms for advanced CM, outcomes (incidence and prevalence rates) and terms related to UK were used in two independent searches that were subsequently combined. The first search (Search 1) combined terms for advanced CM and outcomes while the second search (Search 2) combined terms for CM, outcomes and UK. This approach was helpful to improve the sensitivity of the searches whilst simultaneously limiting the capture of non-UK studies. Searches were limited to studies published in the English language. The search strategy used in MEDLINE is outlined in the supplementary files for review.

Eligibility criteria

Selection of studies was based on pre-specified criteria described earlier. Reports of conferences were retrieved if they provided sufficient information to contribute data to the review. Non-English articles were excluded. Additionally, studies were also excluded if it was not possible to identify patients with advanced CM or if studies involved patients who were not resident in a geographically defined region in the U.K.

Only studies reporting on a defined population of patients with clinically and histologically confirmed CM were included. Patients with distant metastases constituted stage IV disease; the characteristics of stage IIIc patients is summarised in Figure 1.[8] In the event of unclear staging criteria, judgment of CM stage was based on clinical and pathological data provided by authors.

Data extraction and synthesis

Data extraction was performed by one reviewer using a standardised form and checked for accuracy by a second reviewer. Disagreements were resolved by discussion. Data extracted included information on study design, location, staging methods, incidence or proportion of patients with advanced CM. Included studies were assessed according to the Critical Appraisal Skills Programme (CASP) checklist for observational studies.[14] Items were scored as 'yes' (Y); 'no' (N); unclear (U) or not applicable (NA). Due to the heterogeneity of included studies, a narrative synthesis was undertaken.

Results

Figure 2 shows a flow diagram of study selection. After excluding duplicates, there were 5,810 potentially relevant articles retrieved from the searches. Application of the pre-specified inclusion criteria resulted in the inclusion of 6 full-text articles, relating to 3 studies.[15-17] One study was published in four articles over different time periods from 1985 to 2007. The most recently published article [16] was included in this review as it was an updated version of the three earlier publications.[18-20] Overall, the quality of included studies was considered to be of moderate to low risk of bias (presented in the supplementary files for review).

Description of included studies

The review included 16,898 patients with CM over a study period from 1961 - 2004. No eligible cohort or case-control study was identified. All included studies were cross-sectional in design; two [16, 17] were conducted in Scotland while one [15] was undertaken in East Anglia, England. No study was identified that reported on advanced CM patients in Northern Ireland and Wales or on prevalence rates. The characteristics of the included studies are shown in Table 1. Reporting on patient characteristics of all stages and advanced CM varied between studies. Sample sizes ranged from 477 to 12,450 [15-17] with the proportion of affected women approximately twice that of men (61.4% -

66.0% versus 34.0% - 38.6%).[16, 17] In one study,[17] affected men were slightly younger (53.3±1.5 years) compared to women (55.3±1.0 years). Another study[16] classified patients into three age categories (those < 40 years; 40-59 years and 60 years or over); a greater proportion of older patients ('age > 60 years' versus 'age < 40 years' = 43.2%:19.6% respectively) was represented in the study. Sex distribution and mean ages were not reported for patients in the remaining study.[15]

Data Sources

Information on patients in included studies was obtained from the Eastern Cancer Registration and Information Centre (ECRIC) database [15]; the Scottish Melanoma Group database [16]and the Lothian Health Board's computerised hospitals' admission list, the regional cancer registry and diagnostic indicators of three regional pathological departments in the Lothian and Borders region of South-East Scotland. [17]

Data was obtained from the ECRIC database between 1991 and 2004.[15] This database contained records on patients from Norfolk, Suffolk and Cambridgeshire. Information held in the database was obtained from electronic and paper copies of pathology reports as well as patients' hospital notes within the region. The authors, using the flow method,[21] reported that completeness of registration of cases was 96.2%. The flow method incorporates the probabilities of three time-dependent events from which the proportion of patients missing, registered or lost can be calculated.

The Scottish Melanoma Group database, a centralised electronic database, established in 1979 holds population-based records of all newly diagnosed patients with invasive melanoma (Clark level 2 or more) in Scotland. [16] Regular entries were obtained from pathological and clinical records of patients in both the NHS and private sectors. Details considered included histological type of tumour, tumour thickness, affected body site, and treatment. Completeness of case registration in the database during the study period was achieved by cross-checking entries with information held in the Scottish

Cancer Registry. It must be noted that data in the Scottish Cancer Registry does not include tumour thickness. Reported information within the Scottish Melanoma Group database was reported, by authors, to be accurate for more than 95% of cases.[16]

Pondes and colleagues [17] reported on patients from the Lothian and Borders region of South-East Scotland who presented between 1961 and 1976 - before the establishment of the Scottish Melanoma Group database. Besides, the above-mentioned sources of data used in this study, additional information was obtained by examining records from general practitioners, regional radiotherapy and/or dermatology departments, regional cancer records and death certificates.

Patients with advanced melanoma

Staging methods

Diagnosis and description of advanced melanoma was uncertain in all the included studies. Staging in the Levell study [15] was based on an abridged version of the 5th edition of the TNM classification system for malignant tumours. On the other hand, Mackie and colleagues reported staging of CM using an unspecified version of the AJCC criteria.[16] Pondes and colleagues[17] used staging recommendations proposed by the Melanoma Clinical Cooperative Group of the New York University.[22] Patients were categorised as *stage I* (localised disease), *stage II* (regional lymph node disease) and *stage III* (undefined in report). Regional node involvement was defined as metastases (1) within 5 cm of the primary lesion (similar to satellite lesions),[8] (2) between the primary lesion and local glands (resembling in-transit metastases)[8] and (3) locoregional nodal involvement. Metastases to skeletal, visceral and subcutaneous tissues were described as distant metastases but it was not clear whether these patients were those assigned to '*stage III*'. The authors also reported that diagnosis of cases involved, on some occasions, examination of available specimens to determine the level of invasion, the depth of skin involvement as well as the mitotic activity of tumour cells. Tumour cells were stained with haematoxylin and eosin stain or with trichrome stain.

Incidence of advanced melanoma

Incidence data were presented as European age-standardised rates (EASRs) [15], mean annual percentage change (APC) of EASR [16] and the mean annual incidence.[17] A summary of the incidence of advanced melanoma in included studies are presented in Table 2.

Pondes and colleagues[17] estimated annual incidence rates of melanoma in the Lothian and Borders region of South-East Scotland between 1971-1976. Patients with carcinoma in situ (stage 0) were excluded from the analysis in this study. The reported rates did not include information collected from 1960 to 1970 as the robustness of related data was uncertain. For all cases of CMM, the mean annual incidence was 4.6 per 100,000 with a female preponderance. Of the 404 included case records, 385 patients had adequate information for possible staging of CMM. In these patients, 41 patients (10.6%) had 'stage II' disease (defined as regional nodal involvement), while seven patients (2%) had 'stage III' disease (undefined) at the time of initial presentation. From the report, it is unclear if these stages correspond to current staging classifications. Therefore the number of stage IIIc or IV patients could not be established from the available data due to the limited information on the extent of nodal involvement or distant spread.

For the duration of the Levell study [15], the annual incidence (EASR) of all stages of CM increased from 9.39 cases per 100,000 population per year to 13.91 cases per 100,000 population per year. This represented an overall increase by 4.52 cases per 100,000 population per year. On the other hand, the incidence of stage IV cases fell from 0.42-0.13 cases per 100 000 population per year without a significant change in the incidence of stage III cases (actual rates not reported for stage III).

Mackie and others[16] described the mean APC of EASR in Scotland for 5-year periods: 1979-1983, 1984-1988, 1989-1993, 1994-1998 and 1999-2003. Most patients were 60 years or more at the time of diagnosis. Incidence rates of all CM cases demonstrated a three-fold increase from 3.57 to 10.93 per

100,000 population annually in men compared to an increase from 5.6 to 12.96 per 100,000/ year in women. Furthermore, the numbers of diagnosed 'AJCC stage 3 and 4' cases at initial presentation rose during the study period. This translated into a 2% (n=255/12,450) increase in the population studied. These results need to be interpreted with caution as patients were clustered together as 'AJCC stage 3 and stage 4'. The heterogeneity of stage III patients in general must be considered as this makes the proportion of stage IIIc patients in this study population indeterminate.

Discussion

This review provides an overview of the incidence of advanced CM patients in the UK based on 3 cross-sectional studies – two conducted in Scotland and one in East Anglia, England. Estimates of incidence of advanced CM in the review were problematic due to indistinct definitions.

Incidence of melanoma and advanced melanoma

Incidence rates for all stages of CM increased over each study periods and showed a female predominance. This has been observed in other studies.[23-25] According to Levell and others,[15] the increase of CM was due to an increased number of patients with tumours less than 1.5mm thick (thin melanomas). Mackie and colleagues also noted a similar trend. [16] Besides increased exposure to UV light, reasons for increasing trends in CM have also been explained by increased screening and improved diagnostic procedures.[26] The annual incidence of stage IV CM in East Anglia, however, decreased during the study period 1991 to 2004, although the observed incidence rates of stage III cases remained steady (actual data not reported).[15] This may be indicative to early identification and management of CM.

Definition of advanced melanoma

Two studies [15, 16] used the AJCC staging system and the TNM classification, however the nature of reporting limited the usefulness of either method in identifying advanced CM patients. In the Ponder study,[17] patients with regional nodal disease were assigned to '*stage II*' melanoma and it was unclear whether those with '*stage III*' melanoma had distant metastases according to current staging classifications. Hence, the number of stage IIIc or IV patients could not be accurately estimated from the available data due to the limited information on the extent of nodal involvement or distant spread.

Presently, staging involves several investigative procedures including clinical, histological, biochemical and radiographic methods.[27, 28] The range of diagnostic options may result in diverse reported rates. This concern is greater if tests differ significantly in sensitivity and specificity within and between studies. For instance, computerised tomography (CT) scans can detect 27.7% of metastases in patients with stage III disease.[29] Therefore, metastases detected in a study using only x-rays may be lower compared to a study in which this test is combined with CT scans. Identification of advanced CM using a restrictive or uncertain range of diagnostic procedures could lead to unreliable findings.

Historically, there have been shifts in the significance of specific prognostic features resulting in revisions of the description of CM stages.[30] Differences in reported trends have been attributed to changes in histological definitions and descriptions of patients with CM.[31] There are good reasons to believe that the less sophisticated diagnostic work-up for patients during the earlier study periods and ambiguous classification of advanced CM threaten the reliability of results of this review. A recent review of MUP by Kamposioras and colleagues[28], which included 41 articles and one abstract spanning 1917 to 2009, highlighted the difference in MUP incidence on the basis of diagnostic technique. The authors reported an incidence of MUP of 5.05% and 2.7% for before and

after introduction of CT scans, respectively. It is of note that the 'post-CT' incidence of disseminated CM is close to that observed (2%) in the Mackie study. [16]

Data sources

While centralised computerised databases and registries provide vital details of cases, they may fail to accurately capture changes in diagnostic criteria. It must be noted that the completeness of cancer documentation has been challenged. An evaluation in seven UK health districts highlighted issues of miscoding of cases as well as an excessive registration of 'late-stage' melanomas.[32] Regular updating of entries is, therefore, crucial. Perhaps catchment-area based studies, rather than registries or databases, may provide more useful information for identifying specific subgroups of patients.

This review had some limitations. Only 3 relevant studies were included in this review and these involved different time frames, methods and populations - it is possible that other relevant studies were missed. Restricting advanced CM patients to those with stage IIIc and IV CM may have added to challenges in identifying the population of interest. Furthermore, inadequate or unclear description of advanced CM patients may confound advanced CM rates presented here. There was a dearth of epidemiologically appropriate studies relating to this subgroup of patients. Contributing studies examined data in a restricted region in the UK; therefore the reported estimates have limited generalisability. It may be argued that consulting specialist UK registers would be a better alternative for the information this review set out to seek. However, the extensive searches of relevant web-pages demonstrated that this information was not easily accessible.

Over the last 4 decades, incidence rates of all stages of CM have been reported for regions in the UK. However, available evidence regarding the epidemiology of advanced melanoma is restricted. This could be addressed via studies which are designed primarily to identify this sub-group of patients.

Addressing this knowledge gap will contribute information for examining trends and variations of advanced melanoma across the region to improve patient care.

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Tables and Figures

Table 1: Summary of characteristics of included studies

Study reference	Levell 2009[15]	Mackie 2007[16]	Pondes 1981[17]
Outcome of interest	Incidence	incidence	incidence
Study design	Retrospective cross-sectional study	Prospective cross-sectional study	Retrospective cross-sectional study
Study period	1991-2004	1979-2003	1961 - 1976
Location	East Anglia, England (including Norfolk, Suffolk, Cambridgeshire)	Scotland	Lothians and Borders region of the south-east of Scotland (lat. 55°-56 °N)
Data Source	Eastern Cancer Registration and Information Centre database Electronic and paper copies of laboratory reports Patients' notes	Scottish Melanoma Group database (25-year report)	Diagnostic indices of the three pathology departments in the area Regional cancer registry Lothian Health Board's computerised list of hospital admissions

Study reference	Levell 2009[15]	Mackie 2007[16]	Pondes 1981[17]	
			Regional radiotherapy and dermatology department records	
Sample size	3,971	12,450	477 ^a	
Males	Number (%)	not reported	4810(38.6)	162(34.0)
	Mean age/years	not reported	not reported	53.3±1.5 ^b
Females	Number (%)	not reported	7640(61.4)	315(66.0)
	Mean age/years	not reported	not reported	55.3±1.0 ^b

^aOf the 477 patients in the study, case records were available for 404 patients. 385 of these case records had information for determining the clinical stage of the disease.

^bMean age with standard error (SE).

Table 2: Summary of incidence of advanced cutaneous melanoma in included studies

Study reference	Levell 2009[15]	Mackie 2007[16]	Pondes 1981[17]
Criteria for CM diagnosis	Condensed tumour-node-metastasis (TNM) system [5 th edition, abridged]	American Joint Committee on Cancer (AJCC) ^a [unspecified edition]	Malignant Melanoma Clinical Cooperative Group
Incidence rate of all CM: cases/100,000/year	Males 9.39 - 13.91	3.57- 10.93	3.2
	Females	5.6 - 12.96	5.8
Incidence of advanced of CM	cases/100,000/year ^b 0.13-0.42 (stage IV) ^c	not reported	not reported
	<i>% of study¹</i>	<i>2% stage III or IV</i>	<i>11% 'stage II'^d (n=41/385)</i>
	<i>population</i>	<i>(n=255/12,450)</i>	<i>2% 'stage III'^d (n=7/385)</i>

Abbreviations: AJCC, American Joint Committee on Cancer; CM, cutaneous malignant melanoma; n, number; TNM, Tumour-node-metastasis

^aAJCC classification is based on the TNM system.

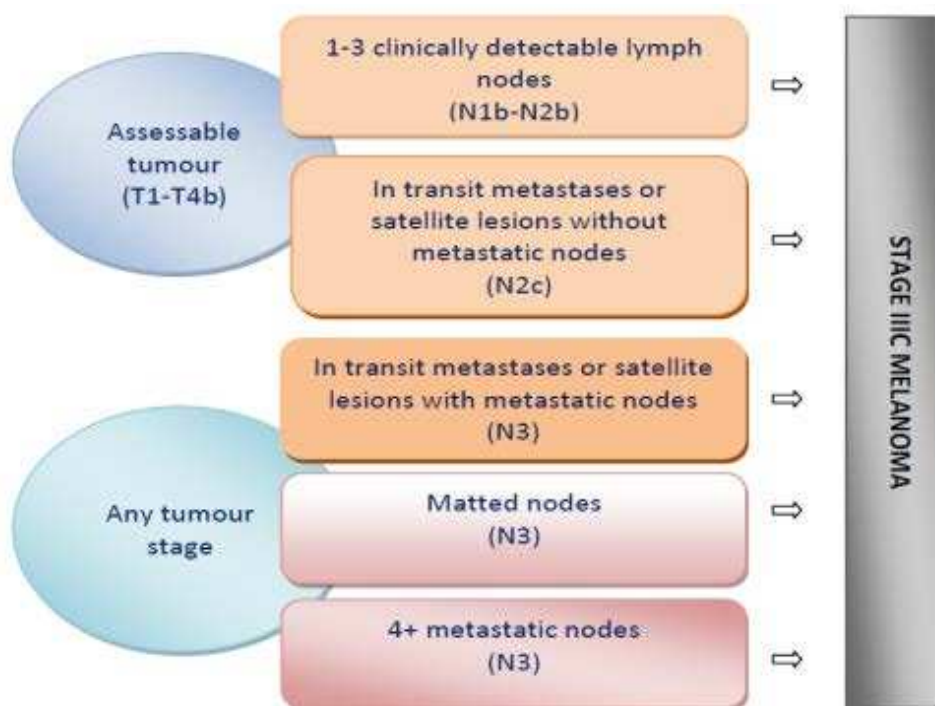
¹ Percentage of patients presented here may indicate the prevalence of advanced CM rather than incidence at the time the study was conducted.

^bEuropean age-standardised rates (EASRs) were reported for incidence of CM.

^cDuring the study period of 1991-2004, the incidence rate dropped from 0.42 -0.13 per 100,000 population per year.

^dIt is not clear whether patients classified as '*stage II*' and '*stage III*' correspond to current staging of CM patients. Stage II was defined in the report as regional node involvement, while stage III was not defined.

Figure 1: Characteristics of stage III CM



Abbreviation: CMM, cutaneous malignant melanoma; T, tumour; N, node

Figure 2: Flow diagram of study selection

