Comparing initial diagnostic excision biopsy of cutaneous malignant melanoma in primary versus secondary care: A study of Irish National data

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KEY MESSAGE
- Initial excision biopsy carried out in general practice does not lead to a poorer outcome.

ABSTRACT

Background: The incidence of melanoma is rising worldwide. Current Irish guidelines from the National Cancer Control Programme state suspicious pigmented lesions should not be removed in primary care. There are conflicting guidelines and research advising who should remove possible melanomas.

Objectives: To determine whether initial diagnostic excision biopsy of cutaneous malignant melanoma in primary versus secondary care leads to poorer survival.

Methods: Analysis of data comprising 7116 cases of cutaneous malignant melanoma from the National Cancer Registry Ireland between January 2002 and December 2011. Single predictor variables were examined by the chi-square or Mann–Whitney U test. The effects of single predictor variables on survival were examined by Cox proportional hazards modelling and a multivariate Cox model of survival based on excision in a non-hospital setting versus hospital setting was derived with adjusted and unadjusted hazard ratios.

Results: Over a 10-year period 8.5% of melanomas in Ireland were removed in a non-hospital setting. When comparing melanoma death between the hospital and non-hospital groups, the adjusted hazard ratio was 1.56 (95%CI: 1.08–2.26); (P = .02), indicating a non-inferior outcome for the melanoma cases initially treated in the non-hospital group, after adjustment for significant covariates.

Conclusion: This study suggests that initial excision biopsy carried out in general practice does not lead to a poorer outcome.

INTRODUCTION

The incidence of malignant melanoma is rising worldwide, with Australia having the highest (10.5%).[1] The average incidence in Europe is 2.8%. Ireland’s incidence is above the European average at 4.6%.[2] In Ireland, the National Cancer Control Programme (NCCP) published guidelines in November 2011 which state suspicious pigmented lesions should not be removed in primary care.[3] This is in agreement with current UK BAD guidelines.[4] In the UK, NICE guidelines state, ‘excision in primary care should be avoided’.[5] These conflict with the Primary Care Surgical Association of Ireland (PCSA), whose guidelines state the initial excision biopsy for melanoma may be carried out by a GP experienced in skin surgery at the earliest possible time.[6] This is based on both Canadian and Australia/New Zealand guidelines.[7,8]

GPs in Ireland now have two conflicting sets of guidelines to follow. Many feel the training of primary care physicians in dermatology and diagnosis of skin cancer is inadequate.[9] However, the PCSA feel that some GPs are very experienced in skin surgery, skin cancer and dermoscopy and may be a valuable resource.[6] Up to 20% of melanomas in the UK are excised in primary care,[10] which is not in keeping with their current guidelines. Figures for Ireland are not known.

There is conflicting evidence about where and by whom the initial excision biopsy of pigmented lesions should take place. There is no current published Irish
research regarding melanoma excision. Within the UK there have been four audits carried out which found primary care excisions were inadequate compared to secondary care.[9,11–13] In contrast, three UK studies found no significant difference in the rate of incomplete excision biopsies.[10,14,15] Two further UK-based studies found no statistically significant difference in outcome for location of excision.[16,17]

NICE performed a comprehensive review of the literature in 2009 in an attempt to identify if outcomes differ when the excisional surgery of a suspicious skin lesion is performed by a general practitioner (GP) compared with a specialist in secondary care. It concluded that the evidence for this subject was poor with only one randomized control trial existing in the literature. The remaining studies—11 in total were made up of non-randomized prospective trials, retrospective studies, audits and published correspondence. Despite insufficient evidence, the study stated it was in favour of specialist care in the management of suspicious skin lesions.[18]

In Ireland, there are no published figures regarding the number of melanomas removed in primary care. There have been no Irish studies comparing primary care versus secondary care excisions and the effect on outcome. Australia has the highest incidence of melanoma worldwide. It also has the highest survival rates for melanomas, a high percentage of which are removed in primary care.[19]

Following the Australian guidelines would allow for the possibility of cost reduction of treatment. Excision of suspicious pigmented lesions in primary care is approximately half the cost of hospital excision which is currently quoted by the HSE as €324.[20]

The aim of this study is to determine the percentage of melanomas removed in primary care in Ireland and determine whether this leads to a statistically significant difference in outcome regarding mortality versus secondary care.

**Methods**

The study data was provided by the National Cancer Registry Ireland (NCRI) who collect cases through Tumour Registration Officers (TROs) based in hospitals around the country. TROs identify all new cancer cases and register all relevant patient, tumour and treatment details. Hospital pathology reports provided to the registry shortly after diagnosis comprise 85% of the information on new cases. TROs also access information from hospital medical records. The registry is provided with all death certificates from the Central Statistics Office (Figure 1).

We applied for data relating to cases of cutaneous malignant melanoma through an online application from the NCRI website. The data provided was in Excel format and was irrevocably anonymized before it was received.

The data consisted of 7116 cases of melanoma from January 2002 until December 2011. The information provided on these cases included; sex, age, marriage status, smoking status, year of diagnosis, anatomical location of lesion, pathological stage of lesion at diagnosis as per the AJCC 5th edition, location of initial treatment of the lesion, initial treatment type, subsequent surgery, biopsy, chemotherapy or radiotherapy, survival in days from date of melanoma diagnosis until the end of the study or until date of death, if before 31 December 2011, and cause of death.

The data recorded for location of initial treatment was recorded as ‘HOSP’ if the initial treatment was carried out in a hospital or ‘nonHOSP’ if performed in a non-hospital setting. Information was not available to identify whether the treatment in hospital was carried out by a dermatologist, plastic surgeon or general surgeon. The non-hospital treatment was presumed to be most commonly in general practice but may also include some private dermatology clinics. The overall percentages for these are unknown. The data set did not record the Breslow thickness; however, this can be inferred from the AJCC staging (see Box 1). There was no information on incomplete excision biopsies or re-excision rates. A complexity sum was calculated which accounted for further treatments following initial excision such as surgery, chemotherapy or radiotherapy.

**Ethics**

Ethical approval was provided by the ICGP research ethics committee.

**Hypothesis**

Patients with melanoma receiving their initial diagnostic excision in the non-hospital setting would have a poorer survival compared to those who had their initial diagnostic excision in the hospital.

**Statistical analysis**

Initially, single variables were examined using the Mann–Whitney U test for continuous variables and the t-test for independent variables. These variables were subsequently compared against survival using Kaplan–Meier plots and Cox proportionate hazards modelling. Next, single variables were compared
against location of initial excision using the chi-square test or Fisher’s exact test as appropriate. Finally, a multivariate Cox hazard proportion model was derived for initial treatment location, which corrected the effect of significant covariates. Adjusted and unadjusted hazard ratios with 95% confidence intervals were derived from these models.

All analyses were carried out under a multilevel model framework using SPSS version 21. Due to the large sample size, many effect sizes of relatively small clinical relevance reached statistical significance at the 0.05 level. Therefore, a more robust significance level of 0.01 was used throughout these analyses.

Results
Cases entered from death certification only were excluded from the data set, which left 7113 cases for analysis. Of these, 6506 (91.5%) had their initial excision in the hospital setting while 607 (8.5%) were excised in the non-hospital setting.

Demographics with survival
The distribution for single variables and their effect on survival are summarised in Table 1. The data showed the majority of melanomas occurred in females, 4082
(57%), however, female survival rates were higher than males with a hazard ratio of 1.68 (95% CI: 1.44–1.96). The mean age at diagnosis was 59 years (STD deviation 17.757) with the peak age group 70–74 years. Within marriage status, the majority of melanomas occurred within the married group, 3681 (51.8%). However, when comparing marriage to survival, those who were married had a significantly better outcome than those who were single or widowed. Most melanoma lesions were removed from limbs 3478 (48.9%). When comparing anatomical position of melanomas, lesions on the head had a better outcome than those on the body and limbs. There was a uniform distribution of melanoma between pathological stages, with the higher stages inferring a statistically poorer outcome.

Location of initial excision

The comparison of location of initial excision against the single variables is summarized in Table 2. The two groups were equally matched for gender, but patients in the non-hospital group were significantly younger (P < .001) and were less likely to be married (P < .001). Lesions removed in the non-hospital group were more likely to be from the trunk and limbs, while those in the hospital group had a higher proportion of lesions removed from the face (P < .001). Lesions excised in the non-hospital group were removed at an earlier pathological stage (P = .03). Despite this 59 (9.8%) of melanomas removed in the non-hospital group were stage 4.

Survival

During follow-up, there were 60 (9.9%) deaths in the non-hospital group, 30 (4.9%) of these were melanoma deaths. This was compared to 1410 (21.7%) deaths in the hospital group, with 721 (11.1%) melanoma deaths (P < .001). When the

| Table 1. Demographics, anatomical location and pathological stage with multilevel model for melanoma specific mortality. | n (%) | Hazard ratio (95% CI) | P value |
|---|---|---|---|
| Sex | Female | 4082 (57.4) | 1 |
| | Male | 3031 (42.6) | 1.68 (1.44–1.96) | <.001 |
| Age | Mean years (SD) | 59 (17.8) | 1.02 (1.01–1.02) | <.001 |
| Marital status | Married | 3681 (51.8) | 1.63 (1.35–1.96) | <.001 |
| | Single | 1201 (16.9) | 1.17 (0.43–3.14) | .76 |
| | Divorced | 44 (0.4) | 1.67 (0.87–2.48) | .152 |
| | Separated | 112 (1.6) | 1.36 (1.07–1.77) | .012 |
| | Widowed | 778 (10.9) | 0.98 (0.75–1.28) | .88 |
| | Unknown | 1297 (18.2) | 0.71 (0.53–0.95) | .2 |
| Smoking status | Current | 626 (8.8) | 0.66 (0.3–0.084) | <.001 |
| | Ex-smoker | 523 (7.4) | 0.51 (0.41–0.63) | <.001 |
| | Never | 1673 (23.5) | 1.02 (1.01–1.02) | <.001 |
| | Unknown | 4291 (60.3) | 1.99 (1.42–2.78) | <.001 |
| Anatomical position | Body and limbs | 4803 (67.5) | 1 |
| | Head | 1979 (27.8) | 0.52 (0.42–0.64) | <.001 |
| | Unknown | 331 (4.7) | 0.51 (0.41–0.63) | <.001 |
| Pathological stage | Stage 4 | 835 (11.7) | 1 |
| | Stage 3 | 1627 (22.9) | 0.66 (0.3–0.084) | <.001 |
| | Stage 2 | 1593 (22.4) | 0.17 (0.13–0.22) | <.001 |
| | Stage 1 | 1982 (27.9) | 0.06 (0.04–0.09) | <.001 |
| | In situ | 113 (1.6) | .889 |
| | Unknown | 963 (13.5) | 0.51 (0.4–0.65) | <.001 |

| aCoefficient was not calculated due to non-convergence. |

| SD, standard deviation; CI, confidence interval. |

| Table 2. Demographics, anatomical location and pathological stage by setting. | HOSP | Non-HOSP | P value |
|---|---|---|---|
| Overall (%) | 6506 (91.5) | 607 (8.5) |  |
| Age, mean years (SD) | 59.53 (17.7) | 53.32 (17.1) | <.001 |
| Sex, male n (%) | 2780 (42.7) | 251 (41.4) | .511 |
| Married, n (%) | 3452 (53.1) | 229 (37.7) | <.001 |
| Single | 1121 (17.2) | 80 (13.2) |  |
| Divorced | 42 (0.6) | 2 (0.3) |  |
| Separated | 110 (1.7) | 2 (0.3) |  |
| Widowed | 748 (11.5) | 30 (4.9) |  |
| Unknown | 1033 (15.9) | 264 (43.5) |  |
| Smoker, n (%) | 3542 (53.1) | 229 (37.7) | <.001 |
| Current | 579 (8.9) | 47 (7.7) | <.001 |
| Ex-smoker | 497 (7.6) | 26 (4.3) |  |
| Never | 1576 (24.2) | 97 (16) |  |
| Unknown | 3854 (59.2) | 437 (72) |  |
| Anatomical location, n (%) | 1885 (29) | 94 (15.5) | <.001 |
| Body | 1188 (18.3) | 137 (22.6) |  |
| Limbs | 3132 (48.2) | 346 (57) |  |
| Unknown | 297 (4.5) | 30 (4.9) |  |
| Pathological stage, n (%) | 891 (13.7) | 63 (10.4) |  |
| In situ | 98 (1.5) | 15 (2.5) | .03 |
| Stage 1 | 1799 (27.7) | 183 (30.2) |  |
| Stage 2 | 1446 (22.7) | 147 (24.3) |  |
| Stage 3 | 1489 (22.9) | 138 (22.8) |  |
| Stage 4 | 776 (11.9) | 59 (9.8) |  |

| SD, standard deviation |


groups were compared with respect to survival, the non-hospital group had a much better outcome with an unadjusted hazard ratio of 2.2 (95%CI: 1.5–3.2); (P < .0001). When we adjusted for known variables which may have an effect on survival or location of initial excision, the adjusted hazard ratio was 1.56 (95%CI: 1.08–2.26; P = .02). This indicated a non-inferior outcome for the non-hospital group. The Kaplan–Meier survival curve for this outcome is illustrated in Figure 2.

**Discussion**

**Main findings**

This study found 8.5% of the melanomas removed in Ireland were removed in the non-hospital setting. These melanoma patients had a non-inferior outcome in terms of mortality when compared to those whose lesions were removed in the hospital setting. This non-inferior outcome persisted following adjustment for multiple variables. It also showed that the non-hospital group removed lesions at an earlier stage. Despite the hospital group removing later stage lesions, many within the non-hospital group removed stage 4 melanomas without significant adverse outcomes.

**Strengths and limitations**

This study was a comprehensive cohort of national data over a 10-year period. The analysis was based on a large number of cases with a wide range of diversity for many variables, ensuring generalizability of data and sufficient statistical power.

The new ‘National melanoma GP guidelines’ from the NCCP were published in November 2010 (3). Unfortunately, the data was collected between January 2002 and December 2011, and so we were unable to assess the full impact of the introduction of these guidelines.

Within the data, we examined hospital versus non-hospital cases. The data for non-hospital excisions was consistent with standard GP practices—with no lymph node biopsies or provision of chemotherapy or radiotherapy. However, we cannot be certain that these lesions were all removed in primary care. Some may have been excised in private health centres by dermatologists or plastic surgeons. Within the hospital group, it was not possible to differentiate between speciality (dermatology, general surgery and plastic surgery). It was also not possible to establish what grade of specialist removed each lesion.

While the data provided by the NCRI included many variables it, unfortunately, did not include
information on co-morbidities, which may have influenced the location of initial excision and the survival outcome.

This is a prospective observational study and not a randomized comparison. Therefore, we cannot rule out that bias occurred, the bigger amount of facial excisions in the in-hospital group and the earlier stage at removal in the non-hospital group support such a view.

**Existing literature**

From this study, we observed 8.5% of lesions in Ireland were removed in the non-hospital setting. This is lower than presumed excision rates in the UK. Murchie et al. [10] looked at 1790 melanomas excised in the UK between January 1991 and July 2007 and found 20% were excised in primary care. This is in spite of UK guidelines recommending that suspected melanomas should not be removed in primary care. Askew et al. [19] examined excision rates in Australia, a country whose guidelines do not stipulate who should excise melanomas. Their study carried out from 2001 to 2005, revealed that GPs performed 34.3% of excisions in 2001, increasing to 35.8% in 2008.

This study also found a non-inferior outcome when comparing hospital versus non-hospital excisions. These findings are comparable to similar studies. McKenna et al. [16] reviewed 1536 melanomas removed between 1979 and 1997 by GPs, general surgeons, plastic surgeons and dermatologists. There was no statistically significant difference in the survival of patients in the GP-treated group versus the dermatologist-treated group, however, there was a significant difference when dermatologists were compared to general surgeons or plastic surgeons, with dermatologists emerging most favourably and general surgeons worst. Unfortunately, for this study we were unable to differentiate between dermatologists and surgeons within the hospital group. Murchie et al. [17] looked at 1263 melanoma cases in Scotland between 1991 and 2007. They examined both mortality and morbidity following initial excision in primary versus secondary care. They also found that initial diagnostic biopsy of melanoma in primary care does not lead to poorer long-term outcomes.

This study was unable to examine the rate of incomplete excisions or need for repeat excision. Murchie performed two previous Scottish studies which examined this issue. His 2007 study found the proportion of inadequate biopsies was similar for GPs and hospital doctors.[14] A further study published in 2011 also found a non-significant difference.[10] Neal et al. [15] analysed 578 melanoma cases in North Wales between 1993 and 2001 and found no evidence that general practice excisions are managed poorly or have a worse outcome.

In contrast, four conflicting UK audits, which looked at melanoma excision, reported that cases in general practice were more likely to have an incomplete excision. A 1991 study reviewing 292 biopsies found that skin lesions were generally less adequately excised by GPs.[9] A case-controlled Scottish study published in 1992 of 42 melanomas removed in general practice found that there was a higher rate of incomplete excision.[11] A study of 819 melanoma cases reported there was inadequacy of excision of melanoma removed in primary care.[12] An audit of 498 melanomas conducted in 2011 showed patients in primary care having a higher rate of incomplete excisions than those in secondary care.[13] However, as observed in this study and previous studies, there is no evidence of a negative effect on mortality. This is independent of the conflicting evidence regarding incomplete excision rates in primary versus secondary care.

**Implications for research and practice**

There was a non-inferior outcome for the melanoma cases initially treated in the non-hospital setting versus the hospital group, after adjustment for significant covariates.

Lesions removed in the non-hospital group were removed at an earlier stage. This may be due to earlier diagnosis or possibly because higher stages were more likely to be referred. If due to earlier diagnosis, this has a direct improvement on prognostic outcome.

Between 2002 and 2011, 607 melanomas were removed in a non-hospital setting and this study has assured us that this has not resulted in adverse outcomes or a worse prognosis. Given the increasing hospital waiting lists and delay in treatment for patients at a hospital level, referral to hospital for treatment of melanoma may not necessarily offer patients the best outcome. GPs with appropriate training in removal of pigmented skin lesions may offer quicker, more cost-effective treatment, in a more familiar environment, without any adverse outcomes.

This study is from an Irish data set. In Ireland, as in the UK, general practice is the point of access for all patients; it provides primary care and referral to specialist care if required. Access to general practice is quick, while referral to specialists/secondary care often involves long waiting lists. In many European countries, it is normal for patients to access specialist care directly, attending dermatologists directly with any
suspicous pigmented lesions. Therefore, this study may have limited relevance in these countries.

This study suggests the need for further statistical analysis on a larger data set. This analysis should differentiate between specialities and doctor grades. It may also suggest the need for a randomized control trial comparing primary and secondary care removal of suspicious pigmented lesions. It reassures us that this trial can be safely conducted.

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Declaration of interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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