Is Initial Excision of Cutaneous Melanoma by GPs Dangerous? Comparing patient outcomes following excision of melanoma by GPs or in hospital using national datasets and meta-analysis

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Abstract

Background: Melanomas are initially excised in primary care and rates vary internationally. Until now there has been no strong evidence that excising melanomas in primary care is safe. European guidelines make no recommendations and UK melanoma guidelines require all suspicious skin lesions to be initially treated in secondary care based on an expert consensus, which lacks supporting evidence, that primary care excision represents substandard care. Despite this, studies have found up to 20% of melanomas in the UK are excised by GPs. Patients receiving primary care melanoma excision may fear that their care is sub-standard and their long-term survival threatened, neither of which may be justified

Methods: Scottish cancer registry data from 9367 people diagnosed with melanoma in Scotland between 2005 and 2013 were linked to pathology records, hospital data and death records. A Cox proportional hazards regression analysis, adjusting for key confounders, explored the association between morbidity and mortality and setting of primary melanoma excision (primary versus secondary care). A pooled estimate of the relative hazard of death of having a melanoma excised in primary versus secondary care including 7116 patients from a similar Irish study was also performed**.**

Results: The adjusted hazard ratio (95% CI) of death from melanoma for those having primary care excision was 0.82 (0.61-1.10). Those receiving primary care excision had a median (IQR) of 8 (3-14) out-patient attendances compared to 10 (4-17) for the secondary care group with an adjusted RR (95% CI) of 0.98 (0.96-1.01). Both groups had a median of 1 (0-2) hospital admissions with an adjusted rate ratio of 1.05 (0.98-1.13). In the meta-analysis, with primary care as the reference, the pooled adjusted hazard ratio (95% CI) was 1.26 (1.07-1.50) indicating a significantly higher all-cause mortality among those with excision in secondary care.

Conclusions: The results of the Scottish and pooled analyses suggest that those receiving an initial excision for melanoma in primary care do not have poorer survival or increased morbidity compared to those being initially treated in secondary care. A randomised controlled trial to inform a greater role for GPs in the initial excision of melanoma is justified in the light of these results.

355 words

INTRODUCTION

Melanoma incidence is increasing worldwide with over 132,000 new cases each year.[1] Melanoma can be hard to diagnose and, perhaps as a consequence, is often excised in primary care.[2] Current European consensus-based interdisciplinary and ESMO guidelines do not make any recommendations at all about which health professionals should biopsy suspicious skin lesions.[3,4] In the UK, skin disease accounts for nearly 9% of GP consultations and with increasing incidence and growing public concern about melanoma it seems likely that melanomas will continue to be excised in primary care[5,6] This is directly contrary to UK melanoma management guidelines, which state that the initial treatment of suspicious skin lesions should never occur in primary care.[7-9] Such guidelines follow a consensus among secondary care specialists in the UK that GP melanoma excision is sub-standard treatment placing patients at risk [10,11], although the supporting evidence for this view is not strong. The randomised MiSTIC trial concluded that the clinical importance of quality differences existed between minor surgery in primary and secondary care, but that the clinical importance of the difference was uncertain.[12] The true clinical importance of the quality difference, however, is of vital importance to those patients who do have a melanoma excised by a GP. As things stand, these patients may be deeply worried that their care is substandard and that their survival may have been compromised. Furthermore, a greater role for suitably skilled primary care practitioners in the initial management of suspicious skin lesions could benefit patients and health services. However, current guidelines and lacking evidence that initial GP melanoma excision is safe are impeding the large randomised trial needed to inform revised guidance and optimize melanoma management pathways everywhere.

We previously published data from over 1200 patients diagnosed with cutaneous melanoma in Northeast Scotland between 1991 and 2010.[2] We found that patients who had received their primary excision in primary care were no more likely to die within 10 years and had less morbidity than those receiving primary excision in secondary care. Following a search of the international literature the only similar study providing evidence that primary care excision of melanoma does not seriously compromise key patient outcomes comes from an analysis of data from 7116 people diagnosed with cutaneous melanoma between 2002 and 2011 and recorded in the National Cancer Registry of Ireland. This study reported that 8.5% of melanomas in Ireland were removed in primary care with a non-inferior outcome, but adjusted for a limited number of potential confounders.[13]

Using linked national data, we investigated whether patients diagnosed with cutaneous melanoma in Scotland between 2005 and 2013 had different mortality and morbidity outcomes depending on whether excision was performed in primary or secondary care. We controlled for a greater number of confounders and also produced the first international pooled estimate of relative mortality for those having a melanoma initially excised in primary versus secondary care.

METHODS

Data linkage

The Scottish Cancer Registry (including underlying pathology records); the National Records of Scotland (NRS) death registry; the Scottish Morbidity Record Acute Inpatient and Day Case Admission dataset (SMR01); and the Hospital Outpatient Attendance dataset (SMR00) for all patients diagnosed with cutaneous melanoma in Scotland between January 2005 and 31st December 2013 were linked using the Community Health Index (CHI) number, a unique 10-character numeric identifier, allocated to each patient on first registration with NHS Scotland.[14]

The Scottish Cancer Registry (SMR06) and underlying pathology records provided data including: date of diagnosis, setting of melanoma excision (primary or secondary care), age, sex, deprivation measured by the Scottish Index of Multiple Deprivation (SIMD) [15] quintile, health board of residence, melanoma type, anatomical site, Clark level, Breslow thickness, presence of microinvasive disease, and presence of metastatic disease (from linked hospitalisation records (SMR01)). The NRS death registry provided date of death and primary and secondary cause of death for included individuals who had subsequently died. For all patients with melanoma, data were abstracted from the episode-based record (SMR01) on inpatient and day case attendances, as well as outpatient attendances from SMR00 (which provides information about all outpatient attendances at Scottish hospitals). The SMR01 data were also used to calculate a Charlson co-morbidity score for each subject using established methods.[16]

Statistical analysis

Patients diagnosed following their initial diagnostic excision biopsy in either primary or secondary care were followed until death, date of emigration, or end of follow up to 31st

December 2015, whichever occurred first. A standard Cox proportional hazards regression analysis was used to explore the association between all-cause mortality and setting of primary excision (primary or secondary care (reference group) with health board as an indicator variable. The unadjusted hazard ratio (HR) and its 95% confidence interval (CI) for excision in primary versus secondary care (reference group) was calculated. The hazard ratio was then adjusted for: age; sex; deprivation (determined using postcode and the Scottish Index of Multiple Deprivation [15]; melanoma type; anatomical site; Clark's level (a staging system reflecting the depth of melanoma invasion into the dermis [9]); Breslow thickness (the depth in millimetres by which a melanoma has invaded the dermis [9]), Charlson score and the presence or absence of micro-invasive and metastatic disease. The likelihood ratio test was used to find interaction effect of (i) location and morphological melanoma type and (ii) location and Breslow thickness on all-cause mortality.

A similar approach was used to explore melanoma-specific survival between those with lesions excised in primary versus secondary care. The proportional hazard (PH) assumption, based on Schoenfeld residuals was examined and the residuals were found to be independent of survival time, hence no violation of the PH assumption was detected.[17]

To explore morbidity, the number and duration of admissions and outpatient attendances to specialities relevant to their melanoma diagnosis (dermatology, medical and clinical oncology, plastic surgery, palliative medicine) were calculated for each patient following diagnosis. A multilevel generalised linear model with a Poisson distribution and log link function was used to calculate rate ratios (95% CIs) for total hospital admissions, hospital inpatient admission and hospital outpatient attendances between primary and secondary care excised biopsies before and after adjustment for potential confounders.

Finally, using the published estimates, a pooled estimate of the relative hazard of death after having a melanoma excised in secondary care versus primary care (as the reference group) for the 9367 Scottish and the 7116 Irish patients [13] was calculated. In order to utilise the published risk estimates from Doherty et al [13], we had to swap our reference group to be primary care in this pooled analysis.

All analyses were carried out under a multilevel model framework, using STATA version 14. A two-sided p-value <0.05 was considered statistically significant throughout.

Statistical power

In the current Scottish study, the overall rate of excision in primary care was 8.2%. If we assume that the ten year survival rate for people aged 15-99 years diagnosed with melanoma is 67%, then, if there was no impact of setting on mortality, we would expect 254 deaths from 771 patients in the primary care excision group and 2837 deaths from 8596 patients in the secondary care excision group. We have 90% power to detect a 6% difference in ten year mortality between the primary and secondary care groups at the two-sided 5% significance level.

RESULTS

During the study period 9367 patients were diagnosed with melanoma. The mean age at excision was 60.4 years (standard deviation, SD=17.5) and more than half (54%) of the melanomas were diagnosed in women (Table 1). Patients whose melanomas were excised in primary care were younger, more affluent and had fewer co-morbidities than those undergoing secondary care excision, with evidence that primary care excision was commoner in some parts of Scotland than others. Melanomas excised in primary care were more likely to be nodular and were more likely to be have been excised from the body or upper limb.

By the end of follow-up, 16.9% of those who had had their melanoma excised in primary care had died compared to 22.7% of those receiving primary excision in secondary care (Table 2). Following multi-adjustment, the HR (95% CI) of death from any cause for those having primary care excision was 0.85 (0.69, 1.04). Females had a lower all-cause mortality than males, whereas increasing deprivation; melanoma subtypes other than superficial spreading; increasing Clarks level; increasing Charlson score; increasing Breslow thickness; increasing age, and the presence of metastatic disease at diagnosis were all independent predictors for increased all-cause mortality. The interaction effects of (i) location and melanoma type (p=0.157) and (ii) location and Breslow thickness (p=0.190) were not statistically significant. Health board did not significantly predict adjusted all-cause mortality (overall p=0.100) and there was no statistically significant interaction between health board and primary/secondary care setting for melanoma excision (p=0.495).

A total of 8.2% of patients who had had their melanoma excised in primary care died from melanoma compared to 10.2% of those receiving excision in secondary care (Table 3). Following multi-adjustment, the HR (95% CI) of death from melanoma for those having primary care excision was 0.82 (0.61, 1.10). Females and residents of the Borders or Lothian had a lower hazard of death from melanoma, whereas increasing deprivation; nodular, acral or other melanoma subtype, increasing Clarks level, Charlson score of 3 or more; increasing Breslow thickness, increasing age, and the presence of metastatic disease at diagnosis were all independent predictors of melanoma-related mortality. Health board was significantly associated with adjusted melanoma specific mortality (p=0.039), but the interaction between health board and primary/secondary care setting was not statistically significant (p=0.774).

There was great variation in the frequency of primary and secondary care excisions by health board, for example, Lanarkshire performed 2% of its excisions in primary care compared to Borders who performed 19% (Table 4).

Figures 1 and 2 show the multi-adjusted hazard ratios for all-cause and melanoma-specific mortality by health board regions. For all-cause mortality, the 95% confidence limits of each individual health board's hazard ratio crosses 1.00. For melanoma specific mortality, there appears to be a small, but statistically significantly protective effect of living in the Lothian or Borders health board regions.

Table 5 shows number of hospital outpatient attendances, inpatient admissions and total bed days by setting. For outpatient attendances, those receiving primary care excision had a median (IQR) of 8 (3-14) outpatient attendances compared to 10 (4-17) for the secondary care group with a corresponding non-significant adjusted RR (95% CI) of 0.98 (0.96, 1.01). Both groups had a median (IQR) of 1 (0-2) total inpatient admissions with an adjusted RR of 1.05 (0.98-1.13). For both groups, the median (IQR) number of bed days was 0 (0-2) with an adjusted RR of 1.01 (95% CI 0.97, 1.06). By speciality, those with melanomas excised in primary care had significantly fewer dermatology appointments, but significantly more plastic surgery and oncology outpatient appointments than those with melanomas excised in secondary care.

The meta-analysis combining effect sizes of setting for all-cause mortality in the current Scottish and published Irish data is shown in Table 6 and Figure 3. The adjusted model included

the variables: setting of excision [hospital/secondary vs non-hospital/primary (reference group)], sex, age, anatomical position (site) and markers of stage (including Breslow thickness, Clark level and metastatic status). Smoking status, American Joint Committee on Cancer (AJCC) pathological stage and marital status were not available in the Scottish data, but were included in the Irish analyses. In the Irish data, the adjusted HR (95% CI) for increased mortality in the secondary care group was 1.56 (1.08, 2.25) compared to 1.19 (0.99, 1.44) in the Scottish data. The pooled risk estimate of all-cause mortality associated with secondary care excision was 1.26 (1.07, 1.50) indicating an overall increased mortality for the secondary care in comparison with the primary care group.

Discussion

Summary of key findings

In this analysis of 9367 patients in Scotland treated for cutaneous melanoma between January 2005 and December 2013 and followed up until 31st December 2015, we found no evidence of an increased hazard of all-cause mortality for those having initial melanoma excision in primary care. There were marked variations between health boards in the proportion of melanomas initially excised in primary care. However, apart from a small protective effect for melanoma-related death for one health board, most likely due to residual confounding, or chance in the context of, effectively, multiple testing, there were no significant differences in risk of death across regions. Overall, there was no significant difference between primary and secondary care settings in the total number of out-patient appointments, hospital admissions and hospital bed-days post-melanoma diagnosis. Overall, the primary care group appeared to be significantly more likely to be managed subsequently in plastic surgery and medical oncology than those treated in secondary care, although the analysis suggested this varied between health boards. In a meta-analysis where our data were combined the only comparable study we could find following a search of the international literature, the pooled hazard ratio indicated a significantly increased risk of death for those receiving their initial excision of melanoma in secondary care compared to primary care.

Meaning and interpretation

Overall, patients who have their melanoma initially excised in primary care can be reassured that there is no evidence that their survival has been jeopardized. The data provide strong evidence that when GPs do excise melanomas their technical surgical skills are sufficient to

permit equivalent outcomes to hospital care. It seems likely that, in the most part, GPs will adhere to referral guidance and refer skin lesions they strongly suspect to be melanoma to a specialist. Therefore, and though we cannot distinguish those melanomas excised intentionally versus inadvertently in the current data, it seems likely that a proportion of the 8.2% in Scotland and 8.5% in Ireland of melanomas excised in primary care had not been suspected, a view perhaps suggested by the higher proportion of nodular melanomas excised by GPs. It seems further likely that such patients will have been given the alarming impression they were subject to diagnostic error and sub-standard care. This impression is consolidated by the greater input of oncologists and plastic surgeons observed overall for the Scottish primary care group post-diagnosis. Therefore, whilst improved diagnostic skills by GPs should always be aspired to, the current data provide strong evidence on which to reassure patients and GPs when a melanoma is inadvertently excised in primary care.

As to the issue of intentional GP excision of suspicious skin lesions, and despite potential benefits for patients and health services, current European guidelines do not support, and UK guidelines expressly forbid, any primary care role in the management of melanoma beyond making an initial visual diagnosis. Our study provides an evidential basis to revisit and perhaps revise these guidelines. In the Antipodes, where melanoma is commoner, initial management of melanoma is largely a primary care activity which is reflected in those national guidelines.[18,19] We are not suggesting that this should immediately become the case here, however, the accumulating evidence suggests that European and UK guidelines could consider extending greater latitude to suitably experienced GPs with respect to excision of melanomas on accessible anatomical sites where good clearance is possible.[11] Greater involvement of appropriately trained GPs in the initial excision of suspicious skin lesions could actually have several potential benefits: earlier stage diagnosis for a portion of people with melanoma; fewer alarmed patients believing they have received sub-optimal care, and fewer referrals to over-burdened secondary care clinics. The current study in fact provides a strong evidential and ethical basis to inform a randomized trial of primary versus secondary care initial excision of suspicious skin lesions which, hitherto, would have been hard to fund or support or fund in the face of strong opposition from secondary care specialists.

A future randomized trial must also provide definitive evidence of the likely potential impact on secondary care services of expanding the role of primary care in initial melanoma excision. There is a legitimate concern that non-expert GPs may flood pathology departments with benign skin lesions, although one small Dutch audit reporting a conversion rate of 10% for skin

suspicious lesions excised by GPs appears to be reassuring.[20] This possibility cannot be properly addressed with existing routine data since GPs excise pigmented skin lesions and submit them to pathology departments for reasons other than suspected malignancy.[11] Therefore, high quality prospective trial data, including a definitive presumed diagnosis from submitting GPs, is required to address this important question.

The variation in the proportion of melanomas excised in primary care across different Scottish health boards during the study period is striking and not readily explainable. It is plausible that rural populations perceive primary care excision as more acceptable and rural GPs maybe more willing to perform minor surgery for the benefit and convenience of their patients. Similarly, particular local service issues during the study period could have impacted the figures observed. It is reassuring to note, however, that mortality rates do not seem to have varied between the Scottish health boards. Given the current policy focus on reducing cancer diagnostic intervals to a minimum it would indeed have been interesting to consider the impact of primary care excision on melanoma diagnostic delay. This was not possible in our study, but worthy of future research.

Strengths and limitations

The key strength of this study is that it is a whole nation dataset. This has enabled a large and representative sample to be drawn from all treated melanomas in Scotland. We have also been able to follow-up patients for sufficient time and analyse sufficiently large numbers of hospital admissions and outpatient attendances. Furthermore, we have been able to pool our results with another similar, albeit more limited, national study from a country with a similar primary care-led healthcare system. This provides dual reassurance – first that our study is of reproducible quality, and second that primary care is not uniquely disadvantaging patients in the way in which melanoma is managed in the UK.

However, all studies based on cancer registry data have some limitations. Some cases may have been missed or miscoded in the register. Additionally, some key variables such as completeness of biopsy excision were not available. Against this such problems are inherent in all similar research and the Scottish Cancer Registry has been consistently shown to be of high quality.[21] It could be argued that more straightforward lesions in fitter and younger patients were excised by GPs and thus could bias results in favour of primary care, although age and co-morbidity were adjusted for as far as possible in the analysis. Nevertheless, it is with these

patients that primary care may have an underexploited role and with reference to whom we would suggest that guidelines might be revisited. A further limitation is that we were unable to distinguish melanomas excised intentionally versus inadvertently in primary care. This is an important issue since it is possible that a greater proportion of particularly hard to diagnose lesions, such and nodular and amelanotic melanomas which have poorer outcomes, are being excised in primary care. This fact may actually have led to an underestimate of a primary care excision survival benefit and makes a future prospective randomized trial, which can now be justified, where suspicious skin lesions are intentionally randomized to primary versus secondary care initial excision even more important to inform future service re-design. We could also not distinguish between initial incisional and excisional biopsies, although our previous work would suggest that the vast majority of melanomas in our sample had been diagnosed following an excision biopsy.[2] Consequently the current study cannot inform the debate around the role of incisional biopsy in melanoma diagnosis.[22]

Context with other literature

The likely combined effect of increasing incidence and growing public awareness about melanoma [23] and the decision to lower the threshold in England at which an urgent suspected skin cancer referral can be made [8] can only result in increased referrals to already over-stretched under-resourced hospital outpatient departments. However, calls for increased training to improve GPs skills in diagnosing pigmented lesions seem impractical given the current crises in UK general practice.

The main European guidelines do not recognize a role for primary care in melanoma management.[3,4] Despite a lack of good evidence, existing UK guidelines go further, explicitly discouraging primary care involvement beyond initial clinical suspicion, and viewing melanoma excision by a GP as misguided and a clinical error.[7-11] This view has been frequently reinforced by un-blinded audits in secondary care which found that GP melanoma excision was sub-standard.[24-29] However, similar audits, but led from primary care, have contradicted this view.[30,31] Perhaps the key contribution of the current data is to provide evidence on important morbidity and mortality outcomes, as opposed to intermediate process measures, to better inform the ongoing debate. Our data could particularly prompt guideline committees to review recommendations around GP involvement in removal of suspicious skin lesions for those in whom visiting a hospital is particularly burdensome; including the very old, rural-dwellers and those with multi-morbidities. Current developments within primary care too,

such as super-surgeries and Multi-Disciplinary Diagnostic Centres should provoke a rethink of recommendations on the right setting for the initial excision of suspicious skin lesions.

Conclusions and implications for policy

Having a melanoma initially excised in primary care does not lead to increased mortality or morbidity for patients. Patients who have a melanoma excised by a GP can be reassured by these findings. A prospective randomised trial to compare the intentional excision of suspicious skin lesions in primary versus secondary care is now justified.

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Competing interest statement

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributors

PM conceived the study. The study was designed by PM, EAR, DHB, LI and AJL. EAR and AJL conducted the analysis. PM wrote the manuscript with comments and contributions from EAR, DHB, LI and AJL. PM is the guarantor of results.

Transparency declaration

The lead author, PM, affirms that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval

This study was approved by the Public Benefit and Privacy Panel for Health and Social Care of NHS Scotland on 8th July 2015 (reference number 1516-0154). It received ethical approval from NRES Committee South East Coast – Surrey on 04th August 2015 (REC reference number: 15/LO/1385; Protocol number: 2/031/15; IRAS project ID: 183757).

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Role of study sponsors

The University of Aberdeen sponsored the study and took responsibility for the initiation, management and financing of the study. The sponsor did not have any direct involvement in the design, conduction or reporting of this study.

Patient involvement statement

Patients were not directly involved in the design, conduction or reporting of this study.

Trial registration details

This study has been registered with ClinicalTrials.gov ID NCT03169036 protocol ID 183757.

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Data sharing

The data used for this study are archived within the NHS Scotland National Statistics Service (NSS) National Safe Haven and are not freely available. Bona fide researchers wishing to access the data should apply to the authors in the first instance. Subsequent access to the data would be subject to application to, and approval by, the Public Benefit and Privacy Panel for Health & Social Care (PBPP) of NHS Scotland.

Table 1: Demographics and clinical details

		Total (n=9367)	Primary care excision (n=771)	Secondary care excision (n=8596)	P-value
Sex	**Male**	4291	355 (46.0)	3936 (45.8)	0.892
	Female	5076	416 (54.0)	4660 (54.2)	
Age	**Mean (SD)**	60.4 (17.5)	57.0 (16.8)	60.6 (17.5)	<0.001
Deprivation (2009 SIMD)	**Most deprived**	1269	67 (8.7)	1202 (14.0)	<0.001
	2	1623	127 (16.5)	1496 (17.4)	
	3	1885	197 (25.6)	1688 (19.7)	
	4	2092	182 (23.6)	1910 (22.2)	
	Least deprived	2493	197 (25.6)	2296 (26.7)	
Health board of residence	**Ayrshire and Arran**	752	98 (12.7)	654 (7.6)	<0.001
	Borders	247	47 (6.1)	200 (2.3)	
	Dumfries and Galloway	308	51 (6.6)	257 (3.0)	
	Fife	626	49 (6.4)	577 (6.7)	
	Forth Valley	431	11 (1.4)	420 (4.9)	
	Grampian, Orkney and Shetland	959	153 (19.8)	806 (9.4)	
	Greater Glasgow and Clyde	2007	47 (6.1)	1960 (22.8)	
	Highland/Western Isles	637	120 (15.6)	517 (6.0)	
	Lanarkshire	1131	22 (2.9)	1109 (12.9)	
	Lothian	1464	98 (12.7)	1366 (15.9)	
	Tayside	805	75 (9.7)	730 (8.5)	
Melanoma type	**Superficial spreading**	4794	388 (55.4)	4406 (56.0)	<0.001
	Nodular	868	113 (16.1)	755 (9.6)	
	Lentigo maligna	1165	42 (6.0)	1123 (14.3)	
	Acral	231	6 (0.9)	225 (2.9)	
	Other	1510	151 (21.6)	1359 (17.3)	
Anatomical site	**Head and neck**	2177	90 (11.9)	2087 (24.7)	<0.001
	Body	2542	272 (35.8)	2270 (26.9)	
	Upper limb	1928	201 (26.5)	1727 (20.5)	
	Lower limb	2557	196 (25.8)	2361 (28.0)	
Clark's Level	**II**	2043	169 (21.9)	1874 (21.8)	0.734
	III	2535	204 (26.5)	2331 (27.1)	
	IV	2915	241 (31.3)	2674 (31.1)	
	V	503	35 (4.5)	468 (5.4)	
	Unknown	1371	122 (15.8)	1249 (14.5)	
Charlson Score	**0**	8534	730 (94.7)	7804 (90.8)	0.003
	1	381	20 (2.6)	361 (4.2)	
	2	375	19 (2.5)	356 (4.1)	
	3 or more	77	2 (0.3)	75 (0.9)	
Breslow thickness	**Median (IQR)**	0.9 (0.5, 2)	0.95 (0.5, 2.4)	0.9 (0.5, 2)	0.021
Microinvasive disease	**Yes**	230	13 (1.7)	217 (2.6)	0.151
	No	9051	750 (98.3)	8301 (97.5)	
Metastatic disease	**Yes**	458	32 (4.2)	426 (5.0)	0.321
	No	8909	739 (95.9)	8170 (95.0)	

Table 2: Unadjusted and adjusted HR (95% CI) for all-cause mortality

			Death (n=2078)		Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
		Total (n=9367)	N	%		
Setting	**Primary care**	771	130	16.9	0.65 (0.55, 0.70)	0.85 (0.69, 1.04)
	Secondary care	8596	1948	22.7	1.00	1.00
Sex	**Male**	4291	1193	27.8	1.00	1.00
	Female	5076	885	17.4	0.57 (0.52, 0.62)	0.72 (0.65, 0.81)
2009 SIMD quintile (missing=5)	**Most deprived**	1269	336	26.5	1.48 (1.29, 1.72)	1.71 (1.45, 2.03)
	2	1623	409	25.2	1.42 (1.24, 1.62)	1.47 (1.26, 1.72)
	3	1885	451	23.9	1.30 (1.13, 1.48)	1.35 (1.15, 1.58)
	4	2092	427	20.4	1.12 (0.98, 1.29)	1.20 (1.03, 1.41)
	Least deprived	2493	455	18.3	1.00	1.00
Health Board	**Ayrshire and Arran**	752	176	23.4	1.10 (0.90, 1.34)	0.84 (0.66, 1.07)
	Borders	247	56	22.7	1.01 (0.75, 1.36)	0.85 (0.60, 1.22
	Dumfries and Galloway	308	88	28.6	1.34 (1.05, 1.73)	1.22 (0.92, 1.62)
	Fife	626	148	23.6	1.07 (0.87, 1.32)	0.88 (0.69, 1.13)
	Forth Valley	431	101	23.4	1.11 (0.87, 1.41)	1.08 (0.82, 1.43)
	Grampian/Orkney/Shetland	959	204	21.3	1.00	1.00
	Greater Glasgow and Clyde	2007	474	23.6	1.08 (0.92, 1.28)	0.95 (0.78, 1.15)
	Highland/Western Isles	637	163	25.6	1.20 (0.98, 1.48)	1.04 (0.82, 1.34)
	Lanarkshire	1131	245	21.7	0.99 (0.83, 1.20)	1.05 (0.85, 1.31)
	Lothian	1464	246	16.8	0.74 (0.62, 0.90)	0.83 (0.66, 1.03)
	Tayside	805	177	22.0	1.02 (0.83, 1.24)	0.91 (0.72, 1.16)
Anatomical site (missing=163)	**Head & Neck**	2177	706	32.4	2.02 (1.80, 2.27)	0.97 (0.82, 1.14)
	Body	2542	498	19.6	1.12 (0.99, 1.27)	1.12 (0.95, 1.32)
	Arm-upper limb	1928	324	16.8	0.94 (0.81, 1.08)	0.87 (0.74, 1.03)
	Lower limb	2557	461	18.0	1.00	1.00
Melanoma type (missing=799)	**Superficial spreading**	4794	565	11.8	1.00	1.00
	Nodular	868	375	43.2	4.61 (4.04, 5.25)	1.56 (1.34, 1.81)
	Lentigo	1165	309	26.5	2.46 (2.14, 2.83)	1.22 (1.03, 1.47)
	Acral	231	76	32.9	3.37 (2.65, 4.28)	1.44 (1.11, 1.87)
	Others	1510	468	31.0	2.87 (2.53, 3.25)	1.26 (1.09, 1.47)
Clark's level	**II**	2043	218	10.7	1.00	1.00
	III	2535	311	12.3	1.14 (0.95, 1.35)	1.05 (0.87, 1.27)
	IV	2915	802	27.5	2.75 (2.36, 3.19)	1.63 (1.37, 1.94)
	V	503	293	58.3	8.19 (6.87, 9.77)	1.84 (1.47, 2.30)
	Unknown	1371	454	33.11	3.60 (3.05, 4.24)	1.47 (1.19, 1.82)
Charlson score	**0**	8534	1677	19.6	1.00	1.00
	1	381	191	50.0	3.28 (2.82, 3.81)	1.88 (1.58, 2.23)
	2	375	157	41.9	2.66 (2.26, 3.13)	1.59 (1.31, 1.94)
	3+	77	53	68.8	6.40 (4.86, 8.42)	3.13 (2.25, 4.36)
Micro-invasive disease (missing=86)	**Yes**	230	21	9.1	0.37 (0.24, 57)	0.66 (0.40, 1.08)
	No	9051	2019	22.3	1.00	1.00
Metastatic disease	**Yes**	458	296	64.6	6.40 (5.64, 7.25)	3.41 (2.86, 4.07
	No	8909	1782	20.0	1.00	1.00
Breslow thickness Median (IQR)	Whole sample 0.9 (0.5, 2)		Those dying 2.4 (0.9-5)		1.13 (1.13, 1.14)	1.08 (1.06, 1.09)
Age Median (IQR)	Whole sample 62 (47, 74)		Those dying 75 (65-83)		1.07 (1.06, 1.07)	1.06 (1.05, 1.06)

* Model comprised setting, sex, age, deprivation quintile, health board, anatomical site, melanoma type, Clark's level, Charlson score, Breslow thickness, microinvasive and metastatic disease

Table 3: Unadjusted and adjusted HR (95% CI) for melanoma-specific mortality

			Melanoma death (n=937)		Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
		Total (n=9367)	N	%		
Setting	**Primary care**	771	63	8.2	0.72 (0.56, 0.94)	0.82 (0.61, 1.10)
	Secondary care	8596	874	10.2	1.00	1.00
Sex	**Male**	4291	557	13.0	1.00	1.00
	Female	5076	380	7.5	0.53 (0.47, 0.61)	0.70 (0.58, 0.83)
2009 SIMD quintile (missing=5)	**Most deprived**	1269	148	11.7	1.51 (1.21, 1.88)	1.61 (1.23, 2.10)
	2	1623	195	12.0	1.56 (1.27, 1.91)	1.60 (1.26, 2.04)
	3	1885	209	11.1	1.42 (1.16, 1.73)	1.18 (0.91, 1.52)
	4	2092	192	9.2	1.20 (0.99, 1.48)	1.29 (1.00, 1.65)
	Least deprived	2493	193	7.7	1.00	1.00
Health Board	**Ayrshire and Arran**	752	94	12.5	1.26 (0.95, 1.67)	0.72 (0.50, 1.04)
	Borders	247	16	6.5	0.62 (0.37, 1.06)	0.46 (0.25, 0.86)
	Dumfries and Galloway	308	39	12.7	1.29 (0.89, 1.87)	1.09 (0.70, 1.69)
	Fife	626	63	10.1	0.98 (0.72, 1.35)	0.67 (0.46, 0.99)
	Forth Valley	431	45	10.4	1.06 (0.74, 1.51)	0.99 (0.66, 1.49)
	Grampian/Orkney/Shetland	959	96	10.0	1.00	1.00
	Greater Glasgow and Clyde	2007	204	10.2	1.00 (0.79, 1.28)	0.75 (0.55, 1.01)
	Highland/Western Isles	637	73	11.5	1.15 (0.85, 1.57)	1.07 (0.74, 1.55)
	Lanarkshire	1131	125	11.1	1.09 (0.84, 1.42)	0.92 (0.66, 1.27)
	Lothian	1464	112	7.7	0.73 (0.56, 0.96)	0.68 (0.49, 0.95)
	Tayside	805	70	8.7	0.86 (0.63, 1.17)	0.72 (0.50, 1.05)
Anatomical site (missing=163)	**Head & Neck**	2177	198	9.1	1.08 (0.90, 1.31)	0.79 (0.61, 1.03)
	Body	2542	286	11.3	1.24 (1.05, 1.48)	1.19 (0.95, 1.50)
	Arm-upper limb	1928	145	7.5	0.82 (0.66, 1.00)	0.81 (0.63, 1.03)
	Lower limb	2557	236	9.2	1.00	1.00
Melanoma type (missing=799)	**Superficial spreading**	4794	226	4.7	1.00	1.00
	Nodular	868	218	25.1	6.50 (5.39, 7.84)	2.07 (1.68, 2.55)
	Lentigo	1165	49	4.2	0.96 (0.71, 1.31)	1.02 (0.71, 1.46)
	Acral	231	42	18.2	4.56 (3.28, 6.35)	1.80 (1.25, 2.59)
	Others	1510	269	17.8	4.23 (3.54, 5.07)	1.46 (1.17, 1.83)
Clark's level	**II**	2043	23	1.1	1.00	1.00
	III	2535	89	3.5	3.11 (1.97, 4.92)	2.54 (1.54, 4.18)
	IV	2915	386	13.2	12.65 (8.30, 19.28)	6.75 (4.24,10.74)
	V	503	175	34.8	44.86 (29.02, 69.34)	9.38 (5.67, 15.51)
	Unknown	1371	264	19.3	19.53 (12.74, 29.97)	5.21 (3.15, 8.59)
Charlson score	**0**	8534	808	9.5	1.00	1.00
	1	381	51	13.4	1.74 (1.31, 2.31)	1.27 (0.90, 1.78)
	2	375	54	14.4	1.83 (1.39, 2.42)	1.09 (0.76, 1.56)
	3+	77	24	31.2	5.59 (3.71, 8.40)	3.01 (1.71, 5.28)
Microinvasive disease (missing=86)	**Yes**	230	2	0.9	0.08 (0.02, 0.32)	0.55 (0.13, 2.25)
	No	9051	917	10.1	1.00	1.00
Metastatic disease	**Yes**	458	226	49.3	12.44 (10.66, 14.52)	4.22 (3.37, 5.28)
	No	8909	711	8.0	1.00	1.00
Breslow thickness Median (IQR)	Whole sample 0.9 (0.5, 2)		Those dying 3.9 (2-6.5)		1.16 (1.15, 1.17)	1.11 (1.09, 1.12)
Age Median (IQR)	Whole sample 62 (47, 74)		Those dying 69 (56-78)		1.03 (1.03, 1.04)	1.02 (1.01, 1.02)

* Model comprised setting, sex, age, deprivation quintile, health board, anatomical site, melanoma type, Clark's level, Charlson score, Breslow thickness, microinvasive and metastatic disease

Table 4: Relative proportions of primary and secondary care excisions by health board of residence

Health board of residence	Total Excisions	Primary Care	Secondary Care	Primary Care		Secondary Care	
				ALIVE	DEAD	ALIVE	DEAD
Ayrshire and Arran	752	98 (13.0)	654 (87.0)	77 (78.6)	21 (21.4)	499 (76.3)	155 (23.7)
Borders	247	47 (19.0)	200 (81.0)	37 (78.7)	10 (21.3)	154 (77.0)	46 (23.0)
Dumfries and Galloway	308	51 (16.6)	257 (83.4)	48 (94.1)	3 (5.9)	172 (66.9)	85 (33.1)
Fife	626	49 (7.8)	577 (92.2)	42 (85.7)	7 (14.3)	436 (75.6)	141 (24.4)
Forth Valley	431	11 (2.6)	420 (97.4)	10 (90.9)	1 (9.1)	320 (76.2)	100 (23.8)
Grampian/Orkney/Shetland	959	153 (15.9)	806 (84.1)	127 (83.0)	26 (17.0)	628 (77.9)	178 (22.1)
Greater Glasgow and Clyde	2007	47 (2.3)	1960 (97.7)	39 (83.0)	8 (17.0)	1494 (76.2)	466 (23.8)
Highland/Western Isles	637	120 (18.8)	517 (81.2)	104 (86.7)	16 (13.3)	370 (71.6)	147 (28.4)
Lanarkshire	1131	22 (2.0)	1109 (98.0)	14 (63.6)	8 (36.4)	872 (78.6)	237 (21.4)
Lothian	1464	98 (6.7)	1366 (93.3)	87 (88.8)	11 (11.2)	1131 (82.8)	235 (17.2)
Tayside	805	75 (9.3)	730 (90.7)	56 (74.7)	19 (25.3)	572 (78.4)	158 (21.6)

Table 5: Outpatient attendances by speciality, inpatient total admission and bed days by setting

Outpatient (Speciality)-attendance	Setting of first excision		Unadjusted	Unadjusted (multilevel)	Adjusted**
	Primary Care	Secondary care			
	Median (IQR)	Median (IQR)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Total outpatient attendance	8 (3, 14)	10 (4,17)	0.86 (0.84, 0.88)	1.02 (1.01, 1.05)	0.98 (0.96, 1.01)
Outpatient speciality: Dermatology	2 (0,8)	5 (1,11)	0.69 (0.66, 0.71)	0.85 (0.83, 0.89)	0.78 (0.75, 0.81)
Medical Oncology	0 (0,0)	0 (0,0)	1.43 (1.36, 1.51)	1.34 (1.27, 1.42)	1.27 (1.19, 1.35)
Palliative medicine	0 (0,0)	0 (0,0)	0.87 (0.57, 1.35)	0.82 (0.53, 1.27)	N/A *
Plastic surgery	1 (0,4)	2 (0,5)	0.93 (0.89, 0.97)	1.18 (1.13, 1.22)	1.23 (1.18, 1.29)
Clinical Oncology	0 (0,0)	0 (0,0)	1.09 (0.96, 1.22)	0.97 (0.85, 1.10)	1.18 (1.02, 1.35)
Inpatient admission					
Total inpatient admission	1 (0,2)	1 (0,2)	0.96 (0.90, 1.01)	1.03 (0.97, 1.09)	1.05 (0.98, 1.13)
Total Bed days	0 (0,2)	0 (0,2)	0.91 (0.88, 0.95)	0.88 (0.85, 0.92)	1.01 (0.97, 1.06)

*Did not converge

** Model comprised setting, sex, age, deprivation quintile, health board, anatomical site, melanoma type, Clark's level, Charlson score, Breslow thickness, microinvasive and metastatic disease

Table 6: Comparison of HR (95% CI) for all-cause mortality between Doherty et al (2016) and those of the current study

Variables	Doherty et al, 2016** (n=7116)		Current study (n=9367)	
	Death % (n)	HR (95% CI)	Death % (n)	HR (95% CI)
Setting*				
Non-hospital/Primary	9.9 (60)	1.00	16.9 (130)	1.00
Hospital/secondary	21.7 (1410)	1.56 (1.08, 2.26)	22.7 (1948)	1.19 (0.99, 1.44)
Age		1.02 (1.01, 1.02)		1.06 (1.06, 1.07)
Sex				
Female		1.00		1.00
Male		1.68 (1.44, 1.96)		1.50 (1.37, 1.65)
Anatomical position				
Body & limbs		1.00		1.00
Head & Neck		0.52 (0.42, 0.64)		1.04 (0.94, 1.16)
Unknown		1.99 (1.42, 2.78)		1.13 (0.68, 1.85)
Breslow Thickness		N/A		1.09 (1.08, 1.10)
Clark's level		N/A		
II				1.00
III				1.14 (0.95, 1.35)
IV				1.85 (1.58, 2.15)
V				2.14 (1.75, 2.62)
Unknown				1.57 (1.30, 1.91)
Pathological stage				N/A
Stage 4		1.00		
Stage 3		0.49 (0.41, 0.59)		
Stage 2		0.17 (0.13, 0.22)		
Stage 1		0.06 (0.04, 0.09)		
In situ		*		
Unknown		0.51 (0.40, 0.65)		
Metastatic disease		N/A		3.80 (3.23, 4.46)

N/A this variable was not available in the Doherty et al (2016)

* Note the reference group for setting was reversed in the current study to match that of Doherty et al (2016)

** Doherty et al (2016) also included marital status and smoking status

The pooled HR (95% CI) was 1.26 (1.07, 1.50), I^2=38.7%, p=0.202

Figure 1: The effect of setting and Health boards on adjusted all-cause mortality (adjusted hazard ratio (95% CI))

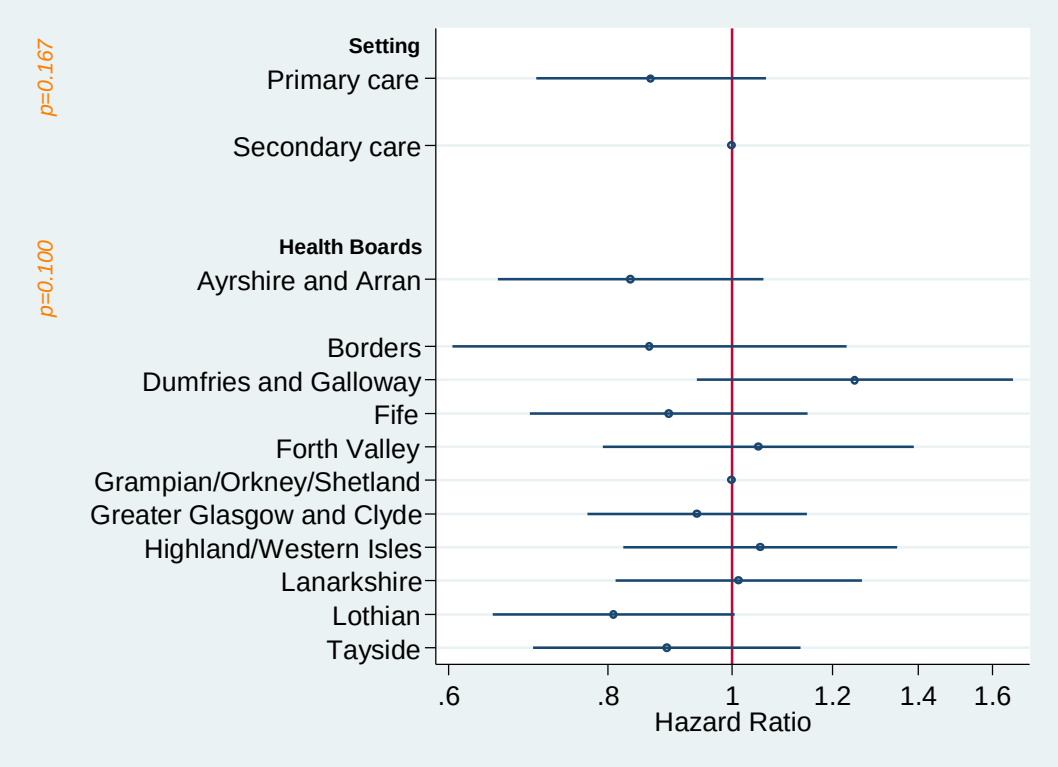

Figure 2: The effect of setting and Health board on adjusted melanoma-specific mortality (adjusted hazard ratio (95% CI))

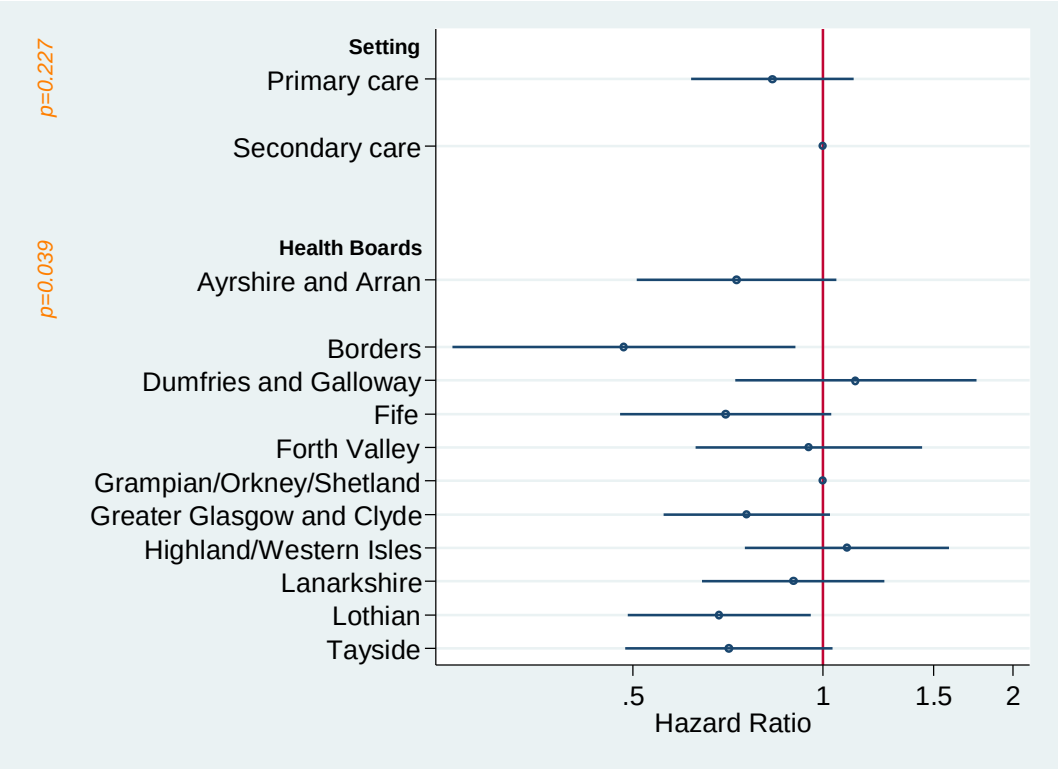

Figure 3: Forest plot of hazard ratio (95% CI) of all-cause mortality from Doherty et al, 2016 and current study

Scottish model included: Setting (hospital/secondary vs non-hospital/primary), gender, age, anatomical position, stage (Breslow thickness, Clark level and metastatic status). Doherty et al [2016] model included: Setting, sex, age, anatomical position, AJCC pathological stage, smoking status and marital status.