TITLE: Does rurality impact processes and outcomes of melanoma care? Results from a whole-Scotland melanoma cohort

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ABSTRACT

BACKGROUND: Rural-dwellers have poorer cancer outcomes, but current evidence on how rurality impacts melanoma care and survival is contradictory.

AIM: To investigate impact of rurality on setting of melanoma excision and mortality in a whole-nation cohort.

DESIGN AND SETTING: Analysis of linked routine healthcare data comprising everyone in Scotland diagnosed with melanoma, January 2005-December 2013.

METHOD: Multivariate binary logistic regression explored the relationship between rurality and setting of melanoma excision, Cox Proportional Hazards regression between rurality and mortality, with adjustments for key confounders.

RESULTS: 9519 patients were included, 54.3% (n= 5167) were female, mean age was 60.2 years (SD 17.5). 91.8% (n=8598) of melanomas were excised in secondary care, 8.2% (n=771) in primary care. The odds of primary care excision increased with increasing rurality/remoteness. Compared with urban-dwellers, the most remote rural-dwellers had almost twice the odds of melanoma excision in primary care (adjusted OR 1.92, 95% CI 1.33-2.77) No significant association was found between urban or rural residency and all-cause mortality. Melanoma-specific mortality was significantly lower in individuals residing in accessible small towns than in large urban areas (adjusted HR 0.53, 95% CI 0.33-0.87) with no trend towards poorer survival with increasing rurality.

CONCLUSION: Scottish rural-dwellers were more likely to have a melanoma excised in primary care. However, rural-dwellers did not have significantly increased mortality from melanoma. Together these findings suggest that current UK melanoma management guidelines could be revised to be more realistic by recognizing the role of primary care in the prompt diagnosis and treatment of rural-dwellers.

Word Count 250

How this fits in

Existing evidence of the impact of rural residence on melanoma management and outcomes is conflicting and drawn from small regional studies with limited external validity. This study was the first to investigate the impact of rurality on processes and outcomes of melanoma treatment using a whole-nation cohort. Conducted in Scotland, and based upon all diagnoses of melanoma between 2007 and 2013, it found that rural-dwellers are significantly more likely to have their melanoma excised in primary care but that this did not confer increased all-cause or melanoma-specific mortality. These results are reassuring for the UK's rural patients and their GPs.

INTRODUCTION

Rural patients appear to have a survival disadvantage following a cancer diagnosis compared to urban counterparts.[1] Melanoma skin cancer is an important cause of mortality and morbidity in the UK, and the incidence of melanoma is rising.[2] Mortality from this visible cancer is strongly influenced by early detection and complete excision, with thin cancers which are fully excised having excellent rates of cure.[3] Patient factors including socioeconomic status and delayed presentation are known to contribute to inequities in survival from melanoma.[4] It seems likely that geography and processes of care could also influence melanoma survival. However, evidence of geographical and treatment inequities for melanoma is understudied and potential mechanisms for rural disadvantage after a cancer diagnosis remain obscure.[1]

Existing evidence on the influence of geography on melanoma treatment and survival is contradictory. A study conducted in Queensland, Australia, found that melanoma patients from rural areas had an adjusted case-fatality rate 20% higher than urban counterparts. The authors concluded that differences in access to services and variation in management practices may partly account for the observation, but they did not adjust for socioeconomic status in their analysis.[5] We have previously reported that people living in rural areas within Northeast Scotland are more likely to have their melanoma excised by a GP than their city-dwelling counterparts.[6] This is contrary to UK guidelines which mandate that all skin lesions suspicious of melanoma should be referred to secondary care for diagnosis and treatment.[7-9] Recently, however we found reassuring evidence in a whole Scotland sample of 9,519 people diagnosed and treated for melanoma between 2005 and 2013 that primary care excision of melanoma does not result in increased mortality and morbidity.[10]

In our earlier work, despite observing higher rates of initial excision of melanoma by GPs we found no evidence that rural patients in Northeast Scotland had higher rates of incomplete excision, nor did they have increased rates of morbidity or mortality.[6,11,12] An acknowledged limitation was that we only studied patients from a single health board (Grampian) in Northeast Scotland.[6,11,12] Grampian's relative affluence could potentially have masked a rural disadvantage compared with other areas, since lower socioeconomic status is associated with later diagnosis of melanoma and poorer survival.[13]

We address the limitation in this study, report the first ever investigation of the influence of rurality on the setting of melanoma excision and mortality in a whole nation cohort.

METHODS

Study Design and Population

This was a data-linkage study comprising a population-based cohort containing every individual in Scotland who received a pathological diagnosis of cutaneous invasive melanoma between January 2005 and December 2013. The primary outcome of interest was melanoma-specific survival based upon urban or rural residence, controlling for important confounders.

Data Sources

The Scottish Cancer Registry (with underlying pathology records supplied electronically at regular intervals by all NHS pathology laboratories in Scotland); 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) were linked using the Community Health Index (CHI) number [14] for all patients diagnosed with cutaneous melanoma in Scotland between 1st January 2005 and 31st December 2013.

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, Breslow thickness (the depth in millimeters by which a melanoma has invaded the dermis [9]), and presence of metastatic disease (from linked hospitalisation records (SMR01)). The NRS death registry provided date of death and primary underlying cause of death as detailed on the death certificate for individuals who had subsequently died. A Charlson co-morbidity score was calculated for each cohort member using SMR01 information, following established methods.[16] Patients diagnosed following their initial diagnostic excision biopsy in either primary or secondary care setting were followed until death, date of emigration or end of follow up to 31st Dec 2015, whichever occurred first. Those patients who were alive at the end of follow up or recorded as emigrated were considered as censored.

Exposure

The exposure of interest was rurality. The Scottish Government Urban-rural Classification [17] provides a standard definition of rural areas in Scotland. The six fold classification categorises Royal Mail postcodes into: 1. Large urban areas of ≥125,000 people; 2. Other urban areas of

10,000 to 124,999 people, 3. Accessible small towns of 3,000 to 9,999 people within 30 minutes' drive of a settlement of 10,000 people; 4. Remote small towns with settlements of 3,000 to 9,999 people outwith a 30 minute drive from a settlement of 10,000 people; 5. Accessible rural are areas with a population of less than 3,000 people and within a 30 minute drive of a settlement of 10,000 or more; and 6. Remote rural are areas with a population of less than 3,000 people and a drive time of more than 30 minutes to a settlement of 10,000 people or more.

Statistical analyses

Demographics, clinical variables, and outcomes were described and compared using tests appropriate to continuous or categorical variables. Associations between the 6-fold urban-rural classification and other categorical variables were examined using the chi-squared test for trend. The association between the 6-fold urban-rural classification and age and Breslow thickness was examined using one way ANOVA and the Kruskal-Wallis test respectively.

Binary logistic regression was used to explore the influence of rurality on the location of the initial diagnostic excision biopsy. The dependent variable was location of excision (primary vs secondary care) with the Scottish 6-fold rural urban classification as the indicator variable (reference category = large urban area). The unadjusted odds ratio (OR) and its 95% confidence interval (CI) for excision in primary (reference group) versus secondary care was calculated. The odds ratio was then adjusted for: sex; age; deprivation; anatomical site; melanoma type; Breslow thickness; the presence of metastatic disease at diagnosis and Charlson score.

To explore the influence of rurality on survival Kaplan-Meier curves were plotted for both cumulative observed survival and cumulative melanoma-specific survival from date of melanoma diagnosis for each of the 6-fold urban-rural categories. We then used Cox proportional hazards modelling with adjustment for estimating the hazard ratio (HR) and associated 95% confidence interval (CI) of all-cause and melanoma-specific survival for each of the 6-fold urban-rural categories with adjustment for: sex; age; deprivation; anatomical site; melanoma type; setting of melanoma excision; Breslow thickness, metastatic disease at diagnosis, and Charlson score. The proportional hazard (PH) assumption is based on Schoenfeld residuals[18, 19]. There was no violations of PH assumption detected in the current

analysis. The interaction effect between setting of excision and 6-fold Urban-rural classification was examined for all cause and melanoma specific mortality outcomes.

In both the binary logistic regression and Cox proportional hazards analysis robust variance and standard error estimates of the regression coefficients were computed to account for the correlation of observations within health boards.[20]

All analyses were conducted using SPSS version 24 and Stata version 14 MP. A two-sided p-value <0.05 was considered statistically significant throughout.

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 4th August 2015 (REC reference number: 15/LO/1385; Protocol number: 2/031/15; IRAS project ID: 183757).

RESULTS

Comparisons of key demographic and clinical characteristics within the Scottish 6-fold Urban-rural Classification Categories

A total of 9,519 patients had a melanoma diagnosis recorded in Scotland between 2005 and 2013. Median follow-up was 71 months (IQR 45-101 months). Over half the cohort (n=5167, 54.3%) were female, and the mean age was 60.2 years (standard deviation (SD) 17.5). Around two thirds of the cohort lived in large urban or suburban settings (n=6349, 66.7%). Patients in remote rural areas were older compared to patients living in large urban areas (mean age= 62.8 years (SD 15.1) versus 59.5 years (SD 18.2), Table 2, p<0.001 for trend. Seventeen percent (n=117 of 689) of patients residing in the most remote rural area had their excision in primary care compared to 4.1% (145 of 3549) of patients residing in large urban settings. Rural patients were less likely to be in the least or most deprived quintiles than urban dwellers: 4.5% of remote rural dwellers were in the least deprived category compared to 34.8% of dwellers from large urban areas, and 2.5% of remote rural dwellers were in the most deprived category compared to 21.1% of urban dwellers (p<0.012 for trend). There was a significantly higher proportion of males in rural (51.4%) than urban areas (44.7%) (p=0.002 for trend). There were no significant

differences in Breslow thickness of tumour at diagnosis, anatomical site of melanoma, death (any cause and melanoma-specific) Charlson comorbidity index, or metastases at presentation between urban and rural dwellers.

Setting of Excision

All patients living outside of large urban areas had significantly greater odds of having their melanoma excised in primary care (Table 3). Those in the most remote rural areas (category six) had nearly twice the odds of having their melanoma excised in primary care than those dwelling in large urban (category one) areas (adjusted odds ratio (OR) 1.92, 95% confidence interval (CI) 1.33-2.77). Those in accessible rural areas also had significantly greater odds of melanoma excision in primary care (adjusted OR 1.75, 95% CI 1.15-2.67). Those in accessible small towns (category 3) and other urban areas (category 2) also had significantly greater odds of having their melanoma excised in primary care than large urban areas, adjusted OR 1.52, 95% CI 1.02-2.27, and adjusted OR 1.83, 95% CI 1.17-2.88, respectively.

After adjusting for important confounders, there was no significant association between deprivation category and primary care melanoma excision. Melanomas on the body and upper limbs had significantly greater odds of being excised in primary care than those on the head and neck: body adjusted OR 2.32, 95% CI 1.77-3.00, and upper limb adjusted OR 2.32, 95% CI 1.77-3.04. Nodular melanomas had significantly greater odds of being excised in primary care compared to superficial spreading melanomas, adjusted OR 2.39, 95% CI 1.84-3.11.

Mortality

There was no significant association between urban or rural residency and overall risk of death from any cause (Figure 1 and Table 4). However, there was a significantly reduced risk of mortality associated with primary care excision in the unadjusted analysis (31% reduction), but this was no longer significant following adjustment. On further investigation, age at diagnosis was the factor that was primarily responsible for the loss of statistical significance.

There were statistically significant associations with higher all-cause mortality and each of lower socioeconomic status, increasing Breslow thickness and nodular melanoma (compared to superficial spreading melanoma). Lower levels of deprivation were associated with lower

hazard of all-cause mortality (SIMD category 5, least deprived, adjusted hazard ratio (HR) 0.56, 95% CI 0.45-0.70, and SIMD category 4, adjusted hazard ratio 0.69 95% CI (0.63-0.77). Nodular melanoma was associated with increased hazard of death (any cause) compared to superficial spreading melanoma, adjusted HR 1.75, 95% CI 1.46-2.10.

Melanoma-specific mortality (Figure 2 and Table 5) was significantly lower in individuals residing in accessible small towns than in large urban areas (adjusted HR 0.53, 95% CI 0.33-0.87) but there were no other significant associations between urban/rural residency and risk of death from melanoma. Remote rural dwellers were no more likely to die from melanoma than those residing in large urban areas (adjusted HR 1.09, 95% CI 0.87-1.37). Setting was significantly associated with melanoma specific mortality in the unadjusted analysis, but this was lost on multiple adjustment, primarily due to the combined impact of several confounders such as age at diagnosis, rurality, SIMD, anatomical site and Breslow thickness. Further analysis revealed that the effect of urban-rural classification on hazard of death from melanoma was significantly different by setting of excision (p=0.005). There was a clearer separation of survival curves between remote and rural locations among those undergoing excision in primary care (Figure 3).

Death from melanoma was significantly associated with increasing age (per year, adjusted HR 1.02, 95% CI 1.02-1.03) and increasing Breslow thickness (adjusted HR 1.13, 95% CI 1.10-1.16). Those in the least deprived SIMD category had lower hazard of melanoma-specific death than the most deprived, adjusted HR 0.61 95% CI 0.45-0.81). Nodular and acral melanomas had an increased hazard of melanoma-specific mortality compared to superficial spreading melanoma, adjusted hazard ratios 2.71 (95% CI 2.11-3.48) and 2.32 (95% CI 1.59-3.40), respectively. A Charlson index of three or more was associated with a near three-fold increase in hazard of melanoma-specific death (adjusted hazard ratio 2.96, 95% CI 1.65-5.28).

DISCUSSION

Summary of main findings

Rural residence did not confer significantly poorer all-cause or melanoma-specific survival for people living in Scotland diagnosed and treated with melanoma between January 2005 and December 2013. Overall 8.1% of melanomas had been excised in primary care, but initial

primary care excision of melanoma was significantly more likely for those living in rural areas. Those living in the most remote rural areas were almost twice as likely to have had an initial excision performed by a GP compared to city-dwellers. Strikingly, in adjusted analysis, those living in accessible small towns had a near 50% reduction in melanoma-specific compared to other urban-rural categories. This may relate to a concentration of favorable sociodemographic and service characteristics, for example relatively affluent patients living close to accessible well-staffed and slightly less-pressured practices, an observation worthy of further study.

Strengths and limitations

The key strength of the study was the quality of the data. It was based on a large national sample of patients followed up for median of 71 months. The data were comprehensive and largely complete. The Scottish Rural-Urban 6-fold classification is an established method of defining rurality and was available for all of the subjects contained in the dataset. Deprivation was also assigned to every subject, although it should be noted that the SIMD provides a measure based on small area estimates of relative deprivation so there exists the potential for some individuals to be misclassified. A further limitation is that despite the Scotland-wide sample numbers in some categories were small. The analysis accounted for clustering by health board, but not at general practice level or by the clinician performing the excisions where outcomes might be more strongly correlated. Additional data on, for example diagnostic intervals, completeness of excision, and details of and the diagnostic impression of the clinician submitting the sample may have enabled a more definitive analysis, and obtaining these data should be considered by future researchers. Although this is a large Scotland-wide sample the data may not apply internationally since international healthcare systems vary markedly with respect to the balance between primary care gate-keeping and direct patient access to secondary care specialists and treatment.[21] In some countries the proportion of primary care excisions occurring in rural areas will be even higher and it would be very interesting to compare these findings with those settings. As they stand, however, the data appear to support the notion of rural GPs excising suspicious skin lesions without detriment to their patients.

Context with existing literature and policy

It is reassuring to note that rural residence did not lead to significantly poorer survival from cutaneous melanoma in this large Scotland-wide sample. Previous work in Scotland has found evidence of poorer survival for rural patients with prostate and lung cancers, but rural versus urban melanoma outcomes have not previously been studied in Scotland, or in fact anywhere

on the scale reported here.[22] The current results also admit the possibility that rurality may impact cancer sites differentially. Since Australian researchers found evidence of poorer survival for rural-dwellers with melanoma, it also seems plausible that there may be international differences in geographical impact on cancer outcomes.[5] The results also cast further doubt on the evidential basis with which existing guidelines mandate that initial excision by GPs has no place in the management of melanoma [7-9]. Policy makers, particularly in Scotland, are calling for "Realistic Medicine" with more effective and efficient use of healthcare resources.[23] Revising existing guidelines to take greater cognizance of the geographical location could result in more satisfying and effective care for patients which at the same time utilizes the wider skill set of many of Scotland's rural GPs.[24] The MiSTIC randomized trial supports this, reporting that GP minor surgery was more satisfying for patients without major difference in quality.[25] Furthermore, primary care excision of melanoma may mean shorter diagnostic delays for patients.[26] By adding the current data to this context it may be time for clinical guidelines to start to consider the realities of geographical healthcare contexts.

Conclusions

In Scotland, rural residence does not appear to confer poorer survival for cutaneous melanoma. This contradicts the balance of evidence on rural cancer outcomes and is therefore reassuring for rural residents with melanoma. These patients are, however, more likely to have their melanomas initially excised by a GP contrary to prevailing UK guidelines. This finding perhaps suggests that, despite guidelines, a pragmatic approach is being practiced with respect to melanoma in rural healthcare settings and it is reassuring to note that this is occurring without adversely affecting the survival of rural melanoma patients. These data provide a basis for current UK melanoma guidelines to be reviewed and consideration given to making management recommendations which consider a patient's place of residence.

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TABLE 1: CHARACTERISTICS OF PATIENTS WITH MELANOMA EXCISED IN SCOTLAND 2005-2013

Characteristic			**N (%)**
Sex	Number male		4352 (45.7)
	Number female		5167 (54.3)
Age		Mean (SD)	60.2 (17.5)
Setting of melanoma excision	Primary care		771 (8.2)
(unknown=150)	Secondary care		8598 (91.8)
Urban-rural (6-fold)	1= Large urban area		3549 (37.4)
(missing=20)	2=Suburban		2800 (29.5)
	3=Accessible small town		886 (9.3)
	4= Remote small town		398 (4.2)
	5=Accessible rural		1177 (12.4)
	6=Remote rural		689 (7.3)
Deprivation (SIMD) category	1 = Most deprived		1292 (13.6)
(missing=5)	2		1652 (17.4)
	3		1923 (20.2)
	4		2124 (22.3)
	5 = Least deprived		2523 (26.5)
Anatomical Site of Melanoma	Head and Neck		2201 (23.5)
(missing=167)	Body		2596 (27.8)
	Upper Limb		1958 (20.9)
	Lower Limb		2597 (27.8)
Melanoma Sub-type	Superficial spreading		4871 (55.9)
(missing=808)	Nodular		882 (10.1)
	Lentigo		1169 (13.4)
	Acral		236 (2.7)
	Others		1553 (17.8)
Metastases at presentation	No		9057 (95.1)
	Yes		462 (4.9)
Vital status at end of follow-up	Alive		7411 (77.9)
	Non-melanoma death		1156 (12.1)
	Died due to Melanoma		952 (10.0)
Charlson Comorbidity Index	0		8677 (91.2)
	1-2		765 (8.1)
	3-4		53 (0.6)
	≥5		24 (0.3)
Breslow thickness (mm)		Median (IQR)	0.9 (0.5, 2)

TABLE 2: CHARACTERISTICS OF INDIVIDUALS WITH MELANOMA EXCISED IN SCOTLAND 2005-2013 BY GEOGRAPHICAL LOCATION OF RESIDENCE

	Large urban area (n=3549)	Suburban (n=2800)	Accessible small town (n=886)	Remote small town (n=398)	Accessible rural (n=1177)	Remote rural (n=689)	P value for trend
Setting of excision							
Primary care	145 (4.1)	253 (9.2)	73 (8.4)	50 (12.7)	131 (11.3)	117 (17.3)	<0.001
Secondary care	3339 (95.8)	2509 (90.8)	797 (91.6)	345 (87.3)	1030 (88.7)	561 (82.7)	
Breslow thickness (mm)							
Median (IQR)	0.90 (0.5, 1.9)	0.90 (0.5, 2)	0.90 (0.5, 2)	1.0 (0.5, 2.5)	0.9 (0.5, 1.9)	0.90 (0.5, 1.9)	0.390
Age (years)							
Mean (SD)	59.5 (18.2)	59.9 (17.6)	61.4 (17.5)	64.0 (16.9)	60.3 (16.1)	62.8 (15.1)	<0.001
Sex							
Male	1587 (44.7)	1248 (44.6)	424 (47.9)	175 (44.0)	556 (47.2)	354 (51.4)	0.002
Female	1962 (55.3)	1552 (55.4)	462(52.1)	223 (56.0)	621 (52.8)	335 (48.6)	
Deprivation – SIMD quintiles							
1 = Most deprived	749 (21.1)	370 (13.2)	91 (10.3)	24 (6.0)	39 (3.3)	17 (2.5)	0.012
2	568 (16.0)	649 (23.2)	147 (16.6)	95 (23.9)	113 (9.6)	76 (11.0)	
3	481 (13.6)	506 (18.1)	167 (18.8)	113 (28.4)	308 (26.2)	342 (49.6)	
4	517 (14.6)	551 (19.7)	205 (23.1)	101 (25.4)	526 (44.7)	223 (32.4)	
5= Least deprived	1234 (34.8)	723 (25.8)	276 (31.2)	65 (16.3)	191 (16.2)	31 (4.5)	
Anatomical site							
Head and neck	787 (22.6)	634 (23)	223 (25.5)	111 (28.4)	274 (23.7)	170 (25.4)	0.066
Body	1000 (28.7)	759 (27.6)	241 (27.5)	76 (19.4)	302 (26.1)	208 (31.0)	
Upper limb	703 (20.2)	594 (21.6)	182 (20.8)	93 (23.8)	262 (22.6)	123 (18.4)	
Groin and lower limb	995 (28.6)	767 (27.9)	229 (26.2)	111 (28.4)	319 (27.6)	169 (25.2)	
Melanoma sub-type							
Superficial spreading	1857 (52.3)	1441 (51.5)	438 (49.4)	177 (44.5)	599 (50.9)	347 (50.4)	0.035
Nodular	291 (8.2)	316 (11.3)	55 (6.2)	50 (12.6)	115 (9.8)	55 (8.0)	
Lentigo	431 (12.1)	322 (11.5)	120 (13.5)	57 (14.3)	154 (13.1)	83 (12.0)	
Acral	100 (2.8)	60 (2.1)	21 (2.4)	13 (3.3)	27 (2.3)	15 (2.2)	
Others	565 (15.9)	430 (15.4)	155 (17.5)	75 (18.8)	201 (17.1)	122 (17.7)	
Missing	305 (8.6)	231 (8.3)	97 (10.9)	26 (6.5)	81 (6.9)	67 (9.7)	
Metastases at presentation							
No	3386 (95.4)	2654 (94.8)	857 (96.7)	364 (91.5)	1123 (95.4)	654 (94.9)	0.532
Yes	163 (4.6)	146 (5.2)	29 (3.3)	34 (8.5)	54 (4.6)	35 (5.1)	
Non-Melanoma death	422 (11.9)	323 (11.5)	119 (13.4)	54 (13.6)	141 (12.0)	97 (14.1)	
Melanoma death	350 (9.9)	298 (10.6)	71 (8.0)	51 (12.8)	109 (9.3)	72 (10.4)	
Charlson Comorbidity Index							
0	3250 (91.6)	2554 (91.2)	812 (91.6)	352 (88.4)	1077 (91.5)	613 (89.0)	0.060
1	140 (3.9)	121 (4.3)	40 (4.5)	24 (6.0)	37 (3.1)	26 (3.8)	
2	136 (3.7)	103 (3.7)	31 (3.5)	18 (4.5)	49 (4.2)	39 (5.7)	
3+	23 (0.6)	22 (0.8)	3 (0.3)	4 (1.0)	14 (1.2)	11 (1.6)	

TABLE 3: FACTORS ASSOCIATED WITH PRIMARY CARE MELANOMA EXCISION

		Setting –Primary care (n)	Unadjusted OR (95% CI)	Adjusted *OR (95% CI)
Urban-rural 6-fold	**1= Large urban area**	145	1	1
	2=Other urban area	253	1.68 (1.06-2.67)	1.83 (1.17-2.88)
	3=Accessible small town	73	1.35 (0.91-2.02)	1.52 (1.02-2.27)
	4= remote small town	50	1.21 (0.82-1.76)	1.18 (0.76-1.83)
	5= Accessible rural	131	1.57 (1.00-2.46)	1.75 (1.15-2.67)
	6=Remote rural	117	1.63 (1.17-2.28)	1.92 (1.33-2.77)
Sex	**Female vs Male**	416	1.04 (0.95-1.13)	1.05 (0.93-1.19)
Age mean (SD)	**(+1 year)**	57.6 (16.8)	0.99 (0.98-0.99)	0.99 (0.98-0.99)
Deprivation (SIMD)	**1 = Most deprived**	67	1	1
	2	127	1.07 (0.89-1.28)	1.13 (0.98-1.31)
	3	197	1.11 (0.72-1.73)	1.05 (0.72-1.54)
	4	182	0.94 (0.64-1.39)	0.84 (0.60-1.17)
	5 = Least deprived	197	1.05 (0.77-1.45)	1.05 (0.75-1.48)
Anatomical Site	**Head and Neck**	90	1	1
	Body	272	3.13 (2.60-3.76)	2.32 (1.77-3.00)
	Upper Limb	201	2.92 (2.40-3.54)	2.32 (1.77-3.04)
	Groin and Lower Limb	196	2.07 (1.63-2.62)	1.59 (1.10-2.28)
Melanoma Sub-type	**Superficial spreading**	388	1	1
	Nodular	113	1.75 (1.39-2.20)	2.39 (1.84-3.11)
	Lentigo	42	0.40 (0.32-0.50)	0.69 (0.50-0.96)
	Acral	6	0.34 (0.16-0.72)	0.46 (0.20-1.06)
	Others	151	1.21 (1.02-1.45)	1.46 (1.25-1.70)
Breslow thickness Median (IQR)		0.95 (0.5, 2.35)	0.99 (0.96-1.01)	0.96 (0.92-1.00)
Metastasis at presentation		32	0.75 (0.38-1.49)	1.15 (0.63-2.08)
Charlson Index	**0**	730	1	
	1	20	0.62 (0.30-1.25)	0.93 (0.42-2.03)
	2	19	0.51 (0.34-0.78)	0.53 (0.39-0.74)
	3+	2	0.24 (0.05-1.12)	0.31 (0.07-1.43)

*Adjusted for sex, age, deprivation, anatomical site, melanoma sub-type, Breslow thickness, metastasis at presentation, Charlson index except where the variable itself is being considered.

TABLE 4: FACTORS ASSOCIATED WITH HAZARD OF DEATH (ANY CAUSE)

		Any cause death (n)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Urban-rural 6-fold	**1= Large urban area**	759	1	1
	2=Other urban area	614	1.02 (0.92-1.13)	0.95 (0.83-1.08)
	3=Accessible small town	187	0.98 (0.82-1.18)	0.82 (0.64-1.04)
	4= remote small town	104	1.27 (1.07-1.50)	0.90 (0.79-1.02)
	5= Accessible rural	246	0.97 (0.82-1.15)	1.02 (0.86-1.22)
	6=Remote rural	169	1.18 (0.99-1.39)	1.03 (0.86-1.22)
Sex	**Female vs Male**	886	0.57 (0.53-0.63)	0.72 (0.64-0.81)
Age mean(sd)	**(+1 year)**	72.8 (14.3)	1.07 (1.06-1.07)	1.06 (1.06-1.07)
Deprivation (SIMD)	**1 = Most deprived**	336	1	1
	2	410	0.95 (0.85-1.06)	0.87 (0.77-0.98)
	3	451	0.89 (0.76-1.05)	0.79 (0.67-0.92)
	4	428	0.76 (0.68-0.86)	0.69 (0.63-0.77)
	5 = Least deprived	455	0.65 (0.57-0.75)	0.56 (0.45-0.70)
Setting of excision	**Secondary care**	1950	1	1
	Primary care	130	0.69 (0.55-0.86)	0.90 (0.71-1.13)
Anatomical Site	**Head and Neck**	706	1	1
	Body	598	0.55 (0.51-0.61)	1.08 (0.92-1.28)
	Upper Limb	324	0.47 (0.43-0.51)	0.85 (0.69-1.05)
	Groin and Lower Limb	461	0.50 (0.46-0.54)	1.02 (0.82-1.27)
Melanoma Sub-type	**Superficial spreading**	565	1	1
	Nodular	375	4.61 (4.04-5.28)	1.75 (1.46-2.10)
	Lentigo	309	2.43 (2.07-2.87)	1.14 (0.91-1.42)
	Acral	76	3.29 (2.58-4.18)	1.54 (1.33-1.79)
	Others	470	2.96 (2.59-3.38)	1.43 (1.26-1.62)
Breslow thickness		0.8 (0.5, 1.4)	1.13 (1.11-1.15)	1.09 (1.06-1.12)
Metastasis at presentation	**Yes**	296	5.83 (4.52-7.51)	3.50 (2.60-4.70)
Charlson Index	**0**	1678	1	1
	1	192	3.30 (2.73-4.00)	1.89 (1.61-2.2)
	2	157	2.63 (2.17-3.19)	1.53 (1.32-1.79)
	3+	53	6.40 (5.11-8.01)	2.93 (2.33-3.68)

*Adjusted for sex, age, deprivation, setting of excision, anatomical site, melanoma sub-type, Breslow thickness, metastasis at presentation, Charlson index except where the variable itself is being examined.

TABLE 5: FACTORS ASSOCIATED WITH MELANOMA-SPECIFIC DEATH

		Melanoma-specific death	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Urban-rural 6-fold	**1= Large urban area**	344	1	1
	2=Other urban area	295	1.08 (0.91-1.30)	0.95 (0.76-1.18)
	3=Accessible small town	69	0.80 (0.64-1.01)	0.53 (0.33-0.87)
	4= remote small town	50	1.34 (1.03-1.75)	1.03 (0.77-1.37)
	5= Accessible rural	107	0.93 (0.77-1.11)	0.90 (0.70-1.17)
	6=Remote rural	72	1.11 (0.92-1.33)	1.09 (0.87-1.37)
Sex	**Female vs Male**	381	0.54 (0.47-0.62)	0.68 (0.57-0.81)
Age mean(sd)	**(+1 year)**	66.4 (15.4)	1.03 (1.02-1.03)	1.02 (1.02-1.03)
Deprivation (SIMD)	**1 = Most deprived**	148	1	1
	2	195	1.03 (0.83-1.27)	1.03 (0.84-1.27)
	3	209	0.94 (0.74-1.20)	0.74 (0.58-0.96)
	4	193	0.78 (0.61-0.99)	0.79 (0.61-1.02)
	5 = Least deprived	193	0.63 (0.53-0.75)	0.61 (0.45-0.81)
Setting of excision	**Secondary care**	875	1	1
	Primary care	63	0.76 (0.58-0.99)	0.91 (0.65-1.29)
Anatomical Site	**Head and Neck**	198	1	1
	Body	286	1.16 (1.04-1.29)	1.38 (1.10-1.74)
	Upper Limb	145	0.76 (0.62-0.92)	0.93 (0.71-1.21)
	Groin and Lower Limb	236	0.93 (0.81-1.05)	1.24 (0.87-1.77)
Melanoma Sub-type	**Superficial spreading**	226	1	1
	Nodular	218	6.53 (5.47-7.81)	2.71 (2.11-3.48)
	Lentigo	49	0.95 (0.65-1.40)	0.82 (0.56-1.22)
	Acral	42	4.44 (3.25-6.05)	2.32 (1.59-3.40)
	Others	270	4.25 (3.52-5.14)	1.83 (1.54-2.19)
Breslow thickness median(IQR)		3.9 (2, 6.5)	1.15 (1.12-1.18)	1.13 (1.10-1.16)
Metastasis at presentation	**Yes**	226	10.75 (8.89-12.99)	4.35 (3.24-5.84)
Charlson Index	**0**	809	1	1
	1	51	1.76 (1.38-2.24)	1.28 (0.96-1.70)
	2	54	1.82 (1.49-2.24)	1.04 (0.70-1.54)
	3+	24	5.56 (3.41-9.06)	2.96 (1.65-5.28)

*Adjusted for sex, age, deprivation, setting of excision, anatomical site, melanoma sub-type, Breslow thickness, metastasis at presentation, Charlson index except where the variable itself is being examined

FIGURE 1: Kaplan Meier curve displaying cumulative all cause survival proportions by six-fold Urban-rural classification (in months) from the date of melanoma diagnosis

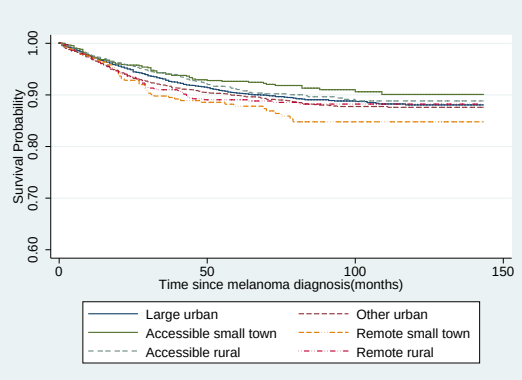


FIGURE 2: Kaplan Meier curve displaying cumulative melanoma-specific survival proportions by six-fold Urban-rural classification (in months) from the date of melanoma diagnosis

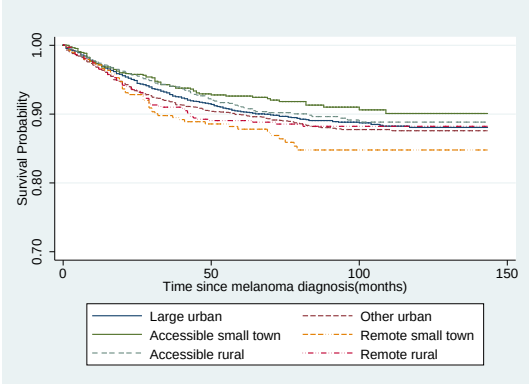
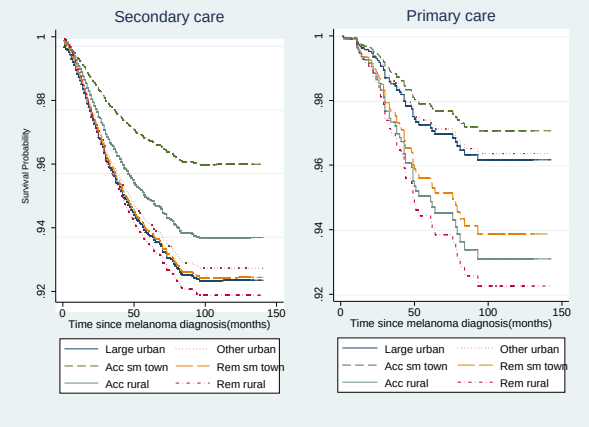


FIGURE 3: Kaplan Meier curve displaying cumulative melanoma specific survival proportions by six-fold Urban-rural classification (in months) from the date of melanoma diagnosis stratified by setting of excision

Abbreviations: Acc accessible; Rem remote; sm small



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 and RA conceived the study. The study was designed by PM, RA, WLK, EAR, DHB, LI and AJL. PM and WLK conducted the analysis supervised by EAR and AJL. PM wrote the manuscript with comments and contributions from RA, WLK, 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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Impact of rurality on melanoma management and outcomes

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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.