Analysing the impact of living in a rural setting on the presentation and outcome of colorectal cancer. A prospective single centre observational study.

Abstract

Introduction

Approximately 17% of the Scottish population lives in a remote or rural location. Current research is contradictory as to whether living a rural location leads to poorer outcomes or affects survival from colorectal cancer (CRC). We aimed to assess if living in a rural location influences outcome of CRC patients in 21st century UK medicine.

Methods

A prospective single-centre observational study was conducted. All patients who underwent resection for colorectal cancer 2005-2016 in NHS Grampian were included. Patients were split into two groups for comparison (urban post-code vs rural) using the Scottish government two-tier classification system. Tumour location, one-year survival, lymph node involvement and extra-mural vascular invasion was recorded and compared between the groups.

Results

Of 2463 patients, 843 (34.2%) lived in a rural area. Rural patients were more likely to be detected through screening (17.4% versus 14.6%, p=0.04). There were no differences in pathology between rural and urban groups if detected through screening. However, rural patients detected through symptomatic pathways were

more likely to be node positive p=0.015. On multivariable analysis, rurality did not independently predict for node positive presentation. Furthermore, there were no differences in cumulative survival between the two groups.

Conclusion

Although there were some differences in pathological characteristics between rural and urban patients, place of residence did not independently predict for outcome in this cohort. Rurality had previously been shown to impact on outcome up to 20 years ago. Improvements in infrastructure and rural healthcare may have influenced this change.

Introduction

Cure from colorectal cancer (CRC) is influenced by a many different characteristics. Tumours detected at an earlier stage have a significantly improved survival profile to those identified with local progression or distant spread. The one-year survival rate for stage one CRC is 98% versus only 40% for stage four. (Cancer research UK, 2016 figures). The pathological factors influencing potential cure include extra-mural vascular invasion[1], nodal status[2], complete excision[3] and location within the colorectum[4]. In addition, patient characteristics such as age[5], co-morbidity[6] and lifestyle choices[7] influence outcome. However, it remains unclear if living in different regions of the country adversely influences the ability to survive a CRC diagnosis[8-10].

At present, environmental influences on cancer presentation and survival have been identified but their interactions are not fully established. The micro-environment in which the colon is exposed has been predicted to be responsible for the development of this disease[11]. Diet, pollutants and smoking status[12] can change the epithelial environment and potentially cause neoplastic change. However, the macro-environment in which an individual lives their daily lives may also have a role in cancer development and outcome. Individuals who live in an urban setting are exposed to more environmental carcinogens in their daily life than those living in more remote areas[13]. However, people living in an urban region may have easier access to healthcare services as they live closer to primary care practitioners and hospitals in comparison to rural patients. It is therefore possible that a patient's place of residence (i.e. living in a rural vs urban location) may influence their potential to develop CRC, and their time to presentation once a malignancy has developed.

Rurality has previously been associated with poorer survival of cancers (not defined into specific organs or body regions)[9,14]. Other analyses have shown that rurality may decrease the uptake of colorectal screening programmes[15] but impair access to specialist care[16]. However, these studies looked at American and Australian populations where patients live in far more remote locations than in the UK. Historical studies from the UK on the influence of rurality on cancer outcomes had demonstrated that living further away from a cancer centre did have an adverse effect on cancer outcome[8]. However, conflicting analysis reported reduced emergency admissions with CRC and an improved outcome in a rural cohort of patients in 1997-1998[10]. There is little contemporary analysis of whether living in a rural region influences CRC presentation and outcome.

Almost one million individuals in Scotland reside in remote and rural areas - 17.1% of the Scottish population[17]. Any disparity in presentation and outcome of people on the basis of their residence is therefore a substantial public health concern. Potentially high risk groups could be specifically targeted with education strategies and information. In this study we aim to analyse patients undergoing resection with curative intent for CRC in the NHS Grampian region (a single Scottish Health Board) to determine if living in rurally is associated with patient age at diagnosis, cancer stage, EMVI, nodal involvement, site of cancer or one-year survival following resection.

Methods

This is a prospective observational review in a single Scottish region. A prospectively maintained pathology database of all patients who had a colorectal cancer resected with curative intent between 2005 - 2016 at Aberdeen Royal Infirmary or Dr Gray's Hospital, Elgin was analysed. These two hospitals are the secondary care facilities for NHS Grampian which covers an area of 8,700 km^2, serves a total population of 586,380 people. (June 2017, National Records for Scotland).

Inclusion/ exclusion criteria

All patients with a CRC diagnosed in the study time frame, undergoing surgical resection with curative intent and whose residential postcode was available at the time of analysis were included. Patients with non-resectable CRC cancer due to frailty, distant metastasis and/ or significant co-morbidities, those whose postcode was not available and those lost to follow-up were excluded.

Definitions: measure of rurality and deprivation

Individual residential postcodes were used to assign a rurality score for each patient using the Scottish Government Rurality Index[17]. Postcodes were collected from patient records and then input into the Scottish Information Services Division database (Information Services Division, Scotland) giving a score of 1-6 for each patient, defined in table 1.

Patients were then grouped into two cohorts for analysis: urban = rurality score 1-4 vs remote = rurality score 5 or 6 using the Scottish Government 2-fold classification system, as previously described[17]. Non-symptomatic patients (those detected via the bowel screening programme) and symptomatic patients were also compared.

Deprivation was also calculated based on residential postcode. Deciles of the Scottish Index of Multiple Deprivation (SIMD) were assessed[18].

Site of cancer

Cancer were defined as proximal (appendix, caecum, ascending colon, hepatic flexure, transverse colon), distal (splenic flexure, descending colon, sigmoid colon) or rectal depending on location within the colorectum.

Outcomes

ISD data were explored to assess if patients were alive or not at the date of censor (21/12/2017).

Statistical analysis

All analysis was performed on SPSS v25 (IBM, New York). Categorical variables between rural and urban groups were assessed using the Chi squared test and ?continuous variables by the Mann Whitney U test. Survival analysis was performed by Kaplan Meier tests. Multivariable analysis for Node positive predictors was performed by binary logistic regression.

Ethical approval

This project was registered with the Research Governance department of the University of Aberdeen. Caldicott approvals were obtained by NHS Grampian Caldicott guardian and the project was reviewed by IRAS proportionate ethical review (IRAS project number 264006).

Results

Of 2562 patients, 2463 had residential postcode data available and were included in the study (96.1%). The remaining patients were of no fixed abode or lived in another region of the country. The number of people who lived in an urban region was 1620 (65.8%) region and 843 (34.2%) lived in a remote area. The median age of patients was younger in the rural group (70.5 years, IQR 62-78 Urban, and 69 years IQR 61-76 Rural; p=0.013). More rural patients were male (urban region 53.1% male vs rural region 57.9% male, p = 0.027). The proportion of rural patients with a rectal cancer that received neoadjuvant therapy (either chemoradiotherapy or radiotherapy) was 67.7% and it was 68.0% for the urban group, p=0.928. Interestingly, cancers detected through the national screening programme were 14.6% in the urban group and 17.4% in the rural group (p=0.04). Demographic data is summarised in table 2.

Patients detected via the bowel screening programme were then compared to those detected via referral for symptoms, summarised in table 3. In the screen-detected group there was no statistically significant difference in site, stage, nodal involvement or EMVI between groups. In the symptomatic group (those tumours detected out with the screening programme) no difference was found in site, stage at presentation or EMVI. There was however a higher degree of nodal involvement in rural patients presenting symptomatically (Rural 44.3% vs Urban 39.2% node positive at surgery, p=0.015).

A multivariable analysis was then performed to determine if a rural residence independently predicted for nodal disease at presentation. Rurality was factored against screening status, gender, age and deprivation. In this model, only screening

status was found to be independently predictive of node positive disease. (table 4). Median follow up of this cohort was 5 years. A Kaplan Meier curve was performed to analyse survival by urban or rural abode (figure 1) and this showed no difference in cumulative survival (p=0.500).

Discussion

In this analysis, the first of its type to be performed after the establishment of the bowel screening programme in the United Kingdom, we have identified some differences in presentation of CRC by rural residence. Patients living in a rural region are more likely to have their CRC detected by screening. In addition, a greater proportion of rural CRC patients were male. Although rurality had no influence on pathological characteristics in the screening group, symptomatic patients were more likely to have nodal disease. However, this was not found to be independent of other factors and did not appear to influence survival up to five years post operation.

Countries around the world have far more remote populations than Scotland: in the US and Australia patients may have to travel hundreds of kilometres for specialist treatment, particularly with the ongoing trend of centralisation of services. An Australian study showed that patients with rectal cancers had on average a 6% increase in mortality risk (95% CI, 3%-8%; $P < 0.001$) per 100km distance that they lived from a radiotherapy treatment centre[19]. Globally, rural dwellers were found to be 5% less likely to survive cancer when compared to their urban counterparts[14]. It is difficult to interpret these results in a smaller country with comparatively shorter distances to cancer centres such as those found in the UK.

In previous analysis of UK data, Campbell et al found that remote CRC patients were more likely to present and die as an emergency cases than urban patients. Rural patients, after diagnosis, had a small survival disadvantage with increasing distance[8]. Previous quantitative work 15 years ago found that delayed treatment

appeared to be more common in the rural population[20]. However each of these studies were conducted before the introduction of the Scottish Referral Guidelines for Suspected Cancer in 2002 and also before the bowel screening programme was widely introduced in the region (pilot commenced in 2006). A more recent qualitative study in 2018 had similar findings, suggesting attitudes amongst the rural population have not changed[21].

Our analysis adds to previous analysis in this field that has been conflicting in nature. In a study of eight cancers (with CRC making up 22.5% of total cases) patients with a journey of more than an hour to the cancer treatment centre were diagnosed more quickly and were more likely to receive treatment within the recommended time but despite this still had an increased mortality at one year following GP referral[9]. In contrast, Murage *et al* found that rural patients with CRC in North East Scotland 1997-1998 had improved three year survival when compared with the urban population despite longer travel times to their nearest GP surgery[10]. In 2008 the Scottish Government published it's 'Delivering for Remote and Rural Healthcare' report, with specific points on improving access to secondary care, infrastructure and emergency response and transport in rural areas. Our study suggests these interventions, alongside the introduction of the CRC screening programme have been effective with regard to CRC in this region. Improved health awareness in the rural community or better infrastructure may also influence this change in outcome. However, the specific reasons why such improvements are seen are beyond the scope of this analysis.

Our observation of a higher rate of screened detected cancers in rural patients is

interesting, since the impact of rurality on cancer-screening uptake has received relatively little attention generally in contrast to the effects of deprivation. Against the context of evidence from Australia that rural patients were less likely to attend for breast screening, a study comparing breast cancer screening uptake in Rural Australia and Scotland was published in 2015[22] and concluded, against expectation, that rural women were not less likely to attend for breast screening in either country. The issue has been largely unexplored in CRC screening so our findings are novel, interesting and should prompt further investigation.

The study has a number of strengths. It is based on a comprehensive database with 12 years of data for patients covering all of NHS Grampian. However, the nature of the study means that it is dependent on the accuracy of data recorded at the time. More than 95% of cases had an available postcode in this study, reducing the risk of bias.

The measure of deprivation was based on area rather than the individual which could affect the result. Access to public transport and variation in individual GP referral times or rates were not assessed. Furthermore, unfortunately it was not possible to compare specific physiological differences between patients in the rural vs urban groups such as BMI, frailty and co-morbid conditions, all factors which may affect survival and outcomes, as these were not available in this dataset. In addition, this study population only included patients with resectable CRC operated on primarily with curative intent: patients with inoperable disease were excluded from the study therefore it has not been possible to compare this group of patients in the rural and urban areas. This would be an interesting area for future research as it

would be useful to determine if there are any difference in stage IV cases between the rural and urban groups and also whether there is a difference in the number of patients in each group who are deemed unsuitable for surgery due to frailty or significant co-morbidities.

Conclusion

This study found no difference in cumulative survival for CRC patients living in more remote areas of the North-East Scotland when compared to patients living in urban areas when analysed over a median follow up period of five years. Patients from a rural region, when controlling for other factors had the same stage of cancer on resection. Our contemporary analysis of the influence of rurality of CRC outcomes show different results to historical papers and suggest that the rural population are no longer adversely affected in the management of CRC. Interestingly however, rural CRC patients are more likely to come from the national screening programme and the reasons for this finding would be an important question in future research.

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Class	Class Name	Definition
1	Large Urban Area	Settlements of 125,000 people and over.
2	Accessible Urban	Settlements of 10,000 to 124,999 people.
3	Accessible Small Town	Settlements of 3,000 to 9,999 people, and within a 30 minute drive time of a Settlement of 10,000 or more.
4	Remote Small Town	Settlements of 3,000 to 9,999 people, and with a drive time of over 30 minutes to a Settlement of 10,000 or more.
5	Accessible Rural	Areas with a population of less than 3,000 people, and within a 30 minute drive time of a Settlement of 10,000 or more.
6	Remote and Rural	Areas with a population of less than 3,000 people, and with a drive time of over 30 minutes to a Settlement of 10,000 or more.

Table 1: Scottish Government Urban Rural Classification Categories 2016.

	Urban	**Remote**	**P value**
Number of patients	1620	843	n/a
Female: Male (%)	759:861 (46.9% : 53.1%)	355: 488 (42.1% : 57.9%)	*0.027*
Age: Median (IQR)	70.5 (62-78)	69 (61-76)	0.031
Screen detected (%)	237 (14.6%)	147 (17.4%)	*0.04*
Site Proximal Distal Rectum	 692 (42.7%) 483 (29.8%) 445 (27.5%)	 351 (41.6%) 249 (29.5%) 243 (28.8%)	 0.766
Deprivation quintiles SIMD 1 (most deprived) SIMD 2 SIMD 3 SIMD 4 SIMD 5 (least deprived)	 92 (5.7%) 240 (14.8%) 383 (23.6%) 314 (19.4%) 591 (36.5%)	 0 (0%) 33 (3.9%) 204 (24.2%) 423 (50.2%) 183 (21.7%)	 <0.001

Table 2: Patient demographic, 2005-2016.

Screen Detected Cancers			
	Urban	**Remote**	**p value**
Number of patients	237	147	
Site			0.470
Proximal	72 (30.4%)	58 (39.2%)	
Distal	93 (39.2%)	47 (32.0%)	
Rectum	72 (30.4%)	42 (28.6%)	
T			
0	14 (5.9%)	3 (2.0%)	0.119
1	20 (8.4%)	20 (13.6%)	
2	45 (19.0%)	34 (23.1%)	
3	135 (57.0%)	73 (49.7%)	
4	23 (9.7%)	17 (11.6%)	
Nodal involvement			
No	148 (62.4%)	101 (68.7%)	0.30
Yes	89 (37.6%)	46 (31.3%)	
EMVI			
No	166 (70%)	112 (76.2%)	0.116
Yes	71 (30%)	35 (23.8%)	
Symptomatic Detected Cancers			
	Urban	**Remote**	**P value**
Number of patients	1383	696	
Site			
Proximal	620 (44.8%)	293 (42.1%)	0.470
Distal	390 (28.2%)	202 (29.0%)	
Rectum	373 (27.0%)	201 (28.9%)	
T			
0	54 (3.9%)	24 (3.4%)	0.683
1	74 (5.4%)	34 (4.9%)	
2	159 (11.5%)	75 (10.8%)	
3	759 (54.9%)	406 (58.3%)	
4	337 (24.4%)	157 (22.6%)	
Nodal involvement			
No	841 (60.8%)	388 (55.7%)	0.015
Yes	542 (39.2%)	308 (44.3%)	
EMVI			
No	933 (67.5%)	457 (65.7%)	0.199
Yes	450 (32.5%)	239 (34.3%)	

Table 3: Pathological characteristics by screening status.

Table 4: Multivariate Analysis for Predicting Nodal Disease

Factor	Odds Ratio	95% CI low	95% CI High	p value
Screening	Ref			*0.037*
Symptomatic	1.278	1.015	1.610	
Rurality	1.121	0.934	1.346	0.218
Urban	Ref			
Gender	1.130	0.961	1.346	0.140
Male	ref			
Age	1.000	0.992	1.007	0.919
SMID1	1.04	0.666	1.624	0.864
SMID 2	0.940	0.706	1.251	0.672
SMID 3	1.06	0.851	1.323	0.599
SMID 4	1.06	0.859	1.322	0.562
SMID 5	ref			

Figure 1: Survival analysis