

## Special Article – Gastric Cancer

# Prognostic Significance of Deprivation in Upper Gastrointestinal Cancer

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The aim of this study was to determine the influence of the Index of Multiple Deprivation (IMD) and Health Deprivation (HD) on upper gastrointestinal (UGI) cancer outcome.

Consecutive 1185 patients (697 oesophageal, 488 gastric cancer) were studied prospectively. Deprivation scores were calculated using the IMD of the Welsh Government. Mortality data were obtained from the Office for National Statistics (ONS) and this data, as well as survival data, were independently verified by the Welsh Cancer Intelligence and Surveillance Unit. Primary outcome measure was survival from diagnosis.

Median survival for gastric cancer patients was 8 months (0.25 to 64) compared with 10 months (0.25 to 62) for oesophageal cancer patients. Open and close laparotomy for all surgical patients was commoner in patients residing in deprived geographical areas with a 6.5% open and close rate in the least deprived IMD quintile versus 13.5% in the most deprived quintile ( $P=0.006$ ). On post-operative histopathology, IMD was associated with pT ( $r=-0.146$ ,  $P=0.043$ ), pN ( $r=-0.158$ ,  $P=0.029$ ), and pM stage ( $r=-0.189$ ,  $P=0.016$ ). On univariate analysis survival was associated with oesophageal versus gastric tumour site ( $P=0.028$ ), histopathological cell type ( $P<0.0001$ ), age ( $P<0.0001$ ), radiological (r) TNM stage ( $P<0.0001$ ), radical treatment intent ( $P<0.0001$ ), IMD ( $P<0.0001$ ) and HD ( $P<0.0001$ ). On multivariate analysis age (HR 1.021, 95% CI, 1.014-1.028,  $P<0.0001$ ), rTNM stage (HR 1.559, 95% CI, 1.427-1.704  $P<0.0001$ ), radical treatment intent (HR 0.338, 95% CI, 0.274-0.418,  $P<0.0001$ ), and IMD rank (HR 1.000, 95% CI, 1.000-1.000,  $P=0.084$ ) were associated with duration of survival.

In conclusion deprivation is an important prognostic indicator in UGI cancer.

**Keywords:** Gastric cancer; Oesophageal cancer; Deprivation; Surgery; Survival

## Introduction

Deprivation is a broad concept which describes limited access to the opportunities and resources which society might expect such as good health, a clean and safe living environment, and protection from crime [1]. Eight types of deprivation, or domains, have been described, including; employment, income, education, health, community, geographical access to services, housing, and physical environment. Multiple deprivation refers to the different types that might occur, and represents a far more profound notion than poverty alone. Deprivation varies geographically, and Wales is recognised as having relatively high levels when compared with England and several other European countries. Indeed, when compared with the UK as a whole, the general health of the population of Wales is significantly poorer with more emergency hospital admissions per capita, and an overall life expectancy one year shorter when compared with England [2].

Linear relationships between levels of deprivation and survival have been reported for no fewer than 44 of 47 specific anatomical cancer sites, including oesophageal, colon and rectal cancer [3]. Deprivation is also associated with an increased incidence of upper

gastrointestinal cancer [4,5], and several reports have highlighted a survival benefit for patients residing in less deprived geographical areas when compared with more deprived areas [6-8]. Discrepancies in cancer related survival cannot be explained entirely by differences in the stage at diagnosis [9,10] or by higher co-morbidity among patients from deprived backgrounds [11]. Moreover, a widening of survival inequality with time has been reported, whereby the improved outcomes experienced by patients living in less deprived geographical areas over the past 25 years have not been shared by patients from the more deprived areas [12-14]. The NHS Cancer Plan of September 2000 [15], and subsequent government targets introduced in 2003, was aimed at reducing such inequalities across the socio-economic divide, and specific and demanding NHS targets were set [16]. It remains to be established whether deprivation per se directly influences outcome in UGI cancer, and if so, whether the effect may be analogue or digital in nature. As prognosis for patients diagnosed with UGI cancer is often poor, the potential benefit from understanding and addressing reversible factors is substantial. The aims of this study were to determine the influence of deprivation on outcomes for patients with UGI cancer, with particular emphasis on survival following potentially curative therapy. The setting was a UK

cancer network serving a population of 1.4 million people.

## Materials and Methods

Between 1<sup>st</sup> August 2008 and 31<sup>st</sup> July 2012, a total of 1185 patients were diagnosed with UGI cancer and managed by the South East Wales UGI multidisciplinary team [median age 72 (22-97) years, 783 male, 402 female, 697 oesophageal, 488 gastric cancer, 903 adenocarcinoma (ACA), 206 squamous cell carcinoma (SCC)]. The details of these patients were collected prospectively and data was cross-referenced with the oncology (CANISC) database. Mortality data were obtained from the Office for National Statistics (ONS) and this data, as well as survival data, were independently verified by the Welsh Cancer Intelligence and Surveillance Unit. Deprivation rankings were designated for each patient using the Welsh Index of Multiple Deprivation (IMD) 2011 [17], as determined by the National Assembly for Wales [1]. This index gives the official measure of multiple deprivation for every postcode in Wales and is based on the eight previously described forms of deprivation. The country is divided into 1,896 areas each having about 1,500 people with the most deprived geographical area ranked 1 and the least deprived area ranked 1,896. The IMD for all areas was sub-classified into equally sized socio-economic quintiles; the most deprived group was labelled quintile 1, and the least deprived quintile 5. These cut-off points allowed subgroup analysis of patients from similarly deprived areas while facilitating comparison across the spectrum. Health deprivation (HD) was also examined, the indicators for which are cancer incidence, all-cause death rate, percentage of live single births <2.5kg, and the number of inhabitants with limiting long-term illness per 100,000 of the population. HD was similarly sub-classified into equally sized quintiles.

### Staging investigations

Patients deemed to have potentially curable tumours underwent diagnostic gastroscopy with histopathological confirmation of oesophageal or gastric cancer and computed tomography (CT) of the thorax and upper abdomen. Patients selected for radical treatment also underwent endoluminal ultrasound (EUS), CT Positron Emission Tomography (CT-PET) and laparoscopy, if appropriate. Tumours were staged according to the unified TNM classification of UGI cancer edition 6 [18] until 2010 and edition 7 [19] thereafter.

### Multidisciplinary management

Patients were initially discussed at one of three local multidisciplinary team (MDT) meetings and if deemed potentially curative they were then referred to and discussed at the regional South East Wales UGI MDT meeting. The MDT consists of seven specialist upper GI surgeons, oncologists, palliative care physicians, radiologists, pathologists, specialist nurses and dieticians. Patients were selected for appropriate radical treatment based on histopathological stage, co-morbidity, the technical feasibility of surgery and patient choice according to an algorithm described previously [20]. Those not suitable or in favour of radical therapy were offered palliative care by specialist palliative care physicians.

### American society of anaesthesiologists grade

The ASA grade was calculated for surgical patients as a measure of co-morbidity. The system has five grades: normal healthy individual; mild systemic disease that does not limit activity; severe systemic

disease that limits activity but is not incapacitating; incapacitating systemic disease which is constantly life-threatening; moribund, not expected to survive 24 hours.

### Surgical treatment

Surgery was performed by one or a combination of seven upper gastrointestinal surgeons working within the parameters of the MDT. For patients with oesophageal cancer a transhiatal resection as described by Orringer was performed in those with T1-2, N0 tumours [21]. It was also employed selectively for patients with adenocarcinomas of the lower third of the oesophagus which were more advanced (T3 N1) and for patients with associated significant comorbidity (ASA grade III). The remaining oesophageal cancer patients underwent standard subtotal oesophagectomy as described by Lewis or Tanner [22,23]. For those with gastric cancers it was the policy to perform a modified radical D2 resection with extended lymphadenectomy but preserving the pancreas and spleen where possible [24-26]. The definition of a potentially curative resection was that all visible tumours were removed and that both proximal and distal resection margins were free of tumour on histological examination. Morbidity and mortality included all in-hospital complications and deaths. Morbidities were recorded against a specific list agreed by all the surgeons involved and graded using the Clavien-Dindo Classification of surgical complications [27].

### Definitive chemoradiotherapy (dCRT)

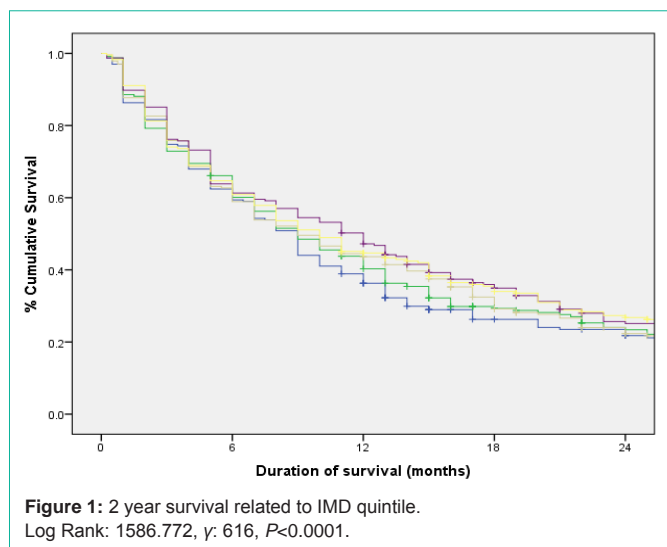
Patients undergoing dCRT received a treatment protocol which involved four 3-weekly cycles of cisplatin (dose 60mg/m<sup>2</sup>) and infusional 5-fluorouracil (5-FU, 300mg/m<sup>2</sup>/day). Cycles three and four were given concurrently with five weeks of radiotherapy (50Gy in 25F), during which time the 5-FU was reduced to 225mg/m<sup>2</sup>/day. If during the course of treatment the glomerular filtration rate (GFR) was less than 40ml/min or the patients experienced significant neuro- or nephrotoxicity, cisplatin was discontinued and replaced with carboplatin.

### Follow-up

Patients undergoing surgery were reviewed every three months for the first year and every six months thereafter. Definitive chemoradiation patients were followed up by the oncologists at equivalent periods. Endoscopy and CT were performed if recurrent disease was suspected. Patients treated with palliative intent were followed up by both oncology and palliative care physicians. All patients were followed up for a minimum of 6 months or until death, and no patients were lost to follow-up. Dates of death were obtained from the Office for National Statistics thus ensuring accurate survival times and dates of death for all patients. Nine hundred and eighty five patients (83.1%) were followed up for two years (n=157) or until death (n=828).

### Statistical analysis

Statistical analysis appropriate for non-parametric data was used. Grouped data were presented as median (range), and quintiles were grouped to allow accurate Cox regression analysis. Bivariate correlations were calculated using Spearman's correlation test. Differences were deemed statistically significant when  $P < 0.05$ . Cumulative overall survival was calculated by the life-table method of Kaplan and Meier [28]. Differences in survival between groups of



patients were analysed using the log-rank method [29]. Factors found to be significantly associated with duration of survival on univariate analysis and with  $P$ -value  $< 0.10$  were entered into a multivariate analysis using Cox's proportional hazards model. To identify any potential confounding factors, a separate stepwise regression was also performed using the univariate effect of deprivation as the first step. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS) version 20 package (IBM Corporation, New York) (Figure 1).

## Results

Demographic details of the patients related to quintile are presented in Table 1.

### Age at presentation

There was a direct correlation between age at diagnosis and IMD rank. Median age in the most deprived quintile (1) was 72 years (range 22-94) compared with 74 years (42-97) for patients in quintile 5 ( $r = 0.058, P = 0.046$ ). There was also a significant correlation between age at diagnosis and anatomical site of the tumour whereby the median age of patients presenting with oesophageal cancers (including type 1 and type 2 junctional tumours) was 71 (24-97) years, compared with 75 (22-97) years for patients presenting with gastric cancer, including type 3 junctional tumours ( $r = 0.146, P < 0.0001$ ).

### Anatomical site of tumour

There was no significant correlation between the anatomical site of the tumour and the IMD ( $r = -0.003, P = 0.905$ ) or HD ( $r = -0.017, P = 0.562$ ).

### Histopathology and stage of cancer at presentation

Details of patient's histopathology related to IMD quintile are presented in Table 1. There were 903 (76.2%) adenocarcinomas (ACA), 206 (17.5%) squamous cell carcinomas (SCC), and the remaining 6.3% comprised of high grade dysplasia (HGD), neuroendocrine tumours, or undifferentiated carcinomas. There was a significant association between a diagnosis of SCC and lower IMD quintiles ( $r = -0.059, P = 0.044$ ), and HD quintiles ( $r = -0.063, P = 0.030$ ). Females accounted for 121 (59%) of the 206 SCC cancers, with males making

**Table 1:** Demographic details of patients related to deprivation quintile.

Deprivation Quintile	1	2	3	4	5
Median IMD Rank	135	407	763	1274	1744
Range	(2-264)	(265-577)	(553-972)	(978-1558)	(1489-1896)
Median HD Rank	134	400	747	1134	1712
Range	(1-283)	(286-561)	(563-911)	(911-1431)	(1431-1895)
Median Age	72 (22-94)	72 (36-95)	73 (24-94)	71 (31-94)	74 (42-97)
Gender (M:F)	148:88	159:77	169:67	151:85	152:84
<b>Histological cell type</b>					
ACA	182	185	179	179	175
SCC	32	8	41	50	45
Undifferentiated	11	10	12	3	10
HGD	11	3	4	4	6
Oesophageal	138	136	145	131	145
Gastric	98	100	91	105	91
Surgery	37	50	46	50	46
dCRT	21	12	20	15	13
EMR	2	3	2	7	4
Palliative Rx	176	171	168	164	173

Figures are numbers of patients: IMD: Index of Multiple Deprivation; HD: Health Deprivation; ACA: Adenocarcinoma; SCC: Squamous Cell Carcinoma; HGD: High Grade Dysplasia; dCRT: Definitive Chemoradiotherapy; EMR: Endoscopic Mucosal Resection.

up the remaining 85 (41%,  $r = 0.241, P < 0.0001$ ). Radiological staging investigations revealed a strong correlation between EUS defined tumour length and both IMD and HD rank ( $r = -0.165, P = 0.025$  and  $0.026$  respectively). No correlation was found between the perceived rTNM stage at presentation and either IMD ( $r = -0.054, P = 0.089$ ), or HD ( $r = -0.048, P = 0.126$ ).

### Details of the surgery

A total of 229 patients (19.3%) were suitable for radical surgical treatment and their details are shown in Table 2. One hundred and nine patients had neoadjuvant therapy followed by surgery, and 120 patients had surgery alone. No correlation was found between IMD and perceived fitness for surgery as defined by the American Society of Anaesthesiology (ASA) grade ( $r = 0.016, P = 0.863$ ). Open and close laparotomy for all surgical patients was commoner in patients residing in deprived geographical areas with a 6.5% open and close rate in the least deprived IMD quintile versus 13.5% in the most deprived quintile ( $P = 0.006$ ). No correlation was found between IMD and operative morbidity (41.4% in quintile 1 versus 39.4% in quintile 5,  $r = 0.016, P = 0.841$ ), or HD and operative morbidity (51.7% in quintile 1 versus 48.4% in quintile 5,  $r = 0.041, P = 0.594$ ) respectively. Furthermore, there was no correlation between IMD or HD and operative mortality within 30 days of surgery (3.3% in quintile 1 versus 0% in quintile 5,  $r = -0.077, P = 0.318, r = -0.016, P = 0.834$  respectively). On post-operative histopathology, IMD was associated with pT ( $r = -0.146, P = 0.043$ ), pN ( $r = -0.158, P = 0.029$ ), and pM stage ( $r = -0.189, P = 0.016$ ).

### Palliative treatment

A total of 857 patients were considered to be of too poor performance status, or were diagnosed with tumours of such

**Table 2:** Details of the patients undergoing surgery.

Deprivation Quintile	1	2	3	4	5
No. of patients (%)	37 (16)	50 (21)	46 (19)	50 (21)	46 (19)
Median Age	67	64	65	67	66
Gender (M:F)	24:13:00	41:09:00	36:10:00	38:12:00	35:11:00
<b>Histopathology</b>					
ACA	34	49	41	45	44
SCC	1	1	4	5	2
HGD	2	0	1	0	0
<b>Site of Tumour</b>					
Oesophageal	15	22	19	23	19
Junctional	5	8	8	9	14
Gastric	17	20	19	18	13
<b>Overall Stage</b>					
HGD	2	0	0	0	1
I	6	16	9	14	14
II	10	9	21	10	16
III	15	19	14	25	14
IV	2	5	1	1	1
<b>Operative Procedure</b>					
TTO	6	3	8	13	12
THO	6	12	8	8	12
Total Gastrectomy	10	6	11	7	7
Subtotal Gastrectomy	6	13	9	12	9
Oesophago-Gastrectomy	1	3	2	2	2
<b>Emergency Procedures</b>	3	4	3	2	1
Open and Close	5	9	5	6	3
CRM positive (%)	5 (13)	6 (12)	7 (15)	11 (22)	13 (28)
<b>Operative Complications</b>					
Morbidity CD ≥ 3 (%)	6 (16)	2 (4)	10 (21)	8 (16)	3 (7)
Operative Mortality	1	0	3	0	0

Figures are numbers of patients: ACA: Adenocarcinoma; SCC: Squamous Cell Carcinoma; HGD: High Grade Dysplasia; TTO: Trans-thoracic Oesophagectomy; THO: Trans-hiatal Oesophagectomy; CRM: Circumferential Resection Margin; CD: Clavien Dindo.

advanced stage that radical treatment was not possible. These patients received palliative chemotherapy, radiotherapy, stent insertion or best supportive care in keeping with the patients' wishes.

### Survival

Median survival from diagnosis for all 1185 patients was 9 (range 0.25 to 64) months. With respect to the 229 patients who underwent potentially curative surgery median survival was 20 (range 1 to 64) months, and 21 (range 3 to 57) months for the 81 patients receiving definitive chemoradiotherapy.

The duration of survival from diagnosis was significantly associated with both IMD ( $P<0.0001$ ), and HD ( $P<0.0001$ ). There was a strong correlation between duration of survival and IMD for Siewert type I and II oesophago-gastric junctional cancers (log-rank 480.930,  $\gamma$  304,  $P<0.0001$ ). The median survival for patients diagnosed with

**Table 3:** Univariate analysis of factors associated with duration of survival.

Factor	Log rank	DF	p-value
Cancer Site	4.852	1	$p=0.028$
Age	178.628	67	$p<0.0001$
Radiological TNM Stage	315.129	4	$p<0.0001$
Histopathological cell type	44.186	3	$p<0.0001$
Radical Rx Intent	367.524	1	$p<0.0001$
Socio-Economic Rank	1586.772	616	$p<0.0001$
Health Deprivation Rank	1586.772	616	$p<0.0001$

oesophageal cancer was 9 months (range 0.25-55), and this increased to 18 months (range 3-55) for patients undergoing oesophagectomy. For patients who underwent oesophagectomy, there was a correlation between greater deprivation and shorter median survival (log-rank 325.504,  $\gamma$  97,  $P<0.0001$ ). When analysed by quintile, the median survival after oesophagectomy for patients in the three most deprived quintiles (1-3) was 16 months (range 3-46) compared with 23 months (range 5-55) for patients in the two least deprived quintiles (4-5).

For the 81 patients with oesophageal cancer treated with dCRT the median duration of survival was 18 months, and again there was a strong correlation between residing in a deprived geographical area and shorter duration of survival (log-rank 241.828,  $\gamma$  69,  $P<0.0001$ ).

The median survival for patients diagnosed with gastric cancer was 7 months (range 0.25-58), and this increased to 22 months (range 1-58) for patients undergoing gastrectomy. There was a strong correlation between duration of survival and IMD for all patients diagnosed with gastric cancer (log-rank 449.383,  $\gamma$  247,  $P<0.0001$ ). For patients who underwent gastrectomy, there was a correlation between greater deprivation and shorter median survival (log-rank 344.364,  $\gamma$  89,  $P<0.0001$ ). When analysed by quintile, the median survival after sub- or total-gastrectomy for patients in the three most deprived quintiles (1-3) was 24 months (range 1-64) compared with 27 months (range 3-57) for patients in the two least deprived quintiles (4-5).

### Univariate analysis

A univariate analysis of the factors influencing survival is shown in Table 3.

### Multivariate analysis

Factors found to be associated with survival at the  $P<0.10$  level on univariate analysis (age, IMD rank, HD rank, pre-operative rTNM stage, histopathology and radical treatment intent) were entered into a multivariate analysis using Cox's proportional hazards model, Table 4.

### Discussion

This is the largest study of the effect of deprivation on outcomes in patients diagnosed with UGI cancer including almost 1200 patients over a four-year period. The principal findings were that both IMD and HD were strongly associated with adverse outcomes for patients diagnosed with UGI cancer, and overall deprivation was associated with duration of survival. Despite developing disease at a younger age, being of similar stage of disease at diagnosis, and being offered similar treatment protocols, patients residing in the most deprived

**Table 4:** Multivariate analysis of factors associated with duration of survival.

Factor	HR	Confidence Interval (95%)	P-value
Age	1.021	1.014-1.028	$p < 0.0001$
Curative Rx Intent	0.338	0.274-0.418	$p < 0.0001$
Radiological TNM Stage	1.559	1.427-1.704	$p < 0.0001$
Index of Multiple Deprivation	1	1.000-1.000	$p = 0.084$

geographical areas were more likely to have significantly shorter median duration of survival than patients in the least deprived geographical areas. No differences were found in the proportion of patients receiving treatment with curative intent related to deprivation quintile, and similar proportions of patients from each quintile were offered surgery, definitive chemoradiotherapy and palliative care. Despite equal proportions of patients from more deprived backgrounds meeting mandatory performance status criteria for surgery, survival was significantly shorter than for patients from less deprived backgrounds.

This study has a number of limitations. Deprivation exists in a number of forms and this multimodal complexity makes quantification challenging. Important discrepancies in outcome and duration of survival between UGI cancer patients from different socio-economic backgrounds were identified, but no explanation emerged as to why this should be so. This study used deprivation scores measured at the area level, i.e. each individual was given a score based on the degree of deprivation of their local community. The use of such area-based deprivation scores, as opposed to individual-based scores, calculated on individuals' incomes or occupations, does introduce potential bias, given that it is unlikely that all residents of a specific postcode will have the attributes of that community (the ecological fallacy) [30]. There is however a clear distinction between poverty (insufficient financial resources) and deprivation (insufficient multiple resources, including financial). IMDs are an accurate measure of true deprivation, taking into account poverty, housing, access to services, health and physical environment. Survival was calculated using all-cause mortality and it is likely that some patients will have died of causes other than progressive or recurrent oesophageal or gastric cancer. This is of particular relevance when considering deprivation, as it is acknowledged that patients from more deprived areas have a higher proportion of many chronic diseases, and their mortality is therefore higher than that of patients from more socio-economically advantaged areas. This latter point is, however, controversial as it has previously been reported that disease-specific mortality provides the most accurate measure of survival when no information regarding co-morbidity is available [31]. Certainly other investigators have reported that the assignment of cancer as a cause of death may be influenced by deprivation [32], and it is therefore probable that the true oesophago-gastric cancer survival rate lies somewhere midway between these two extremes. This was a comparative study, and the definition and analysis of subgroups within a study may lead to bias, while comparisons of groups may prove to be not statistically significant simply because the study has insufficient power to demonstrate real differences. The use of quintiles (as opposed to quartiles or deciles, for example) was arbitrary, and it is not clear from the results presented here whether there is an analogue correlation between deprivation and outcome or whether the effect is binary, with a critical level of deprivation above

which adverse outcomes become more likely.

The strengths of the study are that prospectively collected data for unselected consecutive patients from a well-defined geographical area were used, a significant proportion of whom reside in areas shown to be amongst the most deprived in the United Kingdom. Access to the IMDs for over 99.5% of all the patients adds further strength. The prognostic data are especially robust, with over 83% of patients followed up for at least 24 months or until death. All patients were managed by a specialist MDT whose results are well audited and can stand up to international scrutiny [20]. Furthermore, the accuracy of the survival data is especially robust, as the dates for death were confirmed by the Office for National Statistics and outcomes have also correlated with independent formal analysis by Welsh Assembly Government healthcare statisticians.

The most important prognostic factor in patients diagnosed with oesophageal or gastric cancer has, by tradition, been the stage of disease at diagnosis [33]. This study however, failed to demonstrate any correlation between deprivation and the perceived radiological tumour stage at diagnosis. The study did find that for all patients treated, and particularly those who had undergone surgery, those from least deprived geographic areas had longer median durations of survival. Similar proportions of the more deprived patients progressed to surgery and this could potentially be explained by a more focused input from allied healthcare professionals, dieticians and physiotherapists in particular, to optimise pre-operative performance in patients from more deprived geographical areas who tend to have poorer health and increased rates of cardio respiratory related diseases [34,35]. The findings contrast with a previous study which reported no association between duration of survival after oesophagectomy for cancer and deprivation [30], but were in keeping with Stephens *et al* who reported deprivation was associated with shorter duration of survival following gastrectomy for cancer [20]. Both of these reports utilised an earlier more embryonic version of the Wales IMD.

## Conclusion

In conclusion, the Acheson report highlighted the need for action across the whole of society to address the deep-seated inequalities in our health [36]. The UK Government responded by pledging a commitment to this end, inviting the independent Scientific Reference Group on Health Inequalities to oversee implementation and assess outcomes [37]. In the subsequent decade, life expectancy for males and females living in the 70 local authority areas with the worst health and deprivation indicators in England have increased by 2.9 and 1.9 years respectively, compared with 3.1 and 2.1 years for the population as a whole. This highlights the point that although the health of society's most deprived has improved, the gap between society's most and least deprived has failed to narrow [37,38] and further research and effort to address these health care and deprivation related inequalities is warranted.

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