National Bowel Cancer Audit

Adjuvant Chemotherapy Short Report

NBOCA: Short Report

Date of publication: Thursday 11th July 2019

About HQIP, the National Clinical Audit and Patient Outcomes Programme and how it is funded:

The Healthcare Quality Improvement Partnership (HQIP) is led by a consortium of the Academy of Medical Royal Colleges, the Royal College of Nursing and National Voices. Its aim is to promote quality improvement in patient outcomes, and in particular, to increase the impact that clinical audit, outcome review programmes and registries have on healthcare quality in England and Wales. HQIP holds the contract to commission, manage and develop the National Clinical Audit and Patient Outcomes Programme (NCAPOP), comprising around 40 projects covering care provided to people with a wide range of medical, surgical and mental health conditions. The programme is funded by NHS England, the Welsh Government and, with some individual projects, other devolved administrations and crown dependencies. www.hqip.org.uk/national-programmes

Executive Summary

The benefits of adjuvant chemotherapy for stage III colon cancer are well-established and have been shown to improve overall survival rates. Establishing variation in the use of adjuvant chemotherapy is therefore important. This short report aimed to evaluate current national practice and variation in the use of adjuvant chemotherapy for stage III colon cancer.

60.7% of patients with stage III colon cancer deemed potentially eligible for chemotherapy were found to have received it. The strongest predictor of chemotherapy use was age. Other factors influencing adjuvant chemotherapy use included socioeconomic status, co-morbidity score, performance status, ASA grade, urgency of procedure, type of surgery (laparoscopic/open), stage of disease and unplanned post-operative readmissions.

After risk-adjustment there was significant variation in adjuvant chemotherapy use at a hospital-trust level suggesting that some patients may not be receiving optimal adjuvant therapy. This variation is greatest in patients aged 70 or above suggesting that advanced age alone may be a barrier to chemotherapy use in some hospital-trusts.

Introduction

The benefits of adjuvant chemotherapy (ACT) for stage III colon cancer have been well-established since 1990.[1] Current National Institute for Health and Care Excellence (NICE) guidelines recommend ACT in fit patients.[2] The most recent NBOCA report suggested only 54% of patients with stage III colorectal cancer in the English NHS (National Health Service) received ACT and regional variation existed.[3] ACT has been shown to improve overall survival by 20%-33%, meaning underutilisation is of importance.[4]

In the UK, variation in chemotherapy use has previously been reported[5] but the reasons underlying this are not well understood. Age has consistently been shown to be one of the strongest determinants of chemotherapy receipt.[6-7] This is crucial in the context of an ageing population and with a current focus on the under-treatment of elderly patients with cancer. Establishing variation in practice and understanding the associated underlying factors may facilitate increased rates of ACT use and help to improve survival outcomes. Within the English NHS, hospital-level care is provided by 'hospital- trusts' which may consist of an individual hospital or several hospitals combined.

This short report aims to explore current national practice in the use of ACT in stage III colon cancer in England as well as determinants of ACT use according to patient, clinical and hospital-trust characteristics. In addition, we explore hospital-trust variation in ACT use and possible reasons for this variation.

Methods

National Bowel Cancer Audit (NBOCA) data

NBOCA patients diagnosed with colon cancer between 01 April 2014 to 31 March 2017 who had undergone major resection with pathological stage III disease were identified. Patients were linked to Hospital Episode Statistics Admitted Patient Care (HES-APC). The final NBOCA-HES-APC cohort consisted of 11,932 patients deemed potentially eligible for ACT from all 142 English NHS Trusts.

Systemic Anti-cancer Therapy (SACT) data

The SACT database[8] mandated submission of data by all English NHS providers of chemotherapy in any inpatient, day case, outpatient or community setting from April 2014. SACT data

was available from 01 April 2014 to 30 September 2017 providing a minimum of 4 months chemotherapy data for every patient. SACT includes regimen start date and planned regimen choice.

SACT data is currently not available for Wales and explains why this short report only includes patients diagnosed in England.

Identification of patients receiving ACT

Eligible patients were considered to have received ACT if they linked to a SACT record demonstrating receipt of any potentially curative colorectal chemotherapy regimen within the 4-month post-operative period.

We validated ACT use using HES-APC. All records for inpatient admissions for each patient during their 4-month post-operative period were searched for relevant chemotherapy codes (OPCS-4 (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision) and ICD-10). For the main analysis, 7,239 patients with a chemotherapy record in either SACT or HES-APC were considered to have received ACT.

Statistical analysis

Multivariable random-effects logistic regression was used to estimate associations between ACT use and the explanatory variables including sex, age, pathological tumour, node, metastasis (TNM) staging, surgical urgency, performance status, American Society of Anesthesiologists (ASA) grade (assessment of fitness before surgery), surgical access, RCS Charlson co-morbidity score, socioeconomic status (IMDQ - Index of Multiple Deprivation quintile) and unplanned post-operative readmissions.

Hospital-trust characteristics were also included based on the hospital-trust recorded in NBOCA as performing the surgical procedure. University teaching hospital-trusts were identified from the Association of United Kingdom University Hospitals.[9] On-site chemotherapy presence was collected via the NBOCA organisational survey.[10] Hospital-trusts were categorised as high-volume if they performed, on average, >100 colorectal cancer (CRC) resections per year as this represented the median value.

A random intercept was modelled for each hospital-trust to account for clustering. Missing values for determinants were imputed with multiple imputation using chained equations, creating ten datasets and using Rubin's rules to combine the estimated odds ratios across the datasets.[11]

Hospital-trust variation in ACT use was explored visually using funnel plots.[28] Funnel plots containing two sets of funnel limits helped to establish whether the between-hospital-trust variation in the proportion of patients receiving ACT was greater than expected by chance alone. Separate fully-adjusted funnel plots were generated for all patients (Figure 1a), patients <70 years only (Figure 1b), and patients ≥70 years only (Figure 1c), to explore whether age explained any between-hospital-trust variation. All hospital-trusts had at least 10 patients eligible for ACT and therefore all 142 hospital-trusts were included in the funnel plot for all patients. Hospital-trusts with fewer than 10 patients <70 years or fewer than 10 patients ≥70 years were excluded from both the young and elderly funnel plot analyses (135 hospital-trusts included).

The intra-class correlation coefficient (ICC) was used to quantify the between-hospital-trust variation in a fully-adjusted random-intercept logistic regression model. The ICC is the proportion of the total variance that is between hospital-trusts despite adjustment for all other determinants with larger values demonstrating greater variation.

To identify sources of between-hospital-trust variation the ICC was estimated in 8 strata of the cohort: young (<70 years) versus elderly (≥70 years); non-comorbid (Charlson=0) versus comorbid (Charlson≥1); performance status 0-1 versus performance status ≥2; and low (IMDQ 1-2) versus high (IMDQ 3-5) socioeconomic status. Rather than re-estimate the risk-adjustment model eight times, one

risk-adjustment model was estimated in all patients and used for each stratum. By examining the size of the ICC across the strata, sources of between-hospital-trust variation could be identified and an independent samples t-test used to calculate two-tailed p-values (0.05 significance level) for each factor.

Results

Determinants of ACT use

7,239 patients (60.7%) were identified as receiving ACT. Table 1 (page 6) presents a univariate analysis of patient, clinical and hospital-trust characteristics stratified by receipt of ACT. It also presents results from the multivariable random-effects logistic regression model.

The strongest predictor for ACT use was age. Compared to patients aged <60 years, patients aged 70-74 years, 75-79 years and ≥80 years respectively were increasingly less likely to receive ACT despite adjustment for all other factors. Although ACT use reduced with age, a substantial proportion of younger patients also did not receive chemotherapy.

Other patient characteristics associated with increased ACT use included higher socioeconomic status (IMDQ 3-5), no co-morbidities (Charlson score 0), better performance status (0), and lower ASA grade (ASA I-II). Clinical characteristics associated with increased ACT use included having an elective procedure, undergoing laparoscopic resection, having more advanced disease (T3/T4 or N2 disease) and no unplanned post-operative readmissions. None of the hospital-trust characteristics were associated with ACT use.

Variation between hospital-trusts

ACT use varied substantially between hospital-trusts. The observed hospital-trust proportion of chemotherapy administered ranged from 26%-86%. Amongst patients <70 years, the observed hospital-trust proportion ranged from 46%-100% (80% of hospital-trusts were between 74%- 90%) compared to 10%-81% of patients ≥70 years (80% of hospital-trusts were between 33%-65%).

Adjustment for factors included in the multivariable model did not reduce hospital-trust variation for all patients (Figure 1a, page 7). For patients <70 years, the adjusted proportion was 45%-100% with 10 hospital-trusts outside the 95% funnel limits (Figure 1b, page 7) compared to patients ≥70 years with 14%-76% and 26 hospital-trusts outside the 95% funnel limits (Figure 1c, page 8). Assuming differences arise from random errors alone, the expected number of hospital-trusts outside the 95% funnel limits for all analyses is 7 (5%).

The ICC for patients <70 years was 2.7% (95% CI, 1.2%-5.7%). This provides the proportion of the total variance that is between hospital-trusts in patients aged <70 years despite adjustment for all other factors. In patients ≥70 years this was 9.9% (95% CI, 7.2%-13.4%). A significantly greater proportion of the variance between hospital-trusts is demonstrated in patients aged ≥70 years compared to patients aged <70 years (p=<0.001). Differences in ICCs by co-morbidity, performance status and socioeconomic status were not statistically significant (Figure 2, page 9).

Summary and conclusions

This short report presents an evaluation of current practice and variation in ACT use for stage III colon cancer in England. Overall, we identified that 61% of patients undergoing major resection for pathological stage III colon cancer were given ACT.

We found that patients were more likely to have ACT if they were younger, fitter, less deprived and had more advanced disease. Increasing age shows a major association with reduced

ACT use (despite adjustment) and is unlikely to be completely explained by factors we have not fully adjusted for.

ACT use was increased in those patients having elective surgery, laparoscopic procedures, and those who did not have unplanned post-operative re-admissions. Patients undergoing elective procedures have a reduced mortality compared to those undergoing emergency surgery. However, only 5% of our cohort died, making death before administration of ACT unlikely to explain all of the effect. Reasons are likely multifactorial and include elements that delay recovery such as post-operative complications and stoma presence. Stomas may lead to problems such as dehydration and electrolyte imbalances which can delay or prevent ACT administration.

Similarly, laparoscopic procedures may increase ACT use due to fewer complications, faster recovery and reduced inflammatory response. Unplanned re-admissions are generally due to post-operative complications and, again, may prolong recovery and negate timely ACT administration. Hospital-trust characteristics were not associated with ACT use.

We were unable to account for clinical appropriateness of ACT administration. In addition, although we accounted for co-morbidities, performance status and ASA grade, we were unable to measure the presence or severity of individual conditions. For example, significant ischaemic heart disease would be a contraindication to ACT. We could not account for patient refusal although this has been quoted in the literature as being approximately 10%.

There is general variation in ACT use in hospital-trusts across England and this variation is most marked in those patients ≥70 years. Advanced age alone should not be a barrier to ACT use and highlights the urgency of geriatric input, education and elderly-specific guidelines. Variation between hospital-trusts did not seem to be explained by socioeconomic status, co-morbidities or performance status.

Individual provider comparative monitoring and reporting would help to monitor and address hospital-trust variation in ACT use. We suggest that all colorectal multidisciplinary teams involving surgeons and oncologists review their pathways for patients with stage III colon cancer and assess their criteria for offering adjuvant chemotherapy with a view to increasing the uptake of this important treatment.

In the future, it would be helpful to better understand the reasons behind which patients are offered chemotherapy for stage III colon cancer. This would include recording why the patient has not been given ACT. This would help to get an understanding of the reasons for not giving ACT e.g. contraindication, frailty and patient choice. In addition, this might provide information as to what degree the use of ACT is determined by individual clinician practice, informed patient choice or multidisciplinary team shared decision-making.

It is expected that future developments in understanding subtypes of colon cancer based on different genetic and molecular patterns will provide additional information for us to make decisions about which patients may benefit from ACT. This may include the development of new ACT agents tailored to specific colon cancers.

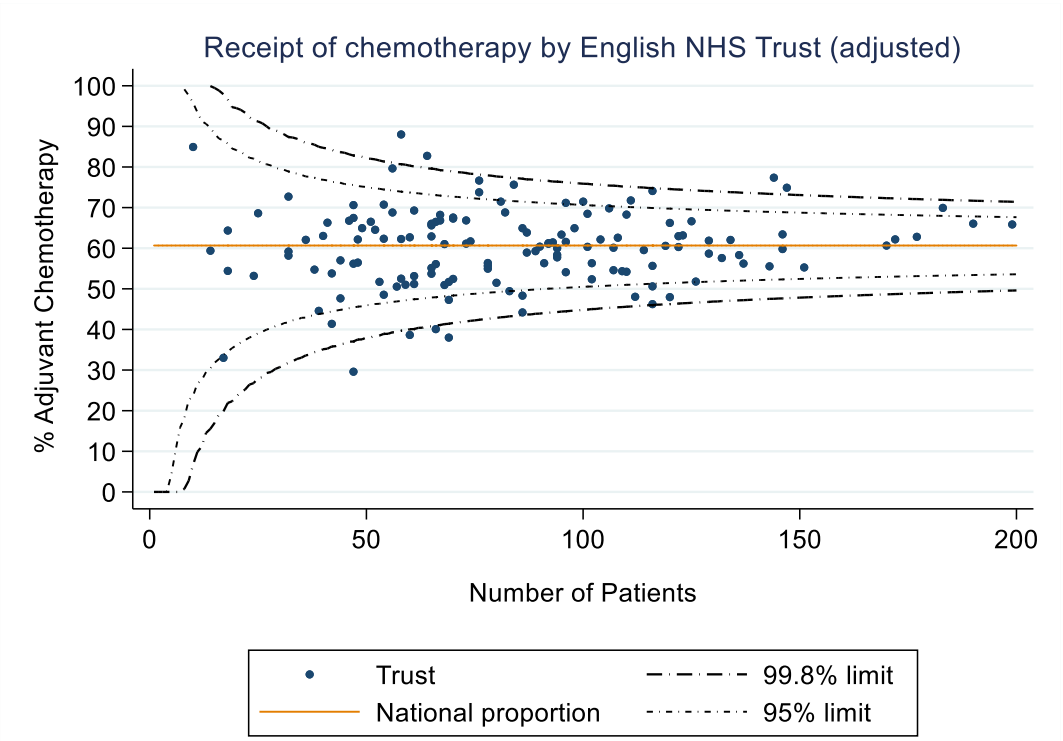
We are not currently making any recommendations on the basis of this short report but will be developing this work in the future within our annual reports. We are planning on reporting unadjusted adjuvant chemotherapy rates for stage III colon cancer in the 2019 annual report.

Table 1 - Patient, clinical and hospital-trust characteristics stratified by ACT use, with adjusted results from multivariable logistic regression analyses for determinants of patients receiving ACT.

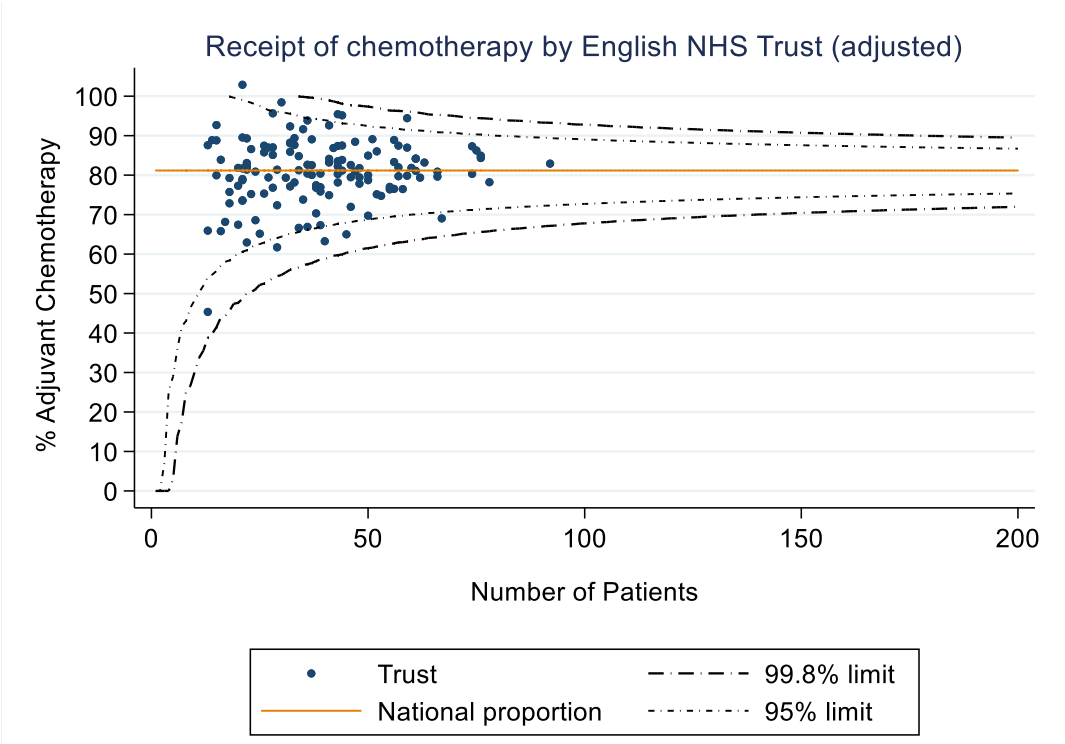
	Total (%) n=11,932	Received ACT (%) n=7,239	p value (X^2)	Adjusted odds ratios (95% CI)	p-value
Patient characteristics					
Sex			0.009		0.368
Male	6,227 (52.2)	3,847 (61.8)		1.0	
Female	5,705 (47.8)	3,392 (59.5)		0.96 (0.88-1.05)	
Age (years)			<0.001		<0.001
<60	2,267 (19.0)	1,933 (85.3)		1.0	
60-64	1,320 (11.1)	1,065 (80.7)		0.76 (0.63-0.93)	
65-69	1,758 (14.7)	1,341 (76.3)		0.63 (0.54-0.74)	
70-74	1,996 (16.7)	1,423 (71.3)		0.53 (0.44-0.62)	
75-79	1,976 (16.6)	992 (50.2)		0.23 (0.19-0.27)	
≥80	2,615 (21.9)	485 (18.6)		0.05 (0.04-0.06)	
Socioeconomic status (IMDQ)			0.149		0.002
1 (most deprived)	1,815 (15.2)	1,061 (58.5)		1.0	
2	1,990 (16.7)	1,193 (60.0)		1.11 (0.93-1.33)	
3	2,603 (21.8)	1,602 (61.5)		1.29 (1.10-1.50)	
4	2,742 (23.0)	1,666 (60.8)		1.22 (1.05-1.42)	
5 (least deprived)	2,759 (23.1)	1,708 (61.9)		1.36 (1.15-1.60)	
Missing	23	9			
RCS Charlson score			<0.001		<0.001
0	6,428 (53.9)	4,425 (68.8)		1.0	
1	3,344 (28.0)	1,913 (57.2)		0.80 (0.72-0.90)	
≥2	1,524 (12.8)	570 (37.4)		0.50 (0.44-0.58)	
Missing	636	331			
Performance status			<0.001		<0.001
0	4,989 (41.8)	3,724 (74.6)		1.0	
1	3,424 (28.7)	1,974 (57.7)		0.83 (0.73-0.95)	
2	1,319 (11.1)	521 (39.5)		0.54 (0.45-0.65)	
≥3	441 (3.7)	67 (15.2)		0.17 (0.13-0.24)	
Missing	1,759	953			
ASA fitness grade			<0.001		<0.001
I	1,469 (12.3)	1,182 (80.5)		1.0	
II	6,091 (51.1)	4,226 (69.4)		0.95 (0.81-1.12)	
III	3,272 (27.4)	1,339 (40.9)		0.56 (0.50-0.63)	
IV or V	365 (3.1)	72 (19.7)		0.24 (0.18-0.32)	
Missing	735	420			
Clinical characteristics					
Urgency of resection			<0.001		0.001
Elective/scheduled	9,005 (75.5)	5,668 (62.9)		1.0	
Emergency/urgent	2,908 (24.4)	1,560 (53.7)		0.80 (0.71-0.91)	
Missing	19	11			
Surgical access			<0.001		<0.001
Open	4,885 (40.9)	2,689 (55.1)		1.0	
Laparoscopic-converted	971 (8.1)	580 (59.7)		1.0 (0.83-1.19)	
Laparoscopic	6,035 (50.6)	3,947 (65.4)		1.28 (1.14-1.44)	
Missing	41	23			
Pathological T-stage			0.001		0.006
T1	241 (2.0)	155 (64.3)		1.0	
T2	706 (5.9)	471 (66.7)		1.35 (0.96-1.88)	
T3	5,976 (50.1)	3,639 (60.9)		1.47 (1.10-1.95)	
T4	5,004 (41.9)	2,971 (59.4)		1.61 (1.20-2.17)	
Missing	5	3			
Pathological N-stage			<0.001		<0.001
N1	7,620 (63.9)	4,464 (58.6)		1.0	
N2	4,312 (36.1)	2,775 (64.4)		1.31 (1.18-1.46)	
30-day post-op readmission			0.001		<0.001
No	10,921 (91.5)	6,675 (61.1)		1.0	
Yes	1,011 (8.5)	564 (55.8)		0.66 (0.56-0.77)	
Hospital-trust characteristics					
University teaching hospital			0.595		0.475
No	8,880 (74.4)	5,375 (60.5)		1.0	
Yes	3,052 (25.6)	1,864 (61.1)		0.93 (0.75-1.15)	
On-site chemotherapy			0.927		0.906
No	1,336 (11.2)	809 (60.6)		1.0	
Yes	10,596 (88.8)	6,430 (60.7)		0.99 (0.81-1.21)	
High volume centre (>100)			0.232		0.864
No	2,643 (22.2)	1,577 (59.7)		1.0	
Yes	9,289 (77.9)	5,662 (61.0)		1.02 (0.81-1.28)	

Figure 1 - Funnel plots demonstrating the proportion of patients who underwent major resection for pathological stage III colon cancer who received ACT at each hospital-trust, adjusted for all factors in Table 1.

a) All patients included (142 hospital-trusts included)



b) Patients aged <70 years only (135 hospital-trusts included).



c) Patients aged ≥70 years only (135 hospital-trusts included).

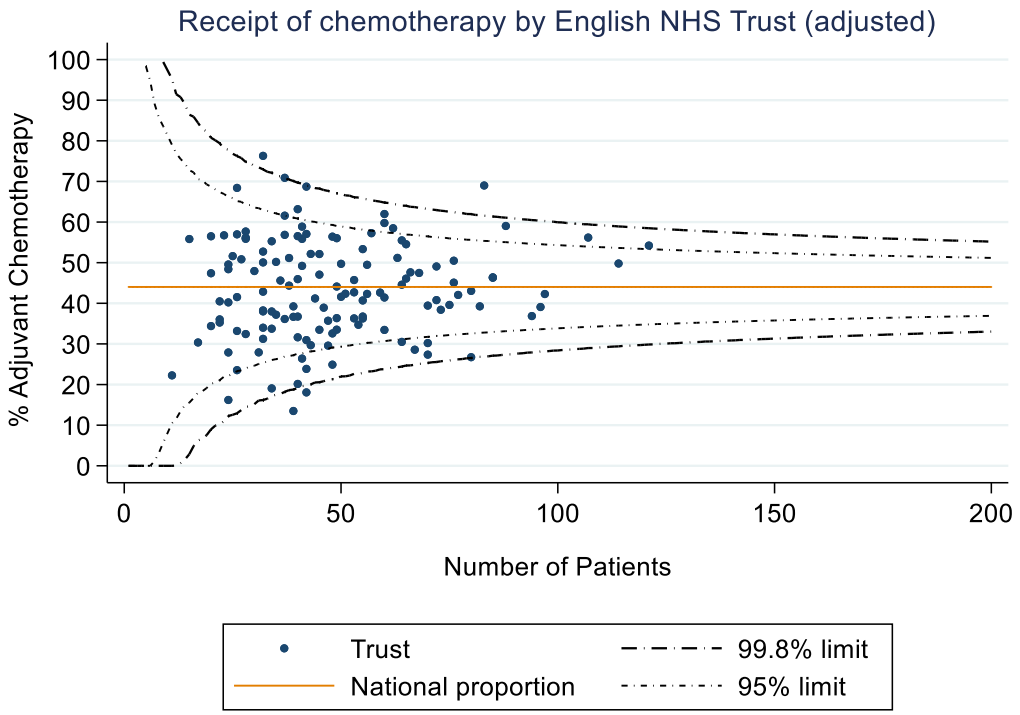
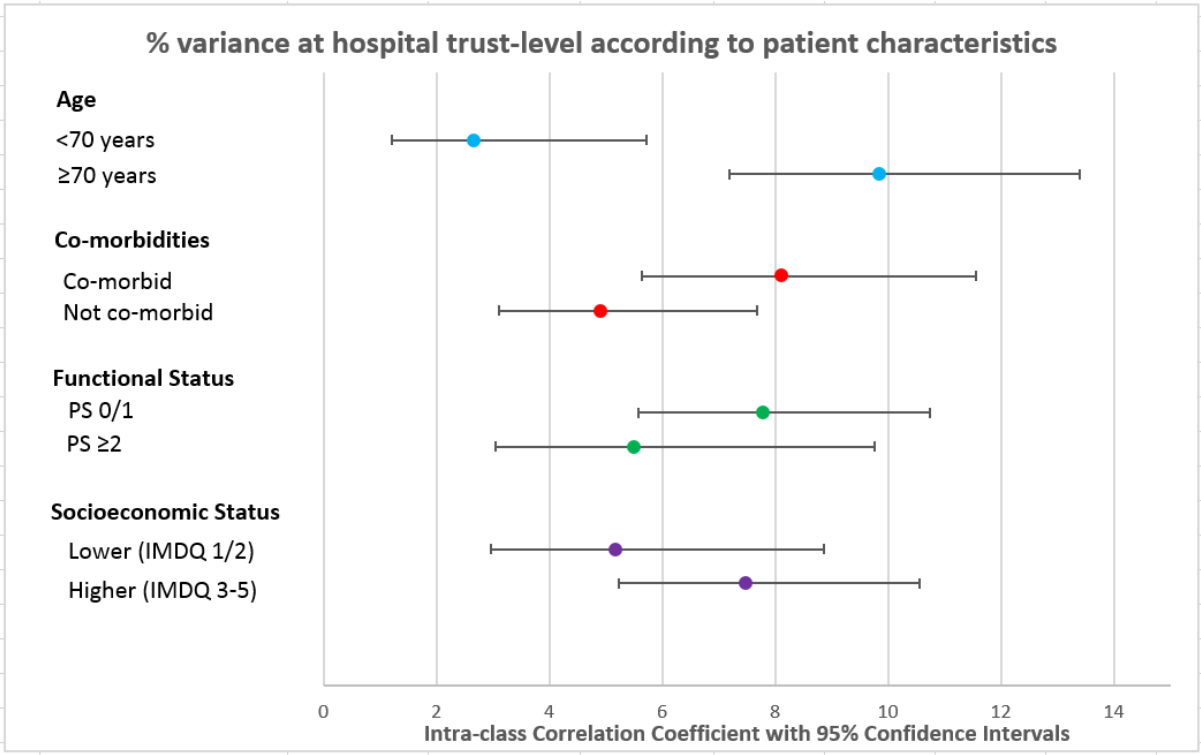


Figure 2 – The proportion of the total variation that is between hospital-trusts dependant on age, co-morbidities, functional status and socioeconomic status.



References

1. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990; 264(11): 1444-50

2. National Institute for Health and Care Excellence: Colorectal cancer: diagnosis and management. Clinical guideline [CG131]; 2011. Available from: https://www.nice.org.uk/guidance/cg131 (Accessed 14th February 2019)

3. National Bowel Cancer Audit: Annual Report; 2018. Available from: https://www.nboca.org.uk/reports/annual-report-2018/ (Accessed 14th February 2019)

4. Casadaban L, Rauscher G, Aklilu M, Villenes D, Freels S, Maker AV. Adjuvant chemotherapy is associated with improved survival in patients with stage II colon cancer. Cancer. 2016; 122 (21): 3277-87

5. Chamberlain C, Owen-Smith A, Donovan J, Hollingworth W. A systematic review of geographical variation in access to chemotherapy. BMC cancer. 2015; 16: 1

6. Macmillan Cancer Support. The age old excxuse: the under treatment of older cancer patients. 2012. Available from: https://www.macmillan.org.uk/documents/getinvolved/campaigns/ageoldexcuse/ageoldexcusereport-macmillancancersupport.pdf (Accessed 14th February 2019)

7. Lawler M, Selby P, Aapro MS, Duffy S. Ageism in cancer care. BMJ. 2014; 348: g1614

8. Systemic Anti-cancer Therapy Monthly Update - SACT dataset: Public Health England. Available from: http://www.chemodataset.nhs.uk/reports/ (Accessed 14th February 2019)

9. Affiliate Groups of The Association of UK University Hospitals. Available from: https://www.universityhospitals.org.uk/ (Accessed 14th February)

10. Organisational Survey: National Bowel Cancer Audit; 2016. Available from: https://www.nboca.org.uk/reports/organisational-survey-results/ (Accessed 14th February)

11. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in medicine. 2011; 30(4): 377-99