Determinants of Variation in the Use of Adjuvant Chemotherapy for Stage III Colon Cancer in England

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ABSTRACT

Adjuvant chemotherapy (ACT) for stage III colon cancer is well-established. This study aimed to explore determinants of ACT use and between-hospital variation within the English National Health Service.

11,932 patients (diagnosed 2014-2017) with pathological stage III colon cancer in the English NHS were identified from the National Bowel Cancer Audit. Records were linked to Systemic Anti-Cancer Therapy and Hospital Episode Statistics databases.

Multi-level logistic regression analyses were performed to estimate independent factors for ACT use including age, sex, deprivation, comorbidities, performance status, ASA, surgical urgency, surgical access, TNM staging, re-admission and hospital-level factors

(University teaching hospital, on-site chemotherapy and high-volume centre). A random intercept was modelled for each English NHS hospital (n=142).

Between-hospital variation was explored using funnel plot methodology. Fully-adjusted random-intercept models were fitted separately in young (<70 years) and elderly (≥70 years) patients, and intra-class correlation coefficients estimated.

60.7% of patients received ACT. Age was the strongest determinant. Compared to patients <60 years, those aged 60-64 (adjusted odds ratio (aOR) 0.76 (95% CI 0.63-0.93), 65-69 (aOR 0.63 (0.54-0.74), 70-74 (aOR 0.53 (95% CI 0.44-0.62)), 75-79 (aOR 0.23 (0.19-0.27)) and ≥80 (aOR 0.05 (0.04-0.06)) were significantly less likely to receive ACT.

With adjustment for other factors, ACT use was more likely in patients with higher socioeconomic status, fewer comorbidities, better performance status, lower ASA grade, advanced disease, elective resections, laparoscopic procedures, and no unplanned readmissions. Hospital-level factors were non-significant.

The observed proportions of ACT administration in the young and elderly were 46%-100% (80% hospitals 74%-90%) and 10%-81% (80% hospitals 33%-65%) respectively. Risk-adjustment did not reduce between-hospital variation. Despite adjustment, age accounted for 9.9% (7.2%-13.4%) of between-hospital variation in the elderly compared to 2.7% (1.2%-5.7%) in the young.

There is significant between-hospital variation in ACT use for stage III colon cancer, especially for older patients. Advanced age alone seems to be a greater barrier to ACT use in some hospitals.

INTRODUCTION

In England, approximately 19,000 cases of colon cancer are diagnosed annually.[1] Of these, 25% present with stage III disease and up to 40% of these develop recurrence after curative resection.[2]

The benefits of adjuvant chemotherapy (ACT) for stage III colon cancer are well-established.[3] Current guidelines in England recommend ACT in fit patients.[4] A recent audit report suggested only 57% of patients with stage III colorectal cancer (CRC) received ACT in the English National Health Service (NHS) with variation between regions (41% to 68%).[1] ACT has been shown to improve overall 5-year relative survival by up to 33%, meaning underutilisation is significant.[5]

Studies outside the United Kingdom (UK) have demonstrated similar rates of ACT use for stage III colon cancer.[6-8] Most studies have been conducted in the United States but often include single-state cancer registries or SEER-Medicare data (only insured patients aged 65 or older) which limits their representativeness. Studies using National Cancer Database data are most representative but still only include one third of inpatient hospitals.[9]

Current International Society of Geriatric Oncology (SIOG) consensus recommendations advise fluoropyrimidine monotherapy for patients aged 70 years or older, with oxaliplatin therapy of uncertain benefit.[10] Age has consistently been shown as one of the strongest determinants of ACT use[6-8,11] which is particularly important in the context of an ageing population. There has been a recent focus on the under-treatment of elderly patients with cancer.[12,13]

Variation in chemotherapy use between hospitals and regions has been observed but the reasons underlying this are not well understood.[14,15] No previous studies have investigated explanations for between-hospital variation in chemotherapy use. Understanding

these reasons is crucial in reducing unwarranted variation, facilitating increased rates of ACT use, and potentially improving survival outcomes.

We linked the National Bowel Cancer Audit (NBOCA)[16], a unique resource involving prospective mandatory data collection for all newly diagnosed CRC patients in the English NHS, to chemotherapy and hospital administrative databases. This enabled us to establish current national practice in the use of ACT in stage III colon cancer, explore determinants for use of ACT according to patient and hospital-level characteristics, establish between-hospital variation and investigate possible reasons for this.

Our dataset includes all centres providing colon cancer treatment in the English NHS with no exclusions based on insurance status, socioeconomic status or age, and with case ascertainment >95% of all adults diagnosed with primary colon cancer in England. This 'real-world' contemporary data from the English NHS, where care is free at the point of need, provides an effective platform for investigating hospital-level variation.

MATERIALS & METHODS

Study population

National Bowel Cancer Audit (NBOCA)

Patients aged 18 years or older with a primary diagnosis of colon cancer, according to ICD-10 codes (International Classification of Diseases, 10th revision), between 1 April 2014 and 31 March 2017 who had undergone major resection with pathological stage III disease were identified in the NBOCA database. Cancers of the appendix were excluded.Identified patients were linked to the Admitted Patient Care records in Hospital Episode Statistics Admitted Patient Care (HES-APC), an administrative database of all inpatient admissions to NHS hospitals.[17]

The linked NBOCA-HES-APC cohort included 11,932 patients deemed potentially eligible for ACT from 142 English NHS hospitals (Figure 1). Patients diagnosed within a private hospital and undergoing major resection in an NHS hospital are included. Patients diagnosed and treated entirely in the private sector are not captured, however, represent a small number of patients.

604 patients (5%) died within 4 months of surgery. This small proportion was retained in the main analysis because it is unlikely to significantly affect the results and provides a full representation of ACT use, including all patients diagnosed with stage III disease.

SACT (Systemic Anti-cancer Therapy) database

The SACT database is the world's first comprehensive, dedicated chemotherapy dataset which mandated submission of data by all English NHS providers of chemotherapy in any inpatient, day case, outpatient or community setting, from April 2014.[18] SACT data was available until 30 September 2017, providing a minimum of 4 months of follow-up from surgery for all patients. SACT provides the regimen start date and regimen name.

Identification of patients receiving ACT

Eligible patients were considered to have received ACT if their NBOCA record linked to a SACT record demonstrating use of any potentially curative colonic chemotherapy regimen within 4 months after surgery. The proportion of patients receiving each type of regimen is listed within Supplementary Table 1.

We validated ACT use utilising HES-APC. All inpatient admissions for each patient within 4 months after surgery 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) (Supplementary Table 2).

Patient and hospital characteristics

Data regarding sex, age, pathological staging (TNM staging), operative date, surgical urgency, performance status,[19] ASA grade,[20] and surgical access were obtained from NBOCA. Comorbidities, socioeconomic status and 30-day unplanned readmission data were obtained from HES-APC. The Royal College of Surgeons' Charlson comorbidity score was used for diagnostic codes identified in the year preceding colon cancer diagnosis.[21]

SIOG recommendations use 70 years as the distinction between elderly and non-elderly; the rationale for our age cut-off.[10] Patients were recorded as having an unplanned 30-day readmission if HES-APC showed an emergency admission within 30 days of surgery.

Socioeconomic status was derived from the Index of Multiple Deprivation (IMD) which ranks 32,482 geographical areas of England according to their level of deprivation across seven domains.[22] Patients are allocated to an IMD quintile (IMDQ) based on the national ranking of the area corresponding to their postcode.

In the English NHS, hospital-level care is provided by 'hospital Trusts'. These may consist of an individual hospital or several hospitals combined. We use 'hospital' to refer to these hospital Trusts. Hospital-level characteristics were derived from the hospital carrying out the surgery according to NBOCA. University teaching hospitals were identified from the Association of United Kingdom University Hospitals.[23] On-site chemotherapy presence was collected in an annual national NBOCA survey of CRC services.[24] Hospitals were categorised as high-volume if they performed on average >100 CRC resections per year as this represented the median value.

Final cohort

Table 1 shows the proportion of the 11,932 patients identified in SACT and/or HES-APC as receiving ACT. For the main analysis, 7,239 patients with a chemotherapy record in either database were considered to have received ACT. 8.0% (579/7,239) of these were identified from HES-APC alone.

Statistical Analysis

Multivariable random-effects logistic regression was used to estimate associations between ACT use and the patient and hospital characteristics described above. A random intercept was modelled for each hospital to account for possible clustering of results within hospitals. Subgroup analyses were performed in the same manner to evaluate patient and hospital characteristics separately in the young (<70 years) and elderly (≥70 years).

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.[25] Multiple imputation was used to impute all missing data for socioeconomic status, RCS Charlson score, performance status, ASA grade, urgency of resection, surgical access and pathological T-stage.

Hospital-level variation in ACT use was explored visually using funnel plots to establish whether the between-hospital variation in the proportion of patients receiving ACT was greater than expected by chance alone.[26] Separate fully-adjusted funnel plots were generated for all patients, patients aged below 70 years only, and patients aged 70 years or older only, to explore whether between-hospital variation was associated with age. All 142 hospitals had 10 or more patients eligible for ACT overall and were included in the funnel plot for all patients. 135 hospitals had 10 or more patients aged below 70 years and 10 or more patients aged 70 years or older, and were included in the young and elderly funnel plots.

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

To identify sources of between-hospital 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. One risk-adjustment model was estimated in all patients and used for each stratum. We compared the ICC between strata using an independent samples t-test to calculate two-tailed p-values (0.05 significance level).

All statistical analyses were conducted using STATA® version 15.1 (StataCorp, College Station, Texas, USA).

RESULTS

Determinants of ACT use

7,239 patients (60.7%) were identified as having received ACT (Table 2). The strongest predictor for ACT use was age, despite adjustment for all other factors. Compared to 85.3% of patients aged <60 years who received ACT, 80.7%, 76.3%, 71.3%, 50.2% and 18.6% of those aged 60-64 years (aOR 0.76 (95% CI 0.63-0.93), 65-69 years (aOR 0.63 (95% CI 0.54-0.74), 70-74 years (aOR 0.53 (95% CI 0.44-0.62)), 75-79 years (aOR 0.23 (0.19-0.27)) and ≥80 years (aOR 0.05 (0.04-0.06)) received ACT respectively. Although the use of ACT decreased with age, a substantial proportion of patients aged below 70 years did not receive ACT.

Other patient characteristics associated with increased ACT use included higher socioeconomic status, fewer comorbidities, better performance status, and lower ASA grade. ACT use was also more likely in the multivariable model in patients who had an elective procedure, had undergone laparoscopic resection, had more advanced disease (T3/T4 or N2 disease), and did not have an unplanned readmission.

Subgroup analyses of patient and hospital-level factors were performed for the young (<70 years) and elderly (≥70 years) (Supplementary Table 3 (a) and (b)). The multivariable results were largely similar to those of the whole sample except that females were less likely to receive ACT if they were old, adjusting for other factors.

Further analysis was carried out on patients aged 70 years or older to investigate ACT use in different age strata according to comorbidities, performance status and ASA grade (Supplementary Table 4). A downward trend in ACT use can be observed with increasing age for each factor, for example, 75% of 70-74 year olds with performance status 0/1 received ACT versus 25% of those aged 80 years or older also with performance status 0/1.

Variation between hospitals

ACT use varied substantially between hospitals. The observed hospital proportion of chemotherapy administered ranged from 26% to 86%. Amongst patients less than 70 years, observed proportions ranged from 46% to 100% (80% of hospitals 74% to 90%). In comparison, amongst patients aged 70 years or older, observed proportions ranged from 10% to 81% (80% of hospitals 33% to 65%).

Adjustment for factors included in the multivariable model did not reduce hospital variation. Assuming differences arise from random errors alone, the expected number of hospitals outside the inner (95%) and outer (99.8%) funnel limits for all analyses is 7 and 0.3 respectively. For patients less than 70 years, 10 hospitals lay outside the inner funnel limits

and 0 hospitals outside the outer limits, compared to 21 and 5 hospitals in patients aged 70 years or older, respectively (Figure 2).

The ICC for patients less than 70 years was 2.7% (95% CI 1.2%-5.7%) compared to 9.9% (95% CI 7.2%-13.4%) in patients aged 70 years or older, which demonstrates a significantly greater proportion of the total variance to be between hospitals in the elderly compared to younger patients (p=<0.001). Differences in ICCs by comorbidity, performance status and socioeconomic status were not statistically significant (Figure 3).

DISCUSSION

This large, representative national study has firstly demonstrated significant variation in the use of ACT for patients with stage III colon cancer within the English NHS. Secondly, it has shown that age has a significant effect on ACT use which persists despite risk-adjustment suggesting underuse of ACT in elderly patients. A significantly greater proportion of between-hospital variation is found in the elderly, indicating that age is a greater barrier to ACT use in some hospitals compared to others. Thirdly, we identified socioeconomic status as a determinant of ACT use, despite case-mix adjustment.

This is the first population-based study evaluating the use of ACT for stage III colon cancer in England. Our finding that 60% of patients received ACT is similar to figures found elsewhere. A recent large US study of 124,008 patients with stage III colon cancer suggested that 66% received ACT between 2003-2011.[7] Two Canadian studies reported that 50% of patients received chemotherapy, despite a healthcare system where access to treatment is free.[27,28] Within Europe, similar ACT rates have been found in Germany (65%)[29], France (65.1%)[30], Italy (64.6%)[30], Belgium (68%)[2], Sweden (55%)[2] and the Netherlands (61%).[2]

Our multivariable analysis demonstrated findings that are largely consistent with those expected. Although we would expect age to influence ACT use, the magnitude of the effect despite risk-adjustment was marked and most apparent in those aged 75 years or older. Patients included in this study have been deemed fit enough to tolerate a major colonic resection suggesting that many have the potential to be candidates for adjuvant chemotherapy, although post-operative status and life expectancy also need to be taken in to consideration.

Previous studies are in agreement with our finding that socioeconomic status is a determinant of ACT use.[31,32] Suggested explanations include delayed presentation,[33] increased comorbidities,[32] and reduced health-seeking behaviours.[31] Socioeconomically deprived patients in our cohort tended to be younger and more comorbid, and had more often undergone emergency resection (results not shown). Education and targeted screening may help facilitate ACT use in this group by reducing emergency presentations. However, socioeconomic status was a significant determinant despite risk-adjustment suggesting it is a barrier to ACT use in its own right.

Comorbidity has been associated with ACT use,[11] but performance status and ASA grade have not previously been reported. These three determinants have been shown to have limited correlation in CRC patients suggesting that they represent independent measures of patient well-being and supporting their inclusion in our model.[34]

As described previously, we have demonstrated that laparoscopic surgery and unplanned readmissions are significant determinants for ACT.[2,35-37] Laparoscopic surgery may increase ACT use because it is associated with fewer complications, faster recovery and reduced inflammatory response. Unplanned readmissions prolong hospital stay which may make the timely use of ACT more difficult.

Patients undergoing emergency surgery were less likely to receive ACT. Previous studies have shown conflicting evidence.[30,38] An explanation for emergency patients being less likely to receive ACT is that they are at increased risk of experiencing post-operative complications and are more likely to have stomas formed.

Hospital-level characteristics, including being a university teaching hospital or having on-site chemotherapy facilities, were not associated with ACT use. A Scottish study demonstrated the significance of on-site chemotherapy facilities but its results were limited because of the absence of staging information.[39]

Other hospital-level factors which we were unable to measure in this study but may influence between-hospital variation in ACT use include rurality, distance to the nearest chemotherapy centre, and oncologist characteristics such as length of practice and volume of consultations for patients with colorectal cancer.[37] A systematic review evaluating geographical variation in access to chemotherapy within the UK suggested that healthcare boundaries, such as which English 'cancer alliance' a hospital lies within, rather than 'natural geographic factors' were most important. The influence of commissioners, policy-makers and individual providers are therefore important.[14] Although most marked in the elderly, variation was also present in the young with up to 55% of patients less than 70 years not receiving ACT in some hospitals. The observed variation in ACT use is important because it suggests that not all patients are receiving optimal adjuvant therapy, particularly those aged 70 years or older.

Wennberg described the concept of 'unwarranted variation' whereby variation in the use of health care services cannot be explained by variation in patient illness or patient preference.[40] Unwarranted variation may consist of overtreatment or undertreatment. Underlying factors can include clinician and patient preferences and attitudes, availability of particular resources, and discrepancies in the treatment of certain patient groups, for example

the elderly and those from a lower socioeconomic background, consistent with our study findings.[41]

Within this study, we accounted for case-mix differences and it is unlikely that the between-hospital variation after adjustment can be fully explained by patient preferences. This suggests that 'unwarranted variation' exists in the use of ACT and highlights the need for a more consistent use of ACT resources in the English NHS.

Patient choice is an important and complex factor determining the use of chemotherapy. Patient-related factors influencing decision-making for cancer treatments are extensive and can include social, cognitive and psychological issues. Physician-related factors such as poor communication, lack of information or distrust in the patient-clinician relationship are also important. Clinician recommendations have been found to be the most important influence in patients' decision-making pathways.[42]

Qualitative studies support our suggestion that unwarranted variation (as identified in this study), especially in the elderly, may be attributable to varying clinician practice. One study showed that clinician recommendations varied more widely according to increasing comorbidity in the elderly compared to the young.[43] Other studies have highlighted bias in clinician decision-making related to advancing age.[44,45]

Given these findings clinicians should recognise the importance of their input in to shared decision-making and be educated in this process. Patients should also be educated about the benefits and risks of adjuvant chemotherapy and support provided as necessary to facilitate informed decision-making and overcome potential barriers. Specialist nurses may provide support in this area.

SIOG recommends the use of comprehensive geriatric assessments (CGAs) which facilitate the formation of individualised treatment plans. There is evidence supporting their use for chemotherapy decision making.[46,47]

Clinical trials need to be enriched through population with more elderly, frail patients.[48] Real-world data can be used to evaluate outcomes in groups under-represented by trials. Both of these can be used to support the development of elderly-specific guidelines and associated educational resources to aid clinical decision making and reduce the observed variation in practice.

The National Bowel Cancer Audit will be implementing a new process measure pertaining to adjuvant chemotherapy use for stage III colon cancer. It will report figures for England at a hospital-level. Other healthcare providers should consider similar evaluations of practice which highlight 'unwarranted variation', facilitate quality improvement and allow monitoring of ACT rates relative to national benchmarking.

There is robust evidence that ACT improves outcomes. Underuse could therefore be a contributing factor to England having lower survival rates for colon cancer compared to other European countries. A recent study suggested that the survival deficit in England is partly attributable to shortfalls in treatment with a steep declining age gradient in the probability of receiving colonic resection (particularly those aged 75 years or older) compared to Denmark, Norway and Sweden.[49] Our results indicate that similar patterns may exist for ACT use.

There were several limitations to our study. Firstly, we considered that patients had received ACT if there was evidence of colonic chemotherapy, irrespective of regimen, within the first 4 months after surgery. This approach is supported by the observation that approximately 96% of observed regimens were in keeping with standard practice (Supplementary Table 1).[4] The remainder could represent atypical practice or palliative treatment. We were also unable to obtain regimen details for patients captured in HES-APC alone. However, a sensitivity analysis performed using SACT data alone to identify patients who had received ACT produced similar results (5 hospitals were excluded from this analysis as they captured <50% of ACT compared to HES-APC).

We could not determine chemotherapy refusal rates but these have been reported to be around 10%[50] and some studies used an offer of chemotherapy as their numerator which did not substantially change their results.[6] Refusal is therefore unlikely to completely explain ACT underuse.

Finally, we were unable to capture all factors which may influence ACT use such as social support, nutrition and cognitive function. Neither could we measure the severity of individual comorbidities, although we captured performance status and ASA grade.

Our study includes a large representative cohort of patients with stage III colon cancer identified in all hospitals providing colon cancer care in the English NHS. SACT provides a unique data source, with data captured directly by chemotherapy providers. Linkage of multiple national datasets facilitated further validation of the data.

CONCLUSIONS

Our study represents an evaluation of current practice in the use of ACT for stage III colon cancer in the English NHS. We found considerable variation in ACT use between hospitals, most prominently in elderly patients. We also demonstrated that, despite case-mix adjustment, there is an association between socioeconomic status and ACT use suggesting possible inequalities in access to ACT. Finally, we highlighted the importance of post-operative recovery in the use of ACT.

We envisage that these findings will be applicable to health care settings outside of the UK. A more considered use of ACT, particularly in elderly patients, may improve outcomes.

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Table 1 – Proportion of patients identified as having ACT according to the SACT and/or HES-APC databases (row and column percentages given).

	Chemotherapy according to SACT		
Chemotherapy according to HES-APC	**Yes**	**No**	**Total**
Yes	4,742 (89.1%)	579 (10.9%)	**5,321**
	(71.2%)	(11.0%)	
No	1,918 (29.0%)	4,693 (71.0%)	**6,611**
	(28.8%)	(89%)	
Total	**6,660**	**5,272**	**11,932**

Table 2 – Distribution of patient and hospital characteristics and their effect on ACT use.

	Total (%) n=11,932	Received ACT (%) n=7,239	p-value (X^2)	Adjusted odds ratios (95% CI)	p-value
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			
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 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)	
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 facilities			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			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)	

*These values were missing prior to the use of multiple imputation. There remained no missing data following imputation.

FIGURES

Figure 1 – Flow chart showing inclusion of patients in study.

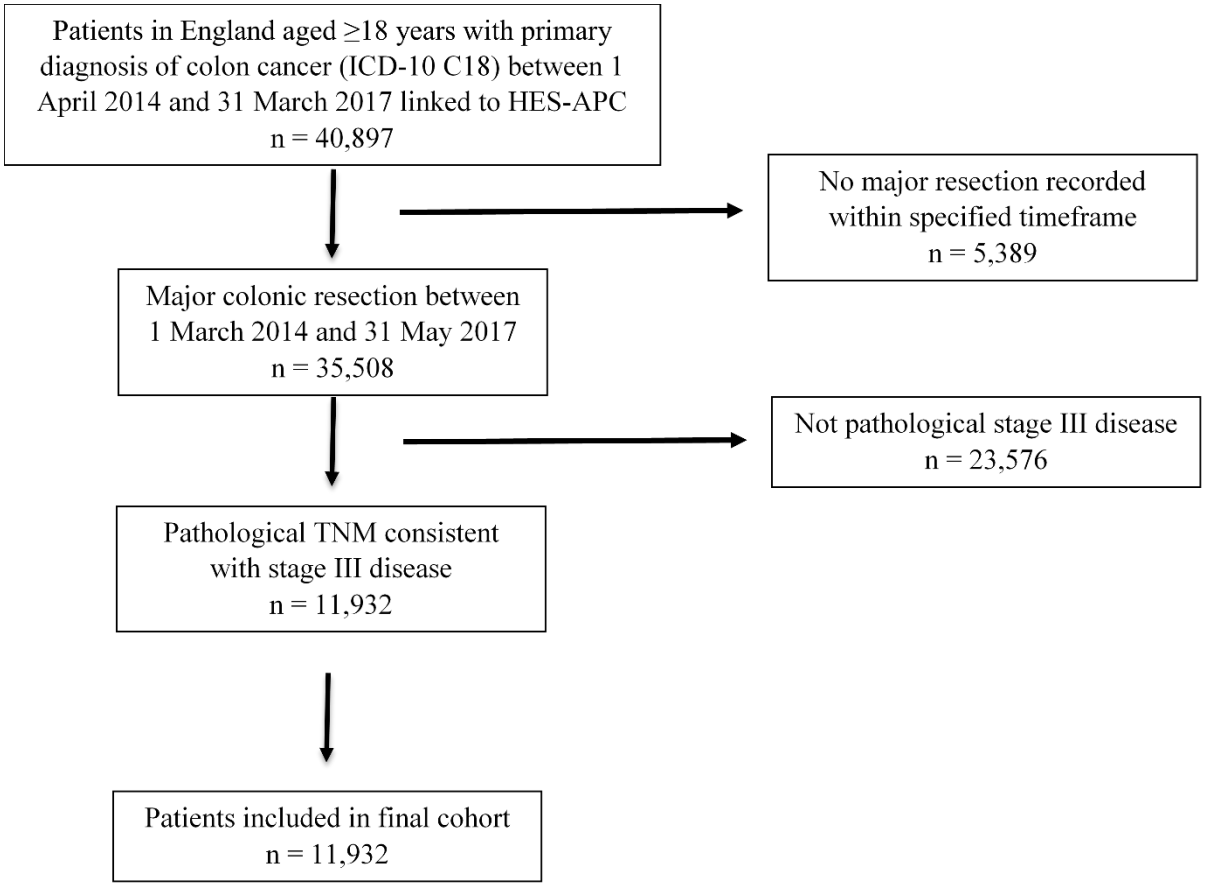
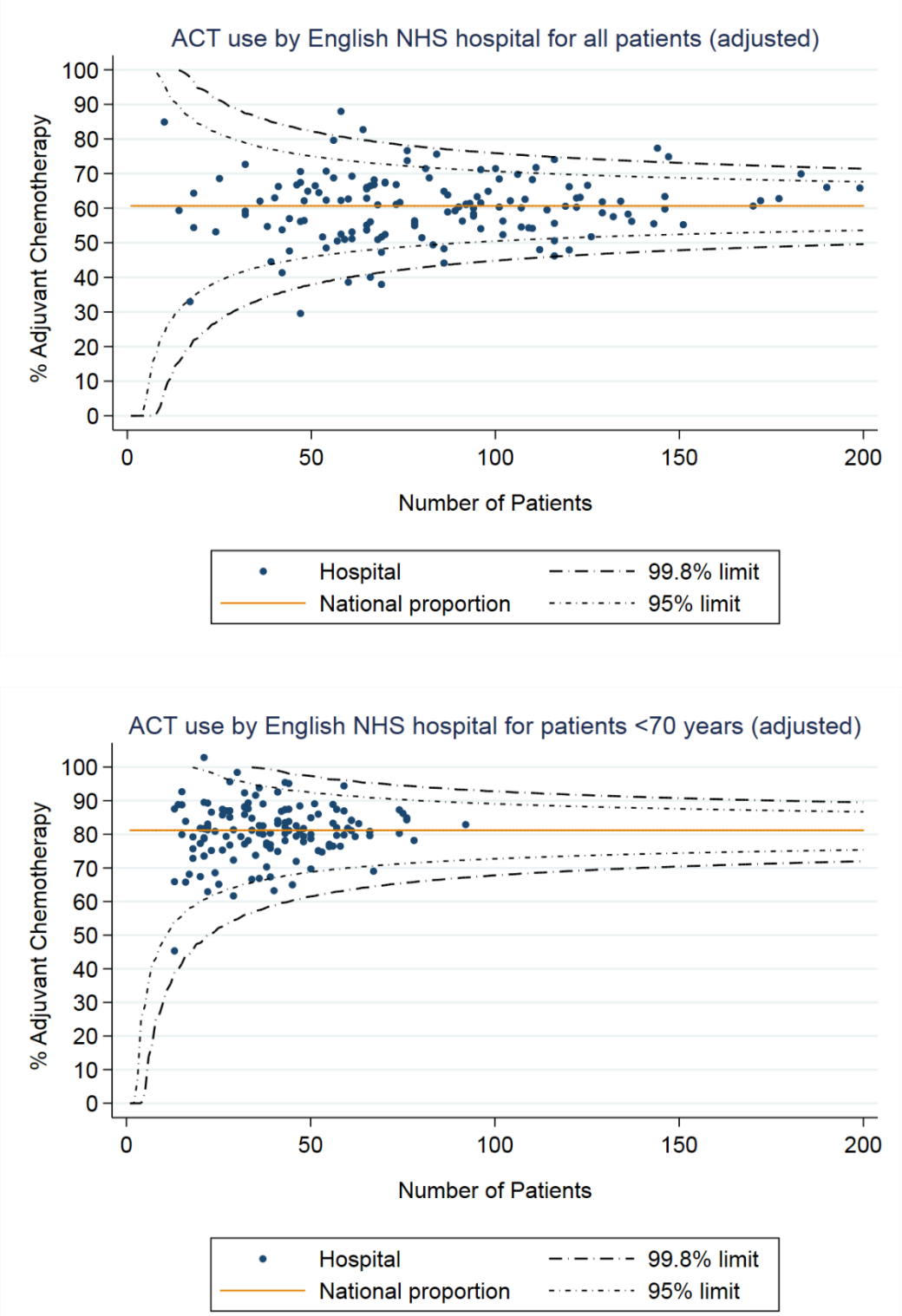


Figure 2 – Funnel plots demonstrating the proportion of patients undergoing major resection with pathological stage III colon cancer who received ACT at each hospital, adjusted for all patient and hospital factors in Table 2 - a) all patients b) young (<70 years) c) elderly (≥70 years).



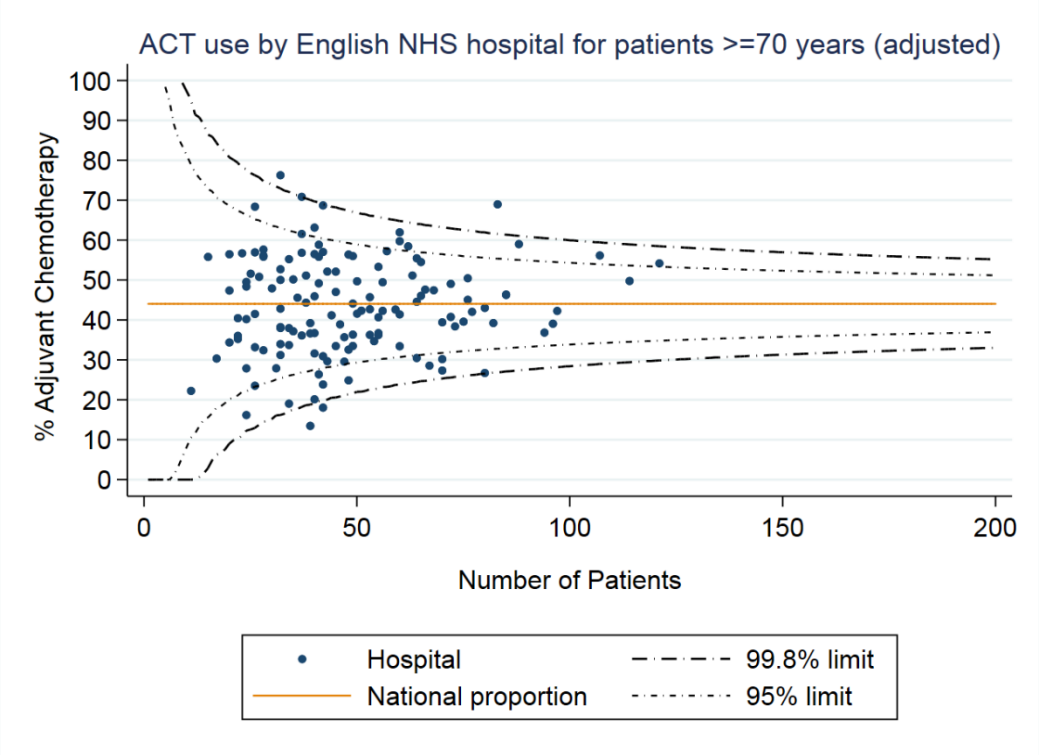


Figure 3 – the proportion of the total variation that is between hospitals according to age, comorbidities, performance status and socioeconomic status.