Development and validation of a coding framework to identify severe acute toxicity from systemic anti-cancer therapy using hospital administrative data

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ABSTRACT

Background: The capture of toxicities from systemic anti-cancer therapy (SACT) in real-world data will complement results from clinical trials. The aim of this study was to develop and validate a comprehensive coding framework to identify severe acute toxicity in hospital administrative data.

Methods: A coding framework was developed to identify diagnostic codes representing severe acute toxicity in hospital administrative data. The coding framework was validated on a sample of 23,265 colon cancer patients treated in the English National Health Service between 1 June 2014 and 31 December 2017. This involved comparing individual toxicities according to the receipt of SACT and according to different SACT regimens as well as assessing the associations of predictive factors and outcomes with toxicity.

Results: The severe acute toxicities captured by the developed coding system were shown to vary across clinical groups with an overall rate of 26.4% in the adjuvant cohort, 53.4% in the metastatic cohort, and 12.5% in the comparison group receiving no chemotherapy. Results were in line with regimen-specific findings from clinical trials. For example, patients receiving additional bevacizumab had higher rates of bleeding (12.5% vs. 2.7%), gastrointestinal perforation (5.6% vs. 2.9%) and fistulation (1.4% vs. 0.5%), and allergic drug reactions (1.4% vs. 0.5%). Severe acute toxicity was associated with pre-existing renal (p=0.001) and cardiac disease (p=0.038), and urgency of surgery (p=0.004). Severe toxicity also predicted lower rates of completion of chemotherapy (p=<0.001) and an increased likelihood of altered administration route (p=<0.001).

Conclusion: These results demonstrate that the developed coding framework captures severe acute toxicities from hospital administrative data of colon cancer patients. A similar approach can be used for patients with other cancer types, receiving different regimens. Toxicity captured in administrative data can be used to compare treatment outcomes, inform clinical decision making, and provide opportunities for benchmarking and provider performance monitoring.

1. INTRODUCTION

Given the widespread use of systemic anti-cancer therapy (SACT), the ability to measure and understand severe acute toxicities is vital for comparing different treatments and informing patient and clinician decision making as well as for facilitating comparative assessment of toxicities across hospital settings to benchmark best practice and stimulate quality improvement.

A study in breast cancer patients showed a hospitalisation rate of 43% in those receiving SACT, with 75% of admissions confirmed as chemotherapy-related adverse events.(1) Despite this significant burden of toxicity on patients and healthcare systems, there remains a lack of data related to real-world practice. Existing evidence usually comes from randomised controlled trials (RCTs) which can be limited in their application to real-world practice.(2, 3) First, there is evidence that acute toxicities are more common in real-world practice than in clinical trials.(4) Second, RCTs often underrepresent patients who are older, comorbid, or less fit, and sometimes ethnic and socioeconomic groups too.(5) Third, rare adverse events may be difficult to capture in RCTs with small sample sizes or short study durations.

To date, some studies of real-world practice have used medical note abstraction or diagnostic and procedural codes from insurance claims to identify acute toxicity.(6-8) Medical note abstraction confers considerable time and cost implications and is impractical for ongoing monitoring. Insurance claims have been shown to provide inconsistent information about specific SACT regimens and incomplete data on the occurrence of events related to SACT.(9, 10)

Many studies of acute SACT toxicity in real-world practice are limited by their lack of generalisability because they only included patients who had a specific toxicity, disease stage, or SACT regimen, or they excluded patients based on age or insurance status.(6-8) In addition, there is often a lack of granularity about SACT details such as administration dates which are important for ascertaining the precise timeframe during which acute toxicities may occur.(4)

Most studies that attempted to validate coding frameworks were designed to identify acute toxicity from insurance claims or hospital administrative data in breast cancer patients.(1, 11, 12) These studies have

included only a small selection of toxicities, often not considering biologic therapies which have unique toxicity profiles.

The aim of our study was to develop a broad and comprehensive coding framework of severe acute toxicity (toxicity necessitating an overnight hospital admission) from SACT across a range of organ systems using hospital administrative data, covering different regimens including biologic therapies. The performance of this coding framework was validated in a large national population-based sample of colon cancer patients treated in the English National Health Service (NHS).

2. METHODS

2.1 Data sources

This study used National Bowel Cancer Audit (NBOCA) data(13), Hospital Episode Statistics (HES) (14, 15), and Systemic Anti-Cancer Therapy (SACT) data(16) linked at patient level for colon cancer patients in the English National Health Service (NHS).

2.2 National Bowel Cancer Audit

NBOCA is a prospective mandatory database for all newly diagnosed colorectal cancer patients in the English NHS. Data items in NBOCA were used to determine sex, age, Eastern Cooperative Oncology Group performance status(17), staging according to the TNM system, date of surgery, and surgical urgency (elective/scheduled or emergency/urgent).

2.3 Systemic Anti-Cancer Therapy dataset

The SACT dataset is a dedicated national chemotherapy dataset held by the English National Cancer Registration and Analysis Service.(18) Data are largely captured via electronic prescribing systems. The SACT dataset includes detailed drug-level information for chemotherapy administered in any inpatient, day-case, outpatient or community setting.(16) Data items in SACT were used to determine the first and last chemotherapy cycle administration dates, regimens, cycle completion, and change in administration route.

Adjuvant chemotherapy was defined as the receipt of a standard regimen (fluoropyrimidine monotherapy or combination therapy with oxaliplatin) commenced within the 4-month period following the NBOCA date of surgery.(19) For patients with Stage IV disease, SACT administered as a first treatment within 4 months of diagnosis was included.

2.4 Hospital Episode Statistics (HES)

The HES dataset is a national administrative dataset of all admissions to English NHS hospitals.(15, 20) This study used HES Admitted Patient Care data which includes records of day-case or overnight admissions. HES records contain a unique patient identifier that allows for longitudinal follow-up. Diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10)(21) and procedures are coded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OPCS-4).(22)

Data items in HES were used to determine the number of comorbidities, as well as specific markers for cardiac and renal impairment (important considerations for SACT use), according to the RCS Charlson Score.(23) HES was used to supplement chemotherapy capture in SACT, as per previous methodology.(24)

2.5 Office for National Statistics

If applicable, date of death was obtained from linkage to official death records provided by the Office for National Statistics (ONS).(25)

2.6 Coding framework for severe acute toxicities

Using a combination of previous studies (1, 11, 12), the CTCAE (Common Terminology Criteria for Adverse Events) dictionary, and adverse events commonly reported for RCTs (26-34), we compiled a comprehensive list of ICD-10 codes likely to represent severe acute toxicities in the context of chemotherapy administration (*'forward coding'*) with expert input (JB & AA). Death was also included.

Toxicities corresponded to Grade 3-5 severe adverse events according to the CTCAE.(35) Grade 3 toxicity includes severe or medically significant adverse events where hospitalisation is required, or adverse events

which are disabling or limit activities of daily living. Grade 4 toxicity includes life-threatening consequences or those requiring urgent intervention, and Grade 5 indicates death.

The most frequently occurring diagnosis codes in the records of overnight admissions during and up to 8 weeks after the last date of chemotherapy administration for patients with stage III and IV colon cancer receiving chemotherapy, were also examined and included if they were likely to represent acute toxicity from chemotherapy (*'backward coding'*). Review of these codes was undertaken independently by two authors (JB & AA) with discrepancies discussed and resolved using clinical expertise (Appendix A). At patient level, diagnostic codes which may reflect chronic conditions were not included if they were recorded within the 12 months preceding administration of the first cycle of chemotherapy to reduce the likelihood of coding pre-existing conditions (Appendix A).

The framework was purposefully kept broad to ensure applicability to most cancer types and chemotherapy regimens, including potential new therapies.

2.7 Validation cohort

Patients aged 18 years and above with a primary diagnosis of colon cancer (ICD-10: C18) were identified in the NBOCA database. Patients undergoing treatments at an English NHS hospital between 1 June 2014 and 30 April 2017 with pathological stage I, II, III and IV disease were identified. This time-period was chosen because not all English NHS chemotherapy providers were submitting SACT data before the end of May 2014.(16) SACT and HES data from 30 June 2014 until 30 April 2018 were used to capture all chemotherapy episodes.

2.8 Validation and statistical analysis

All admissions requiring an overnight stay, from administration of the first cycle of chemotherapy up until 8 weeks after administration of the last cycle of chemotherapy, were examined to identify diagnosis codes from the coding framework.

A three-step validation process of the coding framework was undertaken. First, the toxicity profiles were compared across the three clinical validation groups: patients receiving adjuvant chemotherapy following major resection for stage III disease; patients receiving chemotherapy for stage IV disease; and a comparison

group of patients with stage I and II disease undergoing major resection with no record of chemotherapy receipt. In addition, a multivariable logistic regression model was used to estimate the association between severe acute toxicity and clinical group, adjusting for age, sex, comorbidity, and performance status. Missing values for these patient factors were imputed with multiple imputation using chained equations, creating 10 datasets, and using Rubin's rules to combine the estimated odds ratios across datasets.(36)

As the patients with stage I and II disease had not actually received chemotherapy, pseudo start and end times for their chemotherapy were defined. These corresponded to the 10^{th} centile of the time from major resection to administration of the first cycle of chemotherapy (6 weeks) and the 90^{th} centile (7 months) of this timeframe, using data from the stage III patients who received adjuvant chemotherapy.

Second, toxicity profiles were compared across different chemotherapy regimens known to have different toxicity profiles. Stage III patients receiving capecitabine monotherapy were compared with patients receiving capecitabine and oxaliplatin (CAPOX). This is because oxaliplatin combination chemotherapy is expected to have higher rates of haematological, gastrointestinal, and neurological toxicities compared to monotherapy.(33, 37) Stage IV patients receiving 5-fluorouracil and oxaliplatin (FOLFOX), or 5-fluorouracil and irinotecan (FOLFIRI), were compared with patients receiving FOLFOX or FOLFIRI in addition to biologic agents in the form of either a vascular endothelial growth factor receptor inhibitor (bevacizumab) or epidermal growth factor receptor inhibitor (cetuximab or panitumumab). These are known to be associated with unique acute toxicities including bleeding, gastrointestinal perforation and fistulation, and skin reactions.(27-29)

Third, patient and clinical factors expected to predict acute toxicity were evaluated in patients with stage III disease receiving adjuvant chemotherapy including renal disease, cardiac disease, performance status, and urgency of surgery. Similarly, factors expected to be influenced by severe acute toxicity were evaluated, including completion of chemotherapy and change of administration route.

Chi squared tests were used to compare proportions. Stata® version 15.1 (StataCorp, College Station, Texas,

USA) was used for all data management and analysis.

3. RESULTS

3.1 Description of the validation cohort

We included a total of 42,872 patients (Figure 1). 15,746 patients had stage I or II disease. Of these, 13,573 (86.2%) did not have chemotherapy and were used as a comparison group. 10,680 patients had stage III disease, with 6,012 (56.3%) of these receiving adjuvant chemotherapy. 16,846 patients had stage IV disease, with 3,680 (21.4%) having records of chemotherapy being administered as the first treatment within 4 months of diagnosis.

Appendix B presents the demographics of each of the clinical cohorts. Of note, patients in the stage I/II comparison group were considerably older (29.1% aged 80 and over, compared to 6.5% of stage III patients and 9.2% of stage IV patients, $p<0.001$) and more comorbid (19.4% have ≥2 comorbidities according to the RCS Charlson Score, compared to 8.8% of stage III patients and 10.4% of stage IV patients, $p<0.001$).

3.2 Validation across clinical groups

For all 16 organ systems, those receiving chemotherapy for stage IV disease had more toxicities recorded than those receiving chemotherapy for stage III disease and those in the stage I/II comparison group (Table 1). For example, 23.5% of patients with stage IV disease had a gastrointestinal event captured (e.g. diarrhoea), compared to 12.7% of those with stage III disease, and 3.4% of those in the stage I/II comparison group ($p<0.001$). Similarly, 13.7% of patients with stage IV disease had a haematological event captured (e.g., neutropenia), compared to 4.1% of those with stage III disease, and 1.0% of those in the stage I/II comparison group ($p<0.001$).

The coding framework captured 54 individual toxicities, and toxicity profiles were in keeping with clinical expectation. For example, when comparing stage III patients who received adjuvant chemotherapy with the stage I/II comparison group, we found the most marked differences in the proportion of patients with neutropenia (4.1% versus 0.1%, $p<0.001$), neutropenic sepsis (2.5% versus <0.1%, $p<0.001$), line complications (1.4% versus 0.2%, $p<0.001$), neuropathy (0.8% versus 0.1%, $p<0.001$), and diarrhoea (9.3% vs 1.2%, $p<0.001$).

Overall, 12.5% of patients with stage I/II disease who did not receive chemotherapy had diagnostic codes included in the coding framework for toxicity, which is much lower than the patients with stage III or stage IV disease receiving chemotherapy. Of note, patients with stage I/II disease were considerably older and more comorbid than stage III and IV patients (Appendix B).

The multivariable regression model demonstrated adjusted odds ratios for severe acute toxicity of 2.98 (95% CI: 2.75 to 3.23) for the stage III chemotherapy group and 8.98 (95% CI: 8.22 to 9.80) for the stage IV chemotherapy group compared to the comparison group of stage I/II not receiving chemotherapy, despite adjustment for age, sex, comorbidity, and performance status (p<0.001) (Appendix C).

3.3 Validation across chemotherapy regimens

Toxicity profiles for different chemotherapy regimens were in keeping with clinical expectation (Table 2). For example, when comparing stage III patients that received CAPOX with those that received capecitabine monotherapy, there were increased proportions of haematological (4.0% versus 1.6%, p<0.001), gastrointestinal (15.4% versus 9.1%, p<0.001), neurological (2.9% versus 1.0%, p<0.001), infective (10.9% versus 7.1%), and cardiovascular (6.7% versus 5.1%, p=0.051) toxicities.

In addition, patients with stage IV disease that received FOLFOX/FOLFIRI with bevacizumab had higher proportions of bleeding compared to those receiving FOLFOX/FOLFIRI with cetuximab/panitumumab, or FOLFOX/FOLFIRI alone (12.5% versus 3.4% versus 2.7% respectively, p=<0.001). Although not statistically significant, patients receiving additional bevacizumab compared to those receiving FOLFOX/FOLFIRI alone also had higher rates of hypertension (4.2% versus 3.6%, p=0.98), gastrointestinal perforation (5.6% versus 2.9%, p=0.31) and fistulation (1.4% versus 0.5%, p=0.62), renal failure (9.7% versus 7.2%, p=0.44), and allergic drug reactions (1.4% versus 0.5%, p=0.62).

Patients with stage IV disease that received FOLFOX/FOLFIRI with cetuximab/panitumumab had higher proportions of dermatological toxicities compared to those receiving FOLFOX/FOLFIRI with bevacizumab, or FOLFOX/FOLFIRI alone (5.4% versus 1.5% versus 1.4% respectively, p<0.001). Similarly, those receiving FOLFOX/FOLFIRI with cetuximab/panitumumab had higher proportions of metabolic toxicities (13.2% versus 8.3% versus 7.8% respectively, p=0.003). Specifically, for patients receiving FOLFOX/FOLFIRI with

cetuximab/panitumumab compared to those receiving FOLFOX/FOLFIRI alone there were increased rates of skin reactions (5.2% versus 1.2%, p<0.001), nausea and vomiting (7.8% versus 5.4%, p=0.11), electrolyte disturbances (12.4% versus 7.3%, p=0.004), and ophthalmic disorders (0.8% versus 0.2%, p=0.26).

3.4 Validation according to patient and clinical factors associated with acute toxicity.

In stage III patients, factors demonstrated to be associated with an increased risk of acute toxicity were pre-existing renal (35.5% versus 26.0%, *p*=0.001) and cardiac disease (31.6% versus 26.2%, *p*=0.038), and presentation requiring emergency/urgent surgery (29.7% versus 25.6%, *p*=0.004) (Table 3). Acute toxicity was found to be similar across age groups under 80 and lower in those aged 80 and over (*p*=0.011). Poor performance status was associated with an increased risk of acute toxicity but this was not statistically significant.

Patients who had a severe acute toxicity were less likely to complete standard chemotherapy compared to those that did not have toxicity (*p*=<0.001), and were more likely to have a change in the chemotherapy administration route (*p*=<0.001) (Table 4).

4. DISCUSSION

4.1 Key Findings

This is the first study to develop a comprehensive coding framework to identify a broad spectrum of severe acute toxicities after SACT (including traditional cytotoxics and targeted biologic agents). The toxicities are mapped across organ systems using diagnostic codes from hospital administrative data with reference to the established CTCAE dictionary. The validity of this coding framework has been exemplified using a three-step approach demonstrating its ability to distinguish the 'signal' of severe acute toxicity from the 'noise' of background diagnoses in colon cancer patients.

4.2 Comparison with other studies of SACT toxicities

Our finding that stage IV patients receiving chemotherapy had a considerably higher rate of severe acute toxicity than stage III patients receiving adjuvant chemotherapy is in line with a previous study including breast

cancer patients.(11) Higher rates in the advanced setting are likely multifactorial and might be explained by more prolonged courses of treatment, and increased use of combination SACT regimens in older patients.

We have demonstrated differences in toxicity profiles as expected from RCTs. First, CAPOX had higher rates of haematological, gastrointestinal, and neurological toxicities compared to capecitabine monotherapy.(30, 38-40) Second, the addition of bevacizumab showed increased rates of bleeding, gastrointestinal perforation and fistulation, hypertension, and allergic drug reactions.(41, 42) Third, the addition of cetuximab and panitumumab demonstrated increased rates of skin disorders and electrolyte imbalances.(28, 29)

Our results broadly show higher rates of individual acute toxicities in comparison to RCTs. For example, compared to an RCT for CAPOX, we found a rate of 11.7% versus 8.8% for diarrhoea, 1.9% versus 0.6% for febrile neutropenia, 2.4% versus 11.9% for neutropenia, 4.4% versus 1.3% for vomiting, 1.4% versus 0.9% for mucositis, and 0.6% versus 2.8% for fatigue.(43) Similarly, compared to an RCT for stage IV patients receiving first line FOLFOX or FOLFIRI we found a rate of 11% versus 5.7% for diarrhoea, 5.4% versus 1.6% for vomiting, 3.6% versus 1.6% for mucositis, 12.9% versus 2.1% for febrile neutropenia, and 14.4% versus 42.3% for neutropenia.(44)

It is to be expected that we typically found higher toxicity than observed in RCTs given the older and more comorbid population in real-world practice.(45, 46) The lower rates reported for neutropenia and fatigue are likely explained by RCTs being able to identify these toxicities based on information that we do not have available; namely laboratory results and functional information.

4.3 Relation to existing coding frameworks

Our coding framework for severe acute toxicities includes a large number of diagnostic codes which contrasts with two studies of US insurance claims data which analysed just eight and fourteen toxicities, respectively, in breast and lung cancer patients.(9, 11) These studies are also limited by inherent exclusions based on age, geography, and insurance status. This is in contrast to our use of national hospital administrative data which includes more than 95% of patients diagnosed within the English NHS.

A Canadian study of early breast cancer patients used ICD-10 codes within linked hospital administrative data to ascertain emergency department visits and hospitalisation rates related to SACT.(1, 47) Reasonable accuracy was demonstrated in the identification of SACT-related visits when validated against medical chart records, especially if hospitalisation had occurred (90% sensitivity and 100% specificity). Our study expands on this by reporting a broader range of toxicities and profiles for specific regimens.

4.4 Strengths and limitations

To date, this study represents the largest observational study in colorectal cancer patients to demonstrate real-world severe acute toxicity profiles in a representative cohort of patients across a spectrum of chemotherapy regimens, including biologic therapies.

First, a key strength of this study is the development of a comprehensive and systematic coding framework which aims to maximise the capture of all severe acute toxicities through 'forwards' and 'backwards' coding techniques. Second, we accounted for pre-existing comorbidities to avoid the misclassification of chronic conditions as toxicity. Third, in order to standardise the severity and clinical relevance of toxicities captured for much needed comparisons of regimens, patients groups, and healthcare providers using hospital administrative data, we restricted the analyses to overnight hospitalisations (a measurable consistent outcome).(35) Fourth, given the framework's breadth it can be applied to any chemotherapy regimens, including potential new therapies (e.g., immunotherapy), as well as being transferable to other cancer types.

A limitation of this study is the reliance on the accurate coding of diagnoses in hospital administrative data. However, diagnostic codes in HES have been shown to be accurate compared to clinical notes, thereby supporting its use for research.(48) It was not feasible to validate these results using medical notes although this has already been done in previous studies.(1, 12)

In addition, we found that patients not receiving chemotherapy had diagnostic codes from the coding framework present. However, there were factors present which would have increased the background rate of hospitalisations. First, despite attempting to identify a more homogeneous comparison group by using stage I/II patients not receiving chemotherapy rather than stage III patients not receiving chemotherapy, the cohort

remained significantly older and more comorbid (Appendix B). However, a strong association between severe acute toxicity and clinical group persisted despite adjustment for age, sex, comorbidity, and performance status (Appendix C). Second, a pseudo timeframe was used because these patients did not actually receive chemotherapy meaning a fixed 6-month period was used for identification of diagnostic codes.

Whilst absolute rates of toxicity are informative, these are likely to be overestimates given the inability to determine from hospital administrative data whether the overnight hospitalisations truly represent severe acute toxicity, or other clinical confounders or disease burden. However, it has previously been shown that 75% of hospital visits during chemotherapy treatment were due to toxicity.(1) The coding framework is therefore best suited for comparing groups receiving different chemotherapy regimens or being treated by different chemotherapy providers.

4.5 Implications

The medical management of cancer patients is becoming increasingly complex with new combinations of therapies and biologic agents. However, there remains disconnect between RCT and real-world patient populations.(49) This means that the ability to quantify the burden of SACT in terms of toxicities in real-world clinical practice has many implications. First, it will facilitate improved counselling of patients and enhance patient and clinician decision-making processes, particularly for therapies used towards the end of life.

Second, an improved appreciation for the real-world incidence of regimen-specific toxicities may allow the development of interventions for more prompt identification and treatment of these.(50) It may uncover rarer adverse events that might not be picked up within the trial setting and, unlike RCTs, hospital administrative data is free from observer bias.(51, 52) This is especially important for the novel biologic therapies for which an understanding of their outcomes in real-world populations remains limited.

Third, by using a coding framework based on hospital administrative data, one can start to provide a more detailed understanding of the cost implications of toxicities of novel therapies across different tumour types.

Fourth, the coding frame work for real-world data facilitates comparative provider performance monitoring and quality improvement which is essential given previously demonstrated variation in toxicity across providers.(11)

Finally, using hospital administrative data is more cost-efficient and less labour-intensive than medical note abstraction. It is also readily available and population-based, facilitating ongoing monitoring. In comparison to claims data there are no exclusions limiting the generalisability of results and the data is fit for purpose.

5. CONCLUSION

This study has demonstrated the validity of a coding framework for the identification of severe acute toxicity from SACT using diagnostic codes captured in hospital administrative data, alongside a dedicated national chemotherapy dataset. The breadth of the framework means that it can be readily applied to other chemotherapy regimens and cancer types, following appropriate validation.

Figure 1 – Flow chart of patients included in the study.

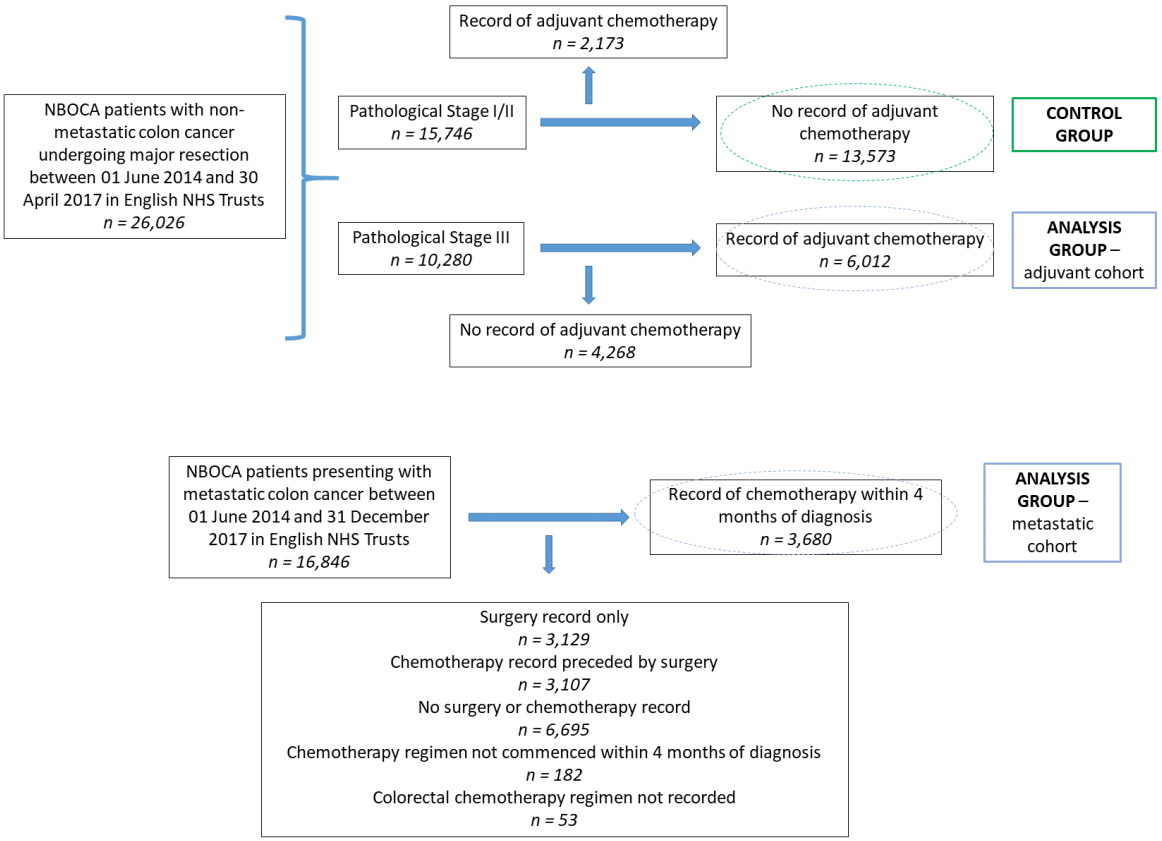

Table 1 – Presence of diagnostic codes per patient, by organ system, according to receipt of chemotherapy and stage of colon cancer

	Chemotherapy		No Chemotherapy	
	Stage III (n=6,012)	**Stage IV (n=3,680)**	**Stage I/II (n=13,573)**	**p value (χ^2)**
Overall	**26.4%**	**53.4%**	**12.5%**	**<0.001**
Gastrointestinal	**12.7%**	**23.5%**	**3.4%**	**<0.001**
Diarrhoea	9.3%	11.3%	1.2%	
Nausea or vomiting	3.6%	6.4%	0.8%	
Constipation	1.2%	6.5%	0.8%	
Oral mucositis	1.6%	3.4%	0.2%	
GI ulceration or perforation	0.3%	2.4%	0.2%	
Stoma dysfunction	0.7%	0.5%	0.7%	
Hepatic failure	0.2%	0.7%	<0.1%	
GI fistulation	0.2%	0.5%	<0.1%	
Infection	**10.5%**	**24.8%**	**5.5%**	**<0.001**
Infection	10.5%	24.8%	5.5%	
Additional neutropenia	*2.5%*	*9.3%*	*<0.1%*	
Cardiovascular	**6.5%**	**14.7%**	**3.9%**	**<0.001**
Pulmonary Embolism	1.6%	4.9%	0.4%	
Arrhythmia*	2.0%	4.7%	1.5%	
Hypotensive episode	1.4%	3.5%	0.9%	
Hypertension*	1.1%	3.6%	1.3%	
Thrombophlebitis	0.6%	1.9%	0.2%	
Arterial or venous thromboembolism	0.6%	0.9%	0.1%	
Heart Failure*	0.5%	0.7%	0.7%	
Cerebrovascular event*	0.5%	0.8%	0.5%	
Angina*	0.4%	0.5%	0.3%	
Acute MI	0.5%	0.3%	0.3%	
Pericardial disease	0.2%	0.2%	0.1%	
Cardiomyopathy	0.0%	0.0%	0.1%	
Metabolic & Endocrine	**4.7%**	**8.9%**	**2.3%**	**<0.001**
Electrolyte abnormalities	4.6%	8.5%	2.1%	
Glucose abnormalities	0.3%	0.7%	0.2%	
Other endocrine	<0.1%	0.0%	<0.1%	
Constitutional	**4.4%**	**9.7%**	**1.9%**	**<0.001**
Hypovolaemia	3.5%	6.1%	1.3%	
Peripheral oedema	0.4%	1.7%	0.2%	
Fatigue	0.5%	1.8%	0.2%	
Anorexia	0.4%	1.4%	0.4%	
Volume overload	0.2%	0.3%	0.1%	
Renal	**4.2%**	**7.7%**	**3.2%**	**<0.001**
Acute renal failure	4.0%	6.8%	3.0%	
Tubulo-interstitial disease	0.4%	1.3%	0.3%	

Haematology	**4.1%**	**13.7%**	**1.0%**	**<0.001**
Neutropenia	3.1%	10.5%	0.1%	
Anaemia*	1.0%	4.1%	0.9%	
Thrombocytopenia	0.3%	0.7%	0.1%	
Disseminated intravascular coagulation (DIC)	0.0%	0.1%	0.0%	
Pain	**3.8%**	**6.3%**	**1.6%**	**<0.001**
Respiratory	**1.1%**	**1.9%**	**0.4%**	**<0.001**
Dyspnoea	0.8%	1.2%	0.2%	
Cough	0.2%	0.6%	0.1%	
Acute Respiratory Distress Syndrome	0.1%	0.1%	<0.1%	
Pulmonary oedema	<0.1%	<0.1%	<0.1%	
Neurological	**2.3%**	**3.3%**	**0.9%**	**<0.001**
Dizziness/syncope	0.9%	1.3%	0.4%	
Neuropathy	0.8%	0.8%	0.1%	
Headache	0.4%	0.7%	0.1%	
Seizures*	0.2%	0.4%	0.2%	
Other neurological	0.1%	0.3%	0.1%	
Laryngeal spasm	0.1%	0.1%	0.0%	
Line Complications	**1.4%**	**3.3%**	**0.2%**	**<0.001**
Psychological*	**1.4%**	**4.4%**	**1.8%**	**<0.001**
Bleeding	**1.1%**	**3.0%**	**0.8%**	**<0.001**
Dermatology & Rheumatology	**1.1%**	**2.0%**	**0.4%**	**<0.001**
Skin reaction	0.7%	1.6%	0.2%	
Gout*	0.4%	0.4%	0.3%	
Ophthalmic*	**0.2%**	**0.5%**	**0.3%**	**0.079**
Drug Reaction	**0.2%**	**0.4%**	**<0.1%**	**<0.001**
Death	**1.9%**	**14.6%**	**2.3%**	**<0.001**

*****Code must not be present in previous 12 months (see Appendix A)

Table 2 – Acute toxicities for patients receiving chemotherapy, according to regimen, including biologic therapies

	Stage III			Stage IV			
	Capecitabine (n=1,413)	**CAPOX (n=2,371)**	**p value (χ^2)**	**FOLFOX or FOLFIRI (n=1,775)**	**FOLFOX/FOLFIRI + Bevacizumab (n=72)**	**FOLFOX/FOLFIRI + Panitumumab or Cetuximab (n=386)**	**p value (χ^2)**
Overall	**18.4%**	**27.8%**	**<0.001**	**54.3%**	**58.3%**	**55.2%**	**0.763**
Gastrointestinal	**9.1%**	**15.4%**	**<0.001**	**23.3%**	**26.4%**	**23.6%**	**0.826**
Diarrhoea	6.9%	11.7%		11.0%	16.7%	10.6%	
Nausea or vomiting	2.1%	4.4%		5.4%	8.3%	7.8%	
Constipation	0.7%	1.4%		6.3%	6.9%	6.2%	
Oral mucositis	1.3%	1.4%		3.6%	8.3%	3.4%	
GI ulceration or perforation	0.4%	0.5%		2.9%	5.6%	2.9%	
Stoma dysfunction	0.5%	0.5%		0.7%	0.0%	0.5%	
Hepatic failure	0.4%	0.1%		0.8%	1.4%	0.5%	
GI fistulation	<0.1%	0.0%		0.5%	1.4%	0.3%	
Infection	**7.1%**	**10.9%**	**<0.001**	**25.6%**	**31.9%**	**28.0%**	**0.330**
Infection	7.1%	10.9%		25.6%	31.9%	28.0%	
Additional neutropenia	1.1%	1.9%		12.9%	9.7%	10.9%	
Cardiovascular	**5.1%**	**6.7%**	**0.051**	**15.1%**	**15.3%**	**18.9%**	**0.175**
Pulmonary Embolism	0.9%	1.9%		5.1%	0.0%	8.0%	
Arrhythmia*	1.6%	1.8%		4.9%	9.7%	5.2%	
Hypotensive episode	1.1%	1.5%		3.2%	4.2%	5.7%	
Hypertension*	1.1%	0.8%		3.6%	4.2%	3.1%	
Thrombophlebitis	0.2%	0.8%		2.6%	2.8%	1.0%	
Arterial or venous thromboembolism	0.4%	0.3%		1.2%	1.4%	0.8%	
Heart Failure*	0.4%	0.3%		0.5%	0.0%	0.8%	
Cerebrovascular event*	0.7%	0.4%		1.0%	1.4%	1.0%	
Angina*	0.4%	0.6%		0.5%	0.0%	0.3%	

Acute MI	0.6%	0.4%		0.3%	0.0%	0.5%	
Pericardial disease	<0.1%	<0.1%		0.0%	0.0%	0.5%	
Cardiomyopathy	0.0%	0.0%		0.0%	0.0%	0.0%	
Metabolic & Endocrine	**4.0%**	**5.6%**	**0.025**	**7.8%**	**8.3%**	**13.2%**	**0.003**
Electrolyte abnormalities	3.9%	5.5%		7.3%	8.3%	12.4%	
Glucose abnormalities	0.1%	0.2%		0.6%	0.0%	1.6%	
Other endocrine	<0.1%	0.0%		0.0%	0.0%	0.0%	
Constitutional	**3.1%**	**5.2%**	**0.002**	**8.7%**	**12.5%**	**11.4%**	**0.168**
Hypovolaemia	2.4%	3.8%		5.0%	8.3%	6.7%	
Peripheral oedema	0.2%	0.6%		1.8%	1.4%	2.1%	
Fatigue	0.4%	0.6%		1.8%	2.8%	2.1%	
Anorexia	0.2%	0.5%		1.3%	1.4%	2.1%	
Volume overload	<0.1%	0.3%		0.3%	1.4%	0.5%	
Renal	**2.9%**	**4.0%**	**0.077**	**7.2%**	**9.7%**	**9.3%**	**0.273**
Acute renal failure	2.8%	3.8%		6.3%	9.7%	7.5%	
Tubulo-interstitial disease	0.1%	0.4%		1.2%	1.4%	2.3%	
Haematology	**1.6%**	**4.0%**	**<0.001**	**17.6%**	**13.9%**	**14.3%**	**0.215**
Neutropenia	1.2%	2.4%		14.4%	11.1%	11.9%	
Anaemia*	0.5%	1.3%		4.4%	5.6%	3.6%	
Thrombocytopenia	0.2%	0.4%		0.6%	0.0%	0.5%	
Disseminated intravascular coagulation (DIC)	0.0%	0.0%		0.2%	0.0%	0.3%	
Pain	**3.0%**	**4.1%**	**0.067**	**6.1%**	**9.7%**	**7.3%**	**0.352**
Respiratory	**0.7%**	**0.9%**	**0.474**	**1.6%**	**1.4%**	**2.9%**	**0.261**
Dyspnoea	0.6%	0.7%		1.1%	1.4%	1.3%	
Cough	0.1%	0.0%		0.6%	0.0%	1.0%	

Acute Respiratory Distress Syndrome	<0.1%	0.2%		0.1%	0.0%	0.5%	
Pulmonary oedema	0.0%	0.0%		0.0%	0.0%	0.0%	
Neurological	**1.0%**	**2.9%**	**<0.001**	**3.3%**	**4.2%**	**3.4%**	**0.914**
Dizziness/syncope	0.7%	0.8%		1.1%	0.0%	1.6%	
Neuropathy	0.0%	1.4%		0.8%	2.8%	1.3%	
Headache	0.0%	0.3%		0.9%	0.0%	0.5%	
Seizures*	<0.1%	0.2%		0.4%	0.0%	0.5%	
Other neurological	0.2%	<0.1%		0.3%	1.4%	0.0%	
Laryngeal spasm	0.0%	0.3%		0.1%	0.0%	0.0%	
Line Complications	**0.2%**	**0.5%**	**0.218**	**4.2%**	**5.6%**	**8.0%**	**0.006**
Psychological*	**1.1%**	**1.4%**	**0.563**	**4.6%**	**1.4%**	**3.9%**	**0.367**
Bleeding	**0.6%**	**1.4%**	**0.032**	**2.7%**	**12.5%**	**3.4%**	**<0.001**
Dermatology & Rheumatology	**0.9%**	**1.2%**	**0.335**	**1.5%**	**1.4%**	**5.4%**	**<0.001**
Skin reaction	0.5%	0.7%		1.2%	1.4%	5.2%	
Gout*	0.4%	0.5%		0.3%	0.0%	0.3%	
Ophthalmic*	**0.2%**	**0.3%**	**0.803**	**0.2%**	**1.4%**	**0.8%**	**0.039**
Drug Reaction	**0.1%**	**0.4%**	**0.188**	**0.5%**	**1.4%**	**0.0%**	**0.182**
Death	**1.6%**	**1.7%**	**0.815**	**13.9%**	**9.7%**	**14.5%**	**0.557**

*****Code must not be present in previous 12 months (see Appendix A)

Table 3 – Patient and clinical characteristics for those with pathological stage III colon cancer receiving adjuvant chemotherapy according to whether or not they have evidence of at least one acute toxicity

Total (n=6,012)		**Severe Acute Toxicity**		***P* value (χ^2)**
		Present (n=1,589)		
		n	**%**	
Age Category				**0.011**
	<60	429	26.8	
	60-69	538	26.8	
	70-79	547	27.2	
	≥80	75	19.2	
Prior renal disease				**0.001**
	Yes	89	35.5	
	No	1,500	26.0	
Prior cardiac disease				**0.038**
	Yes	95	31.6	
	No	1,494	26.2	
Performance Status				0.167
	0	813	25.9	
	1	437	27.0	
	≥2	138	30.2	
	Missing	*791*		
Surgical urgency				**0.004**
	Elective/scheduled	1,229	25.6	
	Emergency/urgent	358	29.7	

Table 4 – Clinical outcomes according to the presence of acute toxicity for patients with pathological stage III colon cancer

	Toxicity Flag		*P* value
	Yes (%)	**No (%)**	
Completion of chemotherapy (n=6,012)			**<0.001**
Yes	556 (18.8)	2,402 (81.2)	
No	1,033 (33.8)	2,021 (66.2)	
Change of route of administration of CAPOX or FOLFOX (n=4,147)			**<0.001**
Yes	54 (51.4)	51 (48.6)	
No	1,165 (28.8)	2,877 (71.2)	

Appendix

Appendix A – Coding framework used to determine acute toxicity

Haematology
D701 D702 D703 D708 D709 D70X D695 D696 D699 M311 R233 D65X D65 D611 D618 D619 D648 D509* D630 D649*
Constitutional
R530 R531 R538 R53X R64 R64X R630 R634 R638 E877 E860 E86X E861 E869 R600 R601 R609 R60X
Cardiovascular*
I200* I201* I208* I209* I210 I211 I212 I213 I214 I219 I220 I221 I228 I229 I230 I231 I232 I233 I234 I235 I236 I238 I500* I501* I509* I440* I441* I442* I443* I444* I445* I446* I447* I471* I472* I480* I483* I484* I489* I48X* I450* I451* I452* I453* I454* I455* I456* I458* I459* I490* I491* I492* I493* I494* I495* I498* I499* R000 R001 R002 R008 I10* I10X* I110* I119* I120* I129* I130* I131* I132* I139* I150* I151* I152* I158* I159* I630* I631* I632* I633* I634* I635* I636* I638* I639* I600* I601* I602* I603* I604* I605* I606* I607* I608* I609* I64* I64X* I610* I611* I612* I613* I614* I615* I616* I618* I619* I620* I621* I629* I690* I691* I692* I693* I694* I698* G450* G451* G452* G453* G454* G458* G459* G460* G461* G462* G463* G464* G465* G466* G467* G468* I950 I951 I952 I958 I959 I260 I269 I313 I319 I427 I429 I740 I741 I742 I743 I744 I745 I748 I749 I822 I823 I828 I829 I800 I801 I802 I803 I808 I809
Respiratory
R05X R05 J80X J80 J81 J81X R060
Infection
R502 R508 R509 R680 R650 R651 R659 A410 A411 A412 A413 A414 A415 A418 A419 A020 A021 A022 A028 A029 A040 A041 A042 A043 A044 A045 A046 A047 A048 A049 A050 A051 A052 A053 A054 A058 A059 A070 A071 A072 A073 A078 A079 A080 A081 A082 A083 A084 A085 A150 A151 A152 A153 A154 A155 A156 A157 A158 A159 A170 A171 A178 A179 A180 A181 A182 A183 A184 A185 A186 A187 A188 A190 A191 A192 A198 A199 A38 A38X A390 A391 A392 A394 A395 A398 A399 A400 A401 A402 A403 A408 A409 A420 A421 A422 A427 A428 A429 A46 A46X A480 A481 A482 A483 A484 A488 A490 A491 A492 A493 A498 A499 A810 A811 A812 A818 A819 A850 A852 A858 A86X A86 A870 A871 A872 A878 A879 A880 A881 A888 A89 A89X B001 B002 B003 B004 B005 B007 B008 B009 B010 B011 B012 B018 B019 B020 B021 B022 B023 B027 B028 B029 B07X B07 B080 B081 B082 B083 B084 B085 B088 B09X B150 B159 B160 B161 B162 B169 B170 B171 B172 B178 B179 B190 B199 B250 B251 B252 B258 B259 B270 B271 B278 B279 B300 B301 B302 B303 B308 B309 B330 B331 B332 B333 B334 B338 B340 B341 B342 B343 B344 B348 B349 B371 B372 B373 B374 B375 B376 B377 B378 B379 B440 B441 B442 B447 B448 B449 B450 B451 B452 B453 B457 B458 B459 B49X B59X B950 B951 B952 B953 B954 B955 B956 B957 B958 B960 B961 B962 B963 B964 B965 B966 B967 B968 B970 B971 B972 B973 B974 B975 B976 B977 B978 B99 B99X J200 J201 J202 J203 J204 J205 J206 J207 J208 J209 J120 J121 J122 J123 J128 J129 J13 J14 J13X J14X J150 J151 J152 J153 J154 J155 J156 J157 J158 J159 J160 J168 J170 J171 J172 J173 J178 J180 J181 J182 J188 J189 J09 J100 J101 J22X J108 J110 J111 J118 J850 J851 J852 J853 J860 J869 N10X N390 N300 N308 N309 N340 N151 N450 N459 N410 N412 N413 L00X L010 L011 L020 L021 L022 L023 L024 L028 L029 L030 L031 L032 L033 L038 L039 L040 L041 L042 L043 L048 L049 L050 L059 L080 L081 L088 L089 N700 N709 N710 N72X N730 N732 N733 N735 N760 N762 N764 N61X T814 G000 G001 G002 G003 G008 G009 G01X G020 G021 G028 G030 G038 G039 G040 G041 G042 G048 G049 G050 G051 G052 G058 G060 G061 G062 G07X G08X A851 M600 I330 I339 I300 I301 I308 I309 I400 I401 I408 I409 I514 I518 H700 K052 K113 J040 J041 J042 H600 H601 H603 H660 J010 J011 J012 J013 J014 J018 J019 J020 J028 J029 J030 J038 J039 M871 K102 M860 M861 M869 M000 M001 M002 M008 M009 K750 K610 K611 K612 K613 K614 K800 K803 K804 K810 K830 K630 K65 K65X
Renal
N170 N171 N172 N178 N179 N19X N19 N10 N10X N12X N12 N130

N131 N132 N133 N134 N135 N136 N137 N138 N139 N141 N142 N144 N158 N159 N280
Line Complications
T825 T827 T828 T829 Z452 T800 T801 T802 T808 T809
Gastrointestinal
K521 K528 K529 A090 A099 R110 R111 R112 R11X R13X K590 K564 K121 K123 B370 K710 K711 K712 K716 K719 K720 K729 R17 R17X K221 K223 K251 K253 K255 K261 K262 K263 K265 K271 K273 K275 K281 K283 K285 K291 K293 K295 K914 K631 N321 N820 N822 N823 N824 K316 K603 K605 K604
Bleeding
R040 R310 R31X N938 N939 R042 J942 K625 I850 K920 K921 K922 K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K292 K294 K296
Metabolic & Endocrine
E870 E871 E872 E873 E874 E875 E876 E878 E833 E835 E838 E839 E883 E834 R730 R739 E15 E15X E160 E161 E162 E032 E058 E064 E273 E231
Pain
R100 R101 R102 R103 R104 M255 M540 M541 M542 M543 M544 M545 M546 M548 M549 R07 R07X R070 R071 R072 R073 R074 R520 R529 H920 K146 H571 M796
Neurological*
R55X R55 R42 R42X G400* G401* G402* G403* G404* G405* G406* G407* G408* G409* G410* G411* G412* G418* G419* R56* R560* R568* G620 G628 G629 R200 R201 R202 R203 R208 R209 H910 H931 J385 G250 G251 G252 G253 G258 G259 G240 G254 G256 G711 G720 R270 R260 G430 G431 G432 G433 G438 G439 G440 G441 G442 G443 G444 G448 R51 R51X
Dermatology & Rheumatology*
R21X R21 L270 L271 L298 L299 L51 L510 L511 L512 L518 L519 L539 R238 R239 M100* M102* M104* M109*
Drug Reaction
L500 T782 T783 T784 T886 T887 T451
Ophthalmic*
H320 H191 H192 H10 H100 H101 H102 H103 H105 H108 H109 H11 H111 H112 H113 B300 B301 B302 B303 B308 B309 H150 H151 H158 H159 H160 H161 H162 H163 H164 H168 H169 M350 H170 H171 H178 H179 H180 H181 H182 H183 H184 H186 H187 H188 H189 H200 H202 H208 H209 H210 H211 H212 H213 H214 H215 H218 H219 H263 H278 H279 H406 H531 H532 H533 H534 H535 H536 H538 H539 H540* H541* H542* H543* H544* H545* H546* H549* H000 H001 H010 H018 H019 H041 H042 H043 H020 H021 H050 H052 H058 H059 H578 H579 H490* H491* H492* H493* H494* H498* H499* H500* H501* H502* H503* H504* H505* H506* H508* H509* H510* H511* H512* H518* H519* H46X* H46* H470* H471* H472* H473* H474* H475* H476* H477* H300* H301* H302* H308* H309* H310* H311* H313* H314* H318* H319* H330* H332* H335* H340* H341* H342* H348* H349* H350* H352* H353* H356* H357* H358* H359* H431 H432 H433 H438 H439 H440 H441 H448 H449
Psychological*
F320 F321 F322 F323 F328 F329* F410 F411 F412 F413 F418 F419*

*Codes excluded if present in the 12 months preceding chemotherapy administration

Appendix B - Patient characteristics according to colon cancer stage and receipt of chemotherapy

	Stage I/II MR – no chemo (n=13,573)		Stage III MR – chemo (n=6,012)		Stage IV – chemo (n=3,680)		P value*
	No.	**%**	**No.**	**%**	**No.**	**%**	
Sex							<0.001
Male	7,217	53.2	3,177	52.8	2,119	57.6	
Female	6,355	46.8	2,835	47.2	1,561	42.4	
Age							<0.001
<60	1,447	10.7	1,599	26.6	1,129	30.7	
60-69	3,148	23.2	2,009	33.4	1,113	30.2	
70-79	5,023	37	2,014	33.5	1,100	29.9	
≥80	3,955	29.1	390	6.5	338	9.2	
RCS Charlson Score							<0.001
0	6,637	48.9	3,787	63	2,176	60.9	
1	4,303	31.7	1,695	28.2	1,024	28.7	
≥2	2,633	19.4	530	8.8	373	10.4	
Missing	0	0	0	0	107	2.9	
Performance Status							<0.001
0	5,459	48.3	3,141	60.2	1,468	45.5	
1	3,798	33.6	1,620	31	1,169	36.2	
≥2	2,040	18.1	460	8.8	590	18.3	
Missing	2,276	16.8	791	13.2	453	12.3	

***Chi-squared test**

Appendix C – Multivariable regression model estimating the association between severe acute toxicity and clinical validation group, adjusting for age, sex, comorbidity, and performance status

	Adjusted Odds Ratio (OR)	95% Confidence Intervals	P value*
Age (years)			0.153
<60	1.0	-	
60-69	0.92	0.84 to 1.02	
70-79	0.96	0.87 to 1.06	
≥80	1.03	0.92 to 1.16	
Sex			0.217
Female	1.0	-	
Male	1.04	0.98 to 1.12	
RCS Charlson comorbidity score			<0.001
0	1.0	-	
1	1.24	1.15 to 1.34	
≥2	1.77	1.60 to 1.95	
Performance status			<0.001
0	1.0	-	
1	1.18	1.08 to 1.28	
≥2	1.75	1.58 to 1.94	
Clinical group			
Stage I/II MR** – no chemo	1.0	-	<0.001
Stage III MR – chemo	2.98	2.75 to 3.23	
Stage IV – chemo	8.98	8.22 to 9.80	

***Wald value**

****Major resection**

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