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ORIGINAL ARTICLE

Variation in the risk of venous thromboembolism in people with colorectal cancer: a population-based cohort study from England

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Summary. *Background:* Patients with colorectal cancer are at high risk of developing venous thromboembolism (VTE), and recent international guidelines have advised extended prophylaxis for some of these patients following surgery or during chemotherapy. However, our understanding of which patients are at increased risk, and to what extent, is limited. *Objectives:* To determine absolute and relative rates of VTE among patients with colorectal cancer according to Dukes stage, surgical intervention, and chemotherapy. *Methods:* We analyzed data from four linked databases from 1997 to 2006: the Clinical Practice Research Datalink, linked to Hospital Episode Statistics, Cancer Registry data, and Office for National Statistics cause of death data, all from England. Rates were compared by the use of Cox regression. *Results:* There were 10 309 patients with colorectal cancer, and 555 developed VTE (5.4%). The incidence varied by Dukes stage, being three-fold higher among Dukes D patients than among Dukes A patients (hazard ratio [HR] 3.08, 95% confidence interval [CI] 1.95–4.84), and 40% higher for those receiving chemotherapy than for those not receiving chemotherapy (HR 1.39, 95% CI 1.14–1.69). The risk following surgery varied by stage of disease and chemotherapy, with Dukes A patients having a low incidence of VTE (0.74%; 95% CI 0.28–1.95) at 6 months, with all events occurring within 28 days of surgery, as compared with Dukes B and Dukes C patients, whose risk at 6 months was ~2%. *Conclusion:* Twenty-eight days of prophylaxis following surgery for colorectal cancer is appropriate for Dukes A patients. However, Dukes B and Dukes C patients receiving postoperative chemotherapy have a longer duration of risk.

Keywords: chemotherapy; colorectal cancer; colorectal surgery; incidence; venous thromboembolism.

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Introduction

Patients undergoing treatment for colorectal cancer are at a high risk of developing venous thromboembolism (VTE) shortly after diagnosis, and this risk appears to vary with severity of disease [1]. This represents a significant source of morbidity and mortality [2], and, in an attempt to reduce the incidence among this patient group, international guidance now recommends 28 days of postoperative thromboprophylaxis for patients with colorectal cancer [2]. However, the authors of these guidelines did highlight the fact that our understanding of which patients are at increased risk, what the magnitude of this increased risk is, and for how long this risk is elevated, is limited [2]. Only by understanding how these factors influence risk and for how long the risk lasts will we be able to identify the right patient groups in which to intervene with appropriate preventive measures [3]. Unfortunately, the influence on VTE risk of stage of colorectal cancer in combination with therapies, including surgery and chemotherapy, remains very unclear. The studies that have reported information on this have focused on high-risk populations, such as those receiving chemotherapy [4,5], have combined data on stage with other cancer types [6], or have used limited staging, such as local, regional, and metastatic [7], rather than the internationally recognized Dukes system. The one available study reporting incidence rates by stage (0–IV) [8] showed a graded increase in risk, with worsening disease with additional risk among those receiving palliative chemotherapy. Inevitably, this trend could be explained by the surgical intervention and chemotherapy regimens received by these patients, which are dependent on stage of disease

[3,6,9–11]. In addition, contradictory findings have been reported for surgically treated patients, with some suggesting an increase in risk and others a decrease. These studies highlight the problem of the selection bias inherent in studying VTE risk, because, for example, Dukes D patients will not be undergoing surgery with curative intent, in contrast to Dukes A, B and C patients. Furthermore, no previous studies have quantified risk from date of surgery, meaning that their results are not easy to translate into clinically meaningful risks, as most guidelines advocate commencement of prophylaxis following surgical intervention.

The aim of this study, therefore, was to use a large, population-based cohort study to determine the risk of VTE and its duration among all patients with a diagnosis of colorectal cancer, taking account of how Dukes stage of disease, surgical intervention and chemotherapy received interact, using nationwide primary-care and secondary-care electronic medical data linked to cancer registries from England.

Methods

Patients and data sources

Our data sources have been described in detail in previous work [12]. Briefly, these were all from England, and comprised a primary-care database (the Clinical Practice Research Datalink [CPRD]), a secondary-care database that contains data from all inpatient hospital admissions in England (Hospital Episode Statistics [HES]), a cancer registry database (National Cancer Intelligence Network), and death certificate data from the Office for National Statistics (ONS). These databases were linked and anonymized by the CPRD, with the linked data covering ~ 4% of the population of England. The study had approval from the Independent Scientific Advisory Committee approval board, which provides scientific advice to the Medicines and Healthcare Products Regulatory Agency (MHRA) on study design, and advises whether further approval is required from the Multi-centre Research Ethics Committee outside the MHRA's current approval for observational studies.

Cohort identification

The cohort was selected from the cancer registry data, and additional information regarding outcome definition and other exposures were identified in the relevant linked primary-care (CPRD) and secondary-care (HES) data. We selected patients who had a colorectal cancer diagnosis in the cancer registry data (ICD-10 sections C18–20, excluding C18.1 – 'Appendix'), between 1 April 1997 and 31 December 2006. Patients were followed up until they developed a VTE event, died, left a participating general practice, or 31 December 2010, whichever was earliest. The earliest date recorded in the cancer registry was used to determine the date of cancer diagnosis. Patients were excluded if they were: < 18 years of age, not in a linked general practice, diagnosed with colorectal cancer outside of the CPRD and HES registration dates, diagnosed in the first year of registration at a participating general practice, or had a VTE prior to the first cancer diagnosis.

Exposures

Cancer stage and grade were determined by using data from the cancer registry database, where stage was recorded in various classification systems, including TNM numerical stage (I–IV) (41.1%), Dukes stage (54.8%), and the individual components of the TNM stage (4.1%). By use of the numerical data and TNM data, patients were recategorized into Dukes stages (A, B, C, and D) if they were not already recorded as such. Most could be directly translated from the numerical stage data, with the exception of patients only recorded as numeric stage I without TNM staging data (whose modified Dukes stage was ambiguous as recorded by the Astler–Coller classification) [13]. These patients were excluded from analyses involving stage. Comorbidity was determined from general practitioner records, and classified according to the Charlson index [14], excluding cancer as a comorbidity. Survival by cancer stage was determined from the linked ONS mortality data, and was measured from the date of cancer diagnosis for all analyses involving death. Surgical procedures were defined from hospital episodes with an associated Office of Population Census and Surveys Classification of Interventions and Procedures (OPCS) code for colorectal surgery. Chemotherapy events were similarly determined by the use of OPCS codes.

Outcome definition

VTE diagnoses were determined from medical codes in the CPRD and HES. These were considered to be valid VTE events if supported by either: a prescription for an anticoagulant or other evidence of treatment in an anticoagulation clinic (such as a medical code) between 15 days before and 90 days after the VTE diagnosis; or a date of death within 30 days of the event. Additionally, an underlying cause of death of VTE was included as evidence of VTE diagnosis. Only the first validated instance of VTE was included in the analysis. The definition from primary-care data alone has been validated previously [15].

Statistical methods

Person-time at risk commenced at the time of cancer diagnosis for our overall analysis. First, we described the basic characteristics of our cohort and 5-year survival by Dukes stage. Absolute rates of VTE (per 1000 person-years) were then calculated by dividing the number of people with VTE

by the person-time at risk. This was performed overall and then separately for each exposure of interest. A Cox proportional hazards model was then created to include all exposures, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We then evaluated the risk of VTE by Dukes stage and according to whether or not patients had undergone surgery by stratifying our analysis by these factors. Following this analysis, it was apparent that risks varied markedly according to stage, so, to evaluate the interaction between Dukes stage, surgical intervention, and chemotherapy, we restricted our cohort to only those patients undergoing surgery with the assumption of curative intent (i.e. Dukes A, B and C patients undergoing surgery). We then reset our follow-up time to start from the date of surgery. Among this restricted cohort, we examined the interaction between chemotherapy and Dukes stage while adjusting for other covariates, using a likelihood ratio test, and we present stratified adjusted HRs from this analysis. Following this, among the surgical cohort, we carried out an analysis of cumulative incidence over the first 6 months of follow-up stratified by Dukes stage (A, B, and C) and chemotherapy, to illustrate how the absolute rates varied by these variables. Data management and all analyses were performed with STATA 11 (Statacorp, College Station, TX, USA).

Results

In the 10 years between 1997 and 2006, 10 309 colorectal cancer patients were identified from cancer registry data (Table 1). The median age at diagnosis was 74 years, and the median follow-up time was 2.2 years. VTE occurred in 555 cases, leading to a rate of 15.8 per 1000 person-years (95% CI 14.5–17.1). Cancer stage was determinable in 71.7% of patients. Among those with a known stage, 8.8% had Dukes A, a large majority had Dukes B and C (37.2% and 33.8%, respectively), and 20.2% had Dukes D. In total, 7407 (71.8%) patients underwent surgery, with 25% of these patients receiving chemotherapy following surgery, and the greatest proportion of chemotherapy being received by Dukes C patients. Among those not undergoing surgery, 338 (11.6%) received palliative chemotherapy. (Fig. 1 shows the distribution of stage by surgery and chemotherapy.) Among patients whose Dukes stage could not be determined, 6% had an ambiguous Dukes stage (recorded only as numerical stage I) and were excluded from analyses involving stage. The overall 5-year survival rate in our cohort was 43.9%, and this varied by stage, with Dukes A patients having the most favorable survival and Dukes D the worst (Table S1). Those with an undetermined stage also had poor survival.

VTE rate varied substantially by stage (Table 2; Fig. 2), with Dukes A patients having the lowest absolute rate (7.3 per 1000 person-years, 95% CI 5.0–10.7) and Dukes D patients the highest (41.3 per 1000 person-years, 95% CI 33.4–51.2). We observed that the rates seemed to be similar in the first few months after diagnosis, and then subsequently diverged. The effects of stage were independent of other measured variables, as shown in the multivariate Cox model (Table 2), with Dukes D patients having a more than three-fold greater risk of VTE than Dukes A patients (HR 3.1, 95% CI 2.0–4.8). From this analysis, it was apparent there were no statistically significant differences in VTE rate between tumor grades in the multivariate model. Overall, patients undergoing surgery had a similar rate of VTE as those not undergoing surgery (HR 0.97, 95% CI 0.77–1.22). However, this effect varied according to how patients were admitted for the first operation, as patients with an emergency admission had a higher rate of VTE than those with an elective admission (HR 1.43, 95% CI 1.15–1.78). There was a significantly higher rate of VTE in those receiving

Table 1 Numbers of patients by patient characteristics

	No VTE	%	VTE	%
Total	9754		555	
Sex				
Male	5241	53.7	312	56.2
Female	4513	46.3	243	43.8
Age bands (years)				
< 40	103	1.1	6	1.1
40–49	365	3.7	27	4.9
50–59	1207	12.4	79	14.2
60–69	2240	23.0	163	29.4
70–79	3358	34.4	204	36.8
≥ 80	2481	25.4	76	13.7
Comorbidities				
0	4724	48.4	257	46.3
1	2597	26.6	156	28.1
2	1371	14.1	88	15.9
3	628	6.4	32	5.8
4	238	2.4	13	2.3
5	85	0.9	6	1.1
6	72	0.7	2	0.4
≥7	39	0.4	1	0.2
Smoking				
No	2997	30.7	192	34.6
Yes	744	7.6	42	7.6
Ex-smoker	2052	21.0	134	24.1
Unknown	3961	40.6	187	33.7
BMI				
Underweight	168	1.7	9	1.6
Ideal	2083	21.4	118	21.3
Overweight	2055	21.1	141	25.4
Obese	687	7.0	44	7.9
Morbidly obese	181	1.9	21	3.8
Missing	4580	47.0	222	40.0
Surgery				
Elective	5216	53.5	337	60.7
Emergency	1707	17.5	115	20.7
Other/unknown	31	0.3	1	0.2
None	2800	28.7	102	18.4
Chemotherapy				
No	7818	80.2	370	66.7
Yes	1936	19.8	185	33.3

BMI, body mass index; VTE, venous thromboembolism.

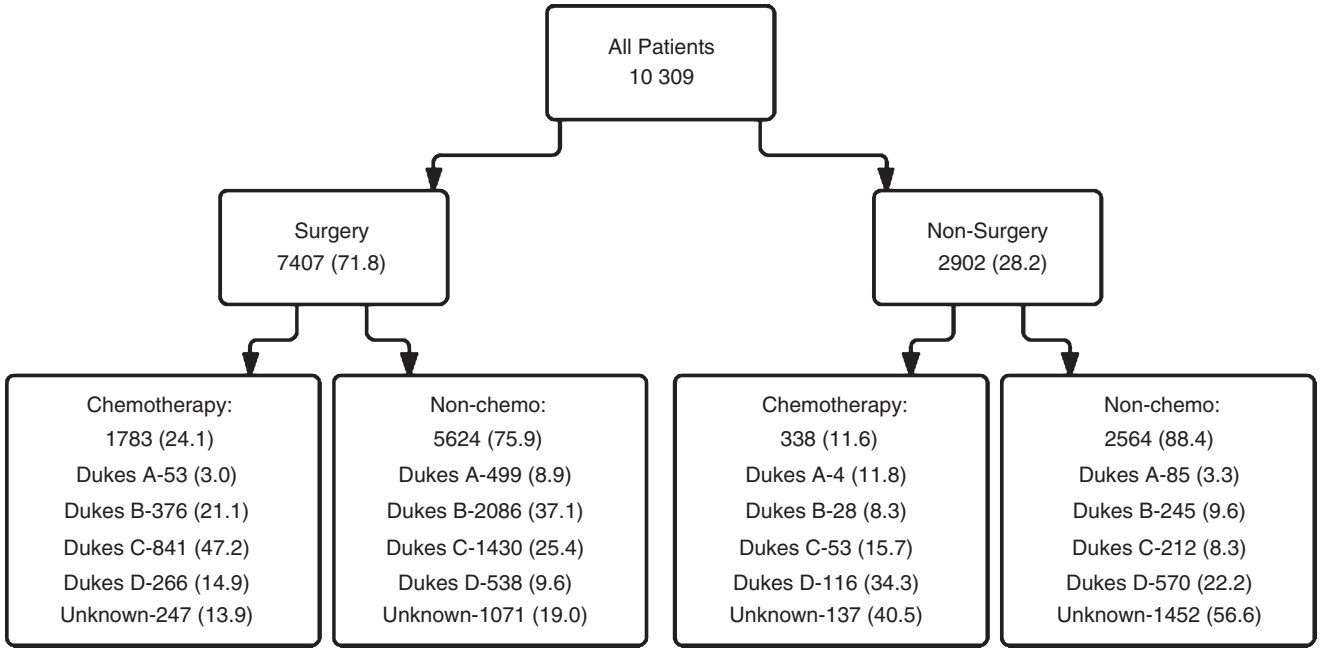

Fig. 1. Distribution of patients by surgery, chemotherapy, and stage of disease.

chemotherapy than in those who not receiving chemotherapy (HR 1.39, 95% CI 1.14–1.69). A number of the other recognized risk factors (smoking, body mass index [BMI], age, and comorbidity) appeared to have relatively little influence on the rate of VTE in this group (Table 2). Although there was a slight trend observed for BMI (with the highest rate in morbidly obese patients), this trend was non-significant ($P = 0.074$).

When we stratified our analysis by stage of disease and surgical intervention, the influence of surgery on the rate of VTE appeared to vary according to the stage of cancer (Fig. 3). In Dukes A patients, the VTE rate was higher in patients undergoing surgery, whereas in Dukes D patients the rate was higher in those not undergoing surgery. Subsequent analyses were all carried out among patients who had undergone surgery with the assumption of curative intent (i.e. Dukes A, B and C patients). These results are presented in Tables 3 and 4. When we fitted our model with an interaction term between stage of disease and chemotherapy, there was some evidence of an interaction (likelihood ratio test, $P < 0.047$). The stratified HRs show that Dukes B and C patients receiving chemotherapy had a two-fold increase in risk of VTE as compared with Dukes B patients not receiving chemotherapy (Table 3), whereas Dukes A patients had no increase in risk.

Table 4 shows the incidence of VTE by time since surgery, stratified by chemotherapy and Dukes stage, and limited to those undergoing surgery. The whole population and this subcohort were similar with respect to gender (46.5% and 45.8% female, respectively), age (median ages of 74 and 73 years), BMI (median of 25.7 kg m^{-2} for both), and Charlson comorbidity score (mean of 0.70 for both). Table 4 shows that the incidence of VTE was lowest in Dukes A patients undergoing surgery, and that their risk was confined to the first 28 days following surgery. In contrast, in Dukes B and C patients receiving chemotherapy following surgery, the risk of VTE persisted for 6 months following surgery (Table 4), with the highest cumulative incidence being observed in Dukes C patients receiving chemotherapy (2.5% at 6 months).

Discussion

Summary of findings

Overall, 5.4% of our cohort of colorectal cancer patients developed a VTE during follow-up, with an absolute rate of 15.8 per 1000 person-years. Increasing Dukes stage was associated with an increased risk of developing VTE, with Dukes D patients having the highest absolute rate (41.3 per 1000 person-years, 95% CI 33.4–51.2), corresponding to a three-fold increase in risk as compared with Dukes A patients. However, these risks were dependent on surgical intervention and chemotherapy. Among patients undergoing surgery with curative intent (Dukes A, B and C patients), Dukes B and C patients receiving chemotherapy had an approximately two-fold increase in risk of developing VTE as compared with Dukes A and B patients not receiving chemotherapy. Analysis of the risk following surgery when stratified by stage, adjuvant chemotherapy and time since surgery demonstrated that Dukes A patients had a low absolute risk that did not extend beyond the first 28 days following surgery. Dukes B and C patients receiving chemotherapy had a persistent risk of VTE that

Table 2 Rates and cumulative incidence of venous thromboembolism (VTE) and multivariate Cox modeling for VTE risk factors from time of diagnosis with colorectal cancer

			Cumulative incidence				Cox model	
			180 days from diagnosis		2 years from diagnosis			
	Events	Person-time (1000s of years)	Events (0–180 days)	Cumulative%	Events (0.5–2 years)	Cumulative%	HR	95% CI
Site								
Colon	358	21.2	135	2.52	97	4.91	Reference	
Rectum	161	11.0	69	2.03	60	4.22	0.92	0.75–1.11
Dukes								
A	26	3.6	7	1.11	2	1.45	Reference	
B	141	13.4	41	1.59	41	3.37	1.30	0.85–1.98
C	186	9.3	60	2.59	58	5.54	2.07	1.36–3.14
D	84	2.0	49	4.58	20	8.32	3.08	1.95–4.84
Unknown	96	4.8	43	2.66	27	5.48	1.99	1.27–3.12
Grade								
Well differentiated	33	2.7	47	2.58	34	5.72	Reference	
Moderately well differentiated	339	23.5	7	1.24	11	3.51	1.09	0.76–1.56
Poorly differentiated	76	3.8	118	2.25	89	4.26	1.16	0.76–1.75
Unknown	107	5.2	32	2.90	23	5.81	1.18	0.78–1.76
Smoking								
No	513	33.2	182	2.24	148	4.56	Reference	
Yes	42	2.0	22	3.53	9	5.74	1.01	0.72–1.42
BMI								
Underweight	9	0.6	4	2.59	2	4.50	0.96	0.49–1.91
Ideal	118	7.9	44	2.30	36	4.77	Reference	
Overweight	141	8.5	47	2.41	38	4.84	1.11	0.87–1.42
Obese	44	2.9	16	2.52	11	4.59	1.04	0.74–1.48
Morbidly obese	21	0.7	13	7.49	3	9.60	1.98	1.24–3.16
Missing	222	14.5	80	2.03	67	4.27	1.31	0.90–1.90
Age (years)								
< 40	6	0.5	1	0.93	1	2.01	Reference	
40–49	27	1.8	11	3.01	10	6.37	1.28	0.53–3.10
50–59	79	5.6	33	2.79	16	4.37	1.23	0.53–2.82
60–69	163	9.9	53	2.41	46	4.95	1.46	0.64–3.32
70–79	204	12.1	82	2.70	61	5.31	1.52	0.67–3.46
80–89	76	5.4	24	1.24	23	3.08	1.17	0.50–2.72
Comorbidity								
0	257	15.5	99	2.35	73	4.72	Reference	
Score								
1–3	276	18.2	100	2.41	80	4.76	1.04	0.85–1.28
≥4	22	1.5	5	1.29	4	2.59	1.15	0.89–1.47
Surgery								
Elective	337	25.4	96	1.81	93	3.80	Reference	
Emergency	115	4.8	48	3.29	37	6.89	1.43	1.15–1.78
Other/unknown	1	0.0	0	0.00	1	11.11	1.10	0.15–7.86
None	102	5.0	60	3.10	26	5.62	1.12	0.89–1.43
Chemotherapy								
No	370	27.1	145	2.13	104	4.21	Reference	
Yes	185	8.1	59	2.88	53	5.88	1.39	1.14–1.69

BMI, body mass index; CI, confidence interval; HR, hazard ratio.

extended to at least 6 months in the postoperative period. Our findings suggest that the current recommendation of a 28-day period of thromboprophylaxis among colorectal cancer patients undergoing major abdominal surgery with high-risk features, which would encompass all of our patients, should be altered to take account of variation by disease stage and identification of those patients receiving chemotherapy who may benefit from an extension of prophylaxis [16,17].

Strengths and limitations

Our study used linked data to identify patients with colorectal cancer from population-based cancer registry data,

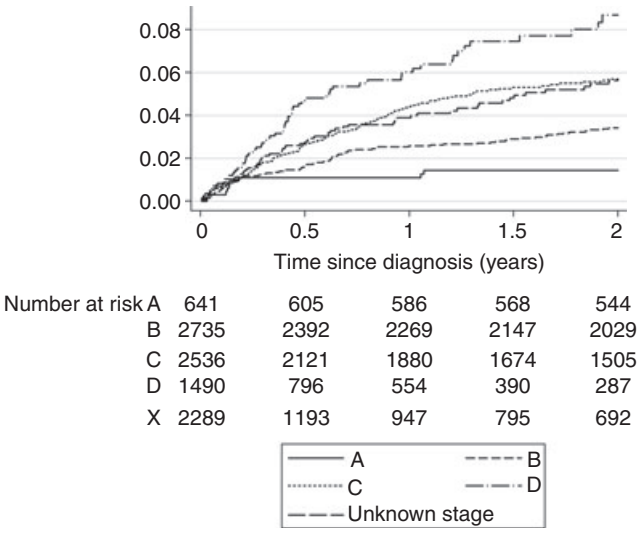

Fig. 2. Rate of venous thromboembolism by Dukes stage from time of diagnosis.

with identification of operative procedures and chemotherapy from secondary care, along with the definition of VTE in a validated manner from primary [15] and secondary care, and in that sense is uniquely placed to quantify VTE risk accurately by these variables. However, Dukes stage was not universally recorded for all patients in the cohort, and, in particular, we were unable to classify Stage 1 patients as either Dukes A or Dukes B when this was missing, and therefore excluded these patients from analyses that were reliant on stage. Nevertheless, the overall proportions of patients in each stage were reasonably similar to national data, with the exception of an increased proportion with Dukes D and unknown stage [18]. There may therefore be some misclassification of Dukes stage, particularly between the Dukes A and B cancers, which could have resulted in higher than expected VTE rates in Dukes A patients, leading to an underestimate of the relative risk of VTE in the other groups, and possibly explaining the use of chemotherapy in a small number of Dukes A patients. This would not have biased the observed absolute

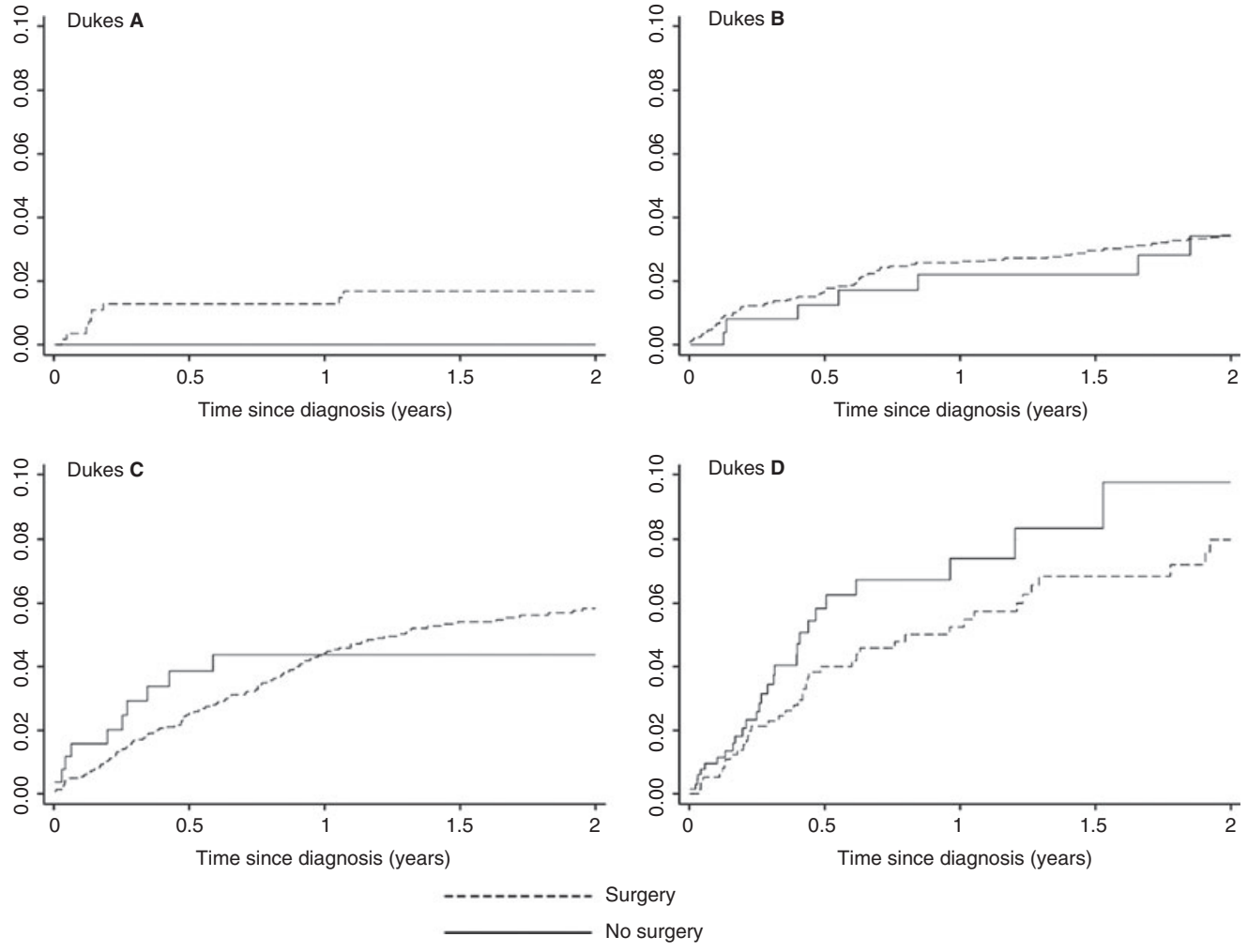

Fig. 3. Rate of venous thromboembolism in surgical and non-surgical patients, stratified by Dukes stage.

Table 3 Interaction between chemotherapy and Dukes stage

	Rate (per 1000 person-years)	95% CI	HR*	95% CI
No chemotherapy				
Dukes A	6.4	4.1–10.2	0.84	0.50–1.40
Dukes B	8.6	6.9–10.5	Reference	
Dukes C	18.4	14.9–22.7	1.92	1.42–2.60
Chemotherapy				
Dukes A	15.7	5.9–41.7	2.00	0.73–5.48
Dukes B	17.8	12.6–25.0	2.05	1.36–3.10
Dukes C	19.8	15.7–25.0	2.17	1.56–3.01

CI, confidence interval; HR, hazard ratio. *Adjusted for site (colon/rectum), grade, smoking, body mass index, age, comorbidity (Charlson), and surgery admission method.

rates in Dukes B and C patients. The recording of surgical intervention is known to be reasonably accurate in secondary-care data in England [19], but separating out patients undergoing palliative and curative surgery and receiving chemotherapy in the Dukes D group is not possible. We therefore excluded them from our stratified analysis of stage and chemotherapy. The size of the secondary-care center may play a role in the outcome of colorectal cancer; however, we were unable to account for the size of the secondary-care center treating patients within this dataset. Although, in our analysis, we were unable to identify those patients receiving thromboprophylaxis at and around the time of surgery during the study period (1997–2006), there were no recommendations for prolonged thromboprophylaxis following surgery in the UK, as this was only introduced in 2010, so patients would, at most, have received low molecular weight heparin while they were inpatients following their surgery [2]. Also, rates of thromboprophylaxis at this time were low, with the ENDORSE study estimating that only 50% of patients received appropriate thromboprophylaxis [20].

Other literature

Our overall absolute rate of VTE of 15.8 per 1000 person-years is very similar to those in previous studies on the subject, as is our observation that rates vary markedly by some measure of severity of disease [21]. Only one prior study, in Asian patients, has reported rates by stage of disease, and found that patients with stage IV disease had a 5.8% cumulative incidence of VTE at 6 months [8], which is similar to the 4.6% cumulative incidence that we found for Dukes D patients. Some prior reports have suggested that patients undergoing surgery have a decreased risk of VTE as compared with patients not undergoing surgery [6,7,22], but we found this only for Dukes C and D patients. This probably reflects the fact that patients not undergoing surgery generally have more advanced disease or other comorbidities that preclude surgery [7]. In contrast, in a recent study of VTE risk following abdominal surgery among cancer patients, an increased risk was observed [23].

Previous population-based studies have lacked good data on the effect of chemotherapy and the risk of VTE [7]. The majority have focused on high-risk populations or mixed populations of cancer patients, and have not reported results for patients with colorectal cancer and receiving chemotherapy separately [6,9–11,24]. Choi *et al.* did report an increased incidence of VTE in patients with colorectal cancer receiving palliative chemotherapy as compared with those not receiving chemotherapy, but did not stratify their results by stage of disease or surgical intervention [8].

The timing of VTE following surgery has not previously been addressed, with studies reporting rates from

Table 4 Cumulative incidence of venous thromboembolism (VTE) following surgery by Dukes stage and chemotherapy

		28 days from surgery			90 days from surgery			180 days from surgery		
	Start number	Events (0–28 days)	Cumulative %	95% CI	Events (28–90 days)	Cumulative %	95% CI	Events (90–180 days)	Cumulative %	95% CI
All patients*	4963	27	0.54	0.37–0.78	29	1.13	0.87–1.46	23	1.62	1.30–2.01
All patients*										
Dukes A	537	4	0.74	0.28–1.95	0	0.74	0.28–1.95	0	0.74	0.28–1.95
Dukes B	2316	10	0.43	0.23–0.79	15	1.08	0.73–1.60	7	1.40	0.99–1.97
Dukes C	2110	13	0.60	0.35–1.04	14	1.28	0.88–1.87	16	2.09	1.55–2.81
No chemotherapy										
Dukes A	485	4	0.82	0.31–2.16	0	0.82	0.31–2.16	0	0.82	0.31–2.16
Dukes B	1947	8	0.40	0.20–0.81	12	1.03	0.67–1.59	4	1.25	0.84–1.85
Dukes C	1282	8	0.61	0.30–1.21	10	1.41	0.89–2.24	4	1.76	1.16–2.67
Chemotherapy										
Dukes A	52	0	0.00	0.00–0.00	0	0.00	0.00–0.00	0	0.00	0.00–0.00
Dukes B	369	2	0.54	0.14–2.15	3	1.36	0.57–3.23	3	2.18	1.10–4.32
Dukes C	828	5	0.60	0.25–1.44	4	1.08	0.57–2.07	12	2.55	1.67–3.89

CI, confidence interval. *Patients with no surgery excluded. This analysis includes Dukes A, B or C patients who underwent surgery and had not had a VTE event prior to surgery. The follow-up time commenced at the date of surgery.

the date of diagnosis rather than time of surgery, or publishing rates on multiple types of surgery and cancer [8,23]; and nor have stratified estimates been presented for the risk of chemotherapy by stage among patients undergoing surgery with curative intent. The latter information is critical in allowing clinicians to decide on the optimum duration of prophylaxis to minimize the risk of VTE for individual patients. Importantly, we found that, in Dukes A patients, the increased risk was confined to the 28 days following surgery. This may be attributable to a relatively lower tumor burden, given the early stage of disease, along with a simpler operative intervention, owing to no involvement of other structures and the lack of chemotherapy given postoperatively. In contrast, Dukes B and C patients continued to have an increase in risk up to 180 days postoperatively, and this was increased further in those receiving chemotherapy, with a two-fold increased risk of VTE as compared with Dukes B patients who only underwent surgery.

Clinical significance

There are ~ 40 000 new diagnoses of colorectal cancer each year in the UK and 143 000 in the USA. At our overall reported incidence of VTE of 5.5%, this represents potentially over 2200 and 7800 preventable VTEs in these populations. However, choosing which patients to administer prophylaxis to and when requires information on VTE risk by stage of disease, treatment given, and the duration of the risk. Current international guidelines focus on extended prevention of VTE only in the immediate postoperative period (up to 28 days) for patients with colorectal cancer, and these lack a sound evidence base. Indeed, some authors have questioned the need to continue thromboprophylaxis to 28 days for all patients undergoing resection, and have focused instead on the role of laparoscopy and enhanced recovery in potentially reducing VTE risk [25]. Our finding that VTE risk following surgery in Dukes A patients was limited to the first 28 days suggests that current guidance is reasonable in this group, and, given evidence from other studies, there may be scope to reduce the duration of prophylaxis further [25]. Importantly, however, we have shown that the risk following surgery in Dukes B and C patients persists for at least 6 months following surgery, with the greatest risk occurring in those receiving chemotherapy. Therefore, it may be the case that, among these patients, we could identify high-risk patients who may benefit from a further extension of prophylaxis beyond 28 days postoperatively to balance the risks of extended prophylaxis against the potential harms of a VTE.

Addendum

A. J. Walker: study concept and design, interpretation and analysis of data, and drafting of the manuscript. J. West: study concept and design, interpretation and analysis of data, drafting of the manuscript, and acquisition of funding and data. T. R. Card: study concept and design, interpretation and analysis of data, drafting of the manuscript, and acquisition of funding and data. D. J. Humes: study concept and design, interpretation and analysis of data, and drafting of the manuscript. M. J. Grainge: study concept and design, interpretation and analysis of data, drafting of the manuscript, and acquisition of funding and data.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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