INCIDENCE OF PULMONARY EMBOLISM IN PATIENTS WITH NEWLY DIAGNOSED COLORECTAL CANCER

Short Running Head:

Incidence of PE in Colorectal Cancer

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Abstract

Aim: Studies have suggested a benefit from extended venous thromboprophylaxis post-operatively in colorectal cancer with an assumed base rate of zero venous thromboembolic events prior to treatment. We aim to establish the incidence of pulmonary embolism in patients with newly diagnosed Stage III or IV colorectal cancer prior to any treatment.

Method: Consecutive patients presenting to a single health service with a new diagnosis of stage III or IV colorectal cancer were identified from a prospective database, for the period between January 2011 and September 2014. Contemporaneous clinical data was reviewed. Included patients had a computerized tomography chest scan for pre-operative staging for cancer. The diagnosis of pulmonary emboli was made on chest computerized tomograph.

Results: Of 330 patients identified 224 had baseline computerized tomography chest imaging available for review, of which 107 (47.8%) were technically adequate scans. Pulmonary emboli were identified on five (4.7%) of these 107, including one of five patients (1.7%) with Stage III and four of five patients (8.3%) with stage IV disease.

None of the 107 patients with adequate scans had postoperative pulmonary emboli or deep vein thrombosis.

Conclusion: There is a clinically significant baseline rate of asymptomatic pulmonary emboli in patients with stage III and IV colorectal cancer that can be demonstrated on the staging chest computerized tomography scan. Pulmonary emboli described as a postoperative event in previous series may have been present prior to surgery.

Keywords: pulmonary embolism, colorectal cancer

Introduction

The relationship between venous thromboembolism (VTE) and malignancy is well established; it forms a significant cause of morbidity and mortality in patients with cancer[1]. For patients with colorectal cancer VTE is a major cause of mortality and morbidity with a reported rate of thromboembolism of 5.0% in the first 6 months from diagnosis[2,3]. The risk of VTE has been established in the neoadjuvant period[4-6], perioperative period[7,8] and in patients with metastatic disease[9,10].

Standard practice in the pre-operative assessment of colorectal adenocarcinoma now includes the use of computed tomography (CT) of the chest, abdomen and pelvis to assess for distant disease[11,12]. Where metastatic disease is detected this may impact on multi-disciplinary management. Incidental findings on CT imaging are not uncommon, and include detection of asymptomatic pulmonary emboli (PE) on staging chest CT. To our knowledge the frequency and significance of this finding has not previously been reported.

We conducted a review of a consecutive series of patients with Stage III and IV colorectal adenocarcinoma to establish the adequacy of initial imaging for detection of PE and the incidence of PE. The clinical course of any patient with

PE was reviewed. A search of our database was also conducted to determine the incidence of postoperative PE.

Materials and Methods

We queried the BioGrid database[13] utilized by Western Health to identify patients with colorectal cancer between January 2011 and September 2014. For our analyses we included all patients diagnosed with Stage III or IV colorectal adenocarcinoma[14]. We reviewed their medical record data and staging CT scans. Exclusion criteria were patients that did not have a CT chest prior to treatment (n= 106), original images not being available for review (n=0), a prior history of VTE (n=0) or documented thrombophilia (n=0).

All CT chests were reviewed separately by two radiologists (ML and MM). A positive study was defined as evidence of PE. We defined negative studies as scans having no evidence of PE and at least 250HU (Hounsfield unit) of contrast enhancement in the pulmonary trunk[15]. CT studies with less than 250HU in the pulmonary trunk were defined as non-diagnostic for PE, that is it was insufficient contrast enhancement to adequately exclude a PE. These studies were excluded from the main analysis.

Our standardized staging scanning protocol included intravenous contrast of 100ml Omnipaque 350 at 3ml/sec via 20- or 22-gauge cannula. The chest scan was performed during the arterial phase from above the lung apices to the below the costophrenic angles. The abdominal / pelvis scan was performed during the portal venous phase from above the diaphragm to the symphysis pubis. Chest and abdominal / pelvis soft-tissue images were reconstructed with 0.6mm thickness and spacing; chest lung window images were reconstructed with 5mm thickness and spacing.

A search of our prospective database was conducted to define the frequency of 30-day post-operative PE in all stage III and IV patients with available imaging.

Data calculations were carried out using Microsoft Excel 2011 and GraphPad Software, Inc. http://www.graphpad.com/quickcalc/ (accessed 6/6/2015). Comparison was made between patients with Stage III and IV disease; statistical analyses comparing age and contrast enhancement (HU) was calculated using a t-test. Analysis comparing gender was calculated using a chi-squared test; whilst analysis comparing incidence of pulmonary embolus was calculated using a Fisher exact test. Proportions of incidence of PE had 95% confidence intervals calculated using the Clopper and Pearson method.

Ethical and institutional approval was gained from the Western Health Low Risk

Human Research Ethics Panel.

Results

There were 330 patients that had Stage III or IV colorectal adenocarcinoma diagnosed between January 2011 and September 2014. Of this cohort 224 had a CT chest prior to any form of treatment that was available for review. Of these studies 117 (52.2%) were considered non-diagnostic due to insufficient contrast enhancement (Figure 1). Five of 107 ((4.7%) 95% CI 0.0153 – 0.1057) studies were positive for PE, including 1 of 59 cases with stage III and 4 of 48 cases with stage IV disease (Table 1).

Of the five cases with PE on pre-treatment imaging (5/107), four had been documented in the initial CT report, and three received anticoagulation with enoxaparin (Table 2). A patient with a main pulmonary artery PE was the only symptomatic patient. One case with a sub-segmental PE did not receive therapeutic anticoagulation as this was deemed not clinically significant. In the one patient where a segmental PE on the initial CT chest was not reported; they became symptomatic postoperatively with a lobar PE formally diagnosed on CT chest approximately 2 months post the original study and was also treated with enoxaparin.

Two patients proceeded to surgery post diagnosis of PE and treatment; standard perioperative anticoagulation was given with a prophylactic dose of enoxaparin at induction, compression stockings and sequential compression devices. The therapeutic dose was given the day prior and restarted the day post operation. There was no documented post-operative bleeding in these 2 cases.

There were no new cases of pulmonary emboli in the 107 patients included in our study, within 30 days of surgery. Two patients with non-diagnostic studies (2/ 117) had PE diagnosed within 30 days of surgery on chest CT. No new deep vein thrombosis (DVT) occurred in either group (0/330) on review of medical records within 30 days of surgery; however our database did not include the total number of patients that had postoperative imaging for suspicion of DVT or PE but only those that had positive studies.

There were no risk factors for VTE in the patients with PE, as well as no history of surgery or admission in the previous 30 days, chemotherapy, prior thromboembolic events or documented thrombophilia. Of the four patients with stage IV disease, three patients had extensive lymphadenopathy, two had hepatic metastases and one extensive pulmonary metastases.

Discussion

Thromboembolic disease is a potentially significant complication of colorectal cancer, with the risk increased in patients with stage IV disease[9,10] and in the postoperative period[7,8]. Pulmonary emboli may be diagnosed following a symptomatic presentation, or as an incidental finding on imaging for staging or other purposes. Our study has established that a significant number of patients have non-diagnostic preoperative imaging for the purposes of detecting asymptomatic PE, and that where scans are adequate the incidence of PE is significant; 4.7% (95% CI 0.0153 – 0.1057). Our data is important as asymptomatic PE do have potential clinical consequences[16]. Also a significant rate of PE at diagnosis could significantly confound any analysis of the rate of postoperative VTE, including in randomized intervention studies where there is an assumption of a base rate of zero PE.

To our knowledge prior studies of the incidence of VTE post-operatively have not examined for the presence of PE at the time of initial diagnosis. This is partly because CT chest imaging at baseline has only become standard practice in recent years. For example, in a survey of clinical practice at multiple Australian sites in 2009, 222 of 257 (86.4%) patients had an abdominal CT at baseline and only 95 (40.0%) a chest CT. Importantly this study also demonstrated the impact of baseline CT chest imaging, with a third of cases with suspicious findings resulted in further investigation or a change in management[17].

Previous studies include an epidemiological study concerning VTE in multiple malignancies, which reported a concurrent rate of 0.2% and 0.6% in colorectal cancer patients with regional and remote disease respectively. Concurrent was defined as a diagnosis of VTE during the hospitalisation of when the cancer was diagnosed. The location of VTE, time of diagnosis and modality of investigation was determined by hospital coding[18]. The authors did not specify whether VTE was confirmed prior to any treatment or make any further comment upon the specific location of VTE. Chandra et al recorded symptomatic VTE post colorectal surgery at a rate of 0.79% as an inpatient and 0.39% at 30 days of which all were PE[19]. Holwell et al reported an incidence of 4.1% at 90 days of which 6 out of 8 patients had PE[20]. A large epidemiological study reported the incidence of VTE in colorectal adenocarcinoma as 5.0% in the first six months after diagnosis. The authors did not specify the timing of diagnosis of VTE[21].

A meta-analysis[22] and four randomized control trials have concluded a statistically significant reduction in risk of VTE with extended DVT prophylaxis post operatively for abdominal and pelvic surgery for cancer. All randomized controlled trials (Table 3) included both asymptomatic and symptomatic DVT confirmed on venography or sonography. CT chest or ventilation / perfusion lung scintigraphy was only performed for investigation of patients with suspected PE[7,23-25]. Vedovati et al[23] examined patients specifically who had undergone laparoscopic colorectal surgery.

In these series often small absolute differences are observed between the study groups, differences that may in part be due to imbalances between study arms due to pre-existing PE (Table 3). Given this we would strongly recommend that any prospective study exploring any type of extended VTE prophylaxis should mandate adequate imaging on all patients at diagnosis as an eligibility criteria, with any patient with PE at diagnosis to be excluded from the study.

Strengths of our study include that this is a consecutive series of patients from a single institution and comprehensive prospective data collection, including documentation of VTE. All images were reviewed by two radiologists that were blinded to the original study report and clinical data, and that quality assurance of imaging was performed prior to including images in our series. The limitations of our study are: the modest number of patients meant we could not do a formal statistical comparison of PE incidence for Stage III or IV disease; we did not examine any patients with stage I or II disease, where the rate of incidental PE may be lower; and, we did not have the pre-operative incidence of DVT. Furthermore given the number of non-diagnostic CT chest scans we may be underestimating the incidence of pretreatment PE.

There is a significant baseline incidence of PE in patients with stage III or IV colorectal cancer that has not been recognized in previous studies. A substantial

proportion of these may be missed due to non-diagnostic imaging, so we would recommend the initial CT chest component of the staging scan be timed by the technician with adequate contrast enhancement of both the pulmonary and systemic circulation to allow for the diagnosis or exclusion of PE. Any future prospective studies of thromboembolic disease should include baseline imaging with adequate contrast to document the true incidence of postoperative VTE.

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Disclosures

The authors have no conflicts of interest to declare.

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Table 1 – Patient characteristics

	Total adequate n =107 (32.4%)		
AJCC stage	III n = 59	IV n =48	P value
Median age (range)	68 (46-87)	70 (30-93)	0.644*
Sex	F 33 (55.9%) M 26 (44.1%)	F 26 (54.2%) M 22 (45.8%)	0.855**
Mean pulmonary contrast enhancement	322HU	317HU	0.685*
PE on CT Chest	1 (1.7%) 95% CI 0.0004 – 0.0909	4 (8.3%) 95% CI 0.0232 - 0.1998	0.171***
	5 (4.7%) 95% CI 0.0153 – 0.1057		

* Calculated with t-test
** Chi-square test
*** Fisher exact test
PE – pulmonary embolus
CT – computerized tomography

Table 2 – PE confirmed patients

Age	Gender	Tumour location	AJCC Stage	CT findings	Contrast enhancement
69	F	Sigmoid	III	Lobar PE	300HU
56	F	Caecum	IV	Segmental PEs	204HU
58	F	Ascending colon	IV	Subsegmental PEs	327HU
68	F	Caecum	IV	Main pulmonary artery PE	295HU
69	F	Caecum	IV	Segmental PE	450HU

Table 3 – Summary of randomized control trials

Author (Year)	Study design	Patients	Intervention	Primary outcome	Result
Bergqvist et al (2002)	Double-blinded	332	LWMH (21 days on discharge) vs placebo (LWMH as inpatient only)	Incidence of VTE (day 25 - 31)	8 (4.8%) LWMH vs 20 (12.0%) placebo (P = 0.02)
Rasmussen et al (2006)	Assessor-blinded	427	Extended LWMH (28 days) vs short-term LWMH (7 days)	Incidence of VTE (day 7 – 28)	29 (7.3%) extended LWMH vs 12 (16.3%) short-term LWMH (P = 0.012)
Kakkar et al (2010)	Double-blinded	488	Bemiparin (28 days) vs bemiparin (8 days) and placebo	Composite of DVT, non-fatal PE and all-cause mortality at day 28	25 (10.1%) bemiparin vs 32 (13.3%) placebo (P = 0.26) †VTE 2 (0.8%) bemiparin vs 11 (4.6%) placebo (P = 0.010)
Vedovati et al (2014)	Assessor-blinded	225	Extended heparin (28 +/- 2 days) vs short heparin (8 +/- days)	Symptomatic or U/S detected VTE at day 28 +/- 2	0 (0%) extended heparin vs 11 (9.7%) short heparin (P = 0.001) at 28 +- 2 days

LWMH – low molecular weight heparin
VTE – venous thromboembolism
DVT – deep venous thrombosis
PE – pulmonary embolus
† Incidence of major venous thromboembolism was not the primary outcome