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ORIGINAL ARTICLE

Thrombotic complications following liver resection for colorectal metastases are preventable

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Abstract

Background. Surgery for colorectal liver metastases (CRLM) can be expected to be associated with a significant rate of thromboembolic complications due to the performance of long-duration oncologic resections in patients aged 60 years. *Aims.* To determine the prevalence of clinically significant thrombotic complications, including deep venous thrombosis (DVT) and pulmonary embolus (PE), in a contemporary series of patients undergoing resection of CRLM with standard prophylaxis. *Material and methods.* A prospectively maintained database identified patients undergoing resection of CRLM from January 2000 to March 2007 and highlighted those developing thromboembolic complications. In addition, the radiology department database was reviewed to ensure that clinically suspicious thromboses had been confirmed radiologically by ultrasound in the case of DVT or computed tomography for PEs. *Results.* During the period of the study, 523 patients (336 M and 187 F) with a mean age of 65 years underwent resection. A major hepatectomy was performed in 59.9%. One or more complications were seen in 45.1% ($n=236$) of patients. Thrombotic complications were seen in 11 (2.1%) patients: DVT alone ($n=4$) and PE ($n=7$). Eight of 11 thrombotic complications occurred in patients undergoing major hepatectomy, 4 of which were trisectionectomies. Patients were anti-coagulated and there were no mortalities. *Conclusions.* The symptomatic thromboembolic complication rate was lower in this cohort than may be expected in patients undergoing non-hepatic abdominal surgery. It is uncertain whether this is due entirely to effective prophylaxis or to a combination of treatment and a natural anti-coagulant state following hepatic resection.

Introduction

Venous thromboembolism in terms of deep venous thrombosis (DVT) or pulmonary embolism (PE) is a well-recognized cause of significant morbidity in patients undergoing resectional surgery for carcinomas [1–4]. The relative risk of thrombosis compared to patients without tumors is 4 times, increasing to 6.5 times for patients who have also received chemotherapy [5]. Furthermore, patients with thromboembolic disease have a 3-fold risk of pulmonary embolism. A number of risk factors for thromboembolism have been recognized (Table I) [6]. The precise reason for the increased prevalence of thromboembolic events in patients with cancer is unclear, although in many cases the thromboembolism is attributed to a hypercoaguable state seen as part of the paraneoplastic syndrome.

When surgical resection is also factored into the equation, the risk is further increased [7–10]. The reasons for the increased risk in the perioperative period include immobility and venous trauma as a result of central venous cannulation. The risk of thromboembolic complications in patients with cancer undergoing surgery is difficult to quantify given the heterogeneity of tumors. The overall risk of asymptomatic DVT has been placed at 20–40%, increasing further in the presence of additional risk factors, mostly a past medical history of DVT or PE [4].

What is not clear is whether the increased thrombotic risk is equal for all tumor types. The risk is said to be high for malignant brain tumors and adenocarcinomas of the ovary, colon, stomach, pancreas, prostate, lung, and kidney [11–13]. There are few data on the risk of DVT and PE in the context of hepatic resection for colorectal liver metastases (CRLM). In a series of 1803 patients undergoing hepatic resection, 1021 of which were for colorectal metastases, Jarnagin and colleagues noted PEs in 16 patients (0.9%) and

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DVTs in 24 (1.3%) [14]. Yates et al., in a small series of 99 resections for primary and secondary malignancies, noted a much higher rate of thrombotic complications, with 7 (7.1%) events, all of which were seen in patients with secondary tumors [15].

The recognition and appreciation of the high risk of thrombotic complications in patients undergoing surgery has led to the introduction of thromboprophylaxis protocols, including both mechanical and pharmacological measures. Patients with cancer are among the group considered most at risk according to the American Association of Chest Physicians [4], since in addition to the presence of cancer most patients are aged 40 or older.

The aims of this study were to document the prevalence of DVT and PE occurring in a contemporary cohort of patients undergoing liver resection for CRLM in whom prophylaxis had been prescribed, and to investigate whether the presence of thromboembolic disease has any bearing on patient outcome.

Patients and methods

All patients with CRLM undergoing hepatic resection at St. James's University Hospital (SJUH), Leeds, United Kingdom, during the period January 2000 to March 2007 were identified from a prospectively maintained hepatobiliary database.

The database was reviewed and the data collected included patient demographics (age and gender); a past medical history of thrombotic disease (DVT or PE); and the extent of the resection performed. In addition to inpatient follow-up, all events occurring after the patient left hospital were also collated and analysed.

In addition, the radiology department database was reviewed to ensure that clinically suspicious thromboses had been confirmed radiologically by ultrasound in the case of DVT or CT for PEs.

During this time period, patients undergoing resection received a combination of low-molecular weight heparin, thromboembolic deterrent stockings and perioperative intermittent pneumatic compression as prophylaxis against venous thrombosis.

Categorical data were presented as frequency and proportions (%) and were analysed using the Pearson chi-squared test. Univariate analysis was performed to assess for a significant difference in clinico-pathological characteristics that influenced the development of thromboembolic complications. All statistical analyses were performed using SPSS for Windows™ version 15.0 (SPSS Inc, Chicago, Ill., USA), and statistical significance was taken at the 5% level.

Results

During the period of the study, 523 patients underwent resections for CRLM. There were 336 (64%) men and 187 (36%) women, and the median age at operation was 65 years (range 32–91 years).

Only four patients had a past medical history of thromboembolic disease, including four of DVT with associated PE and one of isolated DVT. Only one of this subgroup of patients was taking warfarin at the time of admission for liver resection.

Three-hundred-and-ten (59.9%) patients underwent a major hepatectomy (3 or more Couinaud segments) with lesser anatomical or non-anatomical hepatic resections performed in the remaining 213 (40.1%) patients. Overall, 279 (53%) patients had hepatic resection performed for bilobar disease, and 348 (29%) had multiple tumors.

Thrombotic complications were observed in 11 (2.1%) patients (7 M and 4 F). Four presented with symptomatic DVTs and the remaining seven with respiratory symptoms leading to the diagnosis of PE. Seven patients were diagnosed during their initial hospitalization, and the remaining patients (2 DVT and 2 PE) presented to the primary care services and were re-referred to the HPB service for investigation and management.

In all cases of suspected DVT, a Doppler ultrasound scan was performed, and in all cases of suspected PE a CT scan of the chest. In addition, a Doppler scan was performed to document the extent of the lower limb thrombus.

Potential risk factors for venous thrombosis were assessed but no significant factors were identified apart from a previous history of thromboembolic disease (Table I).

Discussion

The primary finding of this study is that in a contemporary series of patients undergoing predominantly major liver resections after receiving prophylaxis, the rate of symptomatic thromboembolic disease is 2.1%. This is the first study specifically to address the issue of thromboembolic disease in patients undergoing liver resection for CRLM. The results were almost identical to the Memorial Sloan-Kettering series, in which all patients undergoing hepatic resection were included [14]. Interestingly, none of the recent series from large institutions has included details of thrombotic complications in the results section [16–19].

Despite these relatively low rates of thromboembolic events, the recent series reported by Yates et al., with a 7.1% rate of thromboembolic complications, is of concern [15]. There are also several papers highlighting the risk of thromboembolic complications following living donor liver transplantation as the consequences in this scenario are greater [20,21]. All these patients have normal livers and are healthy individuals and thus should have a lower risk of thrombosis than patients undergoing resection of liver metastases. Bezeaud et al. investigated the etiology

Table I. Univariate analysis of risk factors for thromboembolic disease in patients undergoing resection of colorectal metastases.

Clinical variables	No DVT or PE ($n=512$)	DVT or PE ($n=11$)	Statistical significance (p-value)
Age (years)			
<40	5 (1%)	0 (0%)	NS
≥40	507 (99%)	11 (100%)	
Gender			
Male	329 (64.3%)	7 (63.6%)	NS
Female	183 (35.7%)	4 (36.4%)	
History of DVT/PE			
Yes	3 (0.6%)	2 (18.2%)	$p<0.05$
No	509 (99.4%)	9 (81.8%)	
History of CVD			
Yes	110 (21.5%)	2 (18.2%)	NS
No	402 (78.5%)	9 (81.8%)	
History of stroke/TIA			
Yes	9 (1.8%)	0 (0%)	NS
No	503 (98.2%)	11 (100%)	
Neoadjuvant chemotherapy			
Yes	90 (17.8%)	2 (18.2%)	NS
No	421 (82.2%)	10 (81.8%)	
Distribution			
Bilobar	343 (67%)	7 (63.6%)	NS
Unilobar	169 (33%)	4 (36.4%)	
Number of tumors			
Multiple	341 (58%)	7 (63.6%)	NS
Single	171 (42%)	4 (36.4%)	
Extent of resection			
Major	304 (59.4%)	6 (54.5%)	NS
Minor	208 (40.6%)	5 (45.5%)	

CVD = cardiovascular disease; TIA = transient ischemic attack.

of the hypercoagulability observed in living donors and confirmed dysregulation of hemostasis with an increase in thrombin-antithrombin complexes (10- to 30-fold) and P selectin (1.5- to 2-fold) following surgery but found no difference between living donors and patients undergoing resection of benign liver tumors who acted as a control group. Levels of both, however, were higher in the group of 4 patients experiencing thromboembolic events compared to the 16 who did not. Unfortunately, no comparison was made with patients undergoing resection of malignant disease [22].

One factor highlighted in the literature is the degree of uncertainty as to whether the correct thromboprophylaxis is actually prescribed. Arnold et al. noted that two-thirds of patients had either inadequate or no thromboprophylaxis even though this was indicated in relation to ACCP guidelines [23]. In a retrospective series such as this, it is not possible to confirm whether low molecular weight heparin was administered correctly, but thromboprophylaxis has been part of the perioperative protocol for all patients undergoing hepatic resection.

Given that almost all the patients are high risk according to the classification published by Geerts and colleagues [4], in that the vast majority are over 40 years of age and undergoing major oncological surgery, the rate of 2.1% would appear acceptable compared to other surgical disciplines. In this series, only a past history of DVT/PE was associated with a higher risk of thromboembolic disease.

The rate of venographically confirmed DVT in patients undergoing abdominal cancer surgery in the absence of prophylaxis has been reported as being between 20% and 40%, rising to 40–60% in the presence of additional risk factors [6]. Although the prevalence of symptomatic DVT is significantly less (1:5 to 1:10), natural history studies have demonstrated a progression, thus indicating a definite benefit for thromboprophylaxis [24].

In a meta-analysis of 59 studies, Mismeti and coworkers showed that the use of low-molecular weight heparin in general surgical patients can reduce the risk of thromboembolic disease by up to 72% [25]. In relation to oncological abdominal and pelvic surgery, the enoxaparin and cancer (ENOXACAN) study demonstrated that the use of prophylaxis for 1 month reduced the incidence of venographically detected thromboembolic events to 4.8% compared to 12% with conventional therapy [26].

In the light of this study and other evidence, the current ACCP recommendations suggest that, for

patients undergoing major abdominal cancer surgery, the thromboprophylaxis should be continued postoperatively for a period of 28–35 days [4]. The recently released American Society of Clinical Oncology (ASCO) guidelines are in keeping with these recommendations [27].

The rate of thromboembolic disease of 2.1% in this study appears very acceptable in comparison to these data; however, it must be remembered that this is a clinical and not a screened rate and thus the true figure for asymptomatic disease may be 5–10 fold higher, i.e. in the order of 10–20%. It has not been our unit policy to prolong prophylaxis; indeed, the majority of events have occurred while individuals have been inpatients, but this policy is currently being audited.

Conclusions

The rate of symptomatic thromboembolic disease in this high-risk cohort receiving mechanical and chemical prophylaxis was acceptable and comparable to the limited clinical data currently available on the topic. Given the recent guidelines on prolongation of therapy postoperatively, further studies will be required to determine whether this is required and indeed beneficial for patients undergoing resection of the colorectal liver metastases.

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