Efficacy and safety of anticoagulant prophylaxis for prevention of postoperative venous thromboembolism in Japanese patients undergoing laparoscopic colorectal cancer surgery

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Abstract

Aim: To investigate the efficacy and safety of anticoagulant prophylaxis to prevent postoperative venous thromboembolism (VTE) during laparoscopic colorectal cancer (CRC) surgery, which is unknown in Japanese patients.

Methods: We conducted this randomized controlled trial at nine institutions in Japan from 2011 to 2015. It included 302 eligible patients aged 20 years or older who underwent elective laparoscopic surgery for CRC. Patients were randomly assigned to an intermittent pneumatic compression (IPC) therapy group or to an IPC + anticoagulation therapy group. Anticoagulation therapy comprised fondaparinux or enoxaparin...
INTRODUCTION

Venous thromboembolism (VTE) is a common surgical complication. The incidence of fatal VTE ranges from 0.1% to 0.8%, and VTE incidence in Japan is almost the same as in Western countries. In Japan, the age-adjusted mortality rate with VTE increased from 1951 to 2000, and the condition arises in 24.3% of abdominal surgery patients, including in asymptomatic cases.

VTE occurs in up to 20% of cancer patients and is a leading cause of death in this patient population. The risk of VTE differs according to cancer subgroup, treatment, and procedure, with the highest risk during the initial period after a diagnosis of malignancy. Thus, VTE can be considered a potentially fatal but preventable complication after major cancer surgery, and prophylaxis is crucial in this setting. Of note, some of the mechanisms that give rise to cancer also can lead to VTE. For example, cancer cells can directly promote blood coagulation by generating thrombin or indirectly promote it by stimulating endothelial cells and circulating mononuclear cells to synthesize and express procoagulant factors.

Since the early 1990s, laparoscopic surgery has revolutionized the field of gastrointestinal surgery, and this approach for major cancer surgery has become increasingly common. However, uniform guidelines are lacking on the use of anticoagulant prophylaxis, with little available evidence to justify its routine use in laparoscopic cancer surgery.

A search of PubMed, PubMed Central, and Google Scholar for the terms "colon or colorectal surgery" and "VTE" and of reference lists of retrieved articles identified 20 relevant papers. Many of these studies were retrospective analyses that relied on database searches. They showed that VTE rates are generally lower in patients undergoing laparoscopic compared to open surgery. Of these identified studies, six had a prospective cohort design, two of which involved laparoscopic surgery. Only one study was a randomized trial, which compared the effectiveness and safety of low-dose heparin versus low-molecular-weight heparin (enoxaparin) as VTE prophylaxis after colorectal surgery. In that study, VTE rates were the same in both groups, without bleeding complications or deaths from pulmonary embolism (PE), suggesting the safety and effectiveness of both anticoagulants. However, the need for anticoagulant prophylaxis to prevent VTE after laparoscopic colorectal cancer (CRC) surgery among patients of Asian descent, including Japanese patients, is unknown.

For this reason, we conducted this randomized study to investigate the clinical need for anticoagulant prophylaxis to prevent postoperative VTE in patients who undergo laparoscopic CRC surgery.
“thrombotic disorder, history of VTE, malignant disease, cancer chemotherapy, serious infection, central venous catheterization, long-term bed rest (more than 24 hours after surgery), leg paralysis, leg cast fixation, hormone therapy, obesity (body mass index 25 kg/m² or more), and varicose veins of the lower extremities.” Other inclusion criteria were as follows: confirmed CRC by endoscopic examination; age ≥20 years or older; sufficient organ function, per laboratory data showing white blood cell count ≥3000/mm³, platelets ≥100 000/mm³, total bilirubin ≤2.0 mg/dL, liver enzymes ≤100 IU/L, and serum creatinine ≤1.5 mg/dL; pre-operative D-dimer <1 μg/mL or less than twice the institution limit for excluding asymptomatic deep vein thrombosis (DVT); symptomatic DVT; and provision of written informed consent.

The exclusion criteria were as follows: active bleeding or with thrombocytopenia (platelets <10 × 10⁹/L); risk of bleeding, including gastrointestinal ulcers, diverticulitis, colitis, acute bacterial endocarditis, uncontrolled severe hypertension, or uncontrolled diabetes mellitus; severe liver dysfunction (Child C); known hypersensitivity to unfractionated heparin, low-molecular-weight heparin, or heparinoids; history of intracranial bleeding; having undergone central cranial surgery, spine surgery, or ophthalmic surgery within 3 months before registration in the study; severe renal dysfunction (creatinine clearance <20 mL/min); known hypersensitivity to contrast media; or any condition that made the patient unfit for the study, as determined by the attending physician.

The study was conducted in accordance with the ethics principles set forth in the Declaration of Helsinki, and the institutional review boards at each hospital approved the study protocol. All patients provided written informed consent before randomization. We did not collect data on the number of patients who were approached and assessed for eligibility.

### 2.2 Randomization and masking

Investigators registered the patients in the study, and treatment allocation was performed preoperatively after study eligibility criteria were confirmed. Patients were randomly assigned (1:1) to either the intermittent pneumatic compression (IPC) therapy group or to the IPC + anticoagulation therapy group, using permuted blocks of four stratified by institution, gender, age, and cancer location (colon or rectum). The surgeon was informed of the patient’s treatment allocation and performed the procedures. Patients and investigators were not masked regarding group assignment. The data center, which was based at the Multicenter Clinical Study Group at Osaka University, was responsible for treatment allocation, central monitoring, and statistical analyses under the supervision of the study statistician.

### 2.3 VTE prophylaxis

All patients wore graduated compression stockings and received IPC. In the IPC therapy group, the attending physician used compression stockings and IPC without anticoagulant therapy for VTE prophylaxis. In the IPC + anticoagulation therapy group, the physician used compression stockings and IPC plus anticoagulant therapy. Either fondaparinux (Arixtra®; GlaxoSmithKline) or enoxaparin (Kurekisan®; Kaken Pharmaceutical Co., Ltd.) was used. The surgeon made the choice of anticoagulant. Unfractionated heparin is also recommended in the Japanese guidelines, but enoxaparin and fondaparinux only were used in this study.33

Administration of fondaparinux or enoxaparin began 24 ± 2 hours after surgery, once hemostasis was established, following the Japanese regimen for VTE prevention. Fondaparinux (2.5 mg) was given once daily for 4-8 days, and enoxaparin (20 000 IU) was given twice daily for 7-14 days. The day of surgery was defined as day 1. The study protocol included the approved use of epidural anesthesia as necessary. The catheter had to be removed at least 2 hours before starting the anticoagulant. The primary endpoint was the incidence of VTE, and the secondary endpoint was the incidence of major bleeding.

### 2.4 Assessment and outcome definitions

#### 2.4.1 Diagnosis of VTE

If clinically suspicious VTE symptoms were noted, such as dyspnea, chest pain, or decreased percutaneous arterial oxygen saturation (SpO₂), we performed enhanced multi-detector helical computed tomography (MDCT) with contrast media, pulmonary scintigraphy, or pulmonary arteriography to immediately diagnose PE. If lower extremity swelling occurred, we performed ultrasonography, MDCT, or ascending phlebography to diagnose DVT.

If VTE was not suspected, the IPC therapy group underwent ≥8-channel MDCT on postoperative days 7-16. In the IPC + anticoagulation therapy group, MDCT was performed after anticoagulant therapy ended on postoperative days 7-16. To diagnose VTE, sections of 0.5-0.625 mm were acquired from the chest, body, and legs. A total of 300 mg/mL (maximum of 150 mL) of iodinated contrast medium was injected into the intravenous catheter. The injection rate was 3.0 mL/s. A radiologist interpreted all multislice computed tomography pulmonary angiography scans. SpO₂, plasma D-dimer, platelet count, and liver function were prospectively recorded preoperatively and on postoperative days 1, 3, and 7. The radiologist interpreted the CT scans without any identifying information about the patients.

#### 2.4.2 Classification of major and minor bleeding

Bleeding was classified as major if it met ≥1 of the following conditions: fatal bleeding; retroperitoneal or intracranial bleeding; bleeding of critical organs (intraocular, adrenal, endocardial, or spinal bleeding); surgical site bleeding that required surgical intervention; or clinically overt bleeding with a decrease in hemoglobin of ≥2 g/dL, or the need for transfusion of ≥800 mL of red blood cells or whole blood within 48 hours from suspicion to bleeding symptoms. Minor bleeding was defined as bleeding that did not meet any of the major bleeding criteria.
2.5 | Statistical analysis

We planned a sample size of 150 patients per treatment group when we designed the trial. The sample size was calculated using the following assumptions to 80% power with a two-sided significance level of 0.05 to detect superiority in reduced VTE frequency.

In earlier studies, the frequency of VTE was 10.8% with fondaparinux prophylaxis and 17.6% with IPC in patients who underwent abdominal surgery. In addition, VTE incidence was 1.2% in the enoxaparin group and 19.4% in the IPC group. Using these data, we estimated that VTE could be anticipated to occur in 17% of patients with IPC therapy and 5% with IPC + anticoagulation therapy, allowing for a loss to follow-up of roughly 20%.

The analysis was performed on an intention-to-treat basis, using JMP Pro 13.1.0 software (SAS Institute Inc., Cary, NC. USA). To evaluate each parameter, the Chi-squared test or Fisher’s exact test was used for categorical data, and Student’s t test was used for continuous variables. The limit for statistical significance was set at P < .05.

3 | RESULTS

3.1 | Patient eligibility

Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the study, which registered 303 patients. One patient declined to participate after registration. The remaining 302 patients were randomly assigned to the IPC therapy group (n = 157) or the IPC + anticoagulation therapy group (n = 145). In the 145 patients in the latter group, anticoagulation therapy was fondaparinux for 81 and enoxaparin for 52. Another 12 patients in this group did not receive anticoagulation therapy because of postoperative hematuria (n = 1), forgotten administration (n = 1), determination by the attending physician (n = 4), or unknown reasons (n = 6). Table 1 shows the baseline clinical characteristics of the two groups, which were similar.

3.2 | Evaluation of VTE

The VTE incidence was 5.10% with IPC therapy and 2.76% with IPC + anticoagulation (P = .382). The incidence of PE was 1.91% with IPC and 0.69% with the combination (P = .623); PE + proximal DVT occurred in 3.82% and 2.76% (P = .752), respectively; and distal DVT arose in 1.34% and 0%, respectively (Table 2). The groups did not differ statistically from each other, and symptomatic VTE did not occur in this study.

3.3 | Safety outcomes

The incidence of all bleeding events was 5/157 (3.18%) for the IPC therapy group and 19/145 (13.1%) for the IPC + anticoagulation therapy group, with significant differences between groups (P = .002). There were no deaths related to bleeding, and major bleeding occurred in two patients in each group (P = .936; Table 3).

Regarding anticoagulant safety, the incidence of all bleeding was 11/81 (13.6%) with fondaparinux and 4/52 (7.69%) with enoxaparin; thus, enoxaparin had fewer postoperative bleeding events than fondaparinux, but there was no statistical difference in each group (P = .5; Table 4). Most of the major bleeding was anastomotic (75%), and minor bleeding was mainly the result of melena (50%) and subcutaneous (36%) bleeding (Table 5).

4 | DISCUSSION

In this study, the incidence of VTE was 5.10% in the IPC therapy group and 2.76% in the IPC + anticoagulation therapy group, with no significant differences between them (P = .382); however, the VTE incidence rate was lower with anticoagulant use. A more detailed analysis showed that PE incidence was 2.01% and 0.69% (P = .623) without and with anticoagulant, respectively, and the incidence of PE + proximal DVT was 3.82% and 2.76% (P = .752), respectively. These findings showed a trend toward lower incidence with use of
an anticoagulant but did not unequivocally confirm the usefulness of anticoagulants.

The incidence of DVT as detected by MDCT was much lower than expected. Sakon et al reported in patients who underwent abdominal surgery without active prophylaxis that the incidence of distal and proximal DVT was 20.8% and 2.9%, respectively, as detected by contrast venography. Other studies have also reported distal DVT incidence of 1.2% with enoxaparin (low-molecular-weight heparin) and 19.4% with IPC using venography. Sugimachi et al reported frequencies of proximal and distal DVT with elastic stocking and IPC prophylaxis of 1.5% and 9.8%, respectively, as determined using duplex scan after laparoscopic gastrointestinal surgery. The incidence of proximal DVT in the present study was comparable to that reported previously for Japanese patients, but the incidence of distal DVT was much lower. This distinction suggests that the detection rate for distal DVT with MDCT might be lower than with venography or duplex scan.

The addition of anticoagulation therapy reduced VTE incidence although not significantly, perhaps because of the low incidence of distal DVT or because of the relatively low number of patients recruited. Perioperative anticoagulant prophylaxis with laparoscopic surgery should be carefully considered in patients of Asian descent with CRC.

The Seventh American College of Chest Physicians (ACCP) guidelines consider patients with a proximal DVT risk of 4%-8% without prophylaxis to be at high risk and needing anticoagulation. In the present study, despite using IPC and IPC + anticoagulant therapy, the incidence of PE + proximal DVT was 3.82% and 2.76% with each,
respectively. With no prevention, the incidence would be expected to be still higher. Thus, according to the ACCP guidelines, the risk of PE + proximal DVT is estimated to be high or greater in these patients. Our results suggested that preventative IPC or IPC + anticoagulant prophylaxis is essential for this patient population. Of note, anticoagulation therapy did not significantly decrease VTE frequency, and anticoagulant prophylaxis may be more appropriate for patients with a high risk of VTE and low bleeding risk.

In this study, there were no bleeding-related deaths, and the incidence of major bleeding was 1.27% and 1.38% without and with anticoagulants, respectively ($P = .936$). Yamaoka et al$^{40}$ reported a major bleeding incidence of 0.6% (2/362) with fondaparinux and 0.8% (5/591) with IPC among colon cancer patients ($P = .715$). We previously reported that the incidence of major bleeding in colon cancer patients with anticoagulant prophylaxis using fondaparinux was 0.81% (5/619; 95% CI 0.3%-1.9%). In that study, there were no bleeding-related deaths or deaths from other causes during the

### TABLE 2 Incidence of VTE in the patients in this study

| Location (n) | IPC therapy group | IPC + anticoagulation therapy group |
|--------------|-------------------|-----------------------------------|
| PE (3)       | 149               | 141                               |
| Pulmonary artery (1) | 1.91% | 0.69% |
| Pulmonary artery + posterior tibial vein (2) | 5.10% | 2.76% |
| Proximal VTE (3) | .382 | .936 |
| External iliac vein/popliteal vein (1) | 2.01 | 2.13 |
| External iliac vein (1) | 1.34 | 0 |
| Superficial femoral vein + deep femoral vein (1) | 1.34 | 0 |
| Distal VTE (2) | 0     | 0     |
| Soleal vein (2) | 0     | 0     |

### TABLE 3 Incidence of bleeding in the patients in this study

| Bleeding | IPC therapy group (%) | IPC + anticoagulation therapy group (%) | $P$  |
|----------|-----------------------|----------------------------------------|------|
| All bleeding | 5/157 (3.18) | 19/145 (13.1) | .002 |
| Major bleeding | 2/157 (1.27) | 2/145 (1.38) | .936 |
| Minor bleeding | 3/157 (1.91) | 17/145 (11.7) | .001 |

### TABLE 4 Incidence of bleeding in patients in this study who were treated with fondaparinux vs enoxaparin

| Bleeding | Fondaparinux (%) | Enoxaparin (%) | $P$  |
|----------|------------------|---------------|------|
| All bleeding | 11/81 (13.6) | 4/52 (7.69) | .500 |
| Major bleeding | 0/81 (0) | 1/522 (0.192) | .386 |
| Minor bleeding | 11/81 (13.6) | 3/52 (5.77) | .296 |

### TABLE 5 Location of bleeding

| Bleeding | IPC therapy group | IPC + anticoagulation therapy group |
|----------|-------------------|-----------------------------------|
| Major bleeding | Anastomosis 1 | Anastomosis 1 |
| Intrapelvic 1 | Enoxaparin | Without administration |
| Minor bleeding | Melena 2 | Melena 3 |
| Bloody drain discharge 1 | Melena 1 | Melena 1 |
| Subcutaneous 5 | Melena 1 | Hematuria 1 |
| Unknown 1 | Unknown 1 |  |

Abbreviation: IPC, intermittent pneumatic compression.
treatment period. The major bleeding rate was similar in these reports, including the current work, and the incidence of clinically problematic bleeding was very low. These findings suggest that VTE prophylaxis using any anticoagulant can be safe with appropriate patient selection.

In the current study, we investigated VTE risk factor-related data in detail to determine their relationship with VTE. However, the number of primary outcome events was lower than expected, and fewer than expected patients had risk factors. Thus, we could not stratify patients according to higher prevalence of VTE.

The study has some limitations. First, the incidence of VTE varies with ethnicity, but this study included only patients of Japanese ancestry. Second, the number of primary outcome events was lower than expected. Finally, the duration of anticoagulation therapy differs in Japan compared to Western countries.

5 | CONCLUSIONS

Anticoagulant prophylaxis did not reduce the incidence of VTE and the incidence of major bleeding was comparable between the two groups. Usefulness of perioperative anticoagulation was not demonstrated in this study. Pharmacological prophylaxis must be restricted in Japanese patients with higher risk of VTE.

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ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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REFERENCES

1. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg. 1998;208:227–40.
2. Sakuma M, Konno Y, Shirato K. Increasing mortality from pulmonary embolism in Japan, 1951-2000. Circ J. 2002;66:1144–9.
3. Sakon M, Maehara Y, Yoshikawa H, Akaza H. Incidence of venous thromboembolism following major abdominal surgery: a multi-center, prospective epidemiological study in Japan. J Thromb Haemost. 2006;4:581–6.
4. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost. 2006;4:529–35.
5. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006;166:458–64.
6. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - A cohort study using linked United Kingdom databases. Eur J Cancer. 2013;49:1401–13.
7. Thodyiil PA, Kakkar AK. Variation in relative risk of venous thromboembolism in different cancers. Thromb Haemost. 2002;87:1076–7.
8. Guyatt GH, Eikelboom JW, Gould MK, Garcia DA, Crowther M, Murad MH, et al. Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based clinical practice guidelines. Chest. 2012;141:e1855–94S.
9. Monroe DM, Hoffman M. Dysregulation of hemostasis by cancer. Cancer Treat Res. 2009;148:3–15.
10. Aharon A, Brenner B. Microparticles, thrombosis and cancer. Best Pract Res Clin Haematol. 2009;22:61–9.
11. Buchberg B, Masoomi H, Lusby K, Choi J, Barleben A, Magno C, et al. Incidence and risk factors of venous thromboembolism in colorectal surgery: does laparoscopy impart an advantage? Arch Surg. 2011;146:739–43.
12. Colvin H, Mizushima T, Eguchi H, Takiguchi S, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost. 2006;4:581–6.
13. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-term endpoints of laparoscopic versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet. 2005;365:1718–26.

14. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M; PEGASUS investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005;92:1212–20.

15. Hata T, Yasui M, Murata K, Okuyama M, Ohue M, Ikeda M, et al. Safety of fondaparinux to prevent venous thromboembolism in Japanese patients undergoing colorectal cancer surgery: a multicenter study. Surg Today. 2014;44:2116–23.

16. Moghadamyeghaneh Z, Masoomi H, Mills SD, Carmichael JC, Pigazzi A, Nguyen NT, et al. Outcomes of conversion of laparoscopic colorectal surgery to open surgery. JSLIS. 2014;18:e2014.00230.

17. Cui G, Wang X, Yao W, Li H. Incidence of postoperative venous thromboembolism after laparoscopic versus open colorectal cancer surgery. Surg Laparosc Endosc Percutan Tech. 2013;23:128–34.

18. Monn MF, Haut ER, Lau BD, Streiff M, Wick EC, Efron JE, et al. Is venous thromboembolism after laparoscopic surgery in patients with colorectal cancer preventable or inevitable? One institution’s experience. J Am Coll Surg. 2013;216:395–401.

19. Henke PK, Arya S, Pannucci C, Kubus J, Hendren S, Engelsbe M, et al. Procedure-specific venous thromboembolism prophylaxis: a paradigm from colorectomy surgery. Surgery. 2012;152:528–36.

20. Xenos ES, Vargas HD, Davenport DL. Association of blood transfusion and venous thromboembolism after colorectal cancer resection. Thromb Res. 2012;129:568–72.

21. Mamidanna R, Burns EM, Bottle A, Aylin P, Stonell C, Hanna GB, et al. Reduced risk of medical morbidity and mortality in patients selected for laparoscopic colorectal resection in England. Arch Surg. 2012;147:219.

22. Shapiro R, Vogel JD, Kiran RP. Risk of postoperative venous thromboembolism after laparoscopic and open colorectal surgery: an additional benefit of the minimally invasive approach? Dis Colon Rectum. 2011;54:1496–502.

23. Verheijen PM, Stevenson AR, Stitz RW, Clark DA, Clark AJ, Lumley JW. Prolonged use of thromboprophylaxis may not be necessary in laparoscopic colorectal surgery. Int J Colorectal Dis. 2011;26:755–9.

24. Yang SS, Yu CS, Yoon YS, Yoon SN, Lim SB, Kim JC. Symptomatic venous thromboembolism in asian colorectal cancer patients, World J Surg. 2011;35:881–7.

25. Weida D, Patrick LYY, Andrew YWC. Is it safe to perform operation for colorectal malignancy in Chinese patients without DVT prophylaxis? An 8-year experience from a regional hospital in Hong Kong, Chin Med J. 2010;123:1973–5.

26. Cheung HY, Chung CC, Yau KK, Siu WT, Wong SK, Chiu E, et al. Risk of deep vein thrombosis following laparoscopic rectosigmoid cancer resection in Chinese patients. Asian J Surg. 2008;31:63–8.

27. Ramirez JL, Vassiliu P, Gonzalez-Ruiz C, Vukasin P, Ortega A, Kaiser AM, et al. Sequential compression devices as prophylaxis for venous thromboembolism in high-risk colorectal surgery patients: reconsidering American society of colorectal surgeons parameters. Am Surg. 2003;69:941–5.

28. McLeod RS, Geerts WH, Snieder KN, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. Ann Surg. 2001;233:438–44.

29. Lee FY, Chu W, Chan R, Leung YF, Liu KH, Ng SM, et al. Incidence of deep vein thrombosis after colorectal surgery in a Chinese population. ANZ J Surg. 2001;71:637–40.

30. Kum CK, Sim EK, Ngii SS. Deep vein thrombosis complicating colorectal surgery in the Chinese in Singapore. Ann Acad Med Singapore. 1993;22:895–7.

31. Tokuhara K, Matsushima H, Ueyama Y, Nakataki K, Yoshioka K, Kon M. Efficacy and safety of thromboembolism prophylaxis with fondaparinux in Japanese colorectal cancer patients undergoing laparoscopic surgery: a phase II study. Int J Surg. 2017;42:203–8.

32. Vedovati MC, Becattini C, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, et al. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. Ann Surg. 2014;259:665–9.

33. JCS Joint Working Group. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009), Circ J. 2011;75:1258–81.

34. Sakon M, Kobayashi T, Shimazu T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. Thromb Res. 2010;125e65–70.

35. Sugimachi K, Tajiri H, Kinjo N, Ikebe M, Wang H, Tanaka K, et al. Incidence and predictors of deep venous thrombosis after abdominal oncologic surgery: prospective Doppler ultrasound screening. J Surg Res. 2012;178:657–61.

36. Loud PA, Katz DS, Bruce DA, Klippenstein DL, Grossman ZD. Deep venous thrombosis with suspected pulmonary embolism: detection with combined CT venography and pulmonary angiography. Radiology. 2001;219:498–502.

37. Karande GY, Hedgire SS, Sanchez Y, Ballyan V, Mishra V, Ganguli S, et al. Advanced imaging in acute and chronic deep vein thrombosis. Cardiovasc Diagn Ther. 2016;6:493–507.

38. Quiroz R, Kucher N, Zou KH, Kipfmueller F, Costello P, Goldhaber SZ, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. JAMA. 2005;293:2012–7.

39. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;126:3385–4005.

40. Yamaoka Y, Ikeda M, Ikenaga M, Haraguchi N, Miyake M, Sekimoto M. Safety and efficacy of fondaparinux for prophylaxis of venous thromboembolism after colorectal cancer resection: a propensity score matched analysis. Dig Surg. 2015;32:190–5.

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