

## Case Report

# Gastric Cancer Receiving Robotic Surgery with Postoperative Pulmonary Thromboembolism: A Case Report with Literature Review

Tomonari Suetsugu, Yoshihiro Tanaka\*, Yuta Sato, Ritsuki Takaha, Masahiro Fukada, Itaru Yasufuku, Naoki Okumura, Nobuhisa Matsuhashi, Takao Takahashi and Kazuhiro Yoshida

Department of Gastroenterological Surgery, Gifu University Graduate School of Medicine, Japan

**\*Corresponding author**

Yoshihiro Tanaka, Department of Gastroenterological Surgery, Gifu University School of Medicine, 1-1 Yanagido, Gifu City 501-1194, Japan, Tel: 81-58-230-6233; Fax: 81-58-230-1074; Email: yoshihirotana11@hotmail.com

**Submitted:** 08 October 2021

**Accepted:** 22 October 2021

**Published:** 23 October 2021

**ISSN:** 2378-9344

**Copyright**

© 2021 Suetsugu T, et al.

**OPEN ACCESS****Keywords**

- Gastric cancer
- Robotic-surgery
- Pulmonary thromboembolism
- Subacute lower limb DVT
- Direct oral anticoagulant

**Abstract**

A 72-year-old woman with early gastric cancer and D-dimer elevation had deep venous thrombosis (DVT) in her soleus, posterior tibial, and sural veins, but no pulmonary thromboembolism (PTE) or proximal lower limb vein thrombosis. Because of anemia and her subacute phase DVT, anticoagulant therapy was not administered preoperatively. She underwent robotic distal gastrectomy with D2 lymphadenectomy and Billroth I reconstruction without intraoperative complications. Her platelets decreased from 263,000/ $\mu$ L to 76,000/ $\mu$ L on postoperative day (POD) 1. Because of potential postoperative bleeding following initiation of anticoagulant therapy under her low platelet count, anticoagulant therapy was postponed until platelets recovered. On POD 3, D-dimer and soluble fibrin monomer complex levels respectively rose to 91.6  $\mu$ g/mL and 64.2  $\mu$ g/mL. She complained of respiratory distress. Saturation of percutaneous oxygen was about 95% on O<sub>2</sub> at 4 L/min, indicating poor oxygenation. Contrast-enhanced CT showed PTE in her right upper and peripheral left pulmonary arteries. After oral rivaroxaban 30 mg/day was started, respiratory distress gradually improved, and O<sub>2</sub> administration became unnecessary with no decrease in platelets or bleeding. She was discharged 17 days postoperatively without complications. It should be recognized that even subacute lower limb-only DVT can result in symptomatic postoperative PE.

**ABBREVIATIONS**

CAT: Cancer-Associated Thromboembolism; CT: Computed Tomography; DOACs: Direct Oral Anticoagulants; DVT: Deep Venous Thrombosis; LMWH: Low-Molecular-Weight Heparin; NCC: National Comprehensive Cancer Network; POD: Postoperative Day; PTE: Pulmonary Thromboembolism; S-FMC: Soluble Fibrin Monomer Complex; UICC: Union for International Cancer Control; US: Ultrasonography; VTE: Venous Thromboembolism

**INTRODUCTION**

Venous thromboembolism (VTE), including both pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT), is an important cause of morbidity and mortality among patients with cancer [1,2]. Cancer frequently causes VTE due to activation of the coagulation system. The incidence of preoperative DVT in patients with gastric cancer is reported to be 7.5% [3]. The risk of VTE in these patients is greatest in those with cancers

of the pancreas, stomach, brain, lung, and ovary; advanced stage disease; and in those undergoing treatment including chemotherapy, hormonal therapy, or surgery [4-6]. In recent years, the efficacy and feasibility of direct oral anticoagulants (DOACs) for cancer-associated thromboembolism (CAT) has been shown [7,8], and active perioperative intervention is also recommended [9]. Therefore, early diagnosis, prevention, and appropriate treatment of DVT are essential for cancer surgery. However, aggressive postoperative anticoagulant use for subacute DVT in the distal leg is controversial [10]. Here, we report a case of a patient with early gastric cancer receiving robotic surgery that developed postoperative symptomatic PTE from a subacute distal type DVT.

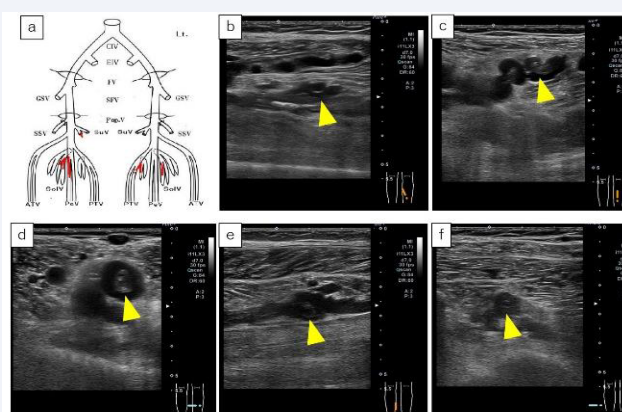
**CASE PRESENTATION**

A 72-year-old woman with gradually progressing anemia was followed for intraductal papillary mucinous neoplasm in our hospital. She underwent esophagogastroduodenoscopy that revealed a type 2 tumor in the lesser curvature of the gastric

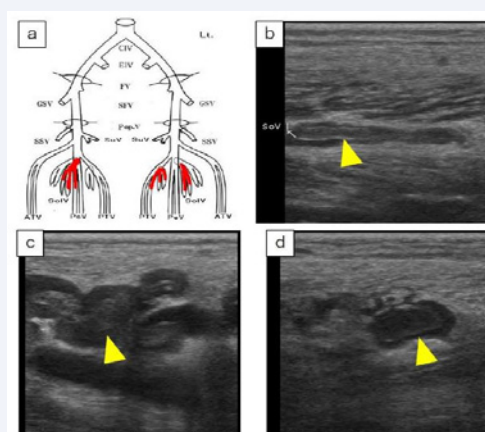
wall (Figure 1). The biopsy result showed adenocarcinoma. Endoscopic ultrasonography (US) was suspicious for infiltration of the ulcerated lesion of the tumor into the muscularis propria layer. Enhanced computed tomography (CT) showed no distant or lymph node metastasis. Therefore, her initial diagnosis was gastric cancer, T2N0M0 cStage I (UICC 8<sup>th</sup> Edition). Robotic distal gastrectomy was planned for her gastric adenocarcinoma. Her height was 147.6 cm, body weight was 50.4 kg and Body Mass index (BMI) was 23.1. Preoperative physical findings showed that no swelling or tenderness in her lower limbs. Laboratory analysis showed a slightly low hemoglobin level of 10.1 g/dL and elevation of D-dimer at 11.2  $\mu\text{g/mL}$ , but tumor markers CEA and CA19-9 were within normal range. US detected venous thrombosis in her soleus, peroneal, and sural veins (Figure 2a). The thrombosis occupied about 10% of the lumen in the sural vein (Figure 2b) but was greatest at 50% in the soleus vein (Figure 2c) and peroneal vein (Figure 2d) in her right leg. In her left leg, the thrombosis occupied almost 30% of a branch of her posterior tibial vein (Figure 2e) and the soleus vein (Figure 2f). Each thrombosis was considered to be in the subacute and organized phase because the echo brightness was relatively high. Neither PTE nor thrombosis in the central femoral vein was noted on enhanced CT. She was referred to a cardiologist for a perioperative strategy to treat her venous thrombosis. Considering her anemia and condition that the subacute phase of thrombus especially only distal lower limb, it was decided to treat her with elastic stockings and postoperative prophylactic anticoagulant therapy. The day before surgery, she underwent US again, which showed the thrombosis in her soleus, posterior tibial, and sural veins to be in almost the same condition as in the previous US examination (Figure 3) and D-dimer was 6.8  $\mu\text{g/mL}$ . The robotic distal gastrectomy with D2 lymph node dissection and Billroth I reconstruction was performed. The operation time was 394 minutes, and blood loss was 5 mL. The surgery was completed without intraoperative complications. The pathological diagnosis of the gastric cancer was T1bN0M0 Stage I (UICC 8<sup>th</sup> Edition) (Figure 4). Although her preoperative platelet count was 263,000/ $\mu\text{L}$ , blood tests on postoperative day (POD) 1 and POD 3 showed decreases in platelets to 76,000/ $\mu\text{L}$  and 46,000/ $\mu\text{L}$ , respectively, so anticoagulant therapy was not started due to concern about postoperative bleeding. On POD 3, her D-dimer level was increased to 91.6  $\mu\text{g/mL}$ , and her soluble fibrin monomer complex (S-FMC) level was increased to 64.2  $\mu\text{g/m}$ , and she complained of respiratory distress. Her saturation of percutaneous oxygen ( $\text{SpO}_2$ ) was about 95% on  $\text{O}_2$  at 4 L/min. Contrast-enhanced CT showed PTE in her right upper pulmonary artery and peripheral left pulmonary artery (Figure 5). After weighing the risk of bleeding and exacerbation of symptomatic PE, we started anticoagulant therapy with oral rivaroxaban at 30 mg/day. Within a few days of starting anticoagulant therapy, her respiratory distress improved. On POD 6, her D-dimer level remained high: 99.8  $\mu\text{g/mL}$ . Platelet count was improved to 83,000/ $\mu\text{L}$  and Hb level was maintained: 10.3g/dL at the same day. Oxygen administration became unnecessary with no decrease in platelets nor bleeding in a week. She was discharged 17 days after surgery without complications. Contrast-enhanced CT obtained one week after discharge showed that the PE had disappeared, and the DVT had disappeared on lower limb US. D-dimer and S-FMC level were decreased to within normal range in 30 POD.



**Figure 1** Preoperative endoscopic image: Type 2 tumor was noted at the lesser curvature of the gastric wall. The biopsy showed adenocarcinoma (tub2).



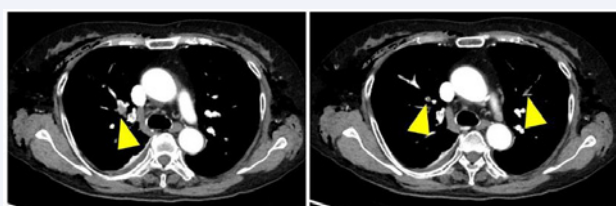
**Figure 2** Lower extremity vein ultrasonography results at first visit (a). The brightness of each thrombosis was relatively high. The thrombi were not floating and were considered to be in the subacute stage. In her right leg, thrombosis occupied about 10% of the lumen in the sural vein (b), about 50% of the lumen in the soleus vein (c), and about 50% of the lumen in the peroneal vein (d). In her left leg, thrombosis occupied about 30% of the lumen in the posterior tibial vein (e) and about 30% of the lumen in a branch of the soleus vein (f).



**Figure 3** (a) Preoperative lower extremity vein ultrasonography results. The brightness of each thrombus was relatively high. The thrombi were not floating and were still considered to be in the subacute stage. In her right leg, thrombosis occupied about 80% of the lumen in both the soleus vein (b) and peroneal vein (c). In her left leg, thrombosis occupied about 70% of the lumen in the posterior tibial vein (d). All thrombi showed a slight increase.



**Figure 4** Surgical specimen of gastric cancer. The pathological findings showed infiltration to SM and no lymph node metastasis. Final diagnosis was pT1bN0M0 Stage I (UICC 8th Edition).



**Figure 5** Contrast-enhanced computed tomography (CT) when symptomatic pulmonary thromboembolism (PTE) occurred. CT findings showed PTE in the right upper pulmonary artery and peripheral left pulmonary artery.

## DISCUSSION

VTE, including both PTE and DVT, is an important cause of morbidity and mortality among patients with cancer [1,2] and is the second leading cause of death in these patients [11]. VTE in cancer patients is called CAT, which is a result of activation of the coagulation system. Cancer cells may induce thrombosis by triggering several complex prothrombotic pathways. Mechanisms of these pathways may include a procoagulant effect of tissue factor expressed by tumor cells, release of cytokines, inhibition of fibrinolysis, and overexpression of membrane adhesion molecules [12-14].

Preoperative screening of DVT and prevention of symptomatic PTE are important. D-dimer assay has a high negative predictive value (96–100%), which allows exclusion of VTE [15-17], although its specificity is only 36–44%. Lower limb venous US has both high sensitivity and specificity [18,19]. Therefore, the combined use of D-dimer assay and US is appropriate for preoperative screening. Further, Tanaka et al., reported that esophageal cancer patients with postoperative VTE had significantly higher levels of D-dimer and S-FMC than those without VTE [20]. The combination of D-dimer and S-FMC seems to be effective as an index reflective of postoperative thrombus activity.

The risk of VTE in patients with cancer is greatest in those with cancers of the pancreas, stomach, brain, lung, and ovary [4,5]. Advanced cancer stage is also a risk factor, and one population-based study showed significantly higher rates of VTE in patients with distant metastases (odds ratio = 19.8; 95% confidence interval, 2.6–149) [21]. Furthermore, a report investigating VTE in patients with both operable and inoperable

gastric cancer showed a 2-year cumulative incidence of VTE after diagnosis of gastric cancer of 3.8% in all patients, and 0.5%, 3.3%, 3.6%, 3.8%, and 24.4% in the patients with stages I, II, III, IV (M0), and IV (M1), respectively [22]. Of course, surgery alone is also one of the risk factors of VTE. Osaki et al. investigated the occurrence of DVT after surgery for gastric cancer and showed that the incidence of DVT was 4.4% (7/160) before and 7.2% (11/153) after surgery. Besides, four of the seven patients with preoperative DVT received pharmacologic thromboprophylaxis, and all patients with DVT were asymptomatic and none suffered symptomatic PTE [23]. Laparoscopic surgery and robotic surgery for gastric cancer are considered to be minimally invasive because they result in less pain and complications than open surgery and the period until the first walk is short [24-26], but there are no reports of increased postoperative thrombosis.

A risk scoring model incorporating 5 clinical and laboratory parameters, such as the site of cancer, platelet count, hemoglobin and/or use of erythropoiesis-stimulating agents, leukocyte count, and body mass index was developed by Khorana et al., to predict chemotherapy-associated thrombosis in ambulatory cancer patients [6]. The Khorana score has been validated retrospectively and prospectively in >18,000 patients and internationally adapted as a risk prediction tool for CAT [27].

Considering these risk factor in our present case, the Khorana score was 2 (intermediate-risk category) and distal lower limb DVT was present preoperatively. It was thought that perioperative anticoagulant therapy should be performed from the viewpoint of PTE prevention. However, previous studies have shown that patients with a first isolated distal DVT and no concomitant PTE have a significantly lower risk of recurrent symptomatic VTE, and possibly of death, than patients with a first proximal DVT [28]. Unfortunately, our patient had a risk of anemia and gastric bleeding before surgery, and platelet levels were decreased after surgery addition to the state of inserting the epidural anesthesia tube, so perioperative prophylactic anticoagulant therapy was not actively administered until 2 POD. Although the patient's preoperative D-dimer level was lower than that at the time of her first visit, the freshness of the thrombus, which can be confirmed in the lower limb US, was in the subacute stage and remained organized. It seems to be difficult to reflect the activity of thrombus with the D-dimer level alone. Therefore, even though early stage of cancer and the thrombus is located only distal lower limbs remaining organized, we should pay more attention that lower limb thrombus may progress to PTE within a few days after the operation.

In recent years, the supportive care guidelines for venous thromboembolism prophylaxis and treatment in patients with cancer were revised by the American Society of Clinical Oncology [9]. This revision indicates the direction of active therapeutic intervention for CAT. To prevent VTE, high risk patients with cancer may be offered thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) with consideration given to the relative benefits and harms, drug costs, and duration of each treatment. Besides, initial anticoagulation may involve LMWH, unfractionated heparin, fondaparinux, or rivaroxaban. Some randomized control trials of DOACs for the treatment of VTE in patients with cancer reported that edoxaban

and rivaroxaban are effective but are linked with a higher risk of bleeding compared with LMWH in patients with GI and potential genitourinary cancers [7,8].

After the symptomatic PTE occurred in our patient, she was treated with rivaroxaban and her symptoms gradually improved in a few days without complications such as bleeding, and it was possible to manage anticoagulant therapy continuously even after discharge. The PTE disappeared within 3 weeks after oral administration of rivaroxaban. Rivaroxaban, which enables a single drug approach, was effective and safe, especially when taken orally from 3POD after gastrectomy.

## CONCLUSION

In conclusion, we report a rare case of symptomatic PTE after surgery for early gastric cancer. Although robotic surgery is minimally invasive and it is possible to get out of bed early after surgery, thromboembolism remains one of the major postoperative complications, requiring timely intervention, including anticoagulant therapy, even for early stage of cancer and for organized thrombosis limited to the lower extremities.

## CONFLICT OF INTERESTS

K. Yoshida has received grants, personal fees, and nonfinancial support from Chugai Pharmaceutical Co., Ltd. during the conduction of the study; grants and personal fees from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., and Yakult Honsha Co., Ltd.; grants from Bristol-Myers Squibb; grants from Kyowa Hakko Kirin Co., Ltd. outside the submitted work; honoraria from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Yakult Honsha Co., Ltd.; and had a consultant or advisory relationship with Taiho Pharmaceutical Co., Ltd. and La Roche, Ltd. T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. All remaining authors declare that they have no conflict of interest.

## Human/animal rights

All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## Informed consent

Consent for publication was obtained from the patient included in this study.

## REFERENCES

- [1] Donnellan E, Khorana AA. Cancer and venous thromboembolic disease: a review. *Oncologist*. 2017; 22: 199–207.
- [2] Lyman GH, Culakova E, Poniewierski MS, Kuderer NK. Morbidity, mortality and costs associated with venous thromboembolism in hospitalized patients with cancer. *Thromb Res*. 2018; 164: S112–S8.
- [3] Tanizawa Y, Bando E, Kawamura T, Tokunaga M, Makuuchi R, Lida K, et al. Prevalence of deep venous thrombosis detected by ultrasonography before surgery in patients with gastric cancer: a retrospective study of 1140 consecutive patients. *Gastric Cancer*. 2017; 20: 878–86.
- [4] Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. *Thromb Haemost*. 2017; 117: 219–30.
- [5] Falanga A, Russo L, Milesi V, Vignoli A. Mechanisms and risk factors of thrombosis in cancer. *Crit Rev Oncol Hematol*. 2017; 118: 79–83.
- [6] Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer*. 2007; 110: 2339–46.
- [7] Raskob GE, van Es N, Verhamme P, Carrier M, Nisio MD, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018; 378: 615–24.
- [8] Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018; 36: 2017–23.
- [9] Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JL, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2020; 38: 496–520.
- [10] Schwarz T, Buschmann L, Beyer J, Halbritter K, Rastan A, Schellong S. Therapy of isolated calf muscle vein thrombosis: a randomized, controlled study. *J Vasc Surg*. 2010; 52: 1246–50.
- [11] Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2019; 20: e566–81.
- [12] Prandoni P, Falanga A, Piccioli A. Cancer and venous thromboembolism. *Lancet Oncol*. 2005; 6: 401–10.
- [13] Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood*. 2007; 110: 1723–9.
- [14] Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med*. 2008; 359: 938–49.
- [15] Legnani C, Pancani C, Palareti G, Guazzaloca G and Coccheri S. Contribution of a new, rapid, quantitative and automated method for D-dimer measurement to exclude deep vein thrombosis in symptomatic outpatients. *Blood Coagul Fibrinolysis*. 1999; 10: 69–74.
- [16] van der Graaf F, van den Borne H, van der Kolk M, J de Wild P, Janssen GW, van Uum SH. Exclusion of deep venous thrombosis with D-dimer testing—comparison of 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis using venography as reference standard. *Thromb Haemost*. 2000; 83: 191–8.
- [17] Fünfsinn N, Caliezi C, Biasiutti FD, Korte W, Z'Brun A, Baumgartner I, et al. Rapid D-dimer testing and pre-test clinical probability in the exclusion of deep venous thrombosis in symptomatic outpatients. *Blood Coagul Fibrinolysis*. 2001; 12: 165–70.
- [18] Mousa AY, Broce M, Gill G, Kali M, Yacoub M, AbuRahma AF. Appropriate use of D-dimer testing can minimize over-utilization of venous duplex ultrasound in a contemporary high-volume hospital. *Ann Vasc Surg*. 2015; 29: 311–7.
- [19] Michiels JJ, Maasland H, Moosdorff W, Lao M, Gadiseur A, Schroyens W. Safe exclusion of deep vein thrombosis by a rapid sensitive ELISA D-dimer and compression ultrasonography in 1330 outpatients with suspected DVT. *Angiology*. 2016; 67: 781–7.
- [20] Tanaka Y, Yamada A, Hirata S, Tanaka H, Sakuratani T, Matsushashi N, et al. Efficacy and safety of enoxaparin for prophylaxis of postoperative venous thromboembolism after esophagectomy: a single-center prospective randomized controlled phase II study. *Anticancer Res*. 2019; 39: 2615–25.

- [21] Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005; 293: 715–22.
- [22] Lee KW, Bang SM, Kim S, Lee HJ, Shin DY, Koh Y, et al. The incidence, risk factors and prognostic implications of venous thromboembolism in patients with gastric cancer. *J Thromb Haemost*. 2010; 8: 540–7.
- [23] Osaki T, Saito H, Fukumoto Y, Kono Y, Murakami Y, Shishido Y, et al. Risk and incidence of perioperative deep vein thrombosis in patients undergoing gastric cancer surgery. *Surg Today*. 2018; 48: 525–33.
- [24] Zhang CD, Yamashita H, Zhang S, Seto Y. Reevaluation of laparoscopic versus open distal gastrectomy for early gastric cancer in Asia: A meta-analysis of randomized controlled trials. *Int J Surg*. 2018; 56: 31–43.
- [25] Uyama I, Suda K, Nakauchi M, Kinoshita T, Noshiro H, Takiguchi S, et al. Clinical advantages of robotic gastrectomy for clinical stage I/II gastric cancer: a multi-institutional prospective single-arm study. *Gastric Cancer*. 2019; 22: 377–85.
- [26] Guerrini GP, Esposito G, Magistri P, Serra V, Guidetti C, Olivieri T, et al. Robotic versus laparoscopic gastrectomy for gastric cancer: the largest meta-analysis. *Int J Surg*. 2020; 82: 210–28.
- [27] Khorana AA, Francis CW. Risk prediction of cancer-associated thrombosis: Appraising the first decade and developing the future. *Thromb Res*. 2018; 164: S70-6.
- [28] Barco S, Corti M, Trincherio A, Picchi C, Ambaglio C, Konstantinides SV, et al. Survival and recurrent venous thromboembolism in patients with first proximal or isolated distal deep vein thrombosis and no pulmonary embolism. *J Thromb Haemost*. 2017; 15: 1436–42.

**Cite this article**

Suetsugu T, Tanaka Y, Sato Y, Takaha R, Fukada M, et al. (2021) Gastric Cancer Receiving Robotic Surgery with Postoperative Pulmonary Thromboembolism: A Case Report with Literature Review. *Ann Vasc Med Res* 8(3): 1133.