Epidemiological Study Regarding the Incidence of Venous Thromboembolism in Patients After Cancer Remission

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ABSTRACT

Introduction: The time course of reduction in the risk of venous thromboembolism (VTE) in patients who were diagnosed with cancer, treated with anticancer therapy, and in remission is unclear. We hypothesized that the risk of VTE will decrease over time after cancer remission.

Methods: We conducted a retrospective analysis using claims data for cancer remission in Japan. Background information of patients who developed VTE after cancer remission was collected, and the VTE incidence rate after cancer remission was analyzed. Subgroup analysis based on VTE history, cancer type, and the presence or absence of surgery during hospitalization was conducted.

Results: A total of 638,908 patients were eligible for the analysis. VTE occurred in 5533 of 638,908 cases, pulmonary embolism occurred in 779 cases, and deep vein thrombosis occurred in 5084 cases after cancer remission. The mean age of patients who developed VTE was 70.1 ± 12.5 years, and the proportion of men was 47.5%. All comorbidities and medications were higher in the VTE group (P < 0.001) than in the non-VTE group after cancer remission. The incidence of VTE was 2.4% per year in the first 30 days, 1.35% per year in 31–60 days, and gradually decreased to 0.48% per year in 181–360 days, becoming almost constant (annual rate 0.3%) 2 years after cancer remission.

Conclusion: Risk of developing VTE decreased to the same level as that in patients without cancer 2 years after cancer remission. Although the guidelines do not specify the duration of anticoagulant prophylaxis for new onset or recurrent VTE after cancer remission and the appropriate duration of such prophylaxis may vary depending on VTE risk factors, determining the period of high risk of VTE for each patient and preventing VTE is considered important.

Keywords: Anticoagulants; Cancer remission; Deep vein thrombosis; Pulmonary embolism; Venous thromboembolism
Key Summary Points

*Why carry out this study?*

Although cancer patients are at a high risk of developing venous thromboembolism (VTE), it is not known whether the risk will continue after cancer remission; thus, the kind of treatment or preventive measure that should be applied to patients after cancer remission remains unclear.

This study was conducted based on the assumption that the risk of VTE will decrease over time after cancer remission.

*What was learned from the study?*

During the 30 days after cancer remission, the incidence of VTE was high, with a risk similar to that in patients with cancer, but this slowly decreased, and after 2 years, the risk of developing VTE decreased to the same level as that in patients without cancer.

Defining the period in which there is a high risk of developing VTE after cancer remission will lead to prevention and early diagnosis of VTE.

INTRODUCTION

Venous thromboembolism (VTE) is one of the complications in patients with cancer, and cancer-related VTE onset is called cancer-associated thrombosis. Various humoral factors produced by cancer cells affect the coagulation fibrinolytic system. In addition, vascular endothelial cell injury caused by anticancer treatment and stagnation of blood flow due to lying down are also considered risk factors [1, 2]. Therefore, it is known that the risk of developing VTE increases in the presence of cancer or anticancer treatment, and the risk of developing VTE in patients with cancer is 4.7 times higher than that in patients without cancer [3]. Furthermore, 20–30% of patients with VTE have cancer [4, 5]. Patients with VTE who have cancer as well as those who do not have cancer are treated with anticoagulants, but long-term anticoagulant treatment is recommended because those with cancer are at an increased risk of VTE recurrence, but the duration of treatment has not been specified [2, 6–8]. Furthermore, in recent years, the number of cancer survivors has increased owing to advances in early cancer detection technology and cancer treatment [9, 10]. With successful cancer treatment and cancer remission or cure, factors that lead to blood clots have been addressed. Some guidelines recommend discontinuing anticoagulant therapy after cancer remission [6, 7]. However, there are no clear data on the duration of the residual effects of cancer or anticancer treatment and appropriate treatment period of anticoagulant therapy. Therefore, questions have arisen, such as (1) should the VTE risk of patients in cancer remission be considered similarly as that of a high-risk group of cancer patients or should these patients be treated as patients who do not have cancer? and (2) after cancer remission, should anticoagulant treatment be continued to prevent VTE recurrence, and if yes, how long should this therapy be continued.

Therefore, we conducted this epidemiological study to investigate the time course of reduction in the risk of VTE in patients who were diagnosed with cancer, treated with anticancer therapy, and cured or in remission, using the medical database of Medical Data Vision Co., Ltd. (MDV, Tokyo), comprising medical information.

METHODS

Study Design

The data of patients diagnosed with malignant tumors (ICD-10; C000-C968) registered in the medical database provided by MDV from April 1, 2008, to July 31, 2021, were extracted. MDV database is an anonymous claims database comprising claims data from 450 acute care hospitals (23% of acute care hospitals with a
combined diagnostic procedure [DPC] system, including approximately 37 million individuals maintained in inpatient and outpatient settings in Japan (as of June 2021). Each patient in the database is associated with a specific ID to which all inpatient and outpatient data are linked.

The study included (1) patients with a confirmed diagnosis of malignancy after April 1, 2008, (2) hospitalized patients scheduled to receive anticancer treatment, such as oncological surgery, stem cell transplant, lymphadenectomy, radiation therapy, topical administration, outpatient chemotherapy, cancer pain relief, and rehabilitation (see Supplementary Table 3 [Table S3]) (primary reason for hospitalization was cancer), and (3) patients with discharged outcome rating for indexed cancer as “cured/improved” or “remission” based on the discharged summary of the DPC system. Patients with active cancer involving two or more organs, those in whom the primary site of cancer occurrence was unknown, or patients for whom sufficient information could not be obtained at baseline prior to cancer diagnosis were excluded.

**Baseline and Follow-up Periods**

In the present study, we defined the final hospitalization of patients whose discharge outcome was “cure/improvement” or “remission” as indexed hospitalization, and the date of the discharge from the indexed hospitalization was defined as the index date, from which a follow-up period was started. The day of discharge from the indexed hospitalization was defined as Day 0. The baseline period was at the most 180 days prior to the index date. Patients with a baseline period of < 6 months were included if the necessary information could be obtained. The 6-month baseline period was used to obtain the clinical and demographic characteristics of the patients. However, because a longer period of time was necessary to determine the history of cancer, all definitive diagnostic information before the index date was used for this purpose in each patient. The follow-up period was up to 1800 days after the index date, and if (1) there was a lack of further records in the database—no further relevant records were added (e.g., no further refills or visits)—the last date of the patient’s record in the database was considered or if (2) the first definitive diagnosis of cancer occurred after the index date or (3) initiation of anticoagulation therapy after the index date, follow-up was terminated on that day. The definitive diagnoses of the first cancer occurrence after the index date were newly developed cancer, relapsed cancer, or metastatic cancer. In this study, to evaluate the risk of VTE in remission, if there was a definitive diagnosis of cancer, follow-up was terminated at that point, and the VTE risk during the follow-up period was evaluated.

**Endpoint and Subgroup Analyses**

The primary endpoint was the time to pulmonary embolism (PE; ICD-10: I26) or deep venous thrombosis (DVT; ICD-10: I80, I81, I82, O222, O223, O225, O870, O871, O882) onset after the index date, using the Kaplan-Meier method. For identification of incidence of PE and/or DVT, we used ICD-10 codes as well as the diagnosis, examination, and treatment based on a validated algorithm [11]. This study has provided a more objective method for identification of DVT and PE in the claims database than the method with only ICD-10 codes. If the diagnosis was only DVT, it was treated as DVT; if the diagnosis was only PE or both PE and DVT, it was treated as PE. Subgroup analysis of previous history of VTE, presence or absence of surgery during hospitalization, and cancer type was performed.

**Definitions**

Outcomes of the patients with cancer at discharge were evaluated based on the discharge summary in the DPC system. In the DPC system, a five-point scale (“cure/improvement,” “remission,” “unchanged,” “worsening,” or “in-hospital death”) is used for determining the discharge outcomes. Patients were considered to be in cancer remission if the outcome at the time of discharge was “cure/improvement” or
“remission.” This outcome rating is only regarding the primary disease (the main disease that caused the hospitalization). Since in this study, only patients hospitalized for cancer were included in the analysis, the outcomes in the DPC discharge summary were considered to be outcomes of indexed cancer.

Drugs were defined using EphMRA ATC codes (see Supplementary Table 1 [Table S1]). Cancer types and other diseases were defined using ICD-10 codes (see Supplementary Table 2 [Table S2]).

Statistics

Patient background is presented as mean ± standard deviation (continuous variables) or patient percentage (%) (categorical variables). Wilcoxon rank-sum test was used to compare the mean values of the two groups, and Fisher’s exact test was used to compare the percentages of the two groups.

The time course of the incidence of VTE after cancer remission, from the index date to the onset of PE, DVT, or VTE is shown by Kaplan-Meier curves. The annual incidence rates with their 95% confidence intervals were estimated at 30, 60, 90, 180, and 360 days and then every 360 days.

The following sub-analyses were also conducted: (1) presence or absence of a VTE history during the baseline period; VTE-free survival curves were drawn using the Kaplan-Meier method and two curves were compared using a log-rank test; (2) presence or absence of anticancer surgery during hospitalization; the incidence rates in each sub-group were calculated and compared; (3) cancer type; VTE incidence rates were calculated by cancer type at baseline. Kaplan-Meier curves were drawn, and incidence rates with 95% confidence intervals were calculated. \( P < 0.05 \) was considered statistically significant.

Data collection, data quality control, and statistical analyses were conducted by Medical Data Vision Co., Ltd. (Tokyo, Japan) and MediStatLab Co., Ltd. (Tokyo, Japan). All calculations and analyses were performed using R

3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Compliance with Ethics Guidelines

This study is a retrospective database study that (1) is not related to the effectiveness and safety of drugs and (2) involves data that does not completely contain personal information. Therefore, in accordance with the “ethical guidelines for medical and biological research involving human subjects,” which are the ethical guidelines for clinical research in Japan, obtaining informed consent from patients and approval by the institutional review board or ethical committee was not required.

RESULTS

Patient Baseline Characteristics in Patients with/without VTE after Cancer Remission

In total, 2,555,651 patients who were diagnosed with cancer were identified. After excluding 1,665,747 patients who did not achieve remission after treatment, 154,556 patients with metastatic cancer, 69,135 with multiple cancers, and/or 27,305 receiving warfarin or direct oral anticoagulants at discharge, totaling 638,908, were included in the analysis (Fig. 1).

Differences in patient background between patients with VTE (VTE group) and those without VTE (non-VTE group) after cancer remission

![Fig. 1 Patient selection flow. Cancer remission was considered when the patient was hospitalized for cancer treatment and the outcome at discharge was confirmed to be cure/improvement or remission. DOAC direct oral anticoagulant](image)
| Variables                  | Entire cohort (N = 638,908) | Patients without VTE (N = 633,375) | Patients with VTE (N = 5,533) (PE: 779, DVT: 5,084) | P       |
|---------------------------|----------------------------|------------------------------------|-----------------------------------------------------|---------|
|                           |                            |                                    |                                                     |         |
| **Demographics**          |                            |                                    |                                                     |         |
| Male                      | 328,426 (51.4)             | 325,798 (51.4)                     | 2628 (47.5)                                         | < 0.001 |
| Age (years)               | 67.8 ± 13.4                | 67.8 ± 13.4                        | 70.1 ± 12.5                                         | < 0.001 |
| **Sites of cancer**       |                            |                                    |                                                     |         |
| Oral cavity/esophagus     | 23,646 (3.7)               | 23,512 (3.7)                       | 134 (2.4)                                           | < 0.001 |
| Stomach                   | 104,571 (16.4)             | 103,744 (16.4)                     | 827 (14.9)                                          | 0.004   |
| Intestine                 | 122,532 (19.2)             | 121,269 (19.1)                     | 1263 (22.8)                                         | < 0.001 |
| Liver                     | 33,006 (5.2)               | 32,578 (5.1)                       | 428 (7.7)                                           | < 0.001 |
| Pancreas                  | 11,309 (1.8)               | 11,151 (1.8)                       | 158 (2.9)                                           | < 0.001 |
| Lung                      | 44,279 (6.9)               | 43,916 (6.9)                       | 363 (6.6)                                           | 0.288   |
| Thymus/heart              | 861 (0.1)                  | 861 (0.1)                          | 861 (0.1)                                           | 1.000   |
| Bone/joint                | 419 (0.1)                  | 414 (0.1)                          | 5 (0.1)                                             | 0.420   |
| Skin                      | 21,803 (3.4)               | 21,638 (3.4)                       | 165 (3.0)                                           | 0.080   |
| Breast                    | 98,229 (15.4)              | 97,676 (15.4)                      | 553 (10.0)                                          | < 0.001 |
| Female reproductive organs| 28,852 (4.5)               | 28,402 (4.5)                       | 450 (8.1)                                           | < 0.001 |
| Male reproductive organs  | 41,863 (6.6)               | 41,636 (6.6)                       | 227 (4.1)                                           | < 0.001 |
| Kidney                    | 66,023 (10.3)              | 65,552 (10.3)                      | 471 (8.5)                                           | < 0.001 |
| CNS                       | 2926 (0.5)                 | 2903 (0.5)                         | 23 (0.4)                                            | 0.764   |
| Endocrine system          | 13,028 (2.0)               | 12,985 (2.1)                       | 43 (0.8)                                            | < 0.001 |
| Lymph/blood               | 25,561 (4.0)               | 25,145 (4.0)                       | 416 (7.5)                                           | < 0.001 |
| **Anticancer treatment**  |                            |                                    |                                                     |         |
| Surgery                   | 476,801 (74.6)             | 473,072 (74.7)                     | 3729 (67.4)                                         | < 0.001 |
| Stem cell transplant      | 1590 (0.2)                 | 1558 (0.2)                         | 32 (0.6)                                            | < 0.001 |
| Lymphadenectomy           | 15,773 (2.5)               | 15,645 (2.5)                       | 128 (2.3)                                           | 0.486   |
| Radiation therapy         | 27,336 (4.3)               | 27,059 (4.3)                       | 277 (5.0)                                           | 0.008   |
| Topical administration    | 9711 (1.5)                 | 9463 (1.5)                         | 248 (4.5)                                           | < 0.001 |
| Outpatient chemotherapy   | 21,242 (3.3)               | 20,978 (3.3)                       | 264 (4.8)                                           | < 0.001 |
| Cancer pain relief        | 5702 (0.9)                 | 5637 (0.9)                         | 65 (1.2)                                            | 0.031   |
| Rehabilitation            | 67,704 (10.6)              | 67,037 (10.6)                      | 667 (12.1)                                          | < 0.001 |
| **Anti-cancer drugs**     |                            |                                    |                                                     |         |
| Alkylating agents         | 24,959 (3.9)               | 24,574 (3.9)                       | 385 (7.0)                                           | < 0.001 |
are shown in Table 1 and Supplementary Table 4 (Table S4). The mean ages of patients in the VTE and non-VTE groups were 70.1 ± 12.5 years and 67.8 ± 13.4 years, respectively (P < 0.001). The percentages of male patients in the VTE and non-VTE groups were 47.5% and 51.4%, respectively (P < 0.001). Patients with cancer of the intestine, liver, pancreas, female reproductive organs, and lymph/blood had a higher incidence of VTE (P < 0.001). The most common medical procedure was surgery in the both patient groups, but fewer cancer-related surgeries were performed in the VTE group (67.4% versus 74.7%, P < 0.001). The second most common medical procedure was cancer rehabilitation (12.1% in the VTE group versus 10.6% in the non-VTE group [P < 0.001]), followed by radiation therapy (5.0% versus 4.3%; P = 0.008), outpatient chemotherapy (4.8% versus 3.3%; P < 0.001), and topical administration of anti-cancer drugs (4.5% versus 1.5%; P < 0.001). Regarding comorbidities, more patients in the VTE group had each investigated comorbidity for all complications (all diseases, P < 0.001). The use of medications, including anti-cancer drug other than anticancer hormonal and hormonal antagonists, was more common in the VTE group (P < 0.001) than in the non-VTE group.

VTE Risk in Patients Who Experienced Cancer Remission

Figure 2 and Table 2 show the risk of developing VTE after cancer remission. The cumulative observation period was 1,043,003 person-years, and VTE occurred in 5533 patients after the index date (the cumulative observation period for the cohort without VTE and with VTE was 1,037,311 person-years and 5692 person-years, respectively). Seven hundred seventy-nine patients had PE during the follow-up period (cumulative observation period of 1,042,157 person-years for cohort without PE and 846 person-years for cohort with PE) and 5084 patients had DVT (cumulative observation period of 1,037,807 person-years for cohort without DVT and 5195 person-years for cohort with DVT). The incidence of VTE was 2.40% per year in the first 30 days, which was decreased to 1.35% per year in 31–60 days and 0.48% per year in 181–360 days. Two years after the index date, the incidence of VTE became almost constant (annual rate of 0.3%). Similarly, the
incidence of DVT and PE was highest in the first 30 days, reduced by half in 31–60 days, and gradually decreased subsequently.

Sub-group Analyses Based on the Presence or Absence of a VTE History, Surgery, and According to Type of Cancer

Figure 3a shows the occurrence of VTE after the index date in patients with or without a history of VTE during the baseline period. A total of 4818 VTE events after cancer remission were observed in the 622,008 patients without a history of VTE (1.8% at 1800 days), and 715 VTE events were observed in the 16,900 patients with a history of VTE (9.4% at 1800 days) ($P < 0.001$). The incidence of VTE in patients with a history of VTE was 11.99% per year in the first 30 days, which was decreased to 6.7% per year in 31–60 days and 1.16% in 1800 days. The incidence of VTE in patients without a history of VTE was 2.14% per year in the first 30 days, which was decreased to 1.20% per year in 31–60 days and 0.26% in 1800 days. The risk of VTE recurrence when adjusted for sex and age had a hazard ratio of 5.69 (5.26–6.16, $P < 0.001$) in patients with a history of VTE (data not shown).

Figure 3b shows the incidence of VTE in patients who underwent surgery during hospitalization and in those who did not. Patients in the non-surgery group had a higher incidence of VTE than those in the surgery group ($P < 0.001$).

Figure 3c shows the incidence of VTE by cancer type at baseline. Patients with pancreatic cancer had the highest risk of developing VTE (4.8%), followed by those with liver cancer (4.0%) and lymph/blood cancer (3.6%) during the follow-up period.

DISCUSSION

The incidence of VTE 1–30 days after cancer remission decreased by 50% in the 31–60 days

**Table 2** Incidence (% per year) of VTE after the index date

| Periods (days after the index date) | VTE          | PE            | DVT          |
|------------------------------------|--------------|---------------|--------------|
| 0–30                               | 2.40 (2.39–2.41) | 0.32 (0.32–0.32) | 2.22 (2.21–2.22) |
| 31–60                              | 1.35 (1.33–1.36) | 0.13 (0.13–0.14) | 1.26 (1.25–1.27) |
| 61–90                              | 1.04 (1.03–1.06) | 0.13 (0.13–0.14) | 0.95 (0.94–0.97) |
| 91–180                             | 0.73 (0.71–0.74) | 0.11 (0.10–0.12) | 0.67 (0.65–0.68) |
| 181–360                            | 0.48 (0.46–0.50) | 0.07 (0.06–0.08) | 0.44 (0.42–0.47) |
| 361–720                            | 0.33 (0.30–0.36) | 0.05 (0.04–0.06) | 0.30 (0.27–0.33) |
| 721–1080                           | 0.27 (0.23–0.31) | 0.04 (0.03–0.06) | 0.25 (0.21–0.28) |
| 1081–1440                          | 0.25 (0.21–0.30) | 0.05 (0.03–0.06) | 0.23 (0.19–0.27) |
| 1441–1800                          | 0.28 (0.23–0.34) | 0.04 (0.02–0.06) | 0.26 (0.21–0.32) |

Figures are presented as incidence (% per year) with 95% confidence intervals

*VTE* venous thromboembolism, *PE* pulmonary embolism, *DVT* deep vein thrombosis
After 2 years, the incidence decreased to a level similar to that in cancer-free patients. This suggests that long-term anticoagulant use for VTE prevention is not required if patients do not have active cancer anymore or if the cancer is in remission. The incidence of VTE varies depending on not only history of VTE but also cancer type, and some types of cancer are associated with a higher rate of VTE development. Therefore, the duration of anticoagulant therapy for VTE prevention could differ depending on the history of VTE and cancer type. Undoubtedly, there should be close monitoring of patients with VTE risk factors to detect VTE development and recurrence.

The risk of new-onset VTE in patients with cancer is 4.7 times higher than that in those without cancer [3] and the risk of VTE recurrence is 3–4 times higher [12–14]. Thus, several guidelines recommend long-term anticoagulant treatment for VTE patients with active cancer [6–8]. However, the time course when the risk of VTE in patients in cancer remission decreases to a level similar to that in cancer-free patients is not known. VTE risk in patients with cancer is related to (1) cancer-related factors such as the site and stage of cancer, (2) treatment-related factors such as surgery and chemotherapy, and (3) patient-related factors such as comorbidities, VTE history, and decreased activity [15]. According to the ASCO guidelines, chemotherapy, angiogenesis inhibitors, hormone therapy, erythrocyte hematopoietic-stimulating factor preparations, blood transfusion, intravenous access device placement, radiation therapy, and a surgery lasting 60 min are risk factors for cancer-associated thrombosis [7]. However, it is unclear how long the effects of these risk factors last after the treatment ends and cancer remission occurs. Our present results show that the risk of VTE development may be decreased to a level similar to that in patients without cancer 2 years after cancer remission, and duration of anticoagulation therapy for both treatment of VTE and prevention of new onset (or recurrence) of VTE is similar to that in patients without cancer.

A study using the UK database to examine the risk of cardiovascular disease in cancer survivors [10] showed that the risk of developing VTE in the period after the initial diagnosis of cancer is high, and then the risk decreases. However, this UK study was for patients who were alive 1 year after being diagnosed with

Fig. 3 Kaplan-Meier curves for VTE, PE, or DVT-free patients during the follow-up period. a Patients with or without a history of VTE, b patients who did or did not undergo surgery as an anti-cancer treatment, c sites of cancer. VTE venous thromboembolism, PE pulmonary embolism, DVT deep vein thrombosis
cancer and not necessarily those who were in remission. In our study, the time course of VTE risk in cancer remission patients was investigated. Although statistical tests have not been performed, the incidence rates may differ significantly between the 30- and 60-day periods since there is no overlap of confidence intervals for the VTE incidence rates for 0–30 days and 31–60 days. The risk of developing VTE in patients with cancer is 13 per 1000 person-years to 68 per 1000 person-years, depending on the type and stage of cancer, and it is reported to be 4.7 times higher than that in patients without cancer [3, 16]. That is, the incidence of VTE in patients without cancer is approximately 2.8–14.5 per 1000 person-years, and the incidence rate of 3 per 1000 person-years after 2 years is thought to decrease to levels similar to those in people without cancer. Since there are various differences among Europe, the USA, and Japan, such as major cancer types and patient backgrounds (e.g., complications), a simple comparison cannot be made. However, it is reasonable to think that soon after cancer remission, the incidence of VTE is similar to that in patients with cancer; the risk decreases after 60 days, and it is estimated that the incidence will decrease in patients without cancer in maximum of a 2-years period. In a previous study that investigated outcomes with anticoagulation treatment in VTE patients with cancer and compared the outcomes between with and without anticoagulation treatment in patients whose cancer was in remission, incidence rate of VTE in patients in cancer remission was much lower than that in the current study. There were many fewer recurrences in patients whose cancer was in remission (< 1%), even after discontinuing anticoagulation treatment [17]. The exact reason why the incidence rate is quite different between the two studies remains unclear. One of the most plausible explanations is the difference in patient characteristics. In the previous study, only patients with a history of VTE were included, whereas in our present study patients with cancer remission, irrespective of a history of VTE, were included in the analysis. In addition, the previous study was conducted at a single site, while our current study included various patients from more than 300 institutes. Furthermore, DPC hospitals are acute-phase hospitals and patient conditions are generally more serious. Awareness of the risk of VTE and the degree to which preventive measures are implemented differ from hospital to hospital. These factors may also contribute to differences in the incidence of VTE. However, since the previous study included both patients with or without anticoagulation therapy, no information as to when anticoagulation therapy should be terminated in patients with cancer remission was provided.

The incidence of VTE after cancer remission in patients with a history of VTE was higher than that in patients without a history of VTE (Fig. 3a). The COMMAND VTE registry in Japan reports that the risk of VTE recurrence in patients with cancer is 11.8% at 1 year after VTE diagnosis, and the VTE recurrence rate in cancer-free patients is 3.7%, which means that the risk of VTE recurrence is approximately three times higher in patients with active cancer [18]. In this study, the risk of VTE in patients with a history of VTE was 11.99% in the 30 days following cancer remission. Taken together, it is suggested that even after cancer remission, patients with a history of VTE could have a higher risk of VTE recurrences and should be carefully monitored.

It has also been reported that the incidence of VTE varies depending on the type of cancer. In the UHC database study by Khorana et al., the pancreas was the site of cancer with the highest incidence of VTE (8.1%), followed by the abdomen (including the liver) (6.6%), ovaries (6%), kidney (5.6%), and lung (5.1%), and the risk of VTE in prostate cancer and breast cancer was low [19]. Similarly, this study also showed that patients who developed VTE after remission had a higher prevalence of cancer of the intestine, liver, pancreas, female reproductive organs, and lymph/blood than those who did not develop VTE. Because the incidence of VTE was high in pancreatic, liver, and lung cancers, whereas it was low in prostate and breast cancers in both studies, cancer associated with a high risk of developing VTE was also associated with a high risk of VTE even after cancer remission. This suggests that if patients have cancer with a high risk of developing VTE,
the patients should be carefully treated or observed even after remission.

From the perspective of treatment-related factors, the proportion of patients with VTE who undergo surgery was low, and the proportion of patients treated with cancer rehabilitation, radiation therapy, outpatient chemotherapy, and topical administration of anticancer drugs was higher than that of the non-VTE group. The reasons for these are not clear, but it seems possible that the non-VTE patients had early-stage cancer that could be relatively easily removed by surgery alone. Since cancer rehabilitation is performed in the hospital, hospitalization may affect VTE risk. As a drug treatment, the prescription ratios of alkylating agents, antimetabolites, microtubule inhibitors, cytotoxic antibiotics, protein kinase inhibitors, monoclonal antibodies, and platinum preparations were higher in patients with VTE than in those without VTE. It has been suggested that some anticancer therapies targeting vascular endothelial cells may lead to development of thrombi due to vascular endothelial damage [20–24]. Although the long-term effects of each of these treatments needs to be investigated in more detail, it was speculated that these anticancer treatments affected thrombus formation and were more likely to lead to VTE even after the discontinuation of the drugs. In addition, the rate of comorbid diseases was higher in patients with than without VTE. Among the comorbid diseases, VTE-risk diseases, such as coagulopathy, valvular disease, heart failure, and peripheral thrombosis, were more common in patients in the VTE group. The proportion of patients taking antithrombotic drugs during the baseline period was higher in the VTE cohort. This is because many of these patients experienced VTE in the follow-up period, for which anticoagulants were used for treatment, and they further developed recurrent VTE in the follow-up period. Patients who have experienced VTE at least once are considered to be at a high risk for recurrent VTE, even if they are treated and cured. Furthermore, patients with a history and complications of lifestyle-related diseases, such as diabetes, hypertension, and hyperlipidemia, and cardiovascular events, such as stroke, angina, myocardial infarction, and heart failure, were prevalent in the VTE group. The relationship between VTE and lifestyle-related diseases, such as metabolic syndrome, dyslipidemia, and diabetes, has also been recently reported [25]. It has been suggested that atherosclerosis and spontaneous VTE are related diseases and that atherosclerosis may induce the development of VTE [26]. Strongman et al. reported a high incidence of VTE and CV events in cancer survivors [27]. It is considered that since patients who develop VTE after cancer remission have various complications, it is important to pay particular attention to the onset of VTE in the early stage after cancer remission and then focus on cardiovascular diseases, including VTE. This study found a period of high risk of VTE after cancer remission and patient characteristics, but it included patients who were not anticoagulated. Outcomes with anticoagulation treatment or anticoagulation prophylaxis were not examined; therefore, it is expected that further studies will be conducted in patients at a high risk for VTE after cancer remission.

**Limitations**

This study has several limitations. First, we could not estimate the number of patients that were lost to follow-up, because we had no data on patients who visited a different hospital or clinic after being registered with one of the hospitals that contribute to the MDV database. This could have led to an underestimation of the rate of VTE development. Second, because information on cancer stage was not obtained from the database, cancer stage was not considered during the analysis. Cancer stage may be associated with the incidence of VTE. Third, we judged cancer remission only from the outcome description in the DPC data. It seems possible that patients who did not experience remission and had hidden cancer were included in the analysis, which may have led to an overestimation of the incidence of VTE. Fourth, since the database we used in this study was an administrative claims database, there is no information on the site and size of the thrombus, and the analysis did not take these factors into account.
into consideration. The site and size of DVT may be an important factor regarding whether DVT is the cause of PE, which could be a limitation of this study. Finally, patients on anticoagulation therapy the day before the index date were excluded from the analysis and patients who started an anticoagulant regardless of the reason (for example, a diagnosis of atrial fibrillation) during the follow-up period were censored at the timing of initiation of the anticoagulation therapy. Therefore, patients on anticoagulation therapy for pathological conditions, such as atrial fibrillation, were not included in the analysis. This might have some impact on generalization of the results.

CONCLUSION

We clearly elucidated the time course of VTE incidence after cancer remission in this study. During the 30 days after cancer remission, the incidence of VTE was high, close to the risk in patients with cancer, but this slowly decreased, and after 2 years, the risk of developing VTE decreased and was similar to that in cancer-free patients. Therefore, it is important to evaluate VTE risk in each patient to determine an appropriate period of anticoagulation therapy to prevent new onset or recurrent VTE.

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Author Contributions M. Imura designed the study, managed the project, interpreted the data, critically reviewed the literature, and reviewed and edited the final manuscript. J. Katada designed the study, interpreted the data, critically reviewed the literature, and reviewed and edited the final manuscript. T. Shiga interpreted the data, critically reviewed the literature, and reviewed and edited the final manuscript.

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Compliance with Ethics Guidelines This study is a retrospective database study that (1) is not related to the efficacy and safety of drugs or a disease and (2) uses data that do not completely contain personal information. Therefore, in accordance with the “ethical guidelines for medical and biological research involving human subjects,” which is the ethical guideline for clinical research in Japan, obtaining informed consent from patients and approval by the institutional review board or ethical committee was not required.

Data Availability The datasets generated during and/or analyzed during the current study are not publicly available due to licensing agreements with Medical Data Vision Co., Ltd. Please contact Miki Imura, the corresponding author of this paper, for data availability.

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