

The Location and Size of Pulmonary Embolism in Anti-neoplastic Chemotherapy Patients¹

Yun Joo Park, M.D., Woocheol Kwon, M.D., Won-Yeon Lee, M.D.², Sang Baek Koh, M.D.³,
Seong Ah Kim, M.D., Myung Soon Kim, M.D., Young Ju Kim, M.D.

Purpose: To retrospectively evaluate the prevalent location and size of pulmonary embolism (PE) in anti-neoplastic chemotherapy patients by multidetector row CT (MD-CT).

Materials and Methods: This study was conducted on 101 patients that were positively diagnosed with PE by CT. Among these patients, 23 had received or were undergoing chemotherapy. The location and the mean size of the largest PE were compared between anti-neoplastic chemotherapy patients and non-cancer patients using the *Chi*-square test and paired *t*-test, respectively. We also used a multiple linear regression to assess the risk posed by the other risk factors of PE.

Results: The most prevalent location of PE in patients on anti-neoplastic chemotherapy was in the lobar or segmental pulmonary arteries and was not significantly different from non-cancer patients. The size of the PE was smaller in patients on anti-neoplastic chemotherapy (1.14 mL [standard error = 0.29]) compared to non-cancer patients. (2.14 mL [standard error = 0.40]) ($p < 0.05$).

Conclusion: The size of PE is smaller in anti-neoplastic chemotherapy patients than in non-cancer patients.

Index words : Pulmonary Embolism

Antineoplastic Combined Chemotherapy Protocols
Tomography, X-Ray Computed

In the general population, the incidence of pulmonary embolism (PE) is two to three patients for every 1,000 who present with nonspecific clinical signs and symp-

toms (1). In patients with a malignant tumor, the incidence of PE is increased by 4-6 times compared to the general population who present with nonspecific clinical signs and symptoms. The risk of thrombus formation increases even more in patients who are receiving chemotherapy and have an increased risk of mortality (2). Therefore, the diagnosis of PE is essential and the diagnostic accuracy must be enhanced using the appropriate diagnostic equipment. Imaging modalities for PE include perfusion-ventilation scan, pulmonary angiography, spiral CT, and MR angiography. CT is less invasive than conventional pulmonary angiography and has the advantage of visualizing the emboli within the pul-

¹Department of Radiology, Wonju Christian Hospital, Yonsei University Wonju College of Medicine

²Department of Internal Medicine, Wonju Christian Hospital, Yonsei University Wonju College of Medicine

³Department of Prevent Medicine, Wonju Christian Hospital, Yonsei University Wonju College of Medicine

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Address reprint requests to : Woocheol Kwon, M.D., Department of Radiology, Wonju Christian Hospital, Yonsei University Wonju College of Medicine, 162, Ilsan-dong, Wonju-si, Gangwon-do 220-701, Korea.

Tel. 82-33-741-1467 Fax. 82-33-732-8281

E-mail: wckwon@yonsei.ac.kr

monary vessels, and it as a result, is accepted as the standard diagnostic tool for PE in many medical institutions (3). If a specific pattern of pulmonary embolus formation including size and location exists, this scan could provide additional diagnostic information in those patients on chemotherapy presenting with signs and symptoms of pulmonary embolism. Knowing the size and location of thrombus formation could help in instances when there is a diagnostic dilemma between the volume averaging artifact and a true pulmonary arterial filling defect. The benefits of increased accuracy include a timely diagnosis and management, and thus a decrease in mortality (4). Prior studies have studied the location and size of pulmonary thrombus formation in the general population, but to the best of our knowledge, there are no reports in the medical literature which have studied the location and size of PE formation in patients that are undergoing chemotherapy. Therefore, the purpose of this study is to evaluate and compare the prevalent location and size of thrombus formation in patients exposed to chemotherapy to non-cancer patients utilizing CT angiography.

Materials and Methods

Patients

This study was conducted in 101 patients who underwent CT pulmonary angiography or chest CT scan and who had a positive diagnosis for PE between July 2005 and February 2008. The patient population consisted of 51 men and 50 women, ranging in age from 26 to 94 years with a mean age of 59 years. Forty nine patients (48.5%) from this group presented with symptoms suspicious for PE and the remaining 52 patients (51.5%) were scanned for other reasons such as cancer surveillance. Twenty three patients (22.7%) had a prior history of chemotherapy or were currently receiving it and had a histologically confirmed diagnosis of malignancy. Among the chemotherapy group, 12 patients had lung cancer, 3 had stomach cancer, 2 had colorectal cancer, 1 had a gastric gastrointestinal stromal tumor, 2 had a thymic carcinoma, and 3 had breast cancer. Among them, 12 patients had metastases to the liver, lung and pleura. The remaining 78 patients had no prior history of cancer or exposure to chemotherapy. Within the chemotherapy group, 6 patients (23.1%) were evaluated by CT for clinical symptoms suspicious of PE, while the remaining 17 patients (76.9%) were scanned for other reasons such as cancer surveillance and the diagnosis of

PE was incidentally detected.

Review of the Medical Records

A retrospective review of the medical charts was performed in order to evaluate the cycle and time frame of chemotherapy treatment in relation to the development of PE, patient demographics, whether the CT scan was performed to evaluate for the presence of PE, or for other reasons such as cancer surveillance. Additionally, other risk factors leading to the development of a pulmonary embolus were assessed including long-term immobilization, recent history of deep vein thrombosis (up to 1 year), presence of congestive heart failure, recent history of a fracture, history of coagulopathy, pregnancy, obesity, or a prior history of oral contraceptive use or anticoagulation therapy.

Scanning Technique

CT pulmonary angiography was performed using 64 multidetector row CT (MDCT) (Brilliance 64, Philips, Cleveland, Ohio) and 16 MDCT (LightSpeed 16, GE, Milwaukee, Wisconsin) along with a power injector and 100 mL of nonionic contrast material administered in the antecubital vein at a rate of 4 mL/sec. CT scanning delay time was determined using the bolus-tracking technique in the lumen of the pulmonary trunk. The threshold value was selected as 120 HU. Parameters for the CT pulmonary angiography using 64 MDCT included a slice thickness of 1 mm, 120 kVp, 220 mA, 18.75 mm/rotation speed of table, pitch of 0.938, and 350 FOV. Parameters for the CT pulmonary angiography using 16 MDCT included a slice thickness of 1.25 mm, 120 kVp, 635 mA, 18.75 mm/rotation speed of table, a pitch of 0.938, and 350 FOV. The reconstructed images were obtained at a slice thickness of 1 mm.

Chest CT was performed using 64 MDCT (Brilliance 64, Philips, Cleveland, Ohio) and 16 MDCT (LightSpeed 16, GE, Milwaukee, Wisconsin) along with a power injector and 100 mL of nonionic contrast material administered in the antecubital vein at a rate of 4 mL/sec. Scanning was started 25 sec after the beginning of contrast administration. Parameters for the chest CT using 64 MDCT included a slice thickness of 1 mm, 120 kVp, 250 mA, 18.75 mm/rotation speed of table, a pitch of 0.673, and 340 FOV. Parameters for the chest CT using 16 MDCT were slice thickness 1.25 mm, 120 kVp, 200 mA, 18.75 mm/rotation speed of table, a pitch of 0.938, and 340 FOV. The reconstructed images were obtained at a slice thickness of 2.5 mm.

Twenty-six patients were scanned by CT pulmonary angiography using 64 MDCT, whereas 23 patients were scanned by CT pulmonary angiography using 16 MDCT, another 34 patients by chest CT using 64 MDCT, and finally, 18 patients by CT pulmonary angiography using 16 MDCT.

Image Review

On CT scans, two parameters (location and volume) of the PE were analyzed. The locations of the emboli included the main pulmonary artery, lobar pulmonary

artery, segmental pulmonary artery, or subsegmental pulmonary artery, based on the location of the largest pulmonary arterial branch involved with PE. The size of the embolus was determined by obtaining the volume of the largest embolus using the three-dimensional reconstruction software VoxelPlus (VoxelPlus. 2. ver. 2.5.6.5009; Mevisys, Daejeon, Korea). The area of the embolus was measured in each slice (slice thickness of 0.1 m) by manually drawing a line along the margin of the embolus. The areas of each slice were summed up to calculate the volume (Fig. 1). The images were then reviewed by 2 independent radiologists and consensus was reached for any discrepancies.

Statistical Analysis

The location and size of the emboli were compared between the following paired groups: Patients exposed to chemotherapy versus those without cancer; patients exposed to chemotherapy who were evaluated for symptoms of PE versus patients exposed to chemotherapy whose PE was incidentally found; those with specific risk factors of PE including long-term immobilization, a recent 1-year history of deep vein thrombosis, congestive heart failure, a recent history of fracture, blood coagulation disorder, pregnancy, obesity and the history of the use of oral contraceptives including estrogen or anti-coagulation therapy versus those without a specific risk factor; female versus male patients. The differences in

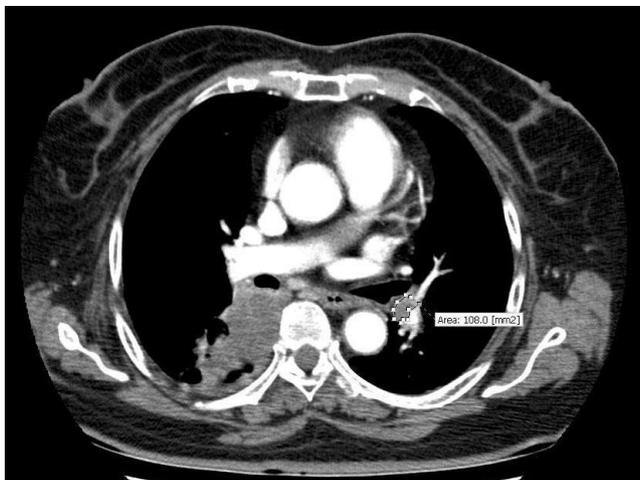


Fig. 1. Axial chest CT scan shows the measurement of the embolus area using VoxelPlus. The measured area of the emboli is summed up to calculate the volume.

Table 1. Location of Largest PE

Patients	Main	Lobar	Segmental	Subsegmental	p-value
Receiving CTx.	5 (21.7)	7 (30.4)	9 (39.1)	2 (8.7)	0.12
Not receiving CTx.	8 (10.3)	42 (53.8)	26 (33.3)	2 (2.6)	
Female	5 (10.0)	25 (50.0)	19 (38.0)	1 (2.0)	0.58
Male	8 (15.7)	24 (47.1)	16 (31.4)	3 (5.9)	
Bed ridden	7 (13.0)	25 (46.3)	21 (38.9)	1 (1.9)	0.56
Not bed ridden	6 (12.8)	24 (51.1)	14 (29.8)	3 (6.4)	
With DVT	2 (12.5)	9 (56.3)	4 (25.0)	1 (6.3)	0.94
Not with	5 (11.4)	22 (50.0)	15 (34.1)	2 (4.5)	
Not evaluated for DVT	6 (13.3)	18 (43.9)	16 (39.0)	1 (2.4)	
Recent surgery	1 (7.7)	3 (23.1)	8 (61.5)	1 (7.7)	0.11
No recent surgery	12 (13.6)	46 (52.3)	27 (30.7)	3 (3.4)	
CHF	2 (18.2)	7 (63.6)	2 (18.2)	0 (0)	0.51
No CHF	11 (12.2)	42 (46.7)	33 (36.7)	4 (4.4)	
Recent fracture	0 (0.0)	5 (55.6)	4 (44.4)	0 (5.0)	0.56
No recent fracture	13 (14.1)	44 (47.8)	31 (33.7)	4 (4.3)	
Symptomatic	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	0.85
Non-symptomatic	4 (23.5)	5 (29.4)	7 (41.2)	1 (5.9)	

Unless otherwise indicated, data represent the number of patients, with percentages in parentheses.

Note.— CTx. = anti-neoplastic chemotherapy, DVT = Deep vein thrombosis, CHF = congestive heart failure

location of the embolus were analyzed using the *Chi*-square test, whereas the differences in size were determined with a *t*-test. A value of $p < 0.05$ was considered statistically significant.

A multiple linear regression was performed to determine whether exposure to chemotherapy had a significant effect on the location and size of PE formation compared to other variables such as other specific risk factors for the development of PE.

Results

Location

In the chemotherapy group, the locations of the largest pulmonary embolus were in the main pulmonary artery in 5 cases (21.7%), lobar pulmonary artery in 7 cases (30.4%), segmental artery in 9 cases (39.1%), and subsegmental artery in 2 cases (8.7%). In the non-cancer group, the locations of the largest embolus were in the main pulmonary artery in 8 cases (10.3%), lobar pulmonary vessels in 42 cases (53.8%), segmental vessels in 26 cases (33.3%), and subsegmental vessels in 2 cases (2.6%). The difference between both groups was not statistically significant ($p = 0.12$) (Table 1).

Sex and other risk factors of PE, including a long-term immobilization, deep vein thrombosis, a recent 1-month history of surgery, congestive heart failure, myocardial infarction, and a recent 1-month history of fracture did not significantly affect the location of PE (Table 1).

Size

The average size of the largest PE was smaller (mean

volume = 1.14 mL [standard error = 0.294]) in the chemotherapy group versus the non-cancer group (mean volume = 2.14 mL [standard error = 0.404]). The difference was statistically significant ($p = 0.04$) (Table 2).

Sex and other risk factors of PE, including long-term immobilization, deep vein thrombosis, a recent 1-month history of surgery, congestive heart failure, myocardial infarction, and a recent 1-month history of fracture did not significantly affect the size of PE (Table 2).

Table 2. Mean Size of Largest PE

Patients	The Mean Size of the Largest Embolus(mL) (Standard Error)	<i>p</i> -value
Receiving CTx.	1.14 (0.29)	0.03
Not receiving CTx.	2.14 (0.40)	
Female	1.70 (0.37)	0.27
Male	2.10 (0.52)	
Bed ridden	2.49(0.56)	0.02
Not bed ridden	1.40(0.34)	
With DVT	2.58(0.86)	0.57
Not with DVT	1.97(0.59)	
Not evaluated for DVT	1.58(0.34)	
Recent surgery	0.91(0.53)	0.11
No recent surgery	2.06(0.36)	
CHF	0.92(0.40)	0.09
No CHF	2.03(0.36)	
Recent fracture	0.80(0.53)	0.11
No recent fracture	2.00(0.35)	
Symptomatic	1.30(0.61)	0.47
Non-symptomatic	1.00(0.34)	

Note.— CTx. = anti-neoplastic chemotherapy, DVT= Deep vein thrombosis, CHF = congestive heart failure

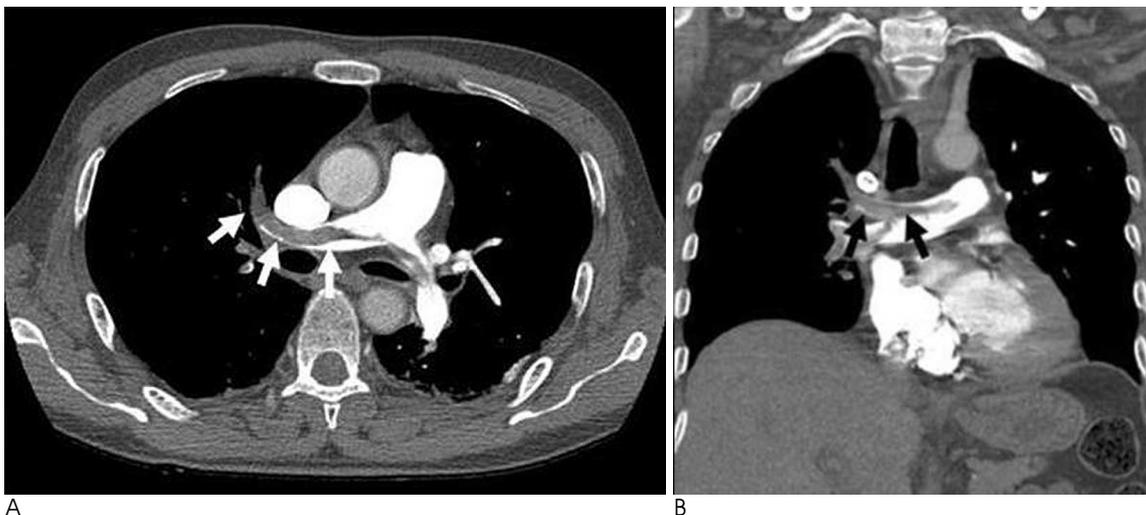


Fig. 2. 63-year-old man without underlying disease. A, B. Axial and coronal CT scan show a large PE (arrow) in the main pulmonary artery.

A multiple linear regression demonstrated that the overall size of the PE was smaller in the chemotherapy group compared to the non-cancer group when similar risk factors for the formation of PE were present ($p = 0.05$) (Table 3).

Discussion

Chemotherapy has traditionally been associated as a risk factor for the development of PE, which is a cause of high mortality rate in this group. In a large autopsy series, a fatal PE was diagnosed before death in only 32% of patients (5). It has also been reported that the proportion of cases in which PE is incidentally diagnosed represented approximately 1% to 4-5% in hospitalized patients, and this further increased to 70-83% in those with a malignant tumor (6). When treated conventionally, there is only an 8% recurrence rate and a 2.5% fatality rate in patients according to the data from the

Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) (3). Having knowledge of the characteristic CT findings such as its prevalent location, size, and the period where it usually occurs, could provide useful information in those instances where there is a difficulty in detecting a pulmonary arterial filling defect or differentiating between a thrombus and partial volume averaging artifact. In a study with 30 patients, peripheral pulmonary arteries down to fifth-order branches were accurately depicted with reconstructed 1.25-mm sections by using multi-detector row spiral CT (7). A low threshold suspicion or a screening CT scan can also be performed at the most prevalent period of thrombus formation in patients undergoing chemotherapy, and thus, increase the detection of PE. To date, many studies have been performed in order to examine the CT findings of PE in a normal patient population. However, to our knowledge, there are no reports in the medical literature that have studied pulmonary embolism detection with CT in patients undergoing chemotherapy.

In more than 70% of the normal population, the largest PE was in the pulmonary arteries whose diameter is greater than the segmental pulmonary arteries. Some studies have reported that the most common location of the largest PE was found to be in the lobar pulmonary vessel (28.5%) (4). Our study also demonstrated similar results; a lobar pulmonary artery was present in 53.8% of patients who did not receive chemotherapy. In patients who had exposure or were receiving chemotherapy, however, the segmental pulmonary vessels were the most prevalent location (39.1%). This difference was however not statistically significant ($p =$

Table 3. Multiple Linear Regression Analysis of Size of PE

Variables	B (Standard Error)	t	p-value
Anti-cancer CTx. and cancer	-1.55 (0.81)	-0.20	0.05
Sex	-0.39 (0.63)	-1.91	0.53
Bed ridden.	-0.75 (0.66)	-1.13	0.25
DVT	0.12 (0.35)	0.36	0.71
Recent surgery	-1.31 (1.03)	-1.26	0.20
CHF	-1.54 (1.06)	-1.44	0.15
Recent fracture	-0.90 (1.19)	-0.75	0.45

Note.— CTx. = anti-neoplastic chemotherapy, DVT = Deep vein thrombosis, CHF = congestive heart failure

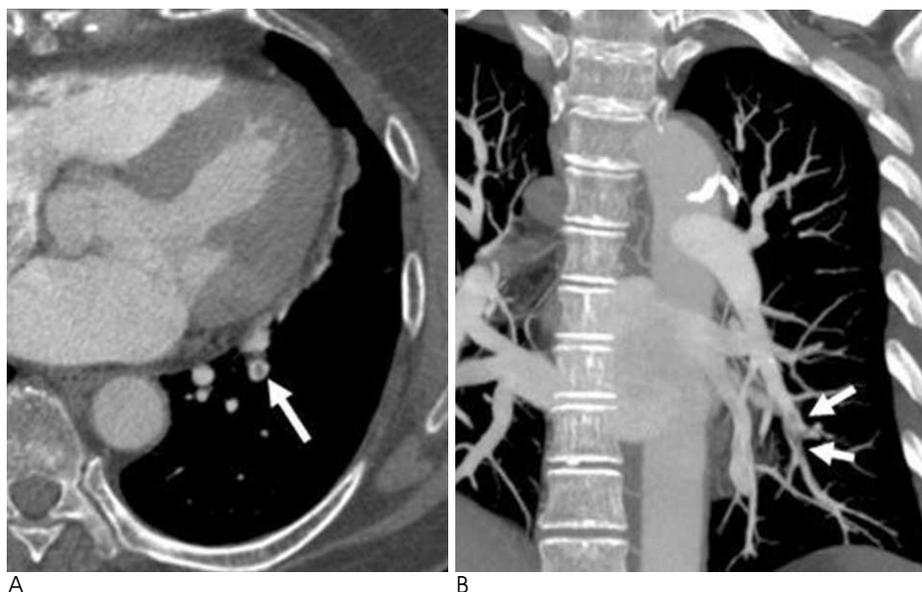


Fig. 3. 64-year-old man with lung cancer. A, B. Axial and coronal CT scan show a small PE in the laterobasal segmental artery of the left lower lobe (arrow).

0.12).

To our knowledge, the size of the largest PE has not been reported in previous studies. In the current study, the size of the largest PE was calculated to have a mean volume of 2.14 mL (standard error = 0.404) in patients without cancer and 1.14 mL (standard error = 0.029) in patients undergoing chemotherapy. These results indicate that chemotherapy had a statistically significant effect on the size of the pulmonary embolus ($p = 0.04$). We assumed that the reason the PE was smaller was that for anti-neoplastic chemotherapy patients the majority of PE were detected in surveillance CT before the symptom developed. Other risk factors including long-term immobilization, deep vein thrombosis, a recent 1-month history of surgery, congestive heart failure, and a recent 1-month history of fracture, were found to not significantly affect the size of PE. The incidence of PE was highest in the third cycle (30.4%) and fourth week following anti-cancer chemotherapy (17.4%).

In more than 50% cases, PE developed earlier than the third cycle and fourth week following anti-neoplastic chemotherapy. However, anti-neoplastic chemotherapy protocols are extremely heterogeneous in our patients. A further study of patients with the same pathology, stage, and anti-neoplastic chemotherapy protocol would enable the determination of the significant prevalent period of developing PE.

Our study had some limitations; first, the study population is small and the number of patients on chemotherapy compared to the control group was uneven. Furthermore, within the study group, there was variability in the chemotherapy regimen as well as the type of cancer studied. The multiple linear regression demonstrated that the size of the PE was smaller in patients undergoing chemotherapy when taking into account other specific risk factors of PE ($p = 0.05$). There was also variability in the CT scan protocol performed,

as some were detected incidentally for other reasons such as cancer surveillance and required different parameters compared to the standard CT angiography performed for the suspicion of PE. This could in turn affect the detection rate and accuracy of measuring the size of the embolus.

In summary, for patients undergoing chemotherapy treatment, there may be a role for screening with thin slice CT pulmonary angiography at the most prevalent periods. Furthermore, chemotherapy appears to decrease the size of thrombus formation, which may affect its location. These may provide useful information for the evaluation of PE, which can lead to a timely diagnosis, management, and reduction in mortality rate.

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항암환자에서 발생한 폐색전증의 호발 혈관 위치 및 색전의 크기¹

¹연세대학교 원주의과대학 원주기독병원 영상의학과

²연세대학교 원주의과대학 원주기독병원 호흡기내과

³연세대학교 원주의과대학 원주기독병원 예방의학과

박연주 · 권우철 · 리원연² · 고상백³ · 김성아 · 김명순 · 김영주

목적: 항암요법을 받는 환자에서 발생한 폐색전증의 호발 혈관 위치 및 색전의 크기를 다중 검출기 CT (MDCT) 를 이용해 알아보하고자 하였다.

대상과 방법: CT에서 폐색전증이 발견된 101명의 환자의 CT소견을 후향적으로 분석하였다. 이 중 23명은 항암요법을 받는 환자이다. 항암요법을 받는 환자와 비종양 환자의 가장 큰 폐색전의 발생 혈관 위치와 폐색전의 평균 크기를 교차분석 및 T-검정을 이용해 비교하였다. 폐색전증의 여러 가지 위험인자가 폐색전증의 호발 혈관 위치 및 색전의 크기에 미치는 영향을 고려하여 선형 회귀 분석을 통해 이를 바로잡았다.

결과: 항암요법을 받는 환자에서 폐색전증의 호발 혈관 위치는 엽성 또는 분절성 혈관이었으며 이는 비종양 환자와 통계학적으로 유의한 차이를 보이지 않았다. 폐색전증의 크기는 항암요법을 받는 환자에서 (1.14 mL [표준오차=0.29]) 비종양 환자보다 (2.14 mL [표준오차=0.40]) 통계학적으로 유의하게 작았다 ($p < 0.05$).

결론: 항암요법을 받는 환자에서 폐색전증의 크기는 비종양 환자보다 작다.