

# Upper-Extremity Deep Vein Thrombosis in Patients With Breast Cancer With Chest Versus Arm Central Venous Port Catheters

Danielle Tippit<sup>1</sup>, Eric Siegel<sup>2</sup>, Daniella Ochoa<sup>3</sup>, Angela Pennisi<sup>4</sup>, Erica Hill<sup>3</sup>, Amelia Merrill<sup>3</sup>, Mark Rowe<sup>3</sup>, Ronda Henry-Tillman<sup>3</sup>, Aneesha Ananthula<sup>1</sup> and Issam Makhoul<sup>4</sup>

<sup>1</sup>Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA. <sup>2</sup>Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, Little Rock, AR, USA. <sup>3</sup>Division of Breast Surgical Oncology, Department of Surgery, University of Arkansas for Medical Sciences, Little Rock, AR, USA. <sup>4</sup>Division of Medical Oncology, Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

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**ABSTRACT:** Most of the patients undergoing treatment for cancer require placement of a totally implantable venous access device to facilitate safe delivery of chemotherapy. However, implantable ports also increase the risk of deep vein thrombosis and related complications in this high-risk population. The objective of this study was to assess the incidence of upper-extremity deep vein thrombosis (UEDVT) in patients with breast cancer to determine whether the risk of UEDVT was higher with chest versus arm ports, as well as to determine the importance of previously reported risk factors predisposing to UEDVT in the setting of active cancer. We retrospectively reviewed the medical records of 297 women with breast cancer who had ports placed in our institution between the dates of December 1, 2010, and December 31, 2016. The primary outcome was the development of radiologically confirmed UEDVT ipsilateral to the implanted port. Overall, 17 of 297 study subjects (5.7%) were found to have UEDVT. There was 1 documented case of associated pulmonary embolism. Fourteen (9.5%) of 147 subjects with arm ports experienced UEDVT compared with only 3 (2.0%) of 150 subjects with chest ports ( $P = .0056$ ). Thus, implantation of arm ports as opposed to chest ports may be associated with a higher rate of UEDVT in patients with breast cancer.

**KEYWORDS:** Upper extremity deep venous thrombosis, breast cancer, chemotherapy, central venous port catheter

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**CORRESPONDING AUTHOR:** Issam Makhoul, Division of Medical Oncology, Department of Internal Medicine, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA. Email: makhoulissam@uams.edu

## Introduction

It is estimated that more than 230 000 women living in the United States were diagnosed with breast cancer in 2015,<sup>1</sup> and 1 in 8 women in the United States will be diagnosed with breast cancer during her lifetime. Despite the increased incidence, outcomes for breast cancer survivors are improving at unprecedented rates with improved screening, targeted chemotherapy regimens, and stringent surveillance guidelines. We are better equipped to fight malignancy, but a diagnosis of cancer remains associated with a myriad of complications. Most standard chemotherapy regimens include drugs that are vesicants, and although they are effective in killing cancer cells, they are also toxic to local tissues if extravasation occurs. Consequently, the route by which these drugs are delivered is critical. These medications must be effectively delivered into the systemic circulation without causing damage to the surrounding tissues, a requirement that is satisfied by totally implanted venous access ports. Despite multiple attempts to deliver chemotherapy through peripheral intravenous catheters, up to 44% of patients with breast cancer over the age of 66 years receive a port to administer their chemotherapy, and patients who are younger or those who need an

extended course of treatment are even more likely to undergo port placement.<sup>2</sup> Historically, chemotherapy ports have been implanted into the chest wall via the subclavian or internal jugular (IJ) veins, but upper-extremity access has become a popular choice in recent years. Various arguments in support of upper-extremity port placement include that arm ports are more cosmetically appealing, allow easier access, and may be medically indicated in certain patient populations.<sup>3–6</sup> In our institution, many patients elect to undergo breast reconstruction after completion of their treatment, and arm ports have been embraced for removing the port from the reconstruction field, thus minimizing the risk for surgical complications. However, despite the popularity of arm port placement, there has been research that suggests that the risk of catheter-related upper-extremity deep vein thrombosis (UEDVT) may be increased in patients with arm ports as opposed to chest ports. Our goal was to determine whether there is a difference in incidence of catheter-related UEDVT in arm ports versus chest ports, as well as to investigate the contribution of previously identified risk factors for clot formation.



## Methods

### *Study design and patient selection*

The study protocol was evaluated by the institutional review board and determined to be low-risk research and therefore not requiring patient consent. We retrospectively reviewed our electronic medical record system to identify patients with a diagnosis of breast cancer who underwent port placement at this institution during the 6-year period from December 1, 2010, to November 30, 2016. We identified a total of 297 women  $\geq 18$  years of age with a histologically confirmed diagnosis of breast cancer who underwent port placement during this time period. The data set was further analyzed to identify patients who reported symptoms commonly associated with UEDVT including upper limb edema, pain, and erythema. Patient charts were used to follow patients for UEDVT from time of port placement to time of port removal, patient death, or January 1, 2017.

Upper-extremity deep vein thrombosis was defined as a UEDVT ipsilateral to the patient's port that was confirmed by Doppler ultrasound or other comparable radiologic studies. Due to both the retrospective nature of our study and the fact that venous Doppler is not a routine test, only patients with clinically symptomatic DVTs were included in this study. Our study was not designed to evaluate the incidence of asymptomatic catheter-related UEDVT. For all 297 patients, information was collected regarding patient age, sex, race, and medical history including oncologic history. Patient charts were also assessed for known risk factors for clot formation including personal history of deep vein thrombosis (DVT), personal or family history of clotting disorder, tobacco use, alcohol use, obesity, recent surgery, immobility, and chronic illness (ie, heart failure, chronic kidney disease). Advanced analysis was not done for several known risk factors for clot formation including personal history of DVT, family history of clotting disorder, chronic disease, and recent surgery for the following reasons: only 2 patients had a personal history of DVT and neither of these patients developed a UEDVT associated with their port. No patients reported a family history of clotting disorder. At the time of port placement, none of the patients in this study had significant comorbidities such as chronic kidney disease or heart failure. All patients underwent surgery either during the time of port placement or 3 months prior, so this particular risk factor was present for all patients in this study.

### *Statistical analysis*

In addition to port placement and UEDVT occurrence, factors collected for analysis consisted of patient demographics (age, race, body mass index [BMI], and self-reported use of alcohol and tobacco), tumor characteristics (breast cancer sidedness, histopathology, American Joint Committee on Cancer [AJCC] stage, and hormone receptor status), and treatment factors (chemo setting, radiotherapy, operator, port placement

sidedness, vein, and catheter size). These factors were assessed for imbalance between patients with ports placed in the arm versus the chest using the Kruskal-Wallis test for continuous factors and Fisher exact test for both binary and multinomial categorical factors, except for operator and vein, which were imbalanced by design. To conduct analysis for risk of UEDVT, all factors not already binary were dichotomized, so that every factor examined would consist of 2 groups. Age was dichotomized as 54 and younger versus 55 and older. The BMI was dichotomized as under 30 (nonobese) versus 30 or more (obese). Histopathology was dichotomized as invasive ductal carcinoma versus all other histopathologies. The AJCC stage was dichotomized 2 different ways, first as stage IV (metastatic) versus stages I to III (nonmetastatic) and then as stage I (very early) versus stages II to IV (more advanced). Chemo setting was dichotomized as adjuvant chemotherapy versus all other settings. Breast cancer sidedness and vein could not be dichotomized sensibly and were excluded from risk analysis. Risk analysis then proceeded as follows. In the 2 groups of each factor, the UEDVT rate was computed as the number of subjects who experienced DVT divided by the number of subjects at risk for DVT. Then, the factor's relative risk between groups was estimated as the ratio of its UEDVT rates, whereas the standard error of this ratio was used to estimate a Wald 95% confidence interval (95% CI). Finally, Fisher exact test was used to assess significance of the estimated risk ratios. Because of the small number of DVTs, multivariate analysis was not conducted to avoid overfitting and consequent spurious results. All tests were 2-sided. All *P* values are reported numerically and interpreted for significance using the sliding-scale approach of Mendenhall et al<sup>7</sup> as follows:  $P < .01$  is "highly significant,"  $.01 < P < .05$  is "statistically significant,"  $.05 < P < .10$  is "trending towards significant," and  $P > .10$  is "not significant."

## Results

Of the 988 patients with breast cancer seen in our institution during the 6-year study period, the number of patients who had a port placed for administration of chemotherapy was 297 (30%), which represents the total study population and is not significantly different from other institutions.<sup>2</sup> We looked at a total of 147 patients with arm ports and 150 patients with chest ports. Among those who had chest ports, 82 (54.7%) were left sided and 68 (45.3%) were right sided. Among those with arm ports, 75 (51.0%) were left sided and 72 (49.0%) were right sided.

The demographic characteristics of all patients included in this study are presented in Table 1. Mean age was 55 years (range: 26-77 years). Of 297 patients, 212 were European American (EA) and 85 were African American (AA). The incidence of breast cancer in EA women in Arkansas is estimated to be 107.7 per 100 000 women, whereas the incidence in AA women is estimated to be 106.1.<sup>1</sup> Although our data set includes a greater number of EA women, we believe that this difference is likely due to differences related to access to health

**Table 1.** Patient and tumor characteristics by port placement.

PATIENT/TUMOR CHARACTERISTIC	ALL SUBJECTS (N=297)	ARM (N= 147)	CHEST (N= 150)	P VALUE <sup>a</sup>
Age, y				.85 <sup>b</sup>
Median	55	54	56	
Interquartile range	45-62	46-62	45-63	
Range	26-77	26-75	27-77	
Race, No. (%) <sup>c</sup>				.31
African American	85 (28.6)	38 (25.9)	47 (31.3)	
European American	212 (71.4)	109 (74.1)	103 (68.7)	
BMI, kg/m <sup>2</sup>				.42 <sup>b</sup>
Median	29.4	29.2	29.7	
Interquartile range	25.1-34.2	24.1-34.9	26.3-33.9	
Range	17.4-51.9	17.4-51.9	19.1-47.8	
Alcohol use, No. (%) <sup>c</sup>				.071
No	213 (71.7)	98 (66.7)	115 (76.7)	
Yes	84 (28.3)	49 (33.3)	35 (23.3)	
Tobacco use, No. (%) <sup>c</sup>				.76
No	243 (81.8)	119 (81.0)	124 (82.7)	
Yes	54 (18.2)	28 (19.0)	26 (17.3)	
Cancer sidedness, No. (%) <sup>c</sup>				.62
Left side	140 (47.1)	73 (49.7)	67 (44.7)	
Right side	148 (49.8)	70 (47.6)	78 (52.0)	
Bilateral	4 (1.3)	1 (0.7)	3 (2.0)	
No primary	5 (1.7)	3 (2.0)	2 (1.3)	
Cancer pathology, No. (%) <sup>c</sup>				.59
Invasive ductal	270 (90.9)	134 (91.2)	136 (90.7)	
Invasive lobular	22 (7.4)	9 (6.1)	13 (8.7)	
Metaplastic	3 (1.0)	2 (1.4)	1 (0.7)	
Neuroendocrine	1 (0.3)	1 (0.7)	0 (0.0)	
Squamous cell	1 (0.3)	1 (0.7)	0 (0.0)	
AJCC stage, No. (%) <sup>c</sup>				.88
I	48 (16.2)	23 (15.6)	25 (16.7)	
II	140 (47.1)	68 (46.3)	72 (48.0)	
III	57 (19.2)	31 (21.1)	26 (17.3)	
IV	52 (17.5)	25 (17.0)	27 (18.0)	
ER status, No. (%) <sup>c</sup>				.80
Negative	96 (32.3)	49 (33.3)	47 (31.3)	
Positive	201 (67.7)	98 (66.7)	103 (68.7)	
PR status, No. (%) <sup>c</sup>				.64

(Continued)

Table 1. (Continued)

PATIENT/TUMOR CHARACTERISTIC	ALL SUBJECTS (N=297)	ARM (N=147)	CHEST (N=150)	P VALUE <sup>a</sup>
Negative	129 (43.4)	66 (44.9)	63 (42.0)	
Positive	168 (56.6)	81 (55.1)	87 (58.0)	
HER2/Neu status, No. (%) <sup>c</sup>				.70
Negative	210 (70.7)	102 (69.4)	108 (72.0)	
Positive	87 (29.3)	45 (30.6)	42 (28.0)	
Triple-negative disease, No. (%) <sup>c</sup>				.78
No	229 (77.1)	112 (76.2)	117 (78.0)	
Yes	68 (22.9)	35 (23.8)	33 (22.0)	

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.

<sup>a</sup>P values are from either Fisher exact tests.

<sup>b</sup>Wilcoxon rank sum tests.

<sup>c</sup>Number (percent of subjects in group).

care in our state. The median BMI was 29.4 (range: 17.4-51.9). In all, 54 patients were current cigarette smokers and 84 patients reported alcohol use. There was no statistically significant difference between the arm and chest port groups regarding age, race, BMI, or tobacco use. However, the percentage reporting alcohol use was 10 points higher with arm ports (33.3%) compared with chest ports (23.3%), and the difference trended toward significance ( $P = .071$ ; see Table 1).

Tumor characteristics for all 297 patients were compared for differences with port placement using Fisher exact test, and the results are found in Table 1. In all, 140 patients had a left-sided tumor, 148 patients had a right-sided tumor, 4 patients had bilateral breast masses, and 5 patients had no breast primary as they were diagnosed with recurrent metastatic disease. More than 90% of patients (270) were diagnosed with invasive ductal carcinoma. The other observed pathologic types consisted of invasive lobular carcinoma (22 or 7.4%), metaplastic carcinoma (3 or 1.0%), neuroendocrine carcinoma (1 or <1%), and squamous cell carcinoma (1 or <1%). In all, 48 patients were diagnosed with stage I disease, 140 with stage II disease, 57 with stage III disease, and 52 with stage IV disease. About 201 tumors were estrogen receptor (ER) positive and 96 were negative; 168 tumors were progesterone receptor (PR) positive and 129 were negative; 87 tumors were HER2/Neu positive and 210 were negative; and 68 patients had triple-negative disease. No significant differences were seen in tumor laterality, pathology, stage, ER status, PR status, or HER2/Neu status between patients with chest ports and those with arm ports (Table 1).

Treatment-related factors were analyzed using Fisher exact test and the results are presented in Table 2. Ports were placed for adjuvant chemotherapy in 89 patients, for neoadjuvant chemotherapy in 154 patients, and for palliative chemotherapy in 52 patients; 2 patients had ports placed but did not receive chemotherapy. Radiation therapy was given to 113 patients, whereas 184 patients did not have radiation. In all, 256 ports

were placed by breast surgery and 41 ports were placed by interventional radiology. At our institution, interventional radiology does not place arm ports, so all 147 arm ports were placed by breast surgery. About 157 ports were left sided and 140 were right sided. For chest port catheters, 6 were placed in the axillary vein, 48 were placed in the IJ vein, and 99 were placed in the subclavian vein. For arm port catheters, 99 were placed in the basilic vein, 36 were placed in the brachial vein, and 2 were placed in the cephalic vein. Seven operative reports did not specify the vein of catheter entry. The catheter size was only recorded for 176 of the 297 total ports placed. The mean catheter size for all patients with nonmissing data was 5.5F (range: 4-8F). No statistically significant differences were seen in chemotherapy setting, radiation therapy, or port laterality between patients with arm ports and chest ports. There was a highly significant difference in venous catheter size between the 2 groups ( $P < .0001$ ), with an average size of 5.0F (range: 5-8F) for arm ports and 6.2F (range: 4-8F) in chest ports (Table 2). Of the 297 catheters placed, 296 were removed by the follow-up cutoff date of January 1, 2017. The number of days the patient's catheter was in place had a median (range) of 556 (10-2182) overall, 473 (11-2182) for arm ports, and 661 (10-2186) for chest ports; means and totals are shown in Table 2. Similarly, the number of days of follow-up for UEDVT had a median (range) of 539 (3-2186) overall, 452 (3-2182) for arm ports, and 661 (7-2186) for chest ports; means and totals are also shown in Table 2.

Figure 1 shows Kaplan-Meier curves for the time in days from port placement to UEDVT development. Among the 150 subjects with chest ports, the 3 UEDVTs occurred at 7, 48, and 124 days after the port placement. Among the 147 subjects with arm ports, the first 10 UEDVTs occurred by the 48th day after the port was placed, whereas the 11th, 12th, 13th, and 14th UEDVTs occurred at 68, 90, 98, and 267 days after port placement, respectively. In neither group did a UEDVT occur

**Table 2.** Cancer treatment factors by port placement.

TREATMENT FACTOR	ALL SUBJECTS (N=297)	ARM (N=147)	CHEST (N=150)	P VALUE <sup>A</sup>
Chemo setting, No. (%) <sup>b</sup>				.13
Adjuvant	89 (30.0)	36 (24.5)	53 (35.3)	
Neoadjuvant	154 (51.9)	85 (57.8)	69 (46.0)	
Palliative	52 (17.5)	25 (17.0)	27 (18.0)	
None	2 (0.7)	1 (0.7)	1 (0.7)	
Radiotherapy, No. (%) <sup>b</sup>				1.00
No	184 (62.0)	91 (61.9)	93 (62.0)	
Yes	113 (38.0)	56 (38.1)	57 (38.0)	
Operator, No. (%) <sup>b</sup>				— <sup>c</sup>
IR	41 (13.8)	0 (0.0)	41 (27.3)	
Surgery	256 (86.2)	147 (100.0)	109 (72.7)	
Port side, No. (%) <sup>b</sup>				.56
Left	157 (52.9)	75 (51.0)	82 (54.7)	
Right	140 (47.1)	72 (49.0)	68 (45.3)	
Vein, No. (%) <sup>d</sup>				— <sup>c</sup>
Basilic	99 (34.1)	99 (70.7)	0 (0.0)	
Brachial	36 (12.4)	36 (25.7)	0 (0.0)	
Cephalic	2 (0.7)	2 (1.4)	0 (0.0)	
Axillary	6 (2.1)	3 (2.1)	3 (2.0)	
IJ	48 (16.6)	0 (0.0)	48 (32.0)	
Subclavian	99 (34.1)	0 (0.0)	99 (66.0)	
(Not recorded)	(7)	(7)	(0)	
Catheter size, F				<.0001 <sup>e</sup>
No. (%) nonmissing	176 (59.3)	110 (74.8)	66 (44.0)	
Mean (SD)	5.5 (1.1)	5.0 (0.3)	6.2 (1.1)	
Range	4.0-8.0	5.0-8.0	4.0-8.0	
Days catheterized <sup>f</sup>				— <sup>c</sup>
Mean; Median	669.4; 556	512.3; 473	823.4; 661	
Range	10-2182	11-2182	10-2186	
Total (ie, catheter-days)	198 817	75 302	123 515	
Days of follow-up for UEDVT <sup>f</sup>				— <sup>c</sup>
Mean; median	655.8; 539	487.5; 452	820.8; 661	
Range	3-2186	3-2182	7-2186	
Total (ie, person-days)	194 785	71 659	123 126	

Abbreviations: IJ, internal jugular; UEDVT, upper-extremity deep vein thrombosis, IR, interventional radiology.

<sup>a</sup>P values are from Fisher exact tests.

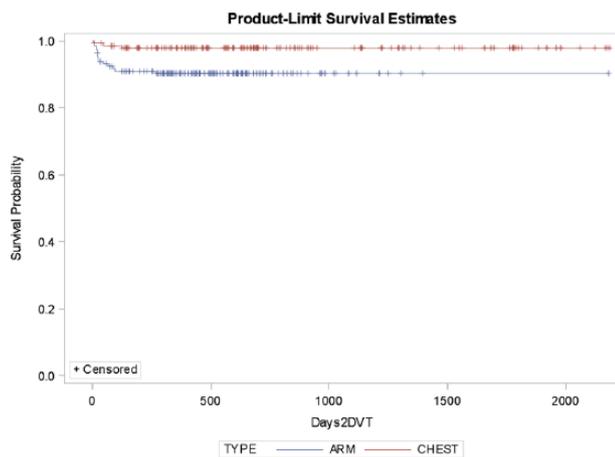
<sup>b</sup>Number (percent of number in group).

<sup>c</sup>Unless not tested.

<sup>d</sup>Number (percent of number nonmissing in group).

<sup>e</sup>Wilcoxon rank sum tests.

<sup>f</sup>Days were calculated using January 1, 2017, as the date when follow-up ended for UEDVT development and catheter removal. One catheter out of 297 remained in place on this date.



**Figure 1.** Kaplan-Meier curves of time in days from port placement to UEDVT development. All DVTs occurred within 9 months of port placement in both groups; see text for specific days of occurrence. DVT indicates deep vein thrombosis; UEDVT, upper-extremity deep vein thrombosis.

more than 365 days after port placement. All UEDVTs were therefore included in subsequent analysis.

Table 3 shows that the symptomatic UEDVT rate was almost 5 times higher in patients with arm ports compared with patients with chest ports (relative risk = 4.76 with 95% CI of 1.40-16.23), and that the difference was highly significant ( $P = .0056$ ). Table 3 also indicates that ports placed on the patient's left side were associated with a 63% decrease in UEDVT rate (relative risk = 0.37 with 95% CI of 0.13-1.03), but this difference only trended toward significance ( $P = .071$ ). Finally, Table 3 suggests that there was no statistically significant risk of UEDVT associated with age, obesity, race, alcohol use, tobacco use, histopathology, metastatic disease, ER/PR/HER2 positivity, triple-negative disease, chemotherapy setting, radiation therapy, or operator.

## Discussion

Malignancy alone is a well-established risk factor for hypercoagulability and deep venous thrombosis. In addition, many patients with cancer are relatively immobile due to advanced disease or debilitating side effects of treatment, further increasing their risk for clot formation. Other factors shown to increase the risk for DVT specifically in patients with cancer include thrombocytosis, anemia, leukocytosis, male sex, factor V Leiden mutation, mechanical factors (eg, port insertion technique, and port revisions), certain types of cancer, metastatic disease, and certain chemotherapy drugs.<sup>8-12</sup> In this study of 297 patients with breast cancer who underwent port placement over a period of 6 years, there was a highly significant difference in catheter-related UEDVT in patients who received arm ports as opposed to those who received chest ports, with the incidence of catheter-related thrombosis being higher with arm ports. Given that most patients who developed UEDVT had an excellent baseline performance status, we expect that

the risk for clot formation and increased morbidity may be even higher in patients who are less healthy. These results could offer guidance regarding the safest option for port placement in each individual patient depending on specific patient attributes, comorbidities, and risk factors.

Of the patients who developed UEDVT during this time period, almost 5 times as many had arm ports despite the total number of patients with arm ports being almost equal to those with chest ports. This increased incidence could be due to the smaller diameter of upper-extremity veins, as it is hypothesized that when the catheter takes up more than 50% of the vessel lumen, there is an increased risk for thrombosis.<sup>3</sup> We were unable to collect information about the catheter-to-vein ratio in this study, but the average vascular catheter size for arm ports was 5 F versus 6.2 F for chest ports, a statistically significant difference. However, the veins in the chest are generally larger and therefore the catheter-to-vein ratio may in fact be smaller than with arm ports. The increased risk may also be related to the presence of a longer vascular catheter,<sup>13</sup> stress applied with everyday use when the port pocket is in the forearm and the vascular catheter crosses the elbow joint, or other factors that have yet to be determined. Current literature (Table 4) suggests that the incidence of UEDVT in arm ports is roughly equivalent to that of chest ports for the most part, with an incidence of 12% to 64% in most retrospective studies and 37% to 66% in a small number of prospective studies.<sup>19</sup> However, most of the current research is looking at incidence of thrombosis as related to implantation technique or operator (ie, surgical versus imaging guided, interventional radiology versus surgery) and is overall more focused on total complications related to port insertion. We know of only 2 large-scale studies<sup>18,20</sup> that specifically looked at data sets that included both arm and chest ports to draw a comparison between the two. We did not find any studies looking at catheter-related UEDVT in patients with breast cancer alone, but the studies below do involve oncology patients, some of which have breast cancer. Furthermore, although the data from the individual studies looking at one port location are quite variable, it is worth noting that the overall incidence of UEDVT in arm ports is higher in both studies comparing the 2 directly, a finding corroborated by the data that we have collected.

Interestingly, this study showed a 63% decrease in rate of thrombosis between ports placed on the right versus the left that trended toward significance ( $P = .071$ ). This is equivalent to a 2.7-fold increased incidence in right-sided ports independent of venous insertion point, a finding consistent with those observed in some studies in the current literature.<sup>8,21</sup> However, other studies, while still coming to the conclusion that the risk for thrombosis is higher in arm ports than chest ports, found either a left-sided predominance or no difference between sides regarding port thrombosis.<sup>18</sup> The patients' handedness was not specifically analyzed in our study but we hypothesize that this increased risk of thrombosis may be

**Table 3.** Relative risks of UEDVT.

BINARY RISK FACTOR	NO. AT RISK	NO. (%) <sup>a</sup> WITH UEDVT	RELATIVE RISK <sup>b</sup> (95% CI)	FISHER EXACT P VALUE
Port location				
Arm	147	14 (9.5)	4.76	.0056
Chest	150	3 (2.0)	(1.40-16.23)	
Port side				
Left	157	5 (3.2)	0.37	.077
Right	140	12 (8.6)	(0.13-1.03)	
Age group				
55 years or older	152	10 (6.6)	1.36	.62
54 years or younger	145	7 (4.8)	(0.53-3.48)	
BMI group				
30 or more (obese)	140	9 (6.4)	1.26	.63
Under 30 (nonobese)	157	8 (5.1)	(0.50-3.18)	
Race				
African American	85	5 (5.9)	1.04	1.00
European American	212	12 (5.7)	(0.38-2.86)	
Alcohol use				
Yes	84	2 (2.4)	0.34	.17
No	213	15 (7.0)	(0.08-1.45)	
Tobacco use				
Yes	54	4 (7.4)	1.39	.52
No	243	13 (5.3)	(0.47-4.08)	
Histopathology				
Invasive ductal carcinoma	270	16 (5.9)	1.60	1.00
All other histopathologies	27	1 (3.7)	(0.22-11.60)	
Metastatic disease				
Yes, AJCC stage IV	52	4 (7.7)	1.45	.51
No, AJCC stages I-III	245	13 (5.3)	(0.49-4.27)	
Very early disease				
Yes, AJCC stage I	48	1 (2.1)	0.32	.33
No, AJCC stages II-IV	249	16 (6.4)	(0.04-2.39)	
Estrogen receptor status				
Negative	96	5 (5.2)	0.87	1.00
Positive	201	12 (6.0)	(0.32-2.41)	
Progesterone receptor status				
Negative	129	9 (7.0)	1.47	.47
Positive	168	8 (4.8)	(0.58-3.69)	
HER2/Neu status				

(Continued)

**Table 3.** (Continued)

BINARY RISK FACTOR	NO. AT RISK	NO. (%) <sup>a</sup> WITH UEDVT	RELATIVE RISK <sup>b</sup> (95% CI)	FISHER EXACT P VALUE
Negative	210	11 (5.2)	0.76	.59
Positive	87	6 (6.9)	(0.29-1.99)	
Triple-negative disease				
Yes	68	4 (5.9)	1.04	1.00
No	229	13 (5.7)	(0.35-3.07)	
Setting				
Adjuvant chemotherapy	89	2 (2.2)	0.31	.11
Neoadjuvant + palliative + none	208	15 (7.2)	(0.07-1.33)	
Radiotherapy				
No	184	11 (6.0)	1.13	1.00
Yes	113	6 (5.3)	(0.43-2.96)	
Operator				
Interventional radiology	41	2 (4.9)	0.83	1.00
Surgery	256	15 (5.9)	(0.20-3.51)	

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; CI, confidence interval; UEDVT, upper-extremity deep vein thrombosis.

<sup>a</sup>Percent of number at risk.

<sup>b</sup>Ratio of the percent with UEDVT.

**Table 4.** Estimated incidence of catheter-related thrombosis in the current literature.

AUTHOR	PORTS ANALYZED	PORT LOCATION	RESULTS	
			% OF PATIENTS AFFECTED	INCIDENCE OF THROMBOSIS (PER 1000 CATHETER-DAYS)
Klößges et al <sup>4</sup>	293	Upper extremity	3.76	0.12
Mori et al <sup>14</sup>	433	Upper extremity	—	0.04
Piran et al <sup>8</sup>	400	Upper extremity	8.50	—
Busch et al <sup>15</sup>	512	Upper extremity	1.56	0.06
Lyon et al <sup>3</sup>	195	Upper extremity	—	0.03
Teichgräber et al <sup>16</sup>	3160	Chest	—	0.11
Beckers et al <sup>12</sup>	43	Chest	9.30	0.68
Goltz et al <sup>17</sup>	52	Chest	1.92	0.02
	152	Upper extremity	9.86	0.09
Kuriakose et al <sup>18</sup>	273	Chest	4.76	—
	149	Upper extremity	11.41	—
Our data	150	Chest	2.00	—
	147	Upper extremity	9.52	—

related to the increased use of the dominant hand in everyday activities, which may result in increased shear stress within the vessel wall, therefore creating a favorable environment for clot formation.

It was also noted that of the 17 patients found to have UEDVT, the average BMI was 31.5 and 76% of these 17 patients were either overweight or obese. The average BMI of patients who did not develop UEDVT was 30.1. According to

the Centers for Disease Control and Prevention (CDC), 70.6% of adults in Arkansas are classified as overweight or obese<sup>22</sup> so this finding may simply be due to the normal distribution of our patient population. However, obesity remains a known risk factor for venous thromboembolism (VTE) and should be considered in choosing the location of port placement in each individual patient.

Catheter-related thrombosis remains a well-documented but poorly understood phenomenon. Furthermore, although the symptoms of UEDVT are often less pronounced than those of lower extremity DVT, outcomes in patients with cancer with UEDVT or LEDVT are consistently worse than that of the general population.<sup>23</sup> In patients with port-associated UEDVT, it is estimated that up to 70% may be asymptomatic.<sup>11</sup> Although the relevance of asymptomatic DVT is not well-understood, studies suggest that the risk of evolution into symptomatic disease is not trivial<sup>24</sup> and the presence of a central venous catheter creates a favorable environment for thrombus formation. The rate of asymptomatic UEDVT is estimated to be between 12% and 66% in patients with cancer, and in 30% to 70% of these patients, this will become clinically significant disease.<sup>11</sup> One lead researcher who had initially found no difference between the risk of thrombosis in chest and arm ports subsequently stated that taking into account the possible progression of asymptomatic UEDVT, the likely incidence of clinically relevant thrombosis in patients with arm ports may be as high as 10.5%,<sup>17</sup> a statistically significant increase. This finding was corroborated by a subsequent retrospective review.<sup>20</sup> Furthermore, it has been hypothesized that even an asymptomatic thrombus may serve as a nidus of infection for bacteria introduced at the catheter site, increasing the risk of bacteremia in an immunocompromised population.<sup>11</sup>

We recognize that our study does have some limitations. With this retrospective review, we were limited to records within our own electronic medical record. As the only University Hospital in the state of Arkansas, we see many patients from all areas of the state, as well as neighboring states. Many patients seek care for acute issues at local institutions and follow-up with us after the acute issue has resolved, so some patients who developed UEDVT may have sought care at a local hospital. Therefore, incidence may be underestimated if UEDVT was reported to an outside facility and patients failed to mention this at their clinic appointment and have confirmatory records uploaded into our system. We also realize that it is impossible to identify all of a patient's underlying risk factors for hypercoagulability. Furthermore, many patients were likely not asked specifically about certain risk factors used in our data collection (eg, family history of clotting disorder, personal history of VTE), and therefore, the existing risk factors for some of these patients may be underestimated. Also, with the exception of port revision, mechanical factors were not taken into account in this analysis, effectively ignoring the contribution of this known risk factor for thrombosis. We were

also limited to articles that were written in English and some studies that would have undoubtedly contributed to our data discussion were not included for this reason. In addition, there were some studies that were not sufficiently powered and these were not included here, although they may have been beneficial to the overall picture. Although not a limitation of our study itself, it is worth noting that much of the research and review articles devoted to this subject are from the 1990s and may not be relevant in their entirety today.

In conclusion, arm ports seem to be associated with a higher incidence of catheter-associated UEDVT than chest ports in patients with breast cancer receiving chemotherapy. These results have the potential to offer guidance in effectively lowering the inherent risk associated with central venous ports while providing necessary treatment for patients with cancer. Further investigation needs to be done regarding the relationship between laterality of port placement and risk for thrombosis, as well as the association of increased BMI and catheter-related thrombosis. Some research has suggested that the cephalic vein presents the highest risk for catheter-associated UEDVT, followed by the basilic and brachial veins, so this could be another consideration in determining the safest location for port placement.<sup>25</sup> Because all DVTs in our study occurred within 9 months of placement, and because most modern adjuvant/neoadjuvant chemotherapy regimens take 3 to 6 months to complete, we would suggest the removal of the port after the completion of chemotherapy to reduce the risk of DVT. It has been suggested that low-dose warfarin is effective for UEDVT prevention<sup>26,27</sup> and that coagulation studies are not affected, and therefore, bleeding risk is negligible. A recent meta-analysis concluded that while the risk of catheter-associated UEDVT was significantly less with LMWH or warfarin use, other benefits and harms were not well defined enough to recommend prophylactic anticoagulation routinely.<sup>28</sup> Ideally, we would be able to identify patients at increased risk for UEDVT and determine whether they may be better served by a traditional chest port versus the arm port, especially in the right side of the body, or whether there is a role for prophylactic anticoagulation on an individual basis to provide safer care for patients with breast cancer.

### Author Contributions

Research idea & design: IM, DT. Data collection: DT, AA, IM. Manuscript writing: DT, IM, AP, DO. Statistical analysis: ES, IM. Patient enrollment: DO, EH, AM, MR, RHT.

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