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ORIGINAL RESEARCH REPORT

Yield of computed tomography pulmonary angiogram in the emergency department in cancer patients suspected to have pulmonary embolism

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Abstract
Objective/background: The use of computed tomography pulmonary angiography (CTPA) in the emergency department (ED) for patients suspected to have pulmonary embolism (PE) has been steadily rising in the last 2 decades. However, there are limited studies that specifically address the use of CTPA in the ED for cancer patients suspected to have PE. The objective of this study is to assess the rate of positive PE by CTPA in the ED in cancer patients and the variables that are associated with positive results.
Methods: A retrospective review of electronic medical records for 208 consecutive patients with cancer who presented to the ED and received a CTPA for suspected PE over a 12-month period. The review included demographics, type and status of cancer, presenting symptoms, CTPA results, calculation of Wells Score, management based on CT findings, and outcome of patients.
Results: Among the 208 patients who met the inclusion criteria during our study period (mean age 57 ± 13.37 years, 73% women, 59% African American, and 32% Caucasians), 5.7% were diagnosed with PE. One hundred and eighty-two (83.7%) had a Wells Score $\leqslant$4, of which 2.2% were found to have to have PE, 22 (16.3%) patients had a Wells Score >4, of which 36.4% were found to have PE ($p < .0001$). Sensitivity and specificity of Wells >4 was 66.7% and 92.9%, respectively, with an odds ratio of 27 (95% CI 6.6–113.6). Receiver operator characteristics area under the

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curve for Wells Score was 0.868. Age, race, sex, malignancy type, stage, status, clinical presentation, D-dimer, and a previous history of venous thromboembolism were not found to have statistically significant predictive values.
Conclusion: The yield of CTPA to rule out PE in patients with cancer presenting in the ED is low. Following a validated decision-making protocol such as Wells Criteria may significantly decrease the number of CTPA used in the ED.

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Introduction

Cancer is a known risk factor for developing venous thromboembolism [1]. Population studies have shown that the incidence of venous thromboembolic disease in cancer patients ranges from 0.6% to 4.0% and is associated with an increased risk of mortality [2—7]. One of the fatal complications of venous thromboembolism is the development of pulmonary embolism (PE). Khorana et al. [3] reported that the mortality rates were 24.8% in cancer patients who developed PE compared with 6.5% of patients that did not have PE ($p < .0001$).

Early detection of PE and treatment with anticoagulation has been shown to improve survival [8]. Clinical decision rules, such as Wells Criteria, have been developed (and validated) to aid in ruling out patients that do not have PE [9]. However, the use of clinical decision rules to exclude those without PE is sporadically used [10]. There is ample evidence that the use of computed tomography pulmonary angiography (CTPA) in the emergency department (ED) for patients suspected to have PE has been steadily rising in the last 2 decades, which exposes patients to increased risks with no significant detection of PE or change in outcomes [11,12]. However, there are limited studies that specifically address the use of CTPA in the ED for cancer patients suspected to have PE. The aim of this study is to assess the rate of positive PE by CTPA in the ED in this patient population and the variables that are associated with positive results.

Methods

Study design and setting

This is a retrospective analysis of a cohort of 208 patients with a history of malignancy who presented to the ED of a tertiary academic hospital with a comprehensive cancer center and underwent CTPA to evaluate PE over 15 months. The study protocol was approved by the Institutional Review Board.

The inclusion criteria for the study were patients with a known history of malignancy and who had a CTPA to assess for PE in the ED. Patients excluded from the study were those who did not have a history of malignancy, those diagnosed with a malignancy post-CTPA, patients in whom the diagnosis of venous thromboembolism was only made with a ventilation—perfusion scan, and/or Doppler venous study. Patients that had insufficient data that would not allow calculation of a Wells Score were also excluded from the study.

Data collection and measurement

Patient demographics, presenting symptoms, documented physical exam, type of cancer including current stage (local, regional, distant, unstageable, unknown), disease status (remission, relapse, new diagnosis), and treatment were reviewed. Laboratory values, chest X-ray, and CTPA results were also recorded. Hospital course was also reviewed assessing for management of the patient, complications from CTPA, and disposition. D-dimer results when available were reviewed if they were obtained in the ED during initial workup.

Wells Score was retrospectively calculated for each patient from the collected data. While our population included only patients with a history of malignancy, patients whose disease was documented as in remission and who had been without chemotherapy for >6 months were not assigned 1 point for malignancy. Special consideration was given to clinician suspicion for PE being the primary diagnosis in Wells Score. Patients meeting the following criteria were assigned 3 points: (1) patients who were started on anticoagulation prior to the CTPA; (2) patients that were specifically sent to the ED for suspicion of PE; (3) documentation from the physician stating that PE was equally likely or most likely; (4) patients receiving ongoing anticoagulation at the time of admission were given 3 points; (5) patients with a history of deep vein thrombosis treated with Greenfield filter in lieu of anticoagulation were also designated to receive 3 points but we had no incidence of this in our study population. Patients that did not meet these criteria were not given any points for PE being the primary diagnosis in Wells Criteria.

The diagnosis of PE was confirmed by a pulmonary arterial filling defect on CTPA with pulmonary protocol. All CTPA with pulmonary protocol were reviewed by a board certified radiologist. The CTPA was also reviewed for an alternative diagnosis that may explain the patient's symptoms.

Complications from CTPA were assessed as contrast-induced nephropathy, extravasation of contrast material, and anaphylaxis from contrast material.

Data analysis

Continuous variables are presented with means and standard deviations. Categorical variables are summarized as percentages. To assess the differences between PE-positive and PE-negative patients in terms of Wells Criteria, Fischer's exact test was used with dichotomous value of

Wells Score ⩽4 and >4 as dichotomous variables for low/-moderate and high risk for PE, respectively. To retrospectively assess the discrimination of Wells Criteria in cancer patients, Wells Score performance was assessed by calculating the receiver operating characteristic curve. To determine if underlying malignancy or presenting complaints had a significant association with the likelihood of PE logistic regression was performed with positive or negative PE as the dichotomous outcome.

Results

During our study period 208 patients met the inclusion criteria and underwent CTPA with pulmonary protocol in the ED to assess for PE. Table 1 presents the baseline characteristics of these patients. The patients included in the study were 57 men (27.4%) and 151 women (72.6%) with a mean age of 56.86 ± 13.7 (years ± standard deviation). Sixty-seven (32.2%) self-identified as Caucasian, 123 (59.1%) African American, and 18 (8.7%) as others. The underlying malignancies were primarily lung 56 (26.9%), breast 52 (25%), hematologic 24 (11.5%), and gynecological 22 (10.6%). In 87 (41.8%) of the study population the disease was classified as in remission, 77 (37%) of these cases the disease had relapsed, and 44 (21.2%) were new or recent diagnoses. Stages of cancer in our study population were classified as 50 (24%) local, 48 (23.1%) regional, 86 (41.3%) distant, and 6 (2.9%) not stageable.

Twelve patients (5.7%) had acute PE based on the CTPA. These patients were four (33.3%) men and eight (66.7%) women. Their mean age was 55.5 years (standard deviation ± 15.95) and six (50%) were African American and six (50%) were Caucasian. The underlying malignancies in these patients, were lung four (33.3%), breast three (25%), endometrial two (16.7%), and one (8.3%) case of testicular, prostate, and malignant thymoma. In seven (58.3%) of these cases the disease had relapsed, three (25%) were classified as in remission, and two (16.7%) were initial diagnoses. Stages of cancer in patients with positive PE were classified as two (16.7%) local, five (41.7% regional), and five (41.7%) distant. Nine (75%) were undergoing current chemotherapy, while three (25%) were not on active treatment.

To study the predictors of having a positive PE when performing CTPA in the ED for patients with cancer, we assessed the following variables: age, race, sex, malignancy type, stage, status, Wells Score, clinical presentation, and previous history of venous thromboembolism.

Only Wells Criteria significantly predicted the presence of PE in these patients. Based on the Wells Criteria 182 (83.7%) were considered low risk (⩽4) and 22 (16.3%) were considered as high risk for PE (>4). Table 2 provides details of the Wells Criteria in low- and high-risk groups. Among low risk patients four (2.2%) were positive for PE compared with eight (36.4%) in the high-risk group ($p < .0001$). The sensitivity of this score (Wells >4) was 66.7% and specificity was 92.9%, with a positive predictive value of 64% and a negative predictive value (NPV) of 98%. The adjusted odds ratio (OR) of PE with a Wells Score of >4 was 27.472 (95% confidence interval (CI): 6.642—113.626, $p < .0005$). Receiver operating characteristic area under the curve was 0.868 (Fig. 1). We further analyzed the odds ratio (OR) for individual Wells Scores (Table 3-only tachycardia (OR: 10.56, $p < .05$), clinical assessment of PE as the most likely diagnosis (OR: 23.55, $p < .001$) were found to have statistical significance. D-dimer values were available for 60 patients-of these, 59 (98%) were positive based on our institutions lab reference cut-off point. This limits the test discriminatory value in the current study. Furthermore, to examine the potential utility of alternative scoring systems in the assessment of pretest probability of PE in our patient population we

Table 1 Patient baseline clinical characteristics.

Characteristic	*N* (%)
No. of patients	208
Demographics	
Age, y (mean ± SD)	56.86 ± 13.7
Sex, *n* (%)	
Male	57 (27.4)
Female	151 (72.6)
Race, *n* (%)	
Black	123 (59.1)
White	67 (32.2)
Other	18 (8.7)
Previous PE or DVT	29 (13.9)
Antiplatelet agent use	36 (17.3)
Anticoagulation use	22 (10.6)
Presenting symptoms, *n* (%)[a]	
Dyspnea	130 (62.5)
Lower extremity swelling	24 (11.5)
Hemoptysis	14 (6.7)
Abdominal pain	13 (6.3)
Leg pain	11 (5.3)
Syncope	6 (2.9)
Palpitations	5 (2.4)
Others	39 (18.7)
Underlying malignancy, *n* (%)	
Lung	56 (26.9)
Breast	52 (25.0)
Hematological	24 (11.5)
Gynecological	22 (10.6)
Genitourinary	16 (7.7)
Abdominal	15 (7.2)
Head and neck	5 (2.4)
Others	18 (8.7)
Disease activity	
Remission	87 (41.8)
Relapse	77 (37)
Ongoing initial treatment	44 (21.2)
Treatment status	
Current chemotherapy	119 (57.2)
No active therapy	89 (42.8)
Disease stage	
Local	50 (24.0)
Regional	48 (23.1)
Distant	86 (41.3)
Not stageable	6 (2.9)
Unknown stage	18 (8.7)

Note: DVT = deep vein thrombosis; PE = pulmonary embolism; SD = standard deviation.

[a] Patient may have more than one presenting symptoms.

Table 2 Frequency and percentages of Wells Criteria in low- and high-risk groups.

	Wells ⩽4 (n = 186) n (%)	Wells >4 (n = 22) n (%)
Clinical signs and symptoms of DVT (+3 points)	3 (1.6)	5 (22.7)
PE #1 diagnosis, or equally likely (+3 points)	4 (2.2)	15 (68.2)
HR >100 (+1.5 point)	93 (50)	19 (86.4)
Immobilization at least 3 d/surgery within 4 wk (+1.5 point)	7 (3.8)	2 (9.1)
Previous DVT/PE (+1.5 point)	20 (10.8)	9 (40.9)
Hemoptysis (+1.0 point)	9 (4.8)	2 (9.1)
Malignancy with treatment within 6 mo or palliative (+1.0 point)	159 (85.5)	22 (100)

Note: DVT = deep vein thrombosis; HR = heart rate; PE = pulmonary embolism.

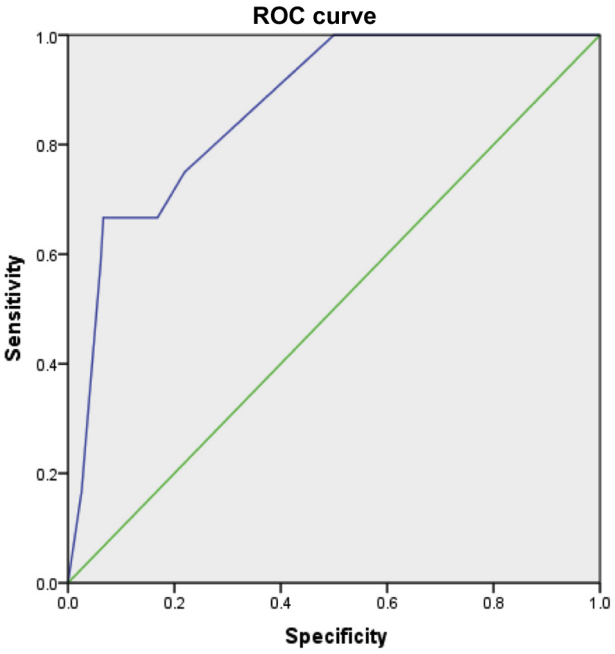

Fig. 1 Receiver operator characteristics (ROC) curve for Wells Criteria. Diagonal segments are produced by ties.

calculated Khorona scores for each patient with the exclusion of brain cancer and multiple myeloma patients for whom the scoring system was not developed (n = 203). This score is used to predict the risk of venous thromboembolism in patients on chemotherapy and includes site of cancer, platelet count, hemoglobin value, and/or use of erythropoiesis stimulating and body mass index [13]. Based on calculated Khorona scores at the time of ED assessment, 46 patients (22.7%) were classified as low risk, 132 patients (65%) as moderate risk, and 25 patients (12.3%) as high risk. Chi-square analysis of the scoring system revealed no statistically significant correlation between risk category and presence of PE in our population (p = .776).

The complications related to performing CTPA in ED were seen in four patients (3.4%) and were primarily related to reversible increase in creatinine. The increase in creatinine was seen in patients who did not have PE (3.4% vs. 0%, p = .51). None of these patients required renal replacement therapy and there were no other complications such as extravasation of iodine contrast, anaphylaxis, or death.

Five (2.4%) patients died during hospitalization. The mortality was two of 12 (16.7%) in those who had PE and three of 196 (1.5%) in those who did not have PE (p = 0.003).

Discussion

The goal of this study was to assess the rate of PE in cancer patients who underwent CTPA in the ED and to determine the variables associated with a positive study in this high-risk population. We found the PE is rare in this situation (5.7%) and that the high-risk Wells Score (>4) was the only predictor among the variables assessed in predicting PE in this patient population.

Table 3 Unadjusted odds ratio (OR) for individual Wells Criteria for positive pulmonary embolism (PE).

	OR	95% CI
PE diagnosis equal or most likely	23.5455**	(6.42, 86.30)
HR >100	10.5600*	(1.34, 83.37)
Immobilization at least 3 d	3.4727	(0.37, 32.34)
Previously diagnosed DVT/PE	1.2519	(0.26, 6.03)
Hemoptysis	2.1364	(0.24, 18.64)
Malignancy/treatment within 6 mo/palliative	1.5349	(0.19, 12.42)
Clinical signs and symptoms of DVT	0	(0, —)

Note: CI = confidence interval; d = days; DVT = deep vein thrombosis; HR = heart rate; mo = months.
* p < .05.
** p < .001.

Previous studies have shown similar findings in the general population of patients who underwent CTPA in the ED. In a study by Crichlow et al. [14] 152 patients underwent CTPA, and PE was diagnosed in 11.8%. One hundred and ten patients (72%) had a low-risk Wells Score (⩽4). Eight of these (7%) had PE as compared with 10 of 42 (24%) patients with a high-risk Wells Score (>4).

Another multicenter prospective study from 11 EDs around the USA showed that imaging to rule out PE was performed on 38% low-risk patients [15]. Imaging was avoidable according to National Quality Forum measures in 32% of patients. The authors concluded that adherence to established diagnostic protocols is likely to result in significantly fewer patients receiving unnecessary imaging with substantially lower risk and savings.

This is the first study to our knowledge that focuses on cancer patients in the ED and shows that CTPA is overused in this patient population and that following a validated decision-making protocol such as Wells Criteria may significantly decrease the number of CTPA used in the ED. Another important finding by this study is that Wells Criteria were the only predictor of PE in this patient population. Other factors such as the type of cancer, stage, disease status, and treatment were not significant in predicting PE.

The criticism for Wells Score is that it is not entirely objective and depends heavily on the clinical judgement. Several studies have included additional steps to further determine the likelihood of PE in ED including the addition of D-dimer and PE rule-out criteria. One study has shown that D-dimer in oncology patients suspected to have PE in an urgent care setting was positive in 85% of patients with confirmed PE. The NPV and sensitivity were 97% and 98%, respectively. The specificity and positive predictive value were 18% and 25%, respectively [16]. In another study, the NPV of D-dimer in both cancer and noncancer patients was 100%. PE was ruled out by a negative D-dimer test in 494/1554 (32%) patients without cancer, and in 18/164 (11%) patients with a malignancy [17]. The authors concluded that enzyme-linked immunosorbent assay D-dimer appears safe to rule out PE in cancer patients but it is negative in only one of 10 patients at the usual cut-off value. Therefore, the majority of cancer patients are likely to have positive D-dimer and may require further testing. Our study shows that using the Wells Criteria provides an additional effective tool in the decision to pursue further diagnostic studies such as CTPA. Further prospective studies on cancer patients are needed to elucidate the role of these approaches–including in combinations–in the decision process of ordering CTPA in the ED in this patient population.

There are other potential benefits in obtaining a CT scan in these patients including influencing further management, which was reported in 16% of our patients, and detecting other incidental findings as reported in other studies. The finding of an alternative diagnosis by CTPA has been shown to be common (43%) in one study. However therapeutic consequences were reported in only 4.9% of these patients. The authors emphasized that CTPA should remain principally to confirm or exclude PE in high probability cases and not to establish alternate diagnoses [18]. Another recent study showed similar results with the majority of findings showing limited clinical significance [19].

Other concerns associated with the overuse of CTPA in the ED include the cost of health services and use of resources including increased length of stay in the ED. There are also potential risks to patients such as allergic reaction, radiation exposure, and contrast-induced nephropathy. Although these complications were rare in our patient population (3.4%), other studies have shown that contrast-induced nephropathy may be as high as 14% [20]. Our study shows that even in cancer patients, following validated criteria to pursue the diagnosis of PE has a significant NPV and may result in avoiding a significant number of CTPA.

Knowledge of validated decision-making rules for pretest probability of PE by emergency physicians has been shown to be variable. In a survey of 555 emergency room clinicians, 68% indicated familiarity with rules, but only 50% reported using them in more than half of the applicable cases [10]. Also, a significant number of respondents could not correctly identify key components of the decision-making rules. Fifty-seven percent of all respondents indicated use of ''clinical gestalt" rather than a decision rule in more than half of the cases. Our study and others have repeatedly shown that decision-making rules such as Wells Criteria correlate with the probability of PE. Healthcare systems should encourage their use in the clinical decision-making process and incorporate such rules in the electronic medical record order sets to drive ordering further investigations such as CTPA. A recent study evaluated the implementation of an evidence-based computerized clinical decision support on the use of CTPA in patients suspected to have PE in the ED. The introduction of this system was associated with decreased CTPA use (55% vs. 49%; absolute difference: 6.3%; 95% CI: 1.0—11.6%; $p = .02$). There were also fewer symptomatic venous thromboembolic events during follow-up in patients with an initial negative diagnostic evaluation for PE [21]. However, such initiatives should be coupled with repeated educational programs since it has been shown that a single educational intervention had no effect on appropriate utilization rates for CTPA in ED [22].

The study provides an important insight on the evaluation of PE in the ED in high-risk cancer patients. However, it does have limitations. The retrospective nature of the analysis limits our study in several ways. Calculation of the Wells Score, specifically the allocation of points for the ED physician's assessment of the pretest probability of PE, may be the most likely diagnosis. Recognizing that inferring physician clinical assessment is difficult utilizing only retrospective data, we intentionally established strict criteria, as detailed above, in order to avoid overestimation of the Wells Score. While this poses the opposite risk of underestimation in specific clinical scenarios, we find this acceptable given the role Wells Criteria plays in potentially avoiding unnecessary CTPE. We therefore prefer to err on the side of lower scores to avoid increasing the apparent sensitivity of the scoring system. Also, our study is limited only to patients presenting to the ED for evaluation. Our analysis of the OR for individual components of the Wells Score revealed statistically significant results for tachycardia and clinical suspicion of PE only; these results suggest the potential benefit of further study with a larger population to assess if individual factors or a combination of factors included in the criteria would provide simpler or more

accurate predictive values but the low incidence of PE in our study limits our power to address these questions.

We recognize that there is a substantial portion of patients with history of malignancy who undergo evaluation for PE on an entirely outpatient basis, and our study does not purport to address this. The low incidence of PE in our study population also decreases the likelihood of finding alternative positive predictors of PE such as presenting symptoms, age, or cancer type, etc. While we found no statistically significant positive predictive values or NPVs for alternative variables, the low incidence of PE in our study population limits our power to detect the effects these variables may contribute. Although the sample size is large, it does reflect a single center experience. D-dimer was not available in a large number of patients in this study, and was 98% positive among the patients who received this test limiting its discriminatory value. The design of our study limits our ability to calculate cost-benefit analysis of CT-PE in the ED. Further prospective, multicenter trials are warranted to validate the current findings, address the above issues, and study the role of other protocols in diagnosis of PE in cancer patients evaluated in the ED.

Conclusion

Our study shows that PE is rare in cancer patients who undergo CTPA in the ED to rule out PE. Wells Criteria are very good in predicting patients who are unlikely to have PE in this patient population.

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Conflicts of interest

The authors have no conflict of interest related to this manuscript.

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