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### **Performance SPECT-CT and ANGIO-CT for diagnosis of pulmonary thromboembolism in a tertiary oncology centre**

### **Desempenho do SPECT-CT e da ANGIO-CT para o diagnóstico do tromboembolismo pulmonar em um centro terciário de oncologia**

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#### **RESUMO**

O tromboembolismo pulmonar (TEP) é caracterizado pela obstrução da circulação pulmonar por coágulos sanguíneos, sendo comumente observado em pacientes hospitalizados com câncer. É diagnosticado utilizando as técnicas ANGIO-TC de tórax e inalação/perfusão pulmonar (I/P) por SPECT-CT. Este estudo teve como objetivo analisar o desempenho dessas duas técnicas no diagnóstico de TEP e avaliar a concordância entre seus resultados, avaliar o perfil dos pacientes, e o impacto na conduta médica. Estudo unicêntrico de coorte descritivo, retrospectivo, quantitativo e qualitativo; realizado através da análise dos exames ANGIO-CT e I/P por SPECT-CT na população de doentes em uma instituição oncológica terciária, de janeiro de 2015 a maio de 2018. Foi analisado um total de 410 exames em 363 pacientes. Foram submetidos a ANGIO-CT 335 pacientes, 75 submetidos a SPECT-CT e 47 pacientes a ambos os testes. Os tipos de câncer que mostraram associação com o diagnóstico de TEP foram os cânceres de pulmão, pâncreas e cérebro. O câncer de pulmão mostrou a maior associação com a suspeita e o diagnóstico de TEP. Os resultados diagnósticos e o tratamento clínico foram compatíveis tanto para o SPECT-CT como para o ANGIO-CT. Ambos os métodos provaram ser confiáveis e altamente precisos para o diagnóstico de TEP na população estudada. O SPECT-CT demonstrou ótima acurácia para o diagnóstico de TEP negativo podendo ser preferível e mais indicado para afastar TEP em pacientes oncológicos dada a sua menor radiação, porém para o diagnóstico de TEP positivo a ANGIO-TC de tórax ainda é mais indicada.

Palavras-chave: Tromboembolismo pulmonar; Angiografia por Tomografia Computadorizada; Anticoagulantes; Neoplasias.

#### **ABSTRACT**

Pulmonary thromboembolism (TEP) is characterized by obstruction of the pulmonary circulation by blood clots, and is commonly seen in hospitalized patients with cancer. It is diagnosed using the ANGIO-TC chest and inhalation/pulmonary perfusion (I/P) techniques by SPECT-CT. The objective of this study is to analyze the performance of these two techniques in the diagnosis of TEP and to evaluate the agreement between their results, evaluate the profile of patients,

and the impact on medical management. A descriptive, retrospective, quantitative, qualitative and unicentric cohort study; carried out through the analysis of ANGIO-CT and I/P tests by SPECT-CT in the patient population in a tertiary oncologic institution, from January 2015 to May 2018. A total of 410 examinations in 363 patients were analysed. Three hundred and thirty five patients underwent ANGIO-CT, 75 SPECT-CT and 47 patients underwent both tests. The types of cancer that showed association with the diagnosis of TEP were lung, pancreas and brain cancers. Lung cancer showed the greatest association with the suspected and diagnosis of TEP. Diagnostic results and clinical treatment were compatible for both SPECT-CT and ANGIO-CT. Both methods proved to be reliable and highly accurate for the diagnosis of TEP in the population studied. The SPECT-CT has proven to be very accurate for the diagnosis of negative TEP and may be preferable and more indicated to rule out TEP in cancer patients due to its lower radiation, but for the diagnosis of positive TEP the chest ANGIO-CT is even more indicated.

Keywords: Pulmonary thromboembolism; Computed Tomography Angiography; Anticoagulants; Neoplasms.

## INTRODUCTION

Pulmonary thromboembolism (TEP) is the third most common acute cardiovascular disease after myocardial infarction and stroke, affecting about 1 in 1000 people a year TEP is a major cause of hospital morbidity and mortality. In Brazil, the estimated incidence is 0.6 cases per 1,000 inhabitants per year, while the worldwide incidence in 2003 was 0.5 cases per 1,000 inhabitants per year.<sup>1,2</sup>

Cancer is a risk factor for both TEP and venous thromboembolism, and there is a four-times higher risk of developing TEP in cancer patients than in the general population. If the patient is undergoing chemotherapy, this risk increases up to six times. The frequency of thrombosis is also largely related to the development of cancer and is considered the second most frequent cause of death in cancer patients.<sup>3-6</sup>

Despite its frequency, the wide array of possible symptoms often leads to confusion with other pathologies.<sup>7</sup>

Therefore, diagnosis of TEP is commonly determined by ANGIO-CT of the thorax or inhalation/perfusion (I/P) SPECT-CT.<sup>8</sup>

Pulmonary I/P by SPECT-CT is the most indicated technique for cancer patients because it uses less radiation than ANGIO-CT. Since cancer patients are often already exposed to radiation during radiotherapy, it is preferable to limit additional exposure. Furthermore, some research has suggested that SPECT-CT offers higher diagnostic accuracy for TEP than does ANGIO-CT. On the other hand, examination time is somewhat longer and many diagnostic centres lack the necessary equipment.<sup>3-5,8</sup>

Perhaps because of its lower cost and its history of excellent performance, ANGIO-CT is now currently considered the gold standard for TEP diagnosis. There has been little research to

correlate diagnostic methods for TEP in cancer patients. The present study aims to analyse the diagnostic performance and agreement between the techniques for the diagnosis of TEP in a cancer centre. The study will assess profiles, evaluate the diagnostic performance of each technique, and determine their impact on medical management.<sup>8-11</sup>

## MATERIAL AND METHODS

A retrospective, descriptive, longitudinal, quantitative, qualitative and unicentric study was performed using pulmonary I/P SPECT-CT and thoracic ANGIO-CT analysis TEP research at the Department of Imaging at A.C. Camargo Cancer Center during the period between January 2015 and May-2018. The information was collected from institutional electronic systems and exported to the Red Cap digital database.

His research project was submitted to and approved by the Research Ethics Committee of the Camargo Cancer Center of A.C. before the start of data collection, CEP number 2503/18, CAAE: 84308118.0.0000.54.32; and Free and Informed Consent (TCLE) was requested, since this is a retrospective work, based on the review of imaging examinations and medical records. The information collected was used solely and exclusively for the project in question and was only disclosed anonymously, preserving the privacy of the research subjects whose data were collected.

Patients' selection: Inclusion criteria- Adult patients aged 18 years or older, cancer patients, have undergone ANGIO-CT or I/P SPECT-CT thoracic examination for suspected TEP. Exclusion criteria- incomplete examinations, examinations performed in another service, non-oncologic patients, patients who underwent a given examination more than once during the period analysed. The following details were collected for each patient: identity, gender, age, date of

examination, hospital record, oncologic diagnosis, cancer staging, radiotherapy and/or chemotherapy treatments, history of comorbidities, inpatient or outpatient, examination performed, result of the examination Positive or Negative for TEP, clinical management plan, and whether both tests were performed within a period of 3 months. Eight hundred and ninety tests were considered; 805 ANGIO-CT and 85 I/P SPECT-CT. Four hundred and eighty tests were excluded due to subjects not being cancer patients or having undergone the same test more than once during the study period. In total, 410 tests and 363 patients were used in the study. Patients were divided into three groups: those who underwent ANGIO-CT examination of the chest for TEP investigation (Group 1) with total 335 patients, those who underwent pulmonary I/P by SPECT-CT for TEP investigation (Group 2) with 75 patients, and those who underwent both tests within a period of three months (Group 3) with 47 patients. Examination protocols: ANGIO-CT thoracic exam and Pulmonary I/P examination by SPECT-CT.

**ANGIO-CT thoracic exam:** Computerized chest angiotomography for suspected TEP equipment was performed using either the Toshiba Aquilion Prime (80 detector rows) or Philips Big Bore (16 detector rows), with administration of intravenous iodinated contrast. Non-contrast localized image acquisition was performed in the coronal plane, then iodinated contrast was injected (40 mL for patients up to 70 kg and 60 mL for patients over 70 kg); followed by 40 mL of saline solution. A non-contrast sequence and post-contrast arterial and venous sequences were performed in the axial planes to visualize perfusion in the pulmonary artery and its segmental and subsegmental branches. A patient was classified as positive for TEP if any defect was observed in the filling of pulmonary arteries and vessels in any segment. A patient was classified as negative for TEP if there was observed normal passage and filling of the pulmonary vessels and arteries by the contrast medium.

**Pulmonary I/P examination by SPECT-CT:** After anamnesis and orientation on the examination, the patient inhales a 99mTc-DTPA nebulized solution (900MBq) in a sitting position; after inhalation is complete, the acquisition of the first set of images begins on a Discovery NM/CT 640 GE Healthcare SPECT-CT gamma camera equipment, and these images will correspond to the distribution of the lung air. The second set of

images, corresponding to intrapulmonary blood perfusion, is obtained after intravenous injection of 99mTc-MAA (100MBq), which will demonstrate the actual perforated lung area. Both images are acquired in the same projections; in the sequence the SPECT images of the perfusion and later the tomography of the lung fields are performed. In the post processing the SPECT images are merged with the CT images. The TEP I/P match / mismatch criteria are applied for diagnosis.

Statistical analysis was performed using the statistical programme SPSS (Statistical Package for the Social Sciences, version 2.5; SPSS Inc., Chicago, IL, USA). The Chi-square and Fischer Exact Test statistics were used, and in some cases the Yates Continuity Correction was applied. The level of statistical significance adopted was 5% ( $p < 0.05$ ). Cohen's kappa was used to measure the concordance of diagnostic methods. For the diagnostic performance analysis of the techniques the ANGIO-TC chest was considered the gold standard in this study.

## RESULTS

TEP was suspected, but not diagnosed, more often in female patients over 60 years of age; this trend has been observed in other studies.<sup>1</sup> Across all patients there was no significant association between oncologic staging and TEP diagnosis (Group 1  $p = 0.36\%$ , Group 2  $p = 0.57\%$  - Positive TEP diagnosis in patients with Primary Ca and Metastasis). The comorbidities associated most strongly with TEP diagnosis were history of TEP, Deep vein thrombosis -TVP, the use of systemic anticoagulants, pulmonary diseases, and benign prostate hyperplasia BPH.<sup>4,6,12</sup> The most prevalent types of cancer in Group 1 were lung, breast, colorectal, and prostate. Lung, pancreas, and brain cancers were significantly associated with a positive TEP diagnosis ( $p=0.021$ ,  $p=0.003$ , and  $p=0.043$ , respectively).

In Group 2 the most prevalent cancer types were lung, breast, colorectal, and prostate, none of which showed significant association with a positive TEP diagnosis. In both groups the most common treatment approach following TEP diagnosis was anticoagulation, but in Group 1 there was some indication for associated treatments such as antithrombus stockings and lower limb ultrasound.

The results of both tests showed good concordance as reflected by kappa coefficient

values ranging from 0.60 to 0.79. Of the 41 patients who were submitted to both tests (Group 3), 87% showed concordant results (Table 1).

We also analysed agreement on the diagnosis of acute and chronic TEP in positive cases performed in both diagnostic methods. Of the 7 concordant positive results, 4 patients were diagnosed as chronic TEP by both diagnostic methods and 3 as acute TEP. Thus, 100% agreement was obtained.

SPECT-CT showed agreement with ANGIO-TC on Sensitivity, Specificity and VPN-Negative Predictive Value, and inferiority on VPP-

Predictive Value Positive and Accuracy. The ANGIO-TC diagnostic parameters were taken from the literature and those of the SPECT-CT calculated based on the diagnostic data from the sample due to the gold standard. The data are shown in (Table 2).

## DISCUSSION

In the present study, comparison of TEP diagnosis between ANGIO-CT and SPECT-CT yielded concordance in 87% of cases and disagreement in 13% of the cases. The diagnostic

Table 1: Concordance between ANGIO-TC diagnostic methods for thorax and pulmonary I/P by SPECT-CT

Methods:		ANGIO-TC – Gold Standard		
SPECT-CT	Positive	Positive	Negative	Total
		7	4	11
		77,8%	10,5%	23,4%
	Negative	2	34	36
		22,2%	89,5%	76,6%
	Total	9	38	47
	Kappa Index 0,62	19,15%	80,85%	100%

Concordant and discordant results in diagnosis of Positive and Negative TEP. Kappa coefficients: 0< No concordance, 0-0.19-Minimum concordance; 0.20-0.39-Discrete concordance; 0.40-0.59-Moderate concordance; 0.60-0.79-Good concordance; 0.80-1.00- Great agreement.

Table 2: Comparison of diagnostic parameters of SPECT-CT and ANGIO-TC techniques

Method	Sensitivity	Specificity	VPP	VPN	Accuracy
Spect-CT	78%	89%	64%	94%	87%
Angio-TC	64-100%	89-100%	93%	94%	93,50%

Accurate diagnostic parameters of SPECT-CT due to gold standard ANGIO-TC

performance of thoracic ANGIO-CT was additionally demonstrated by its agreement with the literature regarding types of cancer most likely to co-occur with TEP.

The diagnostic performance of pulmonary I/P by SPECT-CT was demonstrated through the

parameters of accuracy, sensitivity, specificity, and positive and negative predictive values. This technique yielded sensitivity, specificity, and NPV equivalent to those described in the ANGIO-CT literature. Accuracy and PPV were lower for SPECT-CT than for ANGIO-CT. Other studies

have described pulmonary I/P by SPECT-CT as having TEP, possibly even higher than that of ANGIO-TC and conventional scintigraphy. A 2017 Swiss study comparing the three methods showed SPECT-CT to have a sensitivity of 97% and specificity of 100%.<sup>8,13,14</sup>

What possibly hindered the performance in PPV, Sensitivity and Accuracy of SPECT-CT values in our work was the bias of having few positive cases for TEP in patients who had performed both tests to compare the concordance of methods. Among the 410 patients studied, only 47 performed both tests over a 3-month period, and of these 47 only 11 were diagnosed with positive TEP. Thus, the results obtained by the two diagnostic methods agreed in 7 cases and disagreed in 4 cases, reflecting the 64 % PPV assertiveness of the test in patients with the disease, and in the Sensitivity which is directly related to the ability of the test to detect sick cases, thus impacting the Kappa index and the value of diagnostic accuracy. We used the totality of cases found of the patients who were submitted to the lung I/P test by SPECT-CT in the period, and there was no way to increase the sample to establish a higher number of positive cases for evaluation.

The technique of pulmonary I/P by SPECT-CT could be the most indicated technique for oncologic patients due to the lower amount of radiation used compared to ANGIO-TC radiation, since oncologic patients due to the condition of the malignant disease weaken their immunity, adding the recurrent exposures to which they are irradiated in radiotherapy, it would be preferable to expose them as little as possible; considering also that SPECT-CT has demonstrated through some works an optimal diagnostic accuracy for TEP, even higher than ANGIO-TC. However, the examination time is somewhat longer compared to ANGIO-TC, and there is less availability of this equipment in most diagnostic centres. Perhaps because of the cost and because ANGIO-TC has already shown excellent performance for this purpose, it has so far been considered the gold standard method of choice for TEP diagnosis. Furthermore, there are few studies correlating the results of SPECT-CT and ANGIO-TC chest I/P techniques in cancer patients.<sup>8,11</sup>

The cancro Lung, pancreas and brain were also described in a Brazilian retrospective study and an American cohort study, conducted from 2013 to 2017, which analysed the prevalence of incidental TEP in cancer patients showing a greater

association of these types of cancer with thromboembolic event diagnosis and TEP.<sup>12,15</sup>

Some studies have shown that patients with metastatic cancer had a greater association with the diagnosis of positive TEP.<sup>1,6,12</sup>

However, we did not observe any significant association between metastatic cancer and TEP in our sample. This may be due to the fact that we had such a small number of patients with metastatic disease; future studies could examine this relationship more thoroughly. Although a 2007 work by INCA describes that the frequency of detection of the pro-coagulant factor neoplasia-CP is higher in early stage neoplasms (up to 70%) than in advanced stage neoplasms (20%), which may explain the occurrence.<sup>16</sup> In a retrospective study in the United States and a Brazilian study of cancer patients, a higher prevalence of patients with a history of anticoagulant use, previous TEP/TVP and pre-existing lung diseases with a higher predisposition to the TEP event was also demonstrated, and that smoking had a high prevalence in suspected cases, but a non-association. These data that the patient who uses blood thinners showed prevalence and association and pre-existing lung diseases with a higher predisposition to the TEP event was also demonstrated, and that smoking had a high prevalence in suspected cases, but a non-association. These data that the patient who uses blood thinners showed prevalence and association with TEP are important data, because if the patient uses systemic blood thinners to prevent thrombosis, thromboembolic events and TEP, why did these patients have a higher prevalence of this diagnosis? It may be that the patient who uses anticoagulants periodically conditions their body and circulatory system with the medication, and if there is a treatment failure or if they have stopped taking the medication for a period, they will quickly develop TEP. Having a greater predisposition to the event, especially in oncologic patients who already have an imbalance in the homeostatic system. But it will depend a lot on each case and the patient's conditions, such as: immobilization, limb edema, etc.; also because the vast majority of the patients included in this study (96%) were hospitalized at the time of the examination, which is an important factor.<sup>5,16</sup>

#### Limitations

The number of patients found in Group 2 was much lower than in Group 1 and eventually had some impact on the determination of the

accuracy parameters of SPECT-CT, and also impaired the analysis of cancer types and with the diagnosis of TEP and the analysis of oncologic staging, so we cannot say that these variables showed no association with the diagnosis of TEP. There are also some limitations on performance between the diagnostic methods: it was not possible to calculate the ANGIO-TC accuracy parameters since it was used as the gold standard and its diagnostic parameters were taken from the literature. Furthermore, there are technical differences between the two modalities because ANGIO-TC is an anatomic technique and SPECT-CT is a functional anatomic technique. And the difference between the observers, because generally in this centre it is not the same doctor who evaluates the two tests, but different doctors in Tomography the Radiologist and in Nuclear Medicine the Nuclear Doctor, which depends a lot on the experience of each observer.

## CONCLUSIONS

I/P by SPECT-CT and ANGIO-TC of the thorax have proven to be reliable and highly accurate for the diagnosis of TEP in cancer patients.

There was satisfactory agreement between methods in the diagnosis of acute TEP, chronic TEP, in the positive and negative results for TEP,

including the tests performed even on the day for diagnostic confirmation. And the most prevalent treatment after diagnosis of positive TEP in both groups was anticoagulation, so there was no impact on medical conduct. Both techniques can be used for the diagnosis of TEP in oncologic population. SPECT-CT has shown excellent accuracy especially for the diagnosis of negative TEP and may be preferable and more suitable to exclude TEP in cancer patients due to its lower radiation, but for the diagnosis of positive TEP the chest ANGIO-TC is even more indicated.

The types of cancer that showed association with positive TEP were lung, pancreas, colon and rectum cancer; and the most prevalent in suspected and associated with the presence of TEP was lung cancer.

The comorbidities that showed association with TEP diagnosis in cancer patients were History of TEP/TVP, use of anticoagulants, lung diseases and HAS. And most cancer patients had at least one other comorbidity besides cancer disease.

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