EVALUATING THROMBOTIC RISK IN PATIENTS WITH COLORECTAL AND GASTRIC CANCER

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EVALUATING THROMBOTIC RISK IN PATIENTS WITH COLORECTAL AND GASTRIC CANCER (Abstract): We decided to study the computed tomography appearance and staging of gastric and colorectal cancers in relationship with vein thrombosis and pulmonary embolism because these tumors and their thrombotic complications are leading causes of morbidity and mortality in adult patients. **Materials and methods:** We retrospectively searched the databases of "Sf. Spiridon" County Clinical Emergency Hospital, Iasi, and we discovered 102 patients with gastric and colorectal cancer who underwent computed tomography (CT) with a 64 detectors Incisive Philips CT scan between January and December 2022. The study was focused on the CT appearance of the tumor (location, length and thickness, local invasion), lymphadenopathies, metastases, and the correlation between tumor characteristics and the tendency for vein thrombosis. **Results:** We studied 102 patients (77 with colorectal and 25 with gastric cancer), mean age: 68.85±13.13 years, and among them we discovered 19 (18.62%) cases with vein thrombosis. Cancer-associated thrombosis has a weak negative correlations tumor thickness and length, weak positive correlation with tumor extension outside the digestive wall, number of loco-regional lymphadenopathies, and metastases. **Conclusions:** We found a strong association between vein thrombosis and gastric and colorectal malignant tumors, there is a weak correlation with tumor extension outside the digestive wall, the number of loco-regional lymphadenopathies and the presence of metastases, so we cannot confidently predict thrombosis by studying these tumor characteristics. **Keywords:** GASTRIC CANCER, COLORECTAL CANCER, THROMBOSIS.

INTRODUCTION

Malignancy leads to a hypercoagulable state associating vein thrombosis and / or pulmonary embolism (1), cancer patients having a 4 times higher risk of thromboembolism than general population (2, 3). Cancer-associated thrombosis is the second mortality cause, following the mortality by cancer itself, and preceding the mortality determined by various infections (4); mortality is lower in cancer patients without deep vein thrombosis and / or pulmonary embolism and significantly higher in case of those associating thrombosis (5, 6). Gastric cancer and colorectal cancer are leading causes of morbidity and mortality in

adult patients, many authors studied the frequency of associated venous thromboembolism, and created strategies for prophylaxis and treatment (7). Most patients with gastric cancer and colorectal cancer have no obvious clinical symptoms in the early stage, are diagnosed at an advanced stage, when pain, fatigue, and even jaundice can appear, related to lymphadenopathy or liver metastases (8). Thrombosis can be an early symptom of cancer, but the incidence of varies with cancer type, stage, patient characteristics, and anticancer-associated treatment (9, 10). Computed tomography has a high sensitivity for gastric cancer detection (11) and is the gold standard method for evaluating tumor invasion, regional and distant lymphadenopathy, liver and peritoneal metastases (which are associated with poor prognosis) (12, 13, 14). For colorectal cancer, computed tomography is also the standard method for determining disease stage but staging is improved in case of rectal cancer by using MRI which has been documented to be more accurate than CT (15). Current therapeutic agents of digestive tract cancer-associated thrombosis mainly comprise low weight molecular heparins, and eventually inferior vena cava filters, because oral anticoagulants, and vitamin K antagonists are contraindicated (5, 7, 10).

MATERIALS AND METHODS

We retrospectively searched the databases of "Sf. Spiridon" County Clinical Emergency Hospital Iaşi to identify patients who underwent abdominal and pelvic contrast enhanced CT (CECT) for suspicion of gastric and colorectal cancer during 2022 and we discovered 102 patients with imaging suspicion for these malignancies; among them 24 had also suspicion of vein thrombosis or pulmonary embolism (PE) and computed tomography pulmonary angiography (CTPA) was also performed.

Computed tomography was performed with a 64 detectors Incisive Philips CT scan; for those patients with PE suspicion, CTPA was performed, followed by abdominal and pelvic CT examination, for the other patients only abdominal and pelvic CT was done. All patients with suspicion of gastric cancer ingested immediately prior the investigation 500 mL water to distend the stomach and those with colorectal cancer underwent a colonic cleansing preparation followed by a 1500-2000 mL water enema before the procedure.

A noncontrast enhanced scan was performed on the regions of interest. We injected intravenously up to 100 mL of 400 mg I/mL Iomeprol (Iomeron 400 mg/mL) for CTPA and up to 120 mL of 370 I/mL Iomeprol (Iopamiro 370 mg/mL) for abdominal and pelvic CECT, with an automatic injector, with the speed of 3-4 mL/second, followed by 50 mL of saline chaser; we used bolus tracking technique to choose the moment of arterial phase scanning for CTPA: the scan started with a delay of 22-25 seconds when the density in the pulmonary trunk was over 150-180 HU.

For abdominal and pelvic CT scan we measured the CT densities during contrast injection in the descending aorta just above the diaphragm; when the density was over 120 HU, the scanning started with an injection-to-scan delay for the arterial phase 15-20 seconds, for portal venous phase 60-70 seconds, and 4 minutes for delayed phase.

Gastric cancer and colorectal cancer staging are based on the 8th edition of the AJCC TNM classification of malignant tumors (16, 17).

The study was focused on the following

features: CT appearance of the tumor (location, length and thickness, local invasion), lymphadenopathies, metastases, and the correlation between tumor characteristics and the tendency for vein thrombosis and PE.

RESULTS

We studied 102 patients (77 with colorectal and 25 with gastric cancer), and among them there were 64 (62.75%) males and 38 (37.25%) females, with mean age: 68.85±13.13 years, age range: 18 to 93 years, the majority of patients concentrated in the 60-80 age range (57-55.88% patients), with the highest concentration around the age of 70. We encountered only five sincrone or metacrone large bowel tumors and two associations between colonic and gastric cancer.

The study of the tumor length (fig. 1) and thickness in correlation with age group, shows a wide range of tumor dimensions, with an ascending trend from 20 to 80 years, the 60-80 years group having the highest variability in tumor dimensions, with the median being higher than the previous age groups suggesting that older patients might have tumors detected at later stages.

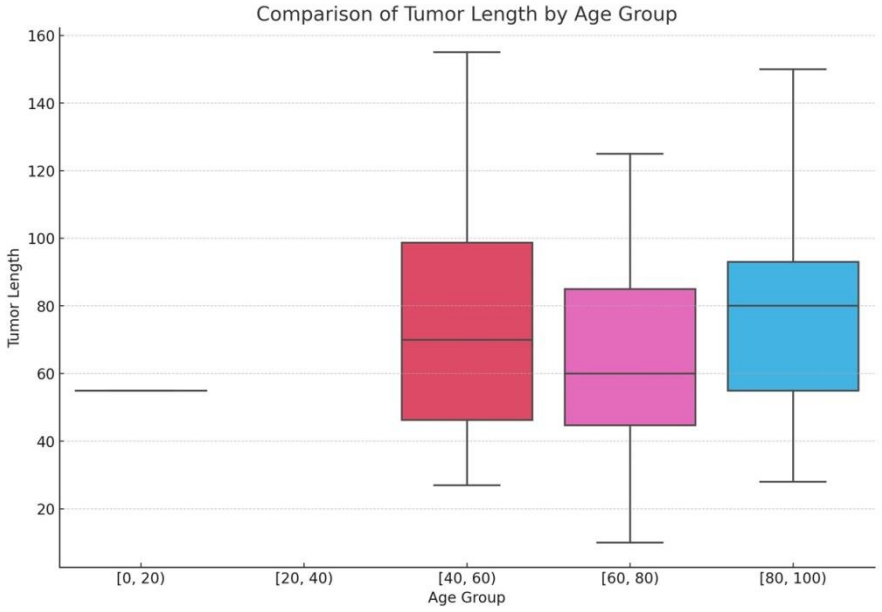

Fig. 1. Relationship between tumor length and age group

We used Pearson correlation coefficient (r) and p-value to measure the strength and direction of the linear relationship between two variables; r ranges from -1 (perfect negative linear relationship) to 1 (perfect positive linear relationship) and p-value is significant between $0.001 \leq$ and < 0.05.

Correlations between tumor characteristics and loco-regional tumor extension

The localization of the tumors influences treatment strategies, so it is important to notice the most frequent locations: in case of the large bowel, rectum and sigmoid have a higher prevalence of tumors (37-48.05%

cases), followed by ascending colon (14-18.18%). Gastric cancer has an equal distribution between antrum: 8 cases (32%), fornix and body (7-28% cases each), other localizations being rarer.

Among all the patients we had studied the highest number of invasive tumors are present in the rectum and sigmoid colon (18-17.64% cases), cecum and ascending colon (10-9.80% cases), and indicating that the lesions with these locations have a higher tendency for local invasion; even if there were only 7 invasive gastric tumors, they represent a significant percentage (6.86% of all lesions and 28% of gastric cancers).

The r values we calculated for tumor thickness reveal that is moderately correlated with both tumor length (0.526) and the extension of the tumor outside the digestive walls (0.325), indicating that as tumors become thicker, they tend to grow larger and invade surrounding tissues more extensively; while there is some relationship between tumor thickness and the number of loco-regional lymphadenopathies, it is relatively weak (0.225), and age appears to have a minor inverse relationship with tumor thickness, but this correlation is also weak (-0.188).

Pearson correlation coefficient and p-values show the significance of tumor thickness correlations with tumor length, extension of the tumor outside the digestive walls, number of loco-regional lymphadenopathies, concluding that they are not likely due to random chance (tab. I).

TABLE I.

Correlations between tumor thickness and other variables

Tumor thickness	Pearson correlation coefficient	p-value	Classification
Tumor length	0.526	<0.001	Highly Significant
Thickness Outside the Digestive Walls	0.325	<0.001	Highly Significant
Number of loco-regional adenopathy	0.225	<0.05	Significant
Age	-0.188	<0.1	Marginally Significant

Tumor length shows a moderate positive correlation with thickness outside the digestive walls (0.470) and a weak positive correlation with locoregional adenopathy number (0.238). Thickness outside the digestive wall shows a moderate positive correlation with locoregional adenopathy number (0.490).

The most frequent metastasis are the liver ones (21-20.58%) (fig. 2), followed by peritoneal and non-regional lymphadenopathies (10-9.80%), pulmonary (8-7.84%), splenic, renal, and bone secondary lesions (1-0.98%). Age distribution of liver metastases ranges from 50 to 89 years, common age group is over 70 years (13-61.90% cases) and the prevalence concerning the gender is in favor of male patients (15-71.42%). The correlation between liver and other metastatic sites is the following:

- with the peritoneal and non-regional lymph node metastases is moderate positive: patients with hepatic metastasis are likely to have peritoneal and non-regional lymph nodes metastasis as well;
- with pulmonary metastasis there is a weak correlation, suggesting a lower likelihood of co-occurrence with liver metastasis;
- splenic, renal, and bone metastasis exhibit a very weak or no correlation with liver metastasis, so they are rarely found together with hepatic metastasis.

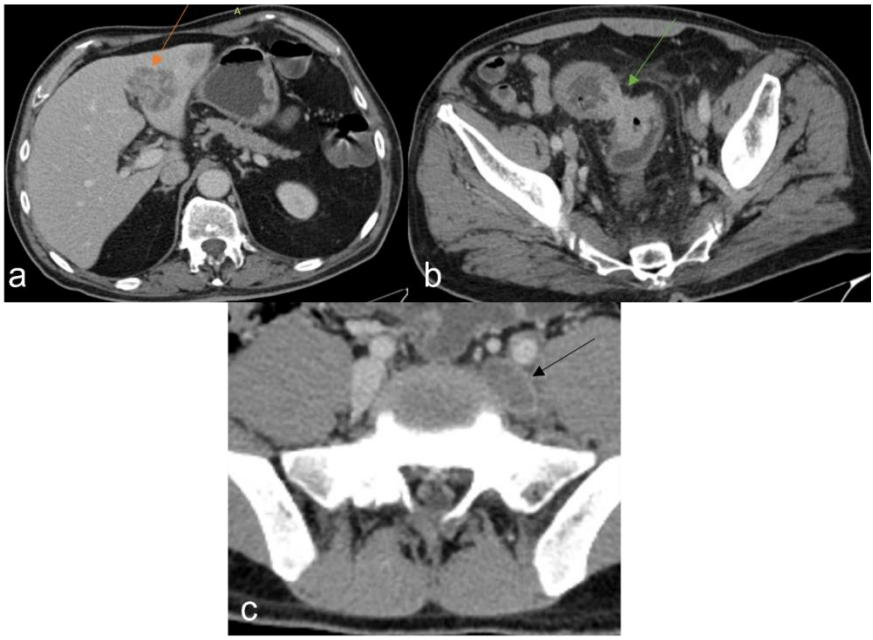

Fig. 2. Abdominal and pelvic CT, portal venous phase: a. liver metastases (orange arrow); b. sigmoid colon cancer (green arrow); c. left common iliac vein thrombosis (black arrow)

Correlations between tumor characteristics and vein thrombosis

Among the patients we had studied we found 19 (18.62%) cases with vein thrombosis associated with pulmonary embolism in 7 (6.86%) cases, most of them (15-78.94%) being males. This study discovered the following correlations between vein thrombosis and tumor characteristics (fig. 3):

- with tumor thickness and length: weak negative correlations; for example, the tendency of vein thrombosis is not increasing with tumor thickness (coefficient is -0.0017), indicating a slight negative relationship with thrombosis, also this relationship is not statistically significant ($p = 0.061$);
- with tumor extension outside the digestive wall: weak positive correlation;
- with number of loco-regional lymphadenopathies: weak positive correlation (0.306), suggesting that higher loco-regional adenopathy numbers are slightly associated with an increased likelihood of thrombosis;
- portal vein thrombosis: weak correlations with tumor thickness (-0.084), tumor length (-0.035), and thickness outside the digestive walls (-0.071), and moderate correlations with other thrombosis types such as iliac vein thrombosis (0.219) and inferior vena cava thrombosis (0.243).

Studying the TNM staging we found only 10 cases of T1-T2 lesions, and most of the patients had locally advanced tumors in 92 (90.19%) cases (T3: 42 cases, T4: 50 cases). The majority of patients (86 cases-84.31%) had lymph node involvement (N1: 52 cases, N2: 22 cases, N3: 12 cases), but distant metastases were present in 37 (36.27%) cases. The correlation of TNM categories and the tendency for vein thrombosis are presented in second table.

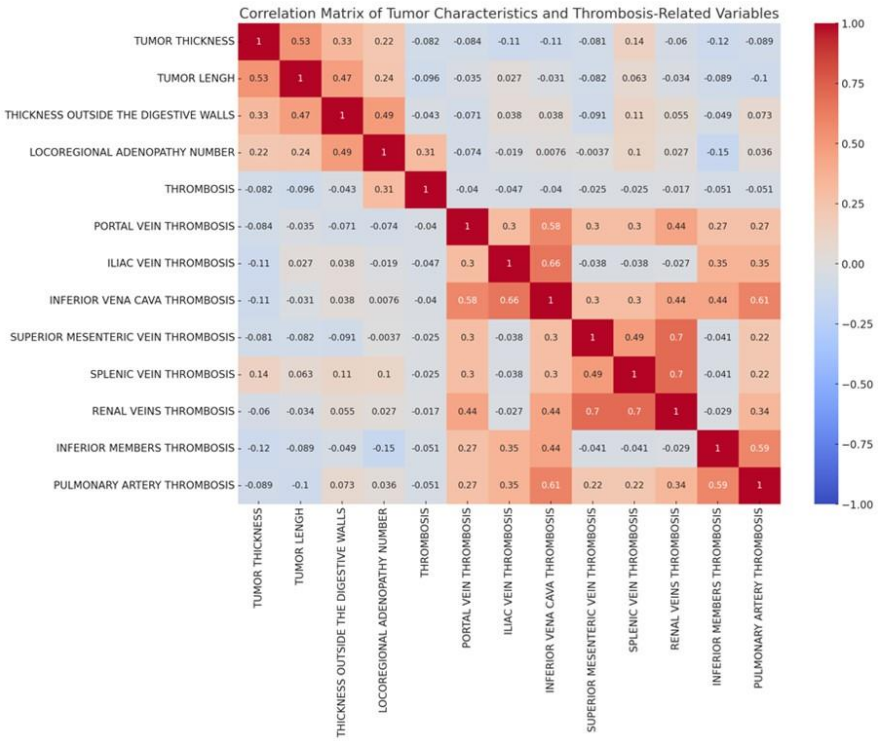

Fig. 3. Correlations between tumor characteristics and thrombosis:
red = positive, blue = negative; the intensity of the color = the strength of the correlation

TABLE II.

Correlation between TNM categories and the tendency for thrombosis

Thrombosis	Pearson correlation coefficient	p-value	Classification
T	-0.327	0.040	Significant
N	0.306	p < 0.001	Highly Significant
M	0.178	0.040	Significant

Tumoral local invasion (T) has the coefficient -0.327, indicating a negative relationship with thrombosis, which is statistically significant (p = 0.040). However, there is a weak correlation between the number of loco-regional lymphadenopathies and thrombosis (r= 0.306), for each additional locoregional adenopathy, the thrombosis score increases; this relationship is statistically significant (p < 0.001), suggesting that patients with more loco-regional lymphadenopathies might have a higher likelihood of developing thrombosis. The presence of metastases has a weak positive(r=0.178), statistically significant (p = 0.040) correlation with vein thrombosis.

DISCUSSION

We studied 102 patients and among them only 25 had gastric cancer, determining an inaccurate statistic for this particular group, so we studied the correlations between tumor characteristics and the rela-

tionship with cancer-associated thrombosis for the whole group of patients.

Gastric and colorectal cancers were frequent (62.75%) in case of male patients, and liver metastases have a higher prevalence in males (71.42%), suggesting the need for gender-specific strategies in early detection and follow-up for this demographic.

The majority of patients are concentrated in the 60-80 age range (55.88% patients), and liver metastases are frequent in case of patients over 70 years old (61.90%) so the surveillance for gastric and colorectal cancers has to be extended also for these age groups.

Although the association between gastric tumors (including neuroendocrine ones) and breast cancer (mainly lobular type) is cited in the literature, we found this association only in 1 case, without any correlation with vein thrombosis (18, 19, 20). Among the patients we had studied we found a significant number (19-18.62%) of vein thrombosis, most of them (15-78.94%) being males; this tendency suggests that the appearance of thrombosis in case of a male subject to ring a bell for the presence of a malignant tumor.

The correlations between thrombosis and tumor thickness and length are weak negative correlations; tumor extension outside the digestive wall has a weak positive correlation with thrombosis.

Tumoral local invasion in other organs has a statistically significant, negative relationship with thrombosis, but between the number of loco-regional lymphadenopathies and the presence of metastases there is a weak positive correlation with vein thrombosis.

For further studies we think about correlating malignant gastric, colonic and pancreatic lesions with vein thrombosis, heart conditions and COVID-19 infection, using artificial intelligence programs (21, 22).

CONCLUSIONS

Most of the patients with metastatic gastric and colorectal cancers from our study were old males, who had also cancer associated thrombosis, so the surveillance for these malignancies has to be focused on them and also extended for older age groups.

Even if we found a strong association between vein thrombosis and gastric and colorectal malignant tumors, there is a weak correlation with tumor extension outside the digestive wall, the number of loco-regional lymphadenopathies and the presence of metastases, so we cannot confidently predict thrombosis by studying these tumor characteristics.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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