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Computed Tomography (CT) in Predicting the Risk of Malignancy in Gastrointestinal Stromal Tumors (GIST) in Correlation with Mitotic Index

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ABSTRACT

Background: Despite being an uncommon form of abdominal neoplasia, gastrointestinal stromal tumors are the most prevalent mesenchymal tumors of the gastrointestinal system.

Objective: This research aimed to identify the predictors of malignancy on computed tomography (CT) for the evaluation of gastrointestinal stromal tumors (GIST) by correlating CT findings with the mitotic index.

Patients and methods: We retrospectively reviewed the radiological and pathological results of forty-five patients who had a histopathological diagnosis of GIST. All underwent post contrast CT for the abdomen and pelvis.

Results: There was a significant correlation among mitotic count and sex, area of necrosis, contour, mesenteric fat infiltration, and distant metastasis with p value < 0.05. The sensitivity of the 20% cut-off value was 74.2%, the specificity was 85.7%, and the accuracy was 77.8%. The sensitivity of 10% cut-off value was 93.5%, the specificity was 78.6%, and the accuracy was 88.9%. Out of 45 patients with GIST lesions, 39 (86.7%) had radiological findings that agreed with the pathological mitotic count. Six patients (13.3%) had mismatches (four favoring pathology and two favoring radiology).

Conclusions: Although, pathology remains the cornerstone in having the final verdict regarding the malignant potential of GIST, the CT-based approach seems to be effective for risk stratification prior to surgery and treatment. This approach in conjunction with other risk variables such as patient age and morbidities could be helpful for a better management of GIST patients, to address them to the best tailored treatment at the time of diagnosis.

Keywords: Computed tomography, Gastrointestinal stromal tumors, Mitotic index.

INTRODUCTION

Despite being an uncommon form of abdominal neoplasia, gastrointestinal stromal tumors account for one to two percent of all gastrointestinal neoplasms and are the most prevalent mesenchymal tumors of the gastrointestinal system [(1)].

The most crucial characteristics of the neoplastic risk in GISTs are the tumour size and mitotic count, which may be categorized using a variety of methods most commonly through surgical excision but also, albeit less precisely by biopsy.

Additionally, several scientists noted that the behavior of GISTs varies depending on the anatomical location [(2)]. The most significant factors for predicting the biological risk or malignant potential of GISTs were proposed to be the anatomic site, tumor size (maximum diameter in centimeters) and mitotic rate. Miettinen and Lasota recently improved their risk assessment table based on follow-up data about over 1900 studied cases who had been affected by GIST over time [(1)].

From a diagnostic perspective, CT is still regarded as the preferred method for identifying and describing GISTs. It provides data on tumor size, anatomic location, growth pattern, evidence of necrosis, invasion of surrounding organs and metastasis. It helps track treatment response and evaluate the course of the disease [(3)]. Some authors have tried to determine whether pathological features—more especially, the biological risk of GISTs—and CT outcomes are related, however the results are still inconclusive. In light of the aforementioned information and the fact that Miettinen & Lasota stated that the combination of the tumor's size, site and mitotic rate, the last two of which may be accurately determined via a CT scan, determines the risk assessment of GISTs, we looked for a potential CT surrogate of the mitotic index that would be beneficial for enhancing the role of CT in the pre-operative prognostic assessment of these tumors [(4)]. Therefore, the purpose of the research was to correlate the mitotic index with CT findings to determine the predictors of malignancy for the evaluation of gastrointestinal stromal tumors.

PATIENTS AND METHODS

This study was performed at Radiology Department. We looked back at the radiological and pathological results of forty-five patients who received treatment & had a histological diagnosis of GIST from July 2023 to December 2023.

Inclusion criteria: Patients with GIST with CT examination performed before the surgery, surgical intervention performed at our hospital & pathological assessment of the specimen was done.

Exclusion criteria: Patients with chronic renal disease or with sensitivity to contrast injection.

CT examination: Abdominal CT scans was performed using a Toshiba Aquillon 16 slice device (made in

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Japan), using a spiral technique in a cranio-caudal direction (from the base of the lungs to the pelvic brim) and supine position. All the contrast-enhanced CTs were done in the portal venous phase (delay 70–80 s) with an intravenous injection of 1 mL/kg of nonionic contrast material. To reduce radiation exposure, an automatic current modulation tube was utilized. To prevent motion artefacts throughout helical imaging, a conventional reconstruction technique was employed & studied cases were urged not to breathe throughout the procedure.

Histopathological analysis: The tumor samples were accurately described macroscopically, considering factors such as tumor size, extra parietal extension, necrotic or hemorrhagic regions & macroscopic ulceration. The samples were dyed with hematoxylin & eosin and embedded in paraffin. By looking for the most mitotically active locations, fifty fields (at 400×) had been used to count the number of mitotic figures. In every instance, the following extra factors were assessed: Ulceration, coagulative necrosis, nuclear atypia, mucosal invasion, degree of parietal diffusion and margin status. The size, mitotic count, anatomic location, margin status, immunophenotyping and Ki67 antibody-evaluated proliferation rate were all contained in the pathology report. According to Miettinen and Lasota, the risk evaluation had been reported [(5)].

Image analysis: Two radiologists (with 10- and 3-years' experience in the oncologic field, respectively), independently reviewed the CT images for each of the 45 GIST patients, blind to surgical and pathological data. They assessed all CT scans for metastases and scans taken throughout the portal venous phase for tumor assessment. The features of each lesion, such as the site, size, area, percentage of necrosis, contour, growth pattern, enhancing pattern, degree of enhancement, mesenteric fat infiltration, ulceration, calcification, regional lymphadenopathy, ascites, direct invasion of nearby organs and distant metastasis were determined by analyzing each CT scan using a reconstruction and image interpretation console. Tumor size was measured in the maximum diameter and lesions were categorized based on the gastrointestinal segment of origin (gastric and non-gastric GIST). If low attenuation area was found within the mass, tumor necrosis was deemed present. The ratio of the hypodensity area to the tumor's overall area was used to compute the percentage of necrosis. Tumor growth patterns were categorized as endoluminal, exophytic, or mixed, and lesion shapes were defined as round or lobulated. Subjectively judged enhancement patterns were used to classify regional lymph nodes as pathological if their enhancement matched the lesion enhancement or if the nodes' short-axis diameter exceeded one cm. In the end, we assessed the relationships among each CT result and the mitotic index to investigate potential CT surrogates for this histological parameter.

Ethical consent: An approval of the study was obtained from The Research Ethical Committee of The Radiology Department of The Faculty of Medicine, Cairo University. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The statistical software for the social sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA) was used to code and enter the data. For quantitative data, the median & interquartile range were used. For categorical data, frequency (count) and relative frequency (%) were used to summarize the data. The non-parametric Mann-Whitney test was used to compare numerical variables [(6)]. We used the Chi square test to compare categorical data. When the anticipated frequency was less than five, an exact test was utilized instead [(7)]. To determine the optimal cutoff value of the area of hypodensity for the detection of mitotic count > 5, a ROC curve was developed and area under curve analysis was conducted. P-values ≤ 0.05 were deemed statistically significant.

RESULTS

This study included 45 patients; their ages ranged from 18 to 75 with the arithmetic median 53. 21 (46.7%) of which were females while 24 (53.3%) were males. There was variability in the site of lesions with gastric lesions being slightly higher (53.3%). While on the other hand, GIST of non-gastric origin: 5 were rectal, 7 were small intestinal, 3 were gastro-esophageal and 6 were duodenal (46.77%). Tumors with internal areas of necrosis were 40 (88.9%) and 5 were with almost no significant necrosis (11.1%). Regarding the contour, 19 had rounded contour (42.2%) and 26 of non-gastric origin showed lobulated contour (57.87%). Of the 45 patients of GIST, 7 had endophytic lesions, 34 had exophytic lesions and 4 had mixed endophytic and exophytic lesions. Tumor ulceration was found in 35 patients (77.8%) while 10 patients had no tumor ulceration (22.2%). Intra-tumoral calcific foci were found in 36 patients (80%) while 9 had no calcifications (20%). Our study had 15 patients with surrounding mesenteric fat infiltration (33.3%), and 30 patients with no evidence of mesenteric fat infiltration (66.7%). As regards regional lymph nodes, direct invasion of the adjacent organs and distant metastasis, 5 had enlarged regional LNs (11.1%) while 40 had no evidence of enlarged regional LNs. 39 had no evidence of direct invasion to the adjacent organs (86.7%), 6 were directly invading the adjacent organs (13.3%). While, 28 patients showed no evidence of distant metastasis (62.2%), and 17 patient showed evidence of distant metastasis (mainly to the liver and the peritoneum). There was significant relation between mitotic count and sex, area of necrosis, contour, mesenteric fat infiltration and distant metastasis ($p < 0.05$) (Table 1).

Table (1): Relation between different CT findings and mitotic count

		Mitotic count				P value
		less than 5 (low risk)		More than 5 (high risk)		
		Count	%	Count	%	
Sex	**Male**	11	78.6%	13	41.9%	0.023
	Female	3	21.4%	18	58.1%	
Site of lesion	**Gastric**	7	50.0%	17	54.8%	0.763
	Non-gastric	7	50.0%	14	45.2%	
Area of necrosis	**Yes**	9	64.3%	31	100.0%	0.002
	No	5	35.7%	0	0.0%	
Contour	**Rounded**	10	71.4%	9	29.0%	0.008
	Lobulated	4	28.6%	22	71.0%	
Growth pattern	**Endophytic**	3	21.4%	4	12.9%	0.856
	Exophytic	10	71.4%	24	77.4%	
	Mixed	1	7.1%	3	9.7%	
Enhancement pattern	**Homogenous**	11	78.6%	5	16.1%	< 0.001
	Heterogeneous	2	14.3%	26	83.9%	
Mesenteric fat infiltration	**Yes**	0	0.0%	15	48.4%	0.001
	No	14	100.0%	16	51.6%	
Ulceration	**Yes**	3	21.4%	7	22.6%	1
	No	11	78.6%	24	77.4%	
Calcification	**Yes**	3	21.4%	6	19.4%	1
	No	11	78.6%	25	80.6%	
Regional lymph nodes	**Yes**	1	7.1%	4	12.9%	1
	No	13	92.9%	27	87.1%	
Ascites	**Yes**	0	0.0%	2	6.5%	1
	No	14	100.0%	29	93.5%	
Direct invasion	**Present**	0	0.0%	6	19.4%	0.156
	Absent	14	100.0%	25	80.6%	
Distant metastasis	**Present**	1	7.1%	16	51.6%	0.004
	Absent	13	92.9%	15	48.4%	

Table (2) illustrated the distribution of patients' age, size of the lesions, percentage of necrosis and the degree of enhancement of GIST lesions in relation to the mitotic count, which indicated the risk of aggressiveness. The median size of low-risk tumors was 4.5 cm while the median size of the high-risk tumors was 9.6 cm, the median for the percentage of necrosis of the low-risk tumors was 3 and the median for high-risk tumors was 34.

Table (2): The distribution of patients' age, size of the lesions, percentage of necrosis and the degree of enhancement of GIST lesions in relation to the mitotic count

	mitotic count						P value
	less than 5 (low risk)			more than 5 (high risk)			
	Median	1st quartile	3rd quartile	Median	1st quartile	3rd quartile	
Age (years)	52.00	42.00	62.00	53.00	40.00	60.00	0.971
Size of lesion (cm)	4.55	4.00	6.90	9.60	5.40	12.30	0.001
Percentage of necrosis (area of hypodensity)	3.00	0.00	9.00	34.00	18.70	50.20	< 0.001
Degree of enhancements (HU)	56.00	44.00	67.00	49.00	34.00	55.00	0.035

cm: centimeter, HU: Hounsfield unit

As regards the accuracy of percentage of necrosis (area of hypodensity). The sensitivity of the 20% cut-off value was 74.2%, the specificity was 85.7% and the accuracy was 77.8%.

The sensitivity of the 10% cut-off value was 93.5%, the specificity was 78.6% and the accuracy was 88.9%. According to this cut off value of 10% percentage of tumor necrosis within the lesion to determine the risk of malignancy.

Our study had 45 patients with GIST lesions, 39 patents their radiological findings agreed with pathological mitotic count (86.7%), while 6 patients showed mismatch (13.3%), 4 of them were in favour of pathology (radiologically the percentage of necrosis was less than 10, while the lesions proved to be high risk by pathology) and the other 2 mismatch were in favour of radiology (pathology showed to be of low risk while the lesions was metastasizing by radiology) **(Table 3).**

Table (3): The percentage of agreement and disagreement between the percentage of necrosis and the mitotic count of the GIST lesions

		Count	%
Agreement	**Match**	39	86.7%
	Mismatch	6	13.3%
Mismatch	**Match**	39	86.7%
	Mismatch in favour for pathology	4	8.9%
	Mismatch in favour of radiology	2	4.4%

A 50-years-old male complaining of vague abdominal pain **(**Figure (1).

- **Radiological findings showed A**: Two masses are noted one at gastric greater curvature having lobulated outline, homogenously enhancing and having a smaller endophytic and larger exophytic component (red arrow).
- **B**: The 2nd one is at the 3rd part of the duodenum having rounded outline and homogenous post contrast enhancement being mainly endophytic (yellow arrow).
- **Percentage of necrosis** was less than 10% for both lesions, the gastric one was about 8-9% and the duodenal one was about 1%.
- **Pathological findings** showed that both lesions were GISTs, low risk, with mitotic count less than 2/50 HPFs. Multiple GISTs were more often to be syndromic.

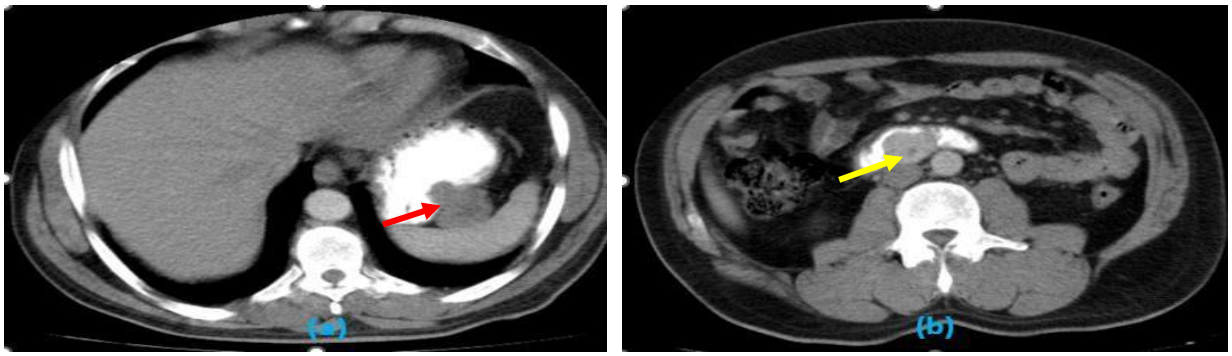

Figure (1): A 50-years-old male complaining of vague abdominal pain

68-years-old male with dysphagia **(**Figure 2).

Radiological findings:

A and B showed lower esophageal mass that was seen extending to the gastroesophageal junction and gastric fundus with heterogeneous post contrast enhancement and internal excusive areas of necrosis, ulceration and cavitation (red arrow).

C showed few small hepatic focal lesions, possibly metastatic (yellow arrow).

D showed porto-caval metastatic lymph nodes (green arrow). Percentage of necrosis was more than 50%. **Pathology:** GIST of high risk, mitotic count more than 5/50 HPFs. Esophageal GIST was considered to be rare (about 1% of all GIST).

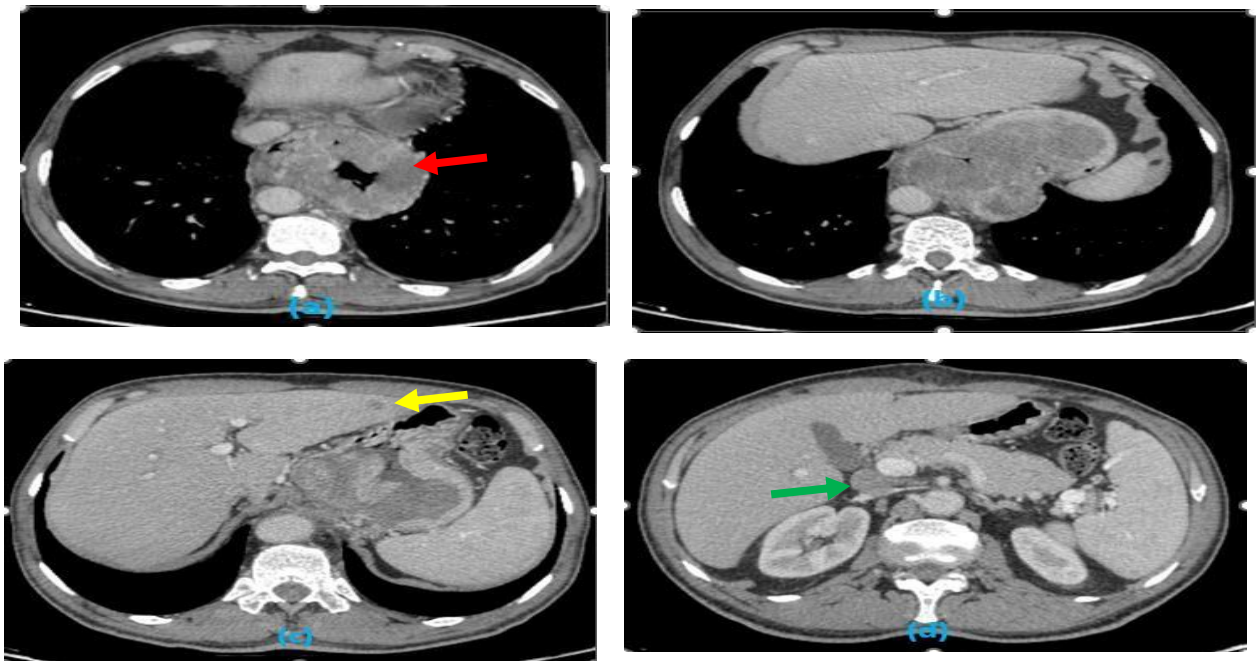

Figure (2): A 68-years-old male with dysphagia.

A 55-years-old male presenting with constipation **(**Figure 3). **Radiological findings:**

A and B showed para-rectal mass with heterogeneous post-contrast enhancement and internal necrosis (red arrow).

C showed hepatic metastatic focal lesion (yellow arrow).

D showed that the lesion was seen compressing both ureters with bilateral hydronephrosis.

Pathology: GIST of high risk, mitotic count was increased 12/50 HPFs.

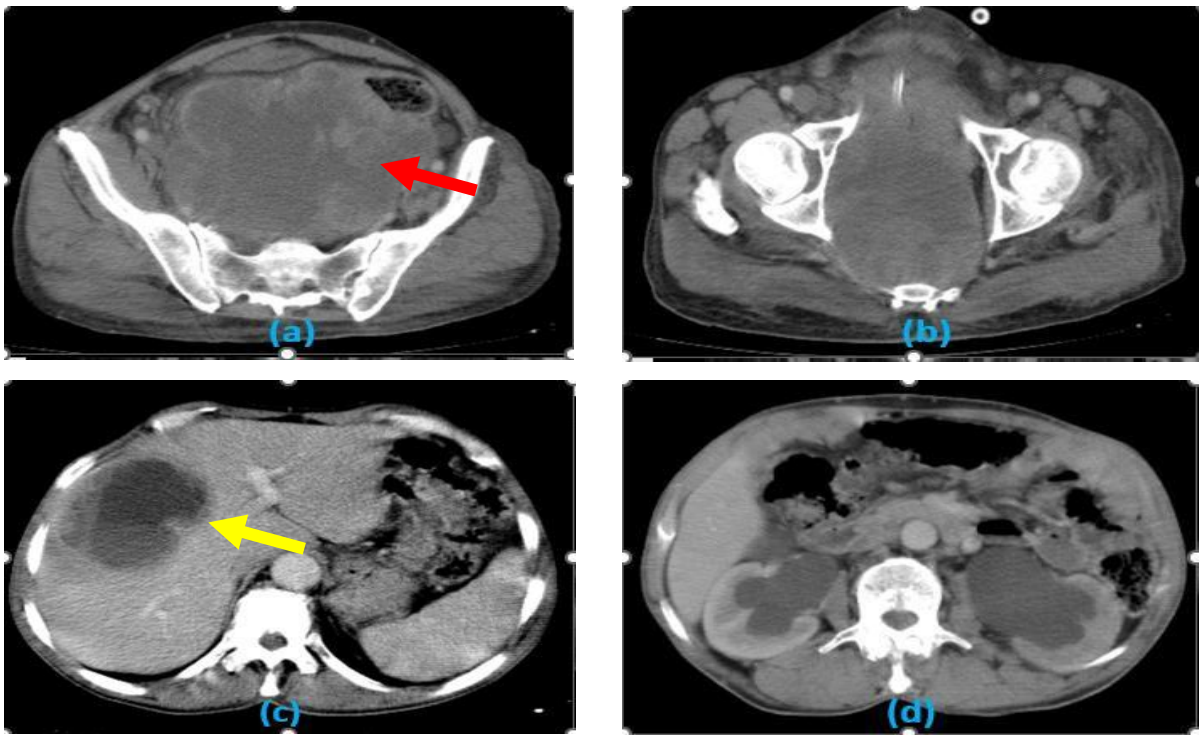

Figure (3): A 55-years-old male presenting with constipation

A 31-years-old female with abdominal pain **(**Figure 4). **Radiological findings: A and B** showed jejunal exophytic lobulated mass with internal necrosis and surrounding fat stranding (red arrow). **C & D** showed multiple hepatic metastatic focal lesions (yellow arrow). **E** showed peritoneal metastatic lesion (green arrow). **Pathology:** Jejunal GIST of high risk with mitotic count more than 5/5

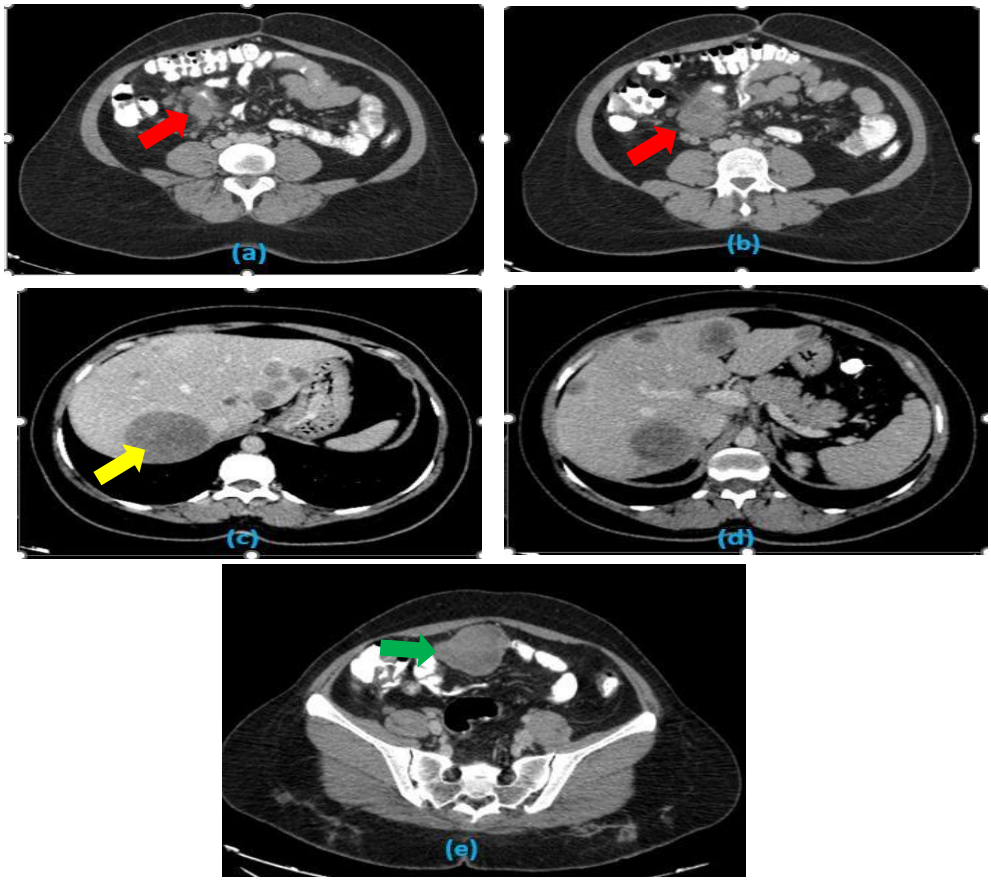

Figure (4): A 31-years-old female with abdominal pain.

DISCUSSION

GISTs have a complex biological behavior which makes predicting their malignant potentially difficult. Because of this, GISTs of any size are all essentially regarded as malignant. Nonetheless, a lot of work has been done over the years to provide practical standards for classifying GISTs based on the likelihood of metastasis or recurrence [(8)].

This study aimed to identify the predictors of malignancy on CT for the evaluation of gastrointestinal stromal tumors (GIST) by correlating CT findings with the mitotic index.

Our study revealed that, out of the 24 patients with gastric GISTs, 17 (70.8%) were of high risk with mitotic count more than 5/50 HPFs, while the rest of them were of low risk. On the other hand, out of the 21 patients with non- gastric GISTs 14 (66.6%) were of high risk with mitotic count more than 5/50 HPFs, while the rest of them were of low risk. These findings conflict with the findings of **Joensuu *et al.*** [(9)] that stated that non-gastric location of GISTS was one of the poor prognostic factors. While, our study showed almost equivalent percentages for both gastric and non-gastric GISTs as regards risk stratification with slight predilection of the gastric lesions to be of high risk.

The lesions had been classified into 2 groups based on the histopathological mitotic count to either low risk gastrointestinal stromal tumor (n=14 (31.1%)) or high risk gastrointestinal stromal tumor (n=31 (68.9%)). This was according to the pathological risk stratification done by **Miettinen and Lasota** [(10)].

In our study regarding the size, we had a range variable CT diameter from 2.7 cm to more than 27 cm, with the low risk GISTs having median size of 4.5 cm while the high risk GISTs having median size of 9.6 cm (P value <0.001) denoting that smaller lesions tended to be of low risk while larger ones tended to be of high risk. For the size, we found a good concordance among CT and pathology which matches with **Wu *et al.*** [(11)].

Upon reviewing the radiological contour of the lesions, our 45 lesions were divided into lesions with rounded outline (19, 42.2%) and lesions with lobulated outlines (26, 57.8%).

Upon correlating them with their pathology, it revealed that, 22 cases (71%) of high risk GISTs had lobulated outline, while 10 cases (71.4%) of low risk GISTs had rather rounded outline, denoting that as regards the contour of the lesions, lobulated contour had more incidence to be of high risk, while rounded contour tended to be a feature associated with low risk GISTs.

This matches with the previous **Wu *et al.* [11] study**.

As regards the enhancement pattern of the lesions, our study revealed that 16 lesions (35.6%) showed homogenous post-contrast enhancement, 11 of them were of low risk GISTs with low mitotic count. 29 lesions (64.4%) showed heterogeneous post-contrast enhancement, 26 of them were of high risk GISTs with high mitotic count. These findings match with **Wu *et al.* [11]** study indicating that heterogeneous post-contrast texture predominated in the high risk gastrointestinal stomal tumors, while homogenous post-contrast predilected among the low risk gastrointestinal stomal tumors.

According **Mazzei *et al.* [12]** study, when the mass includes regions of poor attenuation, a strong correlation (p=0.0056) was observed among high mitotic rate and high CT percentage of intralesional hypodensity. This was determined using the cut-of value of more than twenty percent of internal CT hypodensity with a mitotic index > five. Suggesting that a CT index that can be used to accurately identify the malignant potential of GISTs could be a CT percentage value of hypodensity greater than twenty percent. Comparing these results to our study, we had 45 patients 5 of them (11.1%) showed almost no internal areas of hypodensity, while 8 patients (17.7%) had less than 10% of internal areas of hypodensity, 7 patients (15.5%) had internal areas of hypodensity between 10% and 20%, the remaining 25 patients (55.5%) showed internal hypodensity more than 20%. 100% of the lesions with no internal areas of hypodensity proved to be of low risk, while 100% of the high-risk lesions had internal areas of hypodensity. With the median percentage of internal hypodensity for the low-risk GISTS being 3% while the percentage for the high-risk GISTS was 34%, these results indicated that the more the percentage of internal hypodensity of GIST lesion the higher the risk to be with high mitotic index. These findings match with **Mazzei *et al.* [12]**.

For detection of cutoff value of area of hypodensity to predict high mitotic count > 5/50 HPF, receiver operating characteristic (ROC) analysis was done and showed a significant correlation (p value<0.001) among high mitotic rate & high CT percentage of intralesional hypodensity (internal necrosis).

Using the cut-of value of twenty percent, high risk GISTs with a mitotic index more than five were correctly identified in 92% of the cases with more than 20% internal hypodensity (23 out of 25 patients). On the other hand, low risk GISTS with a mitotic index less than 5 had been correctly detected in 60% of the cases with less than 20% of internal hypodensity (12 out of 20). The sensitivity of the 20% cut- off value was 74.2%, the specificity was 85.7% and the accuracy was 77.8%, which match with **Mazzei *et al.* [12]**.

Furthermore, we attempted to apply a cut-of value of 10 % of internal hypodensity instead of 20 %, and by doing so, we were able to correctly identify high risk GISTs in 29 out of 32 lesions that showed internal hypodensity more than 10% (90.2%). On the other hand, low risk GISTs with mitotic index less than 5 were correctly identified in 11 out of 13 lesions that showed less than 10% of internal hypodensity (84.6%). Hence, the sensitivity of the 10% cut of value proved to be 93.5%, while the specificity was 78.6% and the accuracy was 88.9%.

Comparing the previously demonstrated statistical results of the 10 % cut-off value with those of the 20% ones, we noticed that the 10% cut-off was a better match with the pathology in detecting the low risk GISTs with mitotic index less than 5, while it showed almost comparable results with the 20% cut-off value in detecting high risk GISTs with mitotic index more than 5/50 high power field (HPF), with more sensitivity and accuracy and slightly lower specificity. So, in our study we agree with the **Mazzei *et al.* [12]** study. We also managed to push the cut of value of internal hypodensity down to 10% instead of 20%. Upon applying this new 10% cut of value of internal hypodensity, our study showed some cases with mismatching results.

Out of our 45 patients with GIST lesions, 39 patents showed agreement between their radiological findings and pathological mitotic count (86.7%), while 6 patients showed mismatch (13.3%), 4 of them were in favour of pathology (radiologically the percentage of internal hypodensity was less than 10, while the lesions proved to be high risk by pathology) and the other 2 cases showed mismatch in favour of radiology (the pathology showed mitotic index less than 5, while the lesions were metastasizing at time of examination by radiology). This mismatch proved that although pathology remains the corner stone in having the final word, yet recent advancements in radiological imaging and the eye of an expecting and experienced radiologists should always go hand in hand.

LIMITATIONS

The investigation was conducted retrospectively, despite re-evaluating all CT exams in a prospective setting. Additionally, the number of comparative cohorts was disproportionally low (fourteen GISTs with low mitotic index compared to thirty-one GISTs with high mitotic index) and small size of case population. Third, there were no CT exams conducted using dual-energy CT or CT-perfusion in the era of advanced CT imaging that could be appealing for a better assessment and detection of CT intralesional hypodensity and enhancement of GISTs.

CONCLUSIONS

Although pathology remains the corner stone in having the final verdict regarding the malignant potential of GISTs, our CT-based method for predicting the risk of malignant GISTs seemed to be effective for the pre-operative/pre-treatment prediction of risk stratifications of GISTs. This model, along with other significant risk variables like patient age & comorbidities may be useful for better managing GIST cases and getting them the best customized treatment at the time of diagnosis if its outcomes are validated in a larger case series.

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