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The Value of Computed Tomography Enterography in Diagnosis of Crohn's Disease Activity

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Abstract— Background: The monitoring of the activity in Crohn's disease (CD) may be challenging with endoscopic maneuvers due to difficulties in reaching the affected areas and being restricted to mucosal lesions in endoscope exam ,so the existence of a more tolerable and reliable technique will be highly warranted . In addition to its high accuracy in diagnosis and assessment of this disease. **Objective:** This study aims at detection of the accuracy of computed tomography enterography (CTE) in detection of Crohn's disease activity. **Patient and Methods:** This Prospective study was conducted from October 2015 to the end of November 2016 in Al-yarmook and gastroenterology and hepatology teaching hospitals were Thirty –four patients clinically and histopathologically proven as CD patients and most of them complain recurrent episode of abdominal pain and diarrhea included in this study .patients divided into active and inactive groups according to ileocolonoscopic evaluation. Then all patients underwent CTE as clinically indicated within 1 week of ileocolonoscopy. The radiological signs that used in CTE to suggest Crohn'sdisease activity are mural hyper enhancement, mural thickening, comb sign,mesenteric fat oedema and mesenteric lymph nodes. **Results:** Computed tomography enterography is valuable tool in detecting CD activityand the mural hyper enhancement and comb sign are the main diagnostic CTEcriteria of CD activity. **Conclusion:** CTE is anon invasive and reliable technique that has a significant value inassessment of CD activity in correlation with endoscopy and it is useful infollow up and preoperative guidance.

Key word: Computed tomography enterography(CTE) , Crohn's disease (CD) activity

Introduction:

Crohn's disease (CD) is idiopathic, chronic regional enteritis that most commonly affects the terminal ileum but has the potential to affect any part of the gastrointestinal tract from mouth to anus .(1)
This condition was first described by Crohn, Ginzburg, and Oppenheimer in 1932, but it was not clinically, histological, or radio graphically distinguished from ulcerative colitis until 1959.(2)
Although Crohn's disease is typically starts between the ages of 15 to 40, it can start at any age, approximately one fifth of all people with Crohn's disease have a close relative with some type of inflammatory bowel disease. People ofJewish descent have a higher chance of developing Crohn's disease.(3) Patients present with a range of symptoms, including cramps abdominal pain and diarrhea, which may be complicated by intestinal fistulas, particularlyafter surgical intervention, by intramural abscesses, and by bowel obstruction. (2) Untreated Crohn's disease is characterized by trans mural (full-thickness) inflammation, and the involvement of discontinuous segments of the intestine (skip areas), and in a proportion of cases by non-necrotizing granulomascomposed of epithelioid histiocytes.(4)

With the improved resolution of multidetector computed tomography (CT), CT enterography has become an important method of choice for evaluating small bowel disorders.Although it allow visualization of abnormalities outside the bowel lumen.(5)

The main diagnostic purpose of CT enterography with neutral contrast in crohn's disease is to differentiate active inflammatory strictures from fibrotic strictures in order to guide therapy.
Active bowel disease is more likely to be treated medically, whereas surgery and strictureplasty may be considered in the setting of fibrotic strictures (6,7)CT features of active Crohn disease include mucosal hyper enhancement, wall thickening (thickness > 3 mm), mural stratification with a prominent vasa recta (comb sign), and mesenteric fat stranding.

The capability of CT enterography for depicting extra enteric disease allows the simultaneous diagnosis of complications associated with Crohn's disease, such as obstruction, sinus tract, fistula, and abscess formation. Mura enhancement is the most sensitive indicator of active Crohn's disease withneutral oral contrast as in (figure 1.) (8)

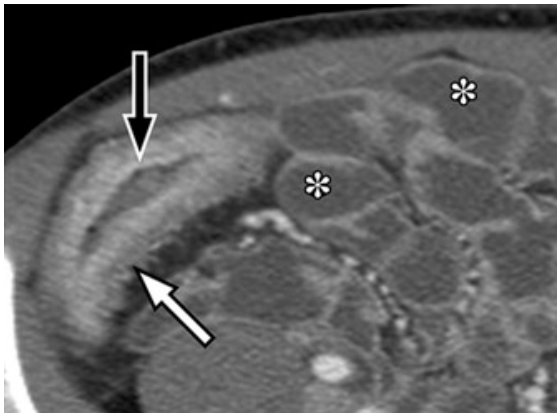

Figure (1): (Axial CT enterographic section shows mucosal hyperenhancement (black arrow) and mural stratification (white arrow) of the terminal ileum, an appearance that contrasts markedly with that of non-diseased ileal segments).

The term *mural stratification* denotes the visualization of bowel wall layers at CT. (9) The edematous bowel wall has a tri laminar appearance, with enhanced outer serosal and inner mucosal layers and an interposed sub mucosal layer of lower attenuation However, this feature is not specific to Crohn'sdisease; it is seen also in other inflammatory bowel diseases and even in some cases of bowel ischemia.

In active Crohn's disease, increased attenuation of the mesenteric fat is often seen, this appearance is due to the trans mural extension of inflammation across the serosa.And the engorgement of the vasa recta which surrounding the inflamed bowel segment. Prominence of the vasa recta adjacent to the inflamed loop of bowel is termed the “comb sign”. (10) This sign, along with increased mesenteric fat attenuation, is the most specific CT feature of active Crohn disease. (11)

Findings that might be seen in inactive longstanding Crohn disease include submucosal fat deposition, pseudosacculation, surrounding fibrofatty proliferation, and fibrotic strictures. (12)

Fibrofatty proliferation in the surrounding mesentery is thought to play a role in sustaining the inflammatory process related to the production of tumor necrosis factor α . (13)

Aim of study:

1- Evaluate the accuracy of CTE in diagnosis of CD activity .

2- Detection of extra enteric complications of the disease which unreliable in endoscope examination

Patient and Methodes:

Patients selection:

This prospective study was conducted during the period from October 2015 to the end of November 2016 at the radiology department in AL-yarmook teaching hospital and Gastroenterology and hepatology teaching hospital and include 34 patients .

A total 34 patient (8 females and 26 male), male to female ratio = 3:1, mean age were (35.5 years) [range of [16-55 years] studied.

All patients were clinically and histopathologically proven to haveCrohn's disease were presented with intermittent abdominal pain and diarrhea ofvariable severity with small and large bowel involvement documented byileocolonoscopy within one week of CTE.

Ileocolonoscopy was performed (long of instrument is 160 cm) and reported by an experienced gastroenterologist in terms of the simple endoscopic score for Crohn's disease [SES-CD] which states that a score between 0 and 2 suggest inactive disease and 3 and more suggested as active disease (tabl;e 1)

Variable	Score			
	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1–0.5)	Large ulcers (diameter 0.5–2)	Very large ulcers (diameter >2)
Ulcerated surface (%)	None	<10	10–30	>30
Affected surface (%)	Unaffected segment	<50	50–75	>75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

*Total SES-CD: sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment (for example, rectum, left colon, transverse colon, right colon and ileum).

Table (1)(13) : Simple endoscopic score

CTE protocol:

All patients who underwent CTE were asked to take nothing by mouth for6 h before scanning .On the day of examination , patients were asked to come60 min before exam time , in which patients were asked to ingest a total of 1.5Lof oral contrast material consist of water mixed with IOHEXOL (350 mg) .40 ml in 1500 ml water to [give concentration of about 1.7 %].Ingestion Divided over 60 min period as follows: 0, 15, 30 and 40 min,the last ingestion is just before the scanning.

Intramuscular buscopan 20 mg is administrated prior to scanning forAdequate luminal distension which is necessary as collapsed bowel loops maymimic pathology and intravenous contrast material [IOHEXOL 350 mg , 100ml] was given at rate 4 ml /sec .only one of our patient ingest only water (asneutral contrast) as he refuse to take positive contrast .

Then patients were scanned using CT scanning is ideally performed on a multidetectorcomputed tomography (MDCT) .[Definition Flash , Siemens MedicalSystems , Berlin , Germany].
From the xiphisternum to the symphysis pubis through single entericphase acquisition and 30-40 s after IV contrast injection .section thicknessused was 1.0 mm and the reconstruction interval was 1.0 mm . the CT scanparameter are 280 -320 m A , 120 KVP a pitch of 1.0.

CT scan were then transferred to view in work station for multi planereconstruction with section thickness 2mm and interval 1 mm and datainterpretation with the use of axial and coronal and sagittal reformatted imagesfor proper evaluation.

CTE image interpretation:
CTE images were interpreted by one radiologist who was blinding withpatients clinical and endoscopic evaluations.They were asked to evaluate the bowel, in each CTE examination formural thickness and report its value in millimeters [mural thickening isconsidered if mural thickness more than 3 mm]and CT signs of active CDwhich include ;mural hyper attenuation [hyper enhancement] which wasdetected visually and quantitatively by measuring the CT density of the bowelwall in Hounsfield units [HU] mural hyper attenuation was defined assegmental hyper enhancement of small bowel wall which exceeds theenhancement of the adjacent small bowel loops . And equal or exceeds thevenous opacification.

Absolute hyper enhancement more than 109 Hounsefield unit [HU]correlates with active disease. mesenteric fat oedema defined as increasedensity and stranding in peri enteric mesenteric fat compared to peri enteric fatadjacent to non inflamed bowel loops , and combs sign which refers tosegmental dilatation of the vasa recta supplying the bowel loops .

Also CTE signs of inactive CD were interpreted as mural thickening ofthe bowel wall or bowel stricture in the absence of CTE signs of active disease.The extra-enteric manifestations and complications of CD were alsoreported with respect to the presence of abscesses, fistula or stricture.

Statistical analysis:
Analysis of data was carried out by using the available statistical packageof SPSS-22 (Statistical Packages for Social Science –Version 22).Data were presented in simple measures of frequency, percentage, mean,standard deviation, and range of (minimum –maximum values) .The significance of difference of different means (quantitative data) weretested using Students-t-test for difference between two independent means .

The significance of difference of different percentages (qualitative data)were tested using Pearson Chi-square test with application of Yates's correctionor Fisher Exact whenever applicable .
The sensitivity, specificity, positive predictive value and negativepredictive value were calculated for the ileocolonoscopic findings (active/inactive) according to CTE enteric finding measurements .statistical significance was considered whenever the P value was equal or less than 0.05.

Results:
This study include total of (34) patients with CD, they were studied by CTE and ileocolonoscopy.
Patients divided according to simple endoscopic score of CD [SES-CD] [in table 2 in chapter 2] into two groups : active group (30 patients) were SES-CD equal and more than 3 and inactive group (4 patients) with SES-CD score < 3.

Ileocolonoscopy detected mucosal oedema and erosions as the commonest findings in all 30 patients of active group, followed by active mucosal ulcers and scars in 21 patients' .while in the inactive group, mucosal congestion were the predominant findings. The most distinguished CTE finding in (table 2) is the mural thickening were 33 patients have mural thickening 30 of those patient reveal active CD andthree patients reveal inactive CD. The mural hyper enhancement noted in 29 patients all of them revealactive CD Twenty two of patients have positive comb sign 21 of them reveal active CD and 20 patients has mesenteric fat oedema 18 of them reveal active CD. Only 11 patients out of 30 active patients have mesenteric lymph nodes (table 3).

The most visualized enteric complication is the fistula which followed by stricture. While the most extra enteric finding is the cholelithiasis (table 2, table 3).

Table (2): The CTE of enteric and extra-enteric findings reported in CD patients included in the study.

	No	%
Mural thickening (>3mm)	33	97.1
Mural enhancement (=>109 HU)	29	85.3
Combs sign	22	64.7
Mesenteric fat oedema	20	58.8
Mesenteric lymph nodes	13	38.2
Abscess	2	5.9
Fistula	5	14.7
Stricture	4	11.8
Cholelithiasis	3	8.8
Sacroiliitis	3	8.8

The CTE enteric and extra-enteric findings reported in CD patientsincluded in the study according to Crhon's type by ileocolonoscopy (table 3) ,the number of inactive CD patient are 4 (out of total 34 patient) were 3 ofthem have mural thickening which represent significant high percentage (75%) of mural thickening in the inactive group .The comb sign has very low percentage (25%) in the inactive groupwhen correlate to the high percentage of comb sign (75 %) in the active group.

No statistically significant difference was found between the two groupswere concerning the mesenteric fat oedema sign and mesenteric lymphadenopathy (table 3) both have equal percentage (50%) between the two groupsof CD patient

Table (3) : The CTE enteric and extra-enteric findings reported in CD patientsincluded in the study according to Crhon's type by ileocolonoscopy.

	Crhon's type by ileocolonoscopy				
	Active (n=30)		Inactive (n=4)		P value
	No	%	No	%	
Mural thickening (>3mm)	30	100	3	75.0	0.005*
Mural enhancement (=>109 HU)	29	96.7	-	-	0.0001*
Mesenteric fat odema	18	60.0	2	50.0	0.703
comb sign positive	21	69.9	1	25.0	0.646
Mesenteric lymph nodes	11	36.7	2	50.0	0.606
Abscess	1	3.3	1	25.0	0.084
Fistula	4	13.3	1	25.0	0.536
Stricture	2	6.7	2	50.0	0.012*
Cholelithiasis	3	10.0	-	-	0.508
Sacroiliitis	2	6.7	1	25.0	0.225

*Significant difference between proportions using Pearson Chi-square test at 0.05 level

As regards to the mucosal hyper enhancement sign ,there was a highly statistical significant difference in terms of mean values between the two groups denoting much higher thickening values of bowel wall in the active group ,while no significant differences was detected in terms of percentage values (table 5) . According to these results Statistical analysis of CTE signs of activity in both active and

inactive groups of patients revealed a highly significant difference in mural hyper enhancement sign (***P*** <0.001) followed by comb sign (P < 0.05) between two groups (table 3) .

Table (5): The mean values of mural thickening (mm) and enhancement (HU) measurements for patients included in the study according to Crhon's type by ileocolonoscopy.

		Crhon's type by ileocolonoscopy	
		Active (n=30)	Inactive (n=4)
Mural thickening (mm)	Mean±SD	8.50±4.20	7.20±2.04
	Range	4---12	3---11
	Percentile 05th	4	3
	25th	6	5
	50th (Median)	10	7
	75th	12	9
	95th	12	11
	99th	12	11
	P value	0.323	
Mural enhancement (HU)	Mean±SD	115.93±12.96`	37.50±5.00
	Range	55---128	30---40
	Percentile 05th	110	30
	25th	110	35
	50th (Median)	119	40
	75th	123	40
	95th	127	40
	99th	128	40
	P value	0.0001*	

*Significant difference between two independent means using Student-t-test at 0.05 level

In correlation to mural thickening as CTE sign of Crohn's disease activity (table 6) it's Sensitivity=90.9%; Specificity=100% Positive predictive value=100% Negative predictive value=25% Accuracy rate=91.2% .

And the mural hyper enhancement as CTE sign of Cronh's disease activity (table 7) Sensitivity=100%; Specificity=80% positive predictive value=96.7% negative predictive value=100% Accuracy rate=97.1%.

So the most significant diagnostic CTE criteria of CD activity is the mural hyper enhancement followed by mural thickening .in addition to the comb sign which have significant percentage(69.9 %) in active CD patient.

Table (6): The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of ileocolonoscopic finding according to CTE enteric measurements of mural thickening and enhancement**.**

Ileocolonoscopic findings of Crhon's type	Mural thickening (mm)				Mural enhancement (HU)			
	Active (>3mm)		Inactive (<=3mm)		Active (=>109)		Inactive (<109)	
	No	%	No	%	No	%	No	%
Active	30	90.9	-	-	29	100	1	20.0
Inactive	3	9.1	1	100	-	-	4	80.0
P value	0.005*				0.0001*			
	Sensitivity=90.9%; Specificity=100% Positive predictive value=100% Negative predictive value=25% Accuracy rate=91.2%				Sensitivity=100%; Specificity=80% Positive predictive value=96.7% Negative predictive value=100% Accuracy rate=97.1%			

*Significant difference between proportions using Pearson Chi-square test at 0.05 level

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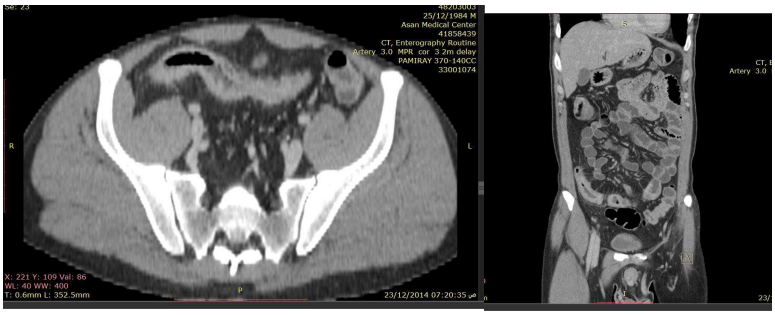

Figure (2) : male patient 30 years old with 4 years history of Crohns disease .CTE withpositive oral contrast (axial a and coronal b) revealed active form of the disease appear as mural thickening and yperenhancementof ileal loops with engorged and increase vascularity , ileocolonoscopy of this case revealed oedema and active ulceration of terminal ileum .

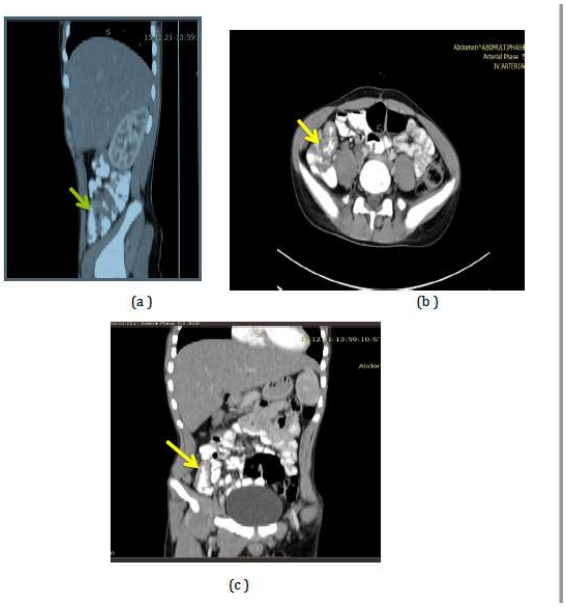

Figure (3) : male patient 19 years old with 2 years history of Crohns disease . CTEwith positive oral contrast (sagitala , axial b and coronal c) shows circumferential wallthickening with mild luminal narrowing involve terminal ileum and caecum withmultiple small mesenteric LAP , reveal active form of the disease , ileocolonoscopy ofthis case revealed oedema and mucosal ulceration and active case of diseases .

Figure (4) : female patient 33 years old with 10 years history of Crohns disease . CTEwith positive oral contrast (axial a and b) shows comb sign with circumferential wallthickening, mesenteric fat oedema and pseudodiverticulumileocolonoscopy revealactive case of CD .

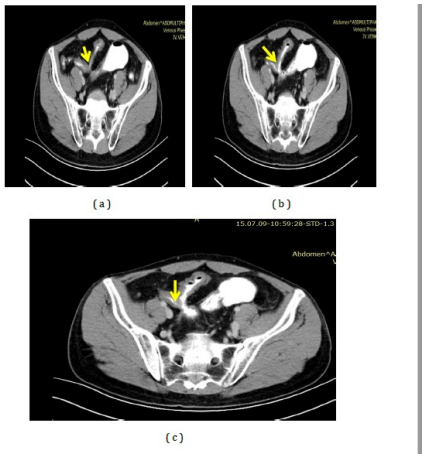

Figure (5) : male patient 32 years old with 10 years history of Crohns disease . CTEwith positive oral contrast (axial a , b and c contagious sections) shows circumferentialmural thickening of terminal ileum with no hyperenhancement and narrowing of thelumen and there is entero colonic fistula between ileum and sigmoid with fat strandingthis is an active case of Crohns disease by CTE which coincides with ileocolonoscopeexamination which reveal multiple mucosal ulcer scars .

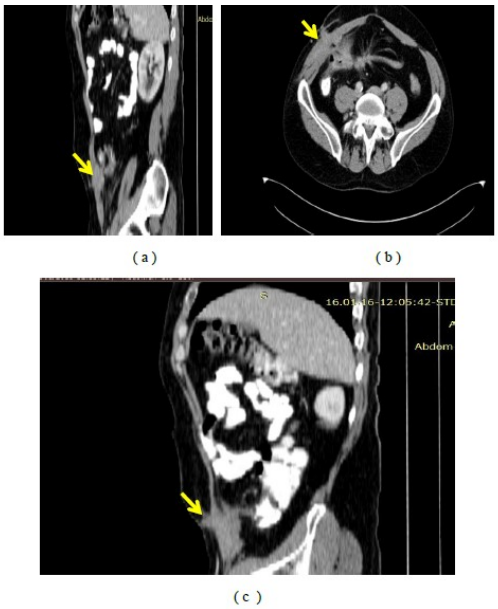

Figure (6): male patient 37 years old with 5 years history of Crohns disease. CTE with positive oral contrast (sagital a, axial b and saggital c) shows healed entero cutaneous fistula leaving adhesions of bowel to anterior abdominal wall with stranding and increase fat density in perenteric and subcutaneous fat tissue.

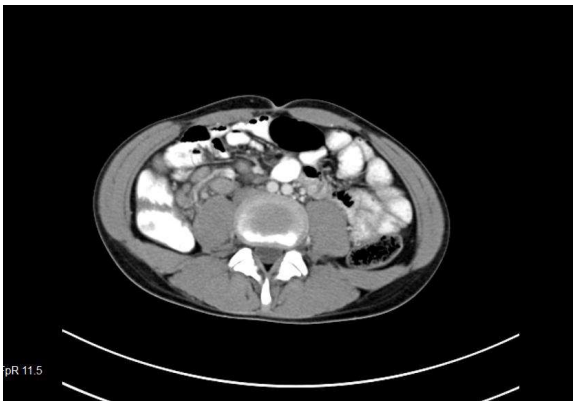

Figure (7) : male patient 19 years old with 2 years history of CD , CTE with positiveoral contrast (axial view) shows enlarged mesenteric lymph nodes ,this is an inactivecase of Crohns disease by CTE which coincides with ileocolonoscope examination whichreveal mucosal congestion .

Discussion:

Crohn's disease (CD) is an incurable chronic condition that can affect any part of GIT Frequently it is manifested by abdominal pain but it is often not clear, whether this pain is caused by active inflammation, stenosis and proximal dilatation, or both. (14) Moreover, there is high prevalence of extra enteric manifestations of the disease that can significantly alter management plans, including the initiation of antibiotic therapy, surgical referral and /or the use of immunosuppressive or biologic agents (14).

Computed tomography enterography (CTE) has been applied to the study of Crohn's disease due to its ability as noninvasive method to differentiate predominant findings, thus helping the physicians to make more informed treatment decision for their patients (15).

In this study we report the CTE findings in CD patient including wall thickening, mural stratification, mucosal hyper enhancement, the comb sign, and increased per enteric fat density, enteric and extra-enteric complication .We found the mural hyper enhancement has highly significant values inpatients with active CD than in patient with inactive CD in respect to bothpercentage and mean values, correlation denoting the significant incidence andquantitative values of mural hyper enhancement in the active CD patients.

The most visually distinguishable CT findings of CD patient are thebowel wall thickening.
There is a high significant difference only in term of mean valuesbetween the two groups in mural thickening, denoting much higher thickeningvalues of bowel wall in the active group, while no significant difference was detected in terms of percentage values revealing the existing incidence of muralthickening in inactive CD.

Hashimoto et al. (16) in which they compared CTE findings with mucosal surface lesions in patients with CD; they revealed a strong correlation between CTE findings and mucosal surface findings were relatively in agreement with Our study results were found strong correlation between CTE finding and CDactivity .

Meyer's and McGuire (17) referred to tortuosity and dilatation of ileal vessels as vascular jejunization of ileum or the "comb sign", noting the occurrence of this finding in patients with CD is common as feature of early CD and associated with activity which correlate well with our study which found high significant percentage value for comb sign (69.9 %) in active CD patient and reported as significant criteria of CD activity.

While in other study comparing CTE, capsule endoscopy, small bowel follow through, and ileocolonoscopy, researchers reported sensitivity of 82% for CTE compared to 74%for ileocolonoscopy and reported that CTE had specificity of 89%compared to 100% to ileocolonoscopy . (18) Which correlate well when compared with our study were all of patient with active Crohn's type by ileocolonoscopy have positive CTE criteria of activity.

Hara and his colleages (19) observed that CTE findings positively correlated with CD disease progression and regression which agree with our study which found mural thickening sensitivity=90.9%; specificity=100% and the accuracy rate=91.2%, and mural hyper enhancement sensitivity=100%; specificity=80% and the accuracy rate=97%. .Booya et al. (20) Demonstrated that CT enterography correctly identifies the presence or absence of fistula in 94% of patients and early adhesions,resulting in changes in the treatment regimen in 61 % of patients. Which agree with our study were found high sensitivity of CTE in diagnosis of enteric complications which are fistula followed by stricture and extra-enteric complications reported in our study included peri-enteric abscess and phlegmon.

Enas Adel GhanyIbrhim et al. (21) found the sensitivity and specificity of CTE in diagnosing CD activity is 83.3% which agree with our study were the CTE findings of active CD patients have high sensitivity and specificity values (mural thickening sensitivity=90.9%; specificity=100% and the mural hyper enhancement sensitivity=100%; specificity=80%). So this study found that CTE provided a significant correlation with ileocolonoscopy in both the active and inactive groups.

CTE criteria for active CD are mural hyper enhancement, mural thickening, and comb sign which are the most predictor signs of CD activity. In addition CTE aided to assess the enteric and extra enteric finding of CD patient.

Conclusions:

We can conclude that CTE has a significant value in diagnosis of Crohn's activity and the mural hyper enhancement, mural thickening and comb sign are the most significant CTE criteria of CD activity with high sensitivity and specificity values.

Those signs should be consider in the diagnostic and management algorithms.

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