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ROLE OF CONTRAST ENHANCED MULTIDETECTOR COMPUTED TOMOGRAPHY IN PRE-OPERATIVE LOCOREGIONAL EVALUATION OF COLONIC CARCINOMA

By

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ABSTRACT

Background: Colorectal cancer is incredibly common. It represents the 4th leading cause of mortality and the second most common malignancy worldwide. With the advent of technological improvement, computed tomography (CT) became one of the important diagnostic tools in the evaluation of local characteristics, preoperative staging, and prognostic factors of colon cancer.

Objective: In this study, we aimed to evaluate the role of contrast enhanced multidetector computed tomography (CEMDCT) in local staging of colorectal carcinoma (CRC).

Patients and methods: MDCT was performed for 37 patients with pathologically proved CRC. All patients submitted to MDCT after IV nonionic iodinated intravenous contrast and oral and rectal positive or negative bowel opacification with water enema. The CEMDCT findings for each patient were recorded and correlated with operative and pathological findings as a reference standard. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated.

Results: In the detection of extramural invasion, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (DC) of CEMDCT were 89.5%, 77.8%, 81%, 87.5%, and 83.8% respectively. In the detection of lymph node status, the sensitivity, specificity, PPV, NPV, and AD were 88.9%, 78.9%, 80%, 68.2%, and 83.8%, respectively. In the detection of retroperitoneal surgical margin (RSM) involvement, the sensitivity was 75%, no false negative patient.

Conclusion: CEMDCT is a sensitive tool in locoregional evaluation of colonic cancer.

Key words: Multidetector CT, opacification, colorectal carcinoma, locoregional**.**

INTRODUCTION

Colorectal cancer is the third most common cancer in both men and women. Conventional colonoscopy is currently considered the reference standard for the detection of colorectal neoplasia (Jemal et al., 2009). However, conventional colonoscopy has various limitations, firstly, it does not allow evaluation of the depth of mural invasion or organs outside the colon, secondly, it fails to show the entire colon in about 5 % of patients, finally, it is invasive and uncomfortable (Narayanan et al., 2014).

The standard treatment of colonic carcinoma is the resection of the tumor with adequate margins including lymphatic drainage without residual tumor

at operative bed (R0 resection) with primary anastomosis. The Surgery is the only curative modality for localized colonic carcinoma (Stage I -III) and potentially curative option for patients with limited metastasis (Stage IV) (Poland and Fakih, 2014).

Imaging techniques play the key role in management of patients with colorectal carcinoma. Accurate staging of colorectal cancer is important to provide the optimal treatment strategy. With the advent of technological improvement, MDCT became one of the important diagnostic tools in the evaluation and preoperative staging of CRC. MDCT may be useful for surgical planning or radiation therapy, particularly when distant metastases or direct invasion of the adjacent organs are seen (Elibol et al., 2016).

Extramural invasion (EMI) is an important factor affecting the prognosis in patients with CRC. Preoperative MDCT can detect EMI in CRC with high sensitivity (Dighe et al., 2010).

Retroperitoneal surgical margin (RSM) was evaluated. RSM involvement occurs within a considerable numbers of caecal and proximal ascending colon carcinoma, suggesting that RSM tumor involvement may be a predictor of recurrence in these tumors (Smith et al., 2007), considering individual anatomical differences, in the colon, not only retroperitoneal ascending and descending colon tumor, but also sigmoid and transverse colon should be kept in mind (Elibol et al., 2016).

The aim of this work was to evaluate the role of CEMDCT in locoregional staging of colorectal carcinoma. The imaging findings were correlated with surgical and pathological findings as reference standards.

PATIENTS AND METHODS

Between October 2013 and April 2016, a total number of 37 patients (24 men and 13 women; mean age 59; age range, 38 - 76 years) diagnosed as colorectal carcinoma were prospectively included in the preset study. All patients underwent surgery within two weeks of MDCT. Curative resection was done in all patients. Patients, patients with renal impairment were excluded. In addition, patients with rectal carcinoma were excluded for two reasons: firstly higher sensitivity of MRI and Trans rectal ultrasound (TRUS) in T staging, secondly, high probability of preoperative chemotherapy which could result in false interpretation with CEMDCT. Written consent was obtained from all patients.

CEMDCT technique: Patient's preparation was performed in all patients by oral administration of 800 - 1200 ml of water (negative or positive contrast medium) two hours before the scanning, and 500 - 1500 ml water enema just before scanning (Negative or positive). MDCT was performed using Toshiba Alexion 16 - row CT scanner, Toshiba medical system Japan and Optima 520 16 row-CT scanner GE USA.) with the following parameters, KV 120, 200-350 MAs, interval 5mm, helical pitch 1.75 :1, 0.8 s gantry rotation time 0.625 mm reconstruction interval with a large field of view.

Unenhanced study was performed firstly in supine position, extending rostrally from the dome of the diaphragm down to the lower aspect of the symphsis pubis using single breath hold in craniocaudal

direction. Enhanced CT study was subsequently performed 70 second after the starting of IV nonionic contrast injection at the rate of 2.5- 3.5 ml/s using an automated power injector system (MEDRAD). Beside axial source images, two dimensional multiplanar reformatted images were performed in coronal, sagittal and oblique planes.

Image analysis: Using axial source images and reformatted images, the findings for each patient were recorded; the presence, location, and morphological characterization of colonic carcinoma were assessed. Tumor localization were categorized under eight regions, cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, and sigmoid. T and N staging was based on the 2010 international TNM classification (Gunderson et al., 2010).

T staging: T1 tumor invading submucosal layer (intraluminal without intestinal wall thickening); T2 tumor invading muscularis propia or subseroa (asymmetrical wall thickening); T3 tumor penetrating serosa and perivesceral fat; T4 tumor invading adjacent organs. In this study, T1 and T2 were considered as the same stage because they are difficult to distinguish from each other on CEMDCT images. Clear pericolonic adipose tissue was assessed as T1/T2, increase density of the pericolonic fat, soft tissue projection or soft tissue strands into the pericolonic fat was assessed as T3, extension of the soft tissue strands into the adjacent organs or structure was assessed as T4.

N staging: For nodal evaluation, NO was evaluated as no lymph nodes, N1 was evaluated as one to three lymph nodes with a short axis more than 5 mm or three or more abnormally clustered normal size lymph nodes. N2 was evaluated as four or more lymph nodes with a short axis larger than 5 mm. In this study, any lymph nodes that have central necrosis, irregular margin, or have calcification were assessed as positive.

Retroperitoneal surgical margin was considered as positive if the distance between the tumor or lymph nodes and retroperitoneal fascia was less than 1 mm.

Pathologic evaluation: Serial sections of 4 microns thickness were prepared from each block and stained by Hematoxylin and Eosin (H&E). Histopathological examination of H&E stained slides was performed for histologic type, patients T and N stage, number of metastatic versus reactive lymph nodes as well as RSM involvement were evaluated and correlated to MDCT staging.

Statistical analysis: Data were analyzed using Statistical Program for Social Science (SPSS) version 22.0. Qualitative data were expressed as frequency and percentage. Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters. Receiver operating characteristic (ROC curve) analysis was used to find out the overall productivity of parameter in and to find out the best cut-off value with detection of sensitivity, specificity, PPV, NPV and accuracy. P value ≤ 0.05 was considered significant.

RESULTS

MDCT was performed in 37 (22 male and 15 female) cases of proved colorectal carcinoma by conventional colonoscopy. No procedural complications were

encountered. The mean age of the patients was 59.6 years. Most of the colonic carcinoma were located in sigmoid colon (16 out of 37, 43.2%), descending colon (No 6, 15.9 %), cecum, cecum/ascending colon (No 5, 13.5 %), transverse colon (No 4, 10.8), hepatic flexure (No 3, 8 %), and ascending colon (No 2, 5.4 %). Histopathology was performed for all patients. Only 1 patient was staged as T1(2.7 %).The majority of the patients (No 17, 45.9 % 100) were staged as T2 (with no pericolonic fat invasion), 15 patients (40.5 %) were staged as T3 (invading through the muscularis propia into the pericolonic fat planes).The remaining 4 patients (10.8 %) were staged as T4 (infiltrating the visceral peritoneum or surrounding organ).Radiologically, both T1 and T2 were assessed as T1/2.

Evidence of extramural extension of the tumor (EMI)was determined and compared with histopathological and surgical results. Radiologic T staging was categorized as understaging, accurate staging and overstaging in correlation with histopathology. On MDCT, 14 out of 18 patients were correctly staged as T1/2, 4 patients were over staged on MDCT, and no understaged patients were recorded. MDCT was correctly staged: 9 out of 15 patients with T3 on histopathology, two patients were understaged, and 4 patients were overstaged. MDCT correctly staged three out of four patients as T4, one patient was understaged. The number of understaged, accurately staged, and overstaged patients were 3 patients (8.1 %0), 26 patients (70.2%) and 8 patients (21,6%) respectively. Regarding to 19 out of 37 patients with extramural invasion (T3 /T4) on histopathology, MDCT was correctly staged 12 patients (63.1%), overstaged 4 patients, (21%), and understaged 3 patients (15.7%) (Table1).

In the present study, MDCT correctly staged 26 out of 37 patients, overstaged 8 patients, (false positive), and understaged 3 patients (false negative). Regarding the correctly staged patients, 14 patients were T1/2 (true negative), and 12 patients were true positive. The overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CEMDCT in detection of EMI (Table 2).

Table (1): Correlation between CEMDCT T staging and histopathological T staging of colorectal carcinoma.

Histopathology / MDCT	T1/2	T3	T4	Total	Chi-square test	
					x^2	p-value
T1/2	14(37.8%)	2(5.4%)	0(0.0%)	16(43.2%)	23.61	**<0.001 (HS)**
T3	4(10.8%)	9(24.3%)	1(2.7%)	14(37.8%)		
T4	0(0.0%)	4(10.8%)	3(8.1%)	7(18.9%)		
Total	18(48.6%)	15(40.5%)	4(10.8%)	37(100.0%)		

Table (2):CEMDCT evaluation of EMI in correlation with histopathological findings.

Histopathology / MDCT	T3/4	T1/2	Sens.	Spec.	FN	FP	PPV	NPV	AUC
T3/4	**TP=17**	**FP=4**	89.5	77.8	10.5	22.2	81	87.5	83.8
T1/2	**FN=2**	**TN=14**							

According to histopathology of the lymph node status, the majority of the patients (No 19, 51.3 %).were staged as N0, N1 in 12 patients, (32.4%), the remaining 6 patients ((16.2%) were staged as N2, MDCT correctly staged 15 out of 19 NO patients, (true negative), the remaining 4 patients were overstaged as N1(false positive). Regarding to N1 patients, MDCT correctly staged 7 out of 12 patients, 2 patients was understaged, and 3 patients were overstaged (false positive). Regarding to N2, MDCT correctly staged 4 out of 6 patients, with two understaged as N1. MDCT correctly staged 26 out of 37 patients (70, 2%), understaging in 4 (10.8%) and overstaging in 7 (18.9. %) patients (Table 3). The overall sensitivity, specificity, PPV, NPV and diagnostic accuracy of CEMDCT (Table 4).

Retroperitoneal surgical margin involvement was reported as positive in 4 patients, three patents were correctly evaluated (true positive) and one patient was false positive. The remaining 32 patient with CEMDCT negative RSM involvement were negative on histopathology.

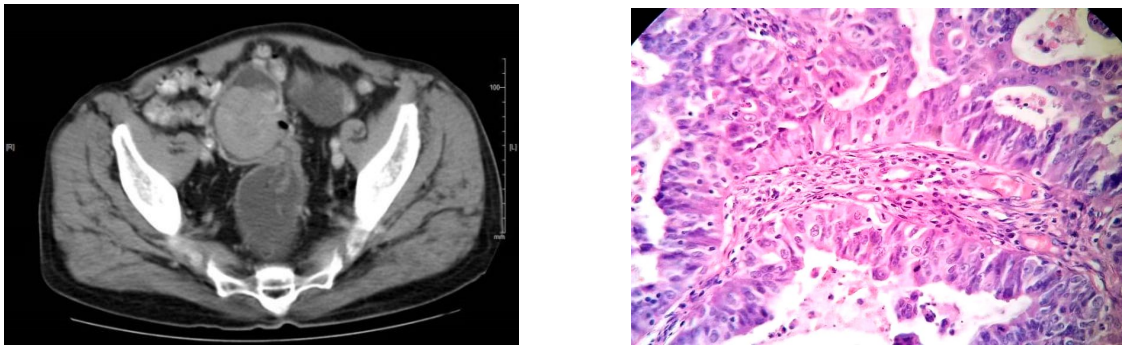
Table (3): Correlation of CEMDCT N staging and histopathological N staging of colonic carcinoma.

Histopathology / MDCT	N0	N1	N2	Total
N0	15(40.5%)	2(5.4%)	0(0.0%)	17(45.9%)
N1	4(10.8%)	7(18.9%)	2(5.4%)	13(35.1%)
N2	0(0.0%)	3(8.1%)	4(10.8%)	7(18.9%)
Total	19(51.4%)	12(32.4%)	6(16.2%)	37(100.0%)

Table (4): CEMDCT evaluation of lymph node status in correlation with histopathological findings

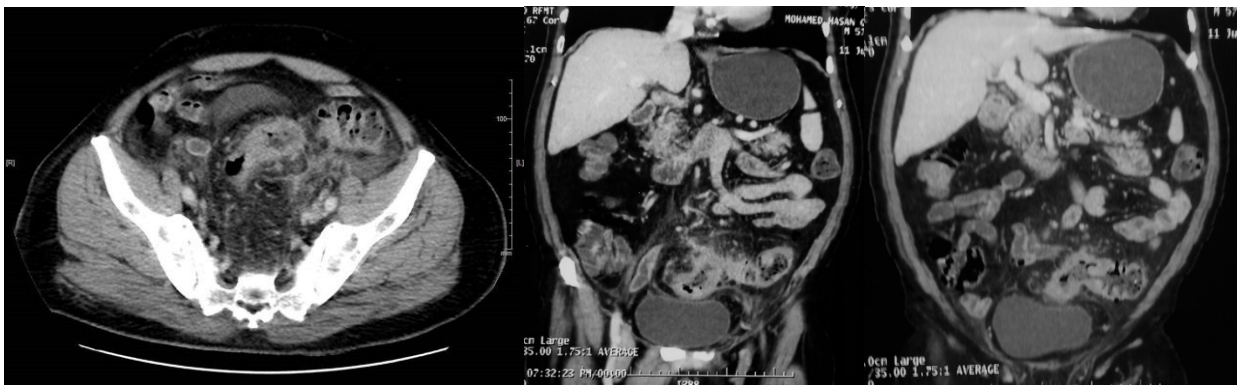
Histopathology / MDCT	N1/2	N0	Sens.	Spec.	FN	FP	PPV	NPV	AUC
N1/2	**TP=16**	**FP=4**	88.9	78.9	11.1	21.1	80.0	88.2	83.8
N0	**FN=2**	**TN=15**							

Figures (1-5) showed cases of colonic carcinoma.



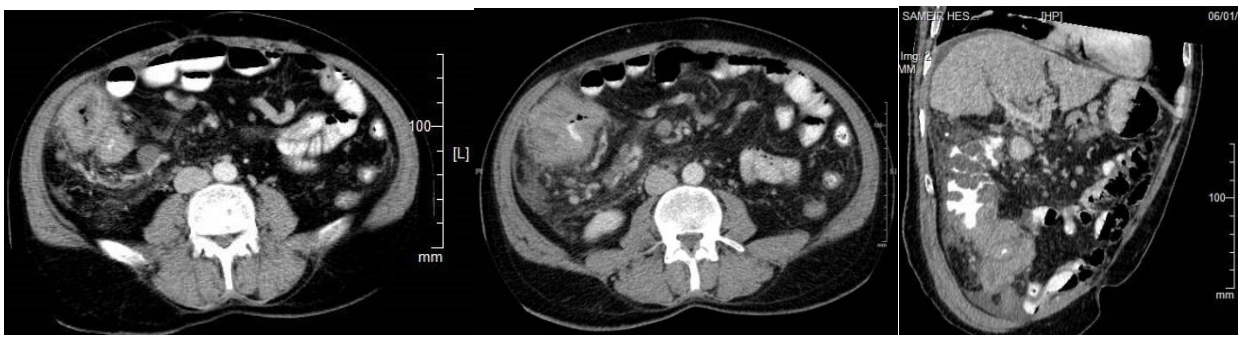
(a) **(b)**

Figure (1): Sigmoid adenocarcinoma**; (a)** CEMDCT of male patient 54-years patient accurately staged of pathologically proven pT1/2 N0 sigmoid carcinoma. **(b)**Grade II of sigmoid colon adenocarcinoma showing malignant cells forming irregular acini, and the cells exhibit large vesicular nuclei with prominent nucleoli (H&E 300x).



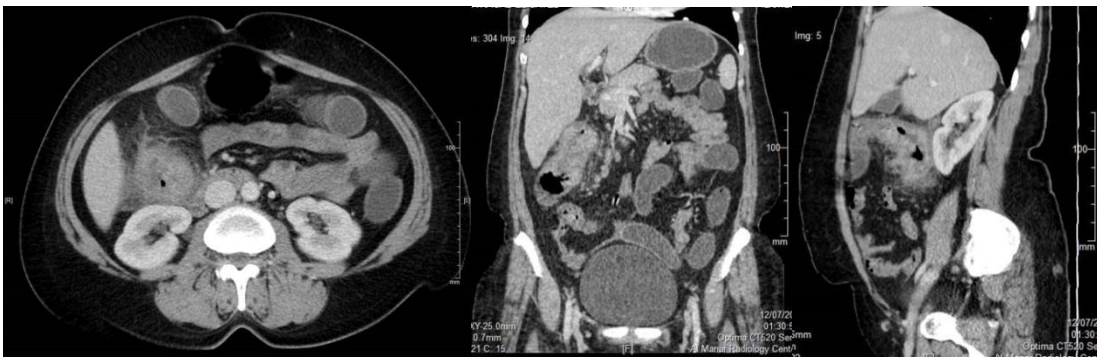
(a) **(b)** **(c)**

Figure (2): CEMDCT **(a)** axial **(b & c)** coronal reformatted images 0f overstaged 62 years.-old male patient with pathologically proven pT3N0, of sigmoid adenocarcinoma, histopathology display reactive lymph node.



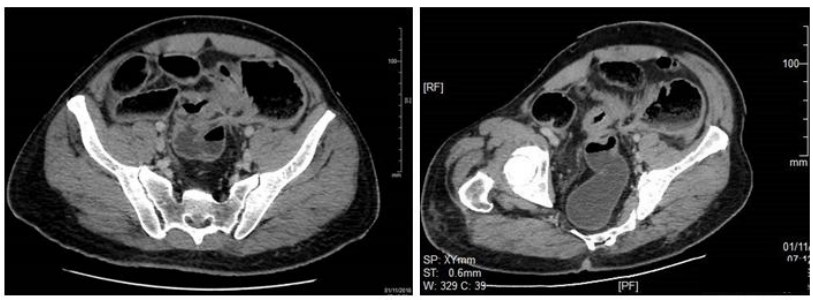
(a) **(b)** **(c)**

Figure (3): CEMDCT axial. (a & b), coronal (c) of accurately staged 65 years old female patient with pathologically proven pT4N2 with positive RSM. CEMDCT display extension of the mass into the terminal ileum (a).

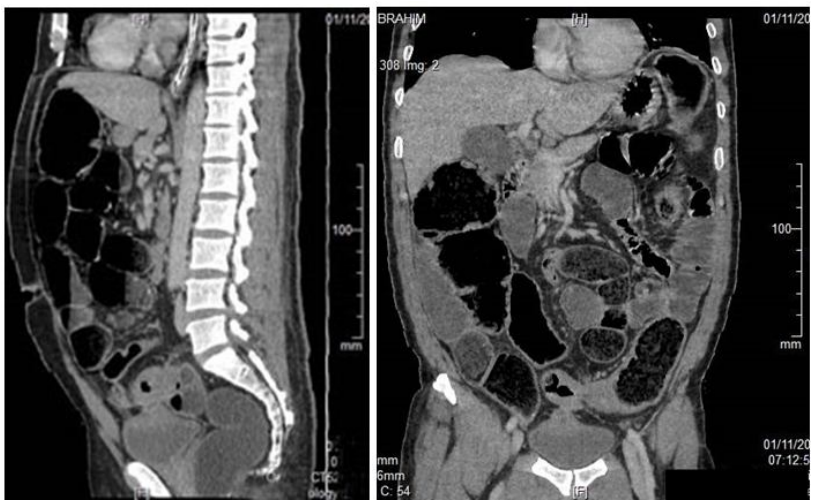


(a) **(b)** **(c)**

Figure (4): CEMDCT (a) axial, (B) coronal and (c) sagittal reformatted image of accurately staged hepatic flexure colonic carcinoma, pathologically proven pT4N2 with positive RSM involvement



(a) **(b)**



(c) **(d)**

Figure (5): a (axial), b (oblique), c & d (sagittal and coronal reformatted images) of overstaged 51 year-old male patient histopathological proven pT2 N1 sigmoid carcinoma, MDCT display invasion of the bladder dome (T4), probably due to desmoplastic / inflammatory reaction. Oblique axial view (b) nicely demonstrates pericolonic enhanced soft tissue strands. Coronal and sagittal (c &d) false positive bladder dome invasion.

DISCUSSION

Colorectal cancer is incredibly common, representing the 4th leading cause of cancer mortality and the 2nd most common malignancy worldwide (Raman et al., 2015) . Preoperative staging is essential for the optimal treatment and surgical planning of CRC. Assessment of the depth of mural invasion of colonic carcinoma (T-stage) and the lymph node status is an important factor in management of patients with colonic carcinoma. The pathological stage of the cancer is the most important predictive factor of overall survival in patients with colorectal carcinoma (Kekelidze et al., 2013).

Dighe et al. (2010), in their meta-analysis, concluded that MDCT accurately distinguish between tumors confined to the bowel wall (T1/2) and those invading beyond the muscularis propria (T3 and T 4), with 86 % sensitivity and 78% specificity, however it is significantly poor at identifying nodal status. Nerad et al. (2016), reported 96% sensitivity and 70 % specificity and he stated that; the use of thin imaging slices (5mm<) improve the detection of tumoral growth beyond the bowel wall (T1-T2 vs. T3-T4). Venera et al. (2015), suggested that water enema MDCT increase the sensitivity and specificity in differentiation of T1/T2 from, T3/T4 (with EMI), he reported 96 % sensitivity and 83 % specificity. In our study, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy was 89.5%, 77.8%, 80.9%, 87.5%, 83.8% respectively, in detecting tumoral invasion beyond the colonic wall into the pericolonic fat planes, with eight (21.1%) patients were overstaged due to stranding pericolonic fat, the explanation probably related to associated inflammatory changes and desmoplastic reaction of the pericolonic tissue without actual tumoral invasion. Our result is almost comparable with Dighe et al. (2010), and Sibileau et al. (2014), they reported 86% sensitivity and 78% specificity for T staging using water enema as negative contrast, and 90% sensitivity and 76 % specificity respectively.

Multiplanar reformatted images enable better delineation of the size and borders of the lymph nodes which are important sign for differentiation of metastatic from reactive lymph nodes. When lymph nodes have irregular border or central necrosis or form a collection or group with a tendency to adhere to each other, radiologist usually suspect metastatic lymphadenopathy (Kijima et al., 2014).

Nerad et al. (2016), in their Meta-analysis stated that thin slices (<5mm) improve the assessment of various criteria such as the size, shape and contour of the lymph nodes, this could be explained the fact that more small lymph nodes are detected using thin slices, which is beneficial; however, small lymph nodes are more difficult to characterized and might be overstaged more frequently by radiologist trying to avoid understaging, this increasing sensitivity, but decreasing specificity. False positive results are caused by benign lymph nodes that are enlarged because inflammation, conversely, false negative results are caused by microscopic metastases in lymph nodes with normal diameter, they reported

sensitivity (71%) but lower specificity (67% versus 78 % in comparable to Dighe et al. (2010).

Elibol et al. (2016), reported that 84% sensitivity and 56% specificity in detection of lymph node metastases. Sibileau al. (2014), showed 90% sensitivity and 85% specificity. In our study, we reported sensitivity, specificity, PPV, NPP and DA 88.9%, 78 %, 80%, 88% and 83% respectively, our result is comparable with Sibileau et al. (2014), with lower specificity (77% versus 85%), which reflect that MDCT cannot reliably differentiate between enlarged lymph node due to metastatic involvement and reactive enlarged lymph node. our specificity was almost the same with Dighe et al. (2010).

With the development of more effective chemotherapeutic agents, neoadjuvent treatment is preferred in patients with high-risk cancer colon (Kekelidze et al., 2013). Preoperative assessment of EMI and RSM positivity can decrease the local recurrence risk and may lead to regression of metastatic lymph node and retroperitoneal extension (Dighe et al., 2010). In a recent retrospective study by Elibol et al. (2016), involving 127 patients with colonic carcinoma, RSM involved in six cases (4.7 %), four of the six, RSM tumor were located on sigmoid with sensitivity and specificity 50% and 80 % respectively, in another retrospective study by Scott et al. (2008), RSM involvement was present in 19 of 228 patients, and 10 of these were due to direct tumoral invasion. Burton et al. (2008) reported 79% as correct prediction of RSM involvement and concluded that; MDCT has potential as the imaging modality of choice in preoperative prediction of poor prognostic feature of colonic carcinoma, In our study, 4 of 37 patients were radiologically positive (10.8%), by direct tumoral invasion, one of them was negative on histopathology (Likely due to desmoplastic reaction or associated perifocal inflammatory changes), resulting in 75% sensitivity, we have no false negative patients in our study.

MDCT can reliably detect extramural invasion and involvement of the RSM which are important prognostic factor in colonic cancer (Tudyka et al., 2015), preoperative detection of RSM involvement may reduce the risk of local recurrence with neoadjuvent chemo-therapy in these patients (Elibol et al., 2016).

In conclusion, CEMDCT was a sensi-tive tool in pre-operative local staging of colonic cancer and has potential as sensitive modality in prediction of poor prognostic features of colonic carcinoma.

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دور الأشعة المقطعية متعددة الكواشف بالصبغة فى التقييم الموضعى لسرطان القولون

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خلفية البحث: يعتبر تقييم مرضى سرطان القولون مرحلة حرجة يتوقف عليها العلاج الأمثل ونوع العملية الجراحية للمريض. ويهدف هذا البحث إلى تقييم دور الأشعة المقطعية متعددة الكواشف بالصبغة الوريدية لتقييم الإنتشار الموضعي لأورام القولون في مرحلة ما قبل العملية الجراحية.

طريقة إجراء البحث: تم إجراء البحث على 37 مريضاً لأورام القولون مع استبعاد أورام المستقيم من البحث وذلك لإحتياج (معظم) المرضى لعلاج كيماوي قبل العملية لتقليص حجم الورم مما يؤثر سلباً على تقييم دور الأشعة مع كل من الجراحة وأمراض الأنسجة. وتم عمل الآتي لجميع المرضى:

1- أشعة مقطعية متعددة الموجات على البطن والحوض بالصبغة الوريدية وتقييم الانتشار الموضعي للورم والغدد الليمفاوية المتعلق به.
2- منظار قولون وأخذ عينة من الورم.
3- عمل تحليل شامل للمريض لإجراء عملية جراحيه.
4- إستئصال الورم جراحياً ومقارنته بفحص الأشعة المقطعيه.
5- التحليل المرضى لأنسجة الورم والغدد الليمفاوية للجزء المستأصل ومقارنتها بالأشعة المقطعية.

نتيجة البحث: أظهر البحث دقة الأشعة المقطعية متعددة الكواشف في وصف الورم السرطاني وتحديد إذا ما كان الورم حبيساً لجدار القولون أو إخترقه وغزا الأنسجة المحيطة به، كما أظهر الدقة في اكتشاف الغدد الليمفاوية المجاورة للورم ولكن ببعض القصور فى التفرقة بين الغدد الناتجة عن أورام ثانوية بها أو نتيجة تفاعل للإلتهابات المصاحبة له.

الخلاصة: أظهر البحث أن الأشعة المقطعية متعددة المجسات بالصبغة الوريدية أداة حساسة في التقييم الموضعي لأورام القولون الخبيثة ولديه إمكانية التنبؤ بحالة المريض بعد إجراء الجراحة وإحتياجه للعلاج بالأدوية الكيماوية.