Original Article

c-MET expression in colorectal adenomas and primary carcinomas with its corresponding metastases

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Background: c-MET plays an important role in tumor proliferation, invasion and metastasis. In this study we examined the expression of c-MET in colorectal adenomas, primary adenocarcinomas and their corresponding lymph node, peritoneal and liver metastases. We correlated our findings with clinicopathological features.

Methods: Twenty three cases of colorectal adenoma and 102 cases of primary colorectal carcinoma and their corresponding metastases (44 lymph nodes, 21 peritoneal deposits and 16 liver metastases) were studied to evaluate c-MET expression by immunohistochemistry. For comparison, 12 sections of adjacent healthy colorectal mucosa were examined.

Results: Statistically significant differences were present among normal tissues, colorectal adenomas and primary colorectal carcinomas (P=0.011). Normal tissues showed a negative or weak reaction in 66.67% and 33.33% of cases respectively. Expression of c-MET was positive in 47.8% of adenomas. A significant positive association was identified between c-MET high expression and degree of dysplasia (P=0.024). c-MET was highly expressed in 66.7% of primary colorectal carcinoma. Significant positive correlations were detected between c-MET expression and TNM stage (P=0.036), lymph node metastasis (LNM), peritoneal deposits and liver metastasis (P=0.038, P=0.094 and P=0.045, respectively). c-MET expression in metastatic tissues was significantly higher than that of the primary tumor.

Conclusions: c-MET expression is gradually up-regulated in the development and progression of colorectal cancer (CRC) from normal epithelium to adenoma to colorectal carcinoma to metastases.

Keywords: c-MET; colorectal adenoma; primary colorectal carcinoma; metastasis; immunohistochemistry

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Introduction

Colorectal cancer (CRC) is currently the third most common cancer type worldwide and it is still the second leading cause of cancer-related deaths worldwide despite of recent advances in neo-adjuvant chemotherapeutic regimens. It is considered the most frequent gastrointestinal malignancy (1,2). In Egypt, CRC constitutes 4.2% being the 7th in men and the 4th in women (3).

Metastatic dissemination of primary colorectal tumors is directly related to patient's survival and is considered as the most frequent reason of treatment failure. It accounts for about 90% of all CRC deaths (4). The 5-year survival of CRC patients with lymph node metastasis (LNM) is only 30% and for those with hepatic metastasis, life expectancy is severely limited (5). Liver metastasis is one of the critical prognostic factors of CRC and 15% of patients with CRC have synchronous or metachronous liver metastases (6).

Molecular targeting on oncogene is now a new therapeutic

approach under intense investigation. The identification of deregulated oncogenic pathways in colonic cancer will lead to new therapeutic options. c-MET, a tyrosine kinase receptor, is overexpressed in a subset of human epithelial malignancies (7) including colorectal (8), ovarian (9), gastric (10), breast (11), endometrial (12), nasopharyngeal (13), hepatocellular (14), and non-small cell lung carcinomas (15) as well as in lymphoma (16). Such overexpression could be the result of c-MET amplification (17).

c-MET (or MET) encodes a cell surface receptor for Hepatocyte Growth Factor/Scatter Factor (HGF/SF), which is a mesenchymal cytokine with pleiotropic effects including mitogenic, monogenic and morphogenic properties (18-20). The c-MET gene has been mapped to chromosome 7 at a subtelomeric position on the q-arm (21). c-MET is expressed in a variety of normal epithelial and endothelial cells while HGF is expressed only by cells of mesenchymal origin (22).

Activation of c-MET by HGF and its signaling pathways promotes tumor cell proliferation, migration, invasion and tumor angiogenesis as well as poor prognosis (7,20,23).

c-MET amplification and overexpression were observed in colonic adenomas and primary tumors, while less expression existed in normal colonic tissues (24). In addition, the system of c-MET and its ligand HGF had been found to play a vital role in distant metastases of CRC (25,26). However, few studies to the best of our knowledge have compared.

c-MET expression in primary CRC and distant metastases, and they have yielded conflicting results (18,27,28). Therefore, it is important to investigate the concordance of results from primary tumors and distant metastases.

This study aimed to analyze the immunohistochemical expression of c-MET in colorectal adenomas and primary colorectal carcinomas including their corresponding metastases; lymph node metastases, peritoneal deposits and liver metastases. We also investigated the correlation of c-MET expression and clinicopathological association of the studied cases.

Patients and methods

Patients

We conducted a retrospective study of colorectal adenoma and carcinoma cases attended at Minia Oncology Center (Egypt), Minia University Hospital (Egypt) and Almowasat Hospital, Almadina Almonawara (Saudi Arabia) during the period between January 2011 and October 2014. Data were extracted from the pathology reports and medical records. Only cases with available adequate tumor tissue and complete clinicopathological data were considered eligible. Patients did not receive neo-adjuvant therapy. The final number available was 23 cases of colorectal adenomas and 102 cases of colorectal carcinomas, representing the study population. For comparison, 12 sections of adjacent healthy colorectal mucosa were also examined.

Diagnosis was done by colonoscopic evaluation of patients presenting with bleeding per rectum, constipation and change in the bowel habits. Multiple biopsies were taken from any suspected lesions or unhealthy mucosa for histopathology. The lesions which were confirmed histopathologically to be colorectal carcinomas were subjected to surgical resection with safety margin together with resection of its corresponding mesentery and lymph nodes according to the lesion's site.

Concerning adenoma cases, the age and gender of patients were recorded. The histological type; tubular, villous, tubulovillous (reviewed according to WHO criteria) (29) and the histological grade of dysplasia (low and high) were obtained from histopathology data files. As regards the carcinoma cases, clinical and pathological data were retrospectively obtained from the files of the hospital medical archive. The included clinical data were histological type of the tumor, histopathological grade, tumor infiltrating lymphocytes, invasion of colonic wall, lymph node, and distant metastasis. Forty-four cases were associated with lymph node metastases, 21 cases were associated with peritoneal dissemination, and 16 cases were associated by liver metastases. Tumor type and grade were reviewed according to the WHO criteria (29). Tumor stage was estimated by the TNM staging system (30).

For the assessment of tumor infiltrating lymphocytes, the entire H&E-stained section of the tumor representing the area with the highest degree of lymphocytic infiltration was examined at low magnification to obtain an overall assessment of the extent of infiltration which was then categorized according to the density of lymphocytic infiltration as: (I) grade 0: absent; (II) grade 1: mild infiltration (scattered lymphocyte aggregates); (III) grade 2: moderate infiltration; (IV) grade 3: marked infiltration (31,32).

Immunohistochemistry

Immunohistochemistry was performed on 10% buffered

formalin fixed, paraffin embedded tissue blocks. On 4-μm tissue sections, pre-diluted rabbit anti-human c-MET monoclonal antibody (clone SP44, spring bioscience, CA, USA) was used as the primary antibody. Briefly, after deparaffinization in xylene and hydration in descending grades of alcohol till distilled water, endogenous peroxidase activity was inhibited by hydrogen peroxide. Antigens were retrieved by using 0.01 M sodium citrate and heated in a microwave oven for 20 min and then incubated with primary antibody for 30 min at room temperature. For the secondary developing reagents, a labeled streptavidin-biotin kit (Novocastra, Germany) was used. Antigens were visualized using Envision system (Novocastra, Germany) and diaminobenzidine (DAB) (Novocastra, Germany). Finally sections were counterstained with hematoxylin (Novocastra, Germany) then dehydrated and mounted. In negative control slides, primary antibody was not included. Human breast carcinoma was used as the positive control.

Evaluation of immunohistochemical staining

The specimens were evaluated independently by two of the authors (N.R. & M.F.) in a blind fashion to the clinic-pathological data. The cytoplasmic/membranous c-MET immunoreactivity in cells was evaluated by considering the intensity of staining as follow: (I) 0, negative immunostaining; (II) 1, weak immunostaining; (III) 2, moderately positive immunostaining; and (IV) 3, strongly positive immunostaining. We defined scores 0 and 1 as c-MET-low expression, and scores 2 and 3 as c-MET-high expression (19,33).

Statistical analysis

All statistical analyses were performed using SPSS 16.0 computer software. To test associations between categorical variables, Chi-square and Fisher exact tests were conducted. Kappa was used a measure of agreement between primary cancer and different metastatic sites. P of 0.05 was used as a significance criterion.

Results

Clinicopathological data of patients

Adenomas

The examined 23 adenoma cases were 15 males (65.2%) and 8 females (34.8%). The M:F ratio was 1.87:1. The mean age was (53.87±7.65) years and a median of 53 years (range, 43-69 years). Adenoma cases were of the following histological types: 15 (65.3%) tubular adenomas, 3 (13%) villous adenomas and 5 (21.7%) tubulovillous adenomas. Eleven adenomas (47.8%) showed low dysplasia, 12 adenomas (52.2%) showed high dysplasia.

Carcinomas

The mean age of the studied colorectal carcinoma cases was (51.49±13.87) years and a median of 51 years (range, 22-79 years). This study included 56 (54.9%) males and 46 (54.9%) females. The M:F ratio was 1.2:1. There were 3 (2.9%), 36 (35.3%), 8 (7.8%), 17 (16.7%), 18 (17.6%) and 20 (19.6%) cases of carcinomas located in the caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum, respectively. According to tumor type, 76 cases (74.55%) were adenocarcinomas, 17 cases (16.7%) were mucoid carcinomas and 9 cases (8.8%) were signet ring carcinomas. Among the 76 adenocarcinoma cases, 4 cases (3.9%) were well-differentiated adenocarcinoma, 42 cases (41.2%) were moderately differentiated adenocarcinoma and 30 cases (29.4%) were poorly differentiated adenocarcinoma. Lymphocytic infiltrate was found in 58 (56.9%) of the cancer cases in which, 23 tumors (22.5%) showed mild lymphocytic infiltrate, 15 (14.7%) tumors displayed moderate lymphocytic infiltrate and 20 tumors (19.6%) had marked lymphocytic infiltrate. Regarding the stage of cases, 55 cases (53.9%) were stages I, II and 47 (36.3%) cases were stages III, IV.

c-MET expression in the study groups

Normal tissues showed either negative or weak reaction in 66.67% and 33.33% of cases respectively (*Figure 1A*). Adenomas had a positive rate of 47.8%, while the positive rate in cancer reached 66.7%. Statistically significant differences were present among the three groups (P=0.011; P=0.594 in normal mucosa *vs.* adenoma, P=0.035 in normal mucosa *vs.* carcinoma and P=0.030 in adenoma *vs.* carcinoma).

c-MET expression in adenoma

c-MET immunoreaction was confined to cytoplasm/membranous staining as shown in (*Figure 1B*,C). Overall, 12/23 (52.2%) of adenomas were c-MET low expression and c-MET high expression was found in 11/23 (47.8%). A significant positive association was identified between c-MET high expression and degree of dysplasia (P=0.009).

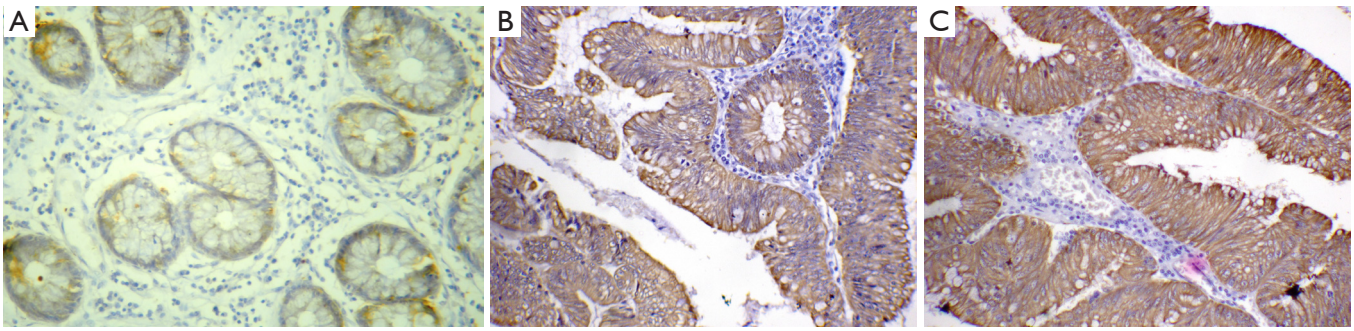

Figure 1 Representative immunohistochemistry for c-MET. (A) c-MET immunostaining in normal colon (low expression). The intense stain is located on membrane and cytoplasm of mucosal cells; (B) c-MET immunoreaction in villous colorectal adenoma (low expression). The intense stain is detected on membrane and cytoplasm of adenomatous cells; (C) c-MET immunostaining in villous colorectal adenoma with dysplasia (high expression). The intense stain is detected on membrane and cytoplasm of adenomatous cells. (DAB chromogen, haematoxylin counterstain. A, ×200; B,C, ×400).

Table 1 The association between c-MET expression and different clinic-pathological parameters in colorectal adenomas (N=23)

Clinic-pathological parameters	No. (%)	c-MET expression		P
		Low (%)	High (%)	
Age				0.611
<50	8 (34.82)	4 (50.0)	4 (50.0)	
≥50	15 (65.2)	8 (53.3)	7 (46.7)	
Sex				0.611
Male	15 (65.2)	8 (53.3)	7 (46.7)	
Female	8 (34.8)	4 (50.0)	4 (50.0)	
Size				0.154
≤1.6 cm	14 (60.9)	9 (64.3)	5 (35.7)	
>1.6 cm	9 (39.1)	3 (33.3)	6 (66.7)	
Type				0.579
Tubular	15 (65.2)	9 (60.0)	6 (40.0)	
Villous	3 (13.0)	1 (33.3)	2 (66.7)	
Tubulovillous	5 (21.7)	2 (40.0)	3 (60.0)	
Degree of dysplasia				0.009*
Low	11 (47.8)	9 (81.8)	2 (18.2)	
High	12 (52.2)	3 (25.0)	9 (75.0)	

Test of significance: Chi-square and Fisher exact tests, *, P<0.05 is considered significant.

The higher the degree of dysplasia, the higher the expression level of c-MET. There was no significant relation between c-MET expression and the histological type (P=0.579). *Table 1* shows the association between c-MET expression and different clinicopathological parameters.

c-MET expression in primary colorectal carcinoma

c-MET immunostaining was located in the cytoplasm/membrane of tumor cells (*Figure 2A-G*). The c-MET high expression was found in 68 cases (66.7%) of primary CRC tumors and low expression in 34 cases (33.3%). Significant positive correlations were detected between c-MET expression and TNM stage (P=0.014), and matched lymph node and liver metastasis (P=0.038, P=0.045 respectively). There was no significant correlation between c-MET expressions with any of other clinicopathological

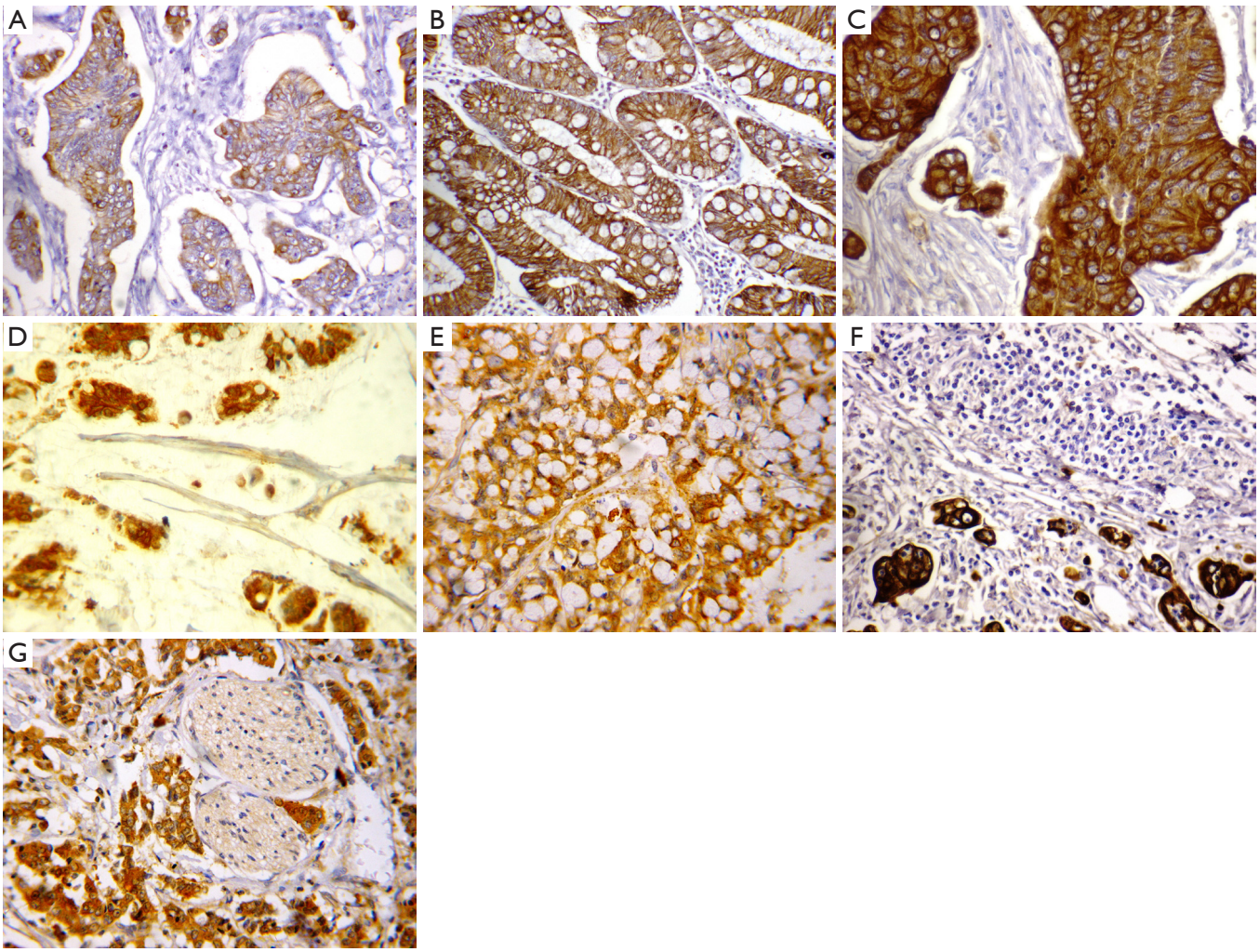

Figure 2 c-MET immunohistochemical expression in colorectal carcinomas. The intense stain is encountered on cytoplasm and membrane of malignant cells. (A) c-MET immunostaining in colorectal carcinoma grade I (low expression); (B) c-MET immunostaining in colorectal carcinoma grade II (high expression); (C) c-MET immunostaining in colorectal carcinoma grade III (high expression); (D) mucoid colorectal carcinoma with high c-MET expression; (E) signet ring colorectal carcinoma with high c-MET expression; (F) high c-MET expression in association with mild tumor lymphocytic infiltration; (G) perineural invasion and high c-MET immunoreactions. (DAB chromogen, haematoxylin counterstain, ×400).

parameters. *Table 2* shows the association between c-MET expression and different clinicopathologic parameters.

c-MET expression in matched metastasis and peritoneal dissemination

In 44 pairs of primary tumors and matched lymph node metastases, c-MET positive expression was found in 35(79.5%) and 38(86.4%) cases of primary tumors and matched lymph node metastases respectively. Only 39 cases (88.6%) positive for c-MET showed concordance result (P<0.001), Kappa=0.601 (*Figure 3A,B*).

In 21 pairs of primary tumors and peritoneal dissemination, c-MET positive expression was found in 14 (66.7%) cases of primary tumors and 15 (71.4%) cases of matched peritoneal dissemination. The concordance result was found in 18 cases (85.7%) positive for c-MET (P=0.002), Kappa=0.667 (*Figure 3C,D*).

In 16 pairs of primary tumors and liver metastases, 13 (81.2%) cases of primary tumors and 15 (93.8%) cases of matched liver metastases showed c-MET positive expression.

Table 2 The association between c-MET expression and different clinic-pathological parameters in primary colorectal carcinomas (N=102)

Clinicopathological parameters	c-MET expression		P
	Low (%)	High (%)	
Age			0.527
<50	15 (34.1)	29 (65.9)	
≥50	19 (32.8)	39 (67.2)	
Sex			0.220
Male	21 (37.5)	35 (62.5)	
Female	13 (28.3)	33 (71.7)	
Site			0.281
Caecum	2 (66.7)	1 (33.3)	
Ascending	14 (38.9)	22 (61.1)	
Transverse	3 (37.5)	5 (62.5)	
Descending	2 (11.8)	15 (88.2)	
Sigmoid	5 (27.8)	13(72.2)	
Rectum	8 (40.0)	12 (60.0)	
Type			0.316
Adenocarcinoma	28 (36.8)	48 (63.2)	
Mucoid	3 (17.6)	14 (82.4)	
Signet ring	3 (33.3)	6 (66.7)	
Tumor grade (for adenocarcinoma only)			0.540
GI	2 (50.0)	2 (50.0)	
GII	16 (38.1)	26 (61.9)	
GIII	10 (33.3)	20 (33.7)	
Perineural invasion			0.144
Yes	3 (18.8)	13 (81.2)	
No	31 (36.0)	55 (64.0)	
Lymphovascular invasion			0.074
Yes	7 (21.9)	25 (78.1)	
No	27 (38.6)	43 (61.4)	
Tumor infiltrating lymphocytes			0.148
Absent	10 (22.7)	34 (77.3)	
Mild	8 (34.8)	15 (65.2)	
Moderate	8 (53.3)	7 (46.7)	
Marked	12 (60.0)	8 (40.0)	
TNM stage			0.014*
Stages I & II	24 (43.6)	31 (56.4)	
Stages III & IV	10 (21.3)	37 (78.7)	
LN metastasis			0.038*
Yes	24 (22.7)	31 (77.3)	
No	24 (41.4)	34 (58.6)	
Peritoneal dissemination			0.094
Yes	4 (19.0)	17 (81.0)	
No	30 (37.0)	51 (63.0)	
Liver metastasis			0.045*
Yes	2 (12.5)	14 (87.5)	
No	32 (37.2)	54 (84.3)	

Test of significance: Chi-square and Fisher exact tests, *, P<0.05 is considered significant.

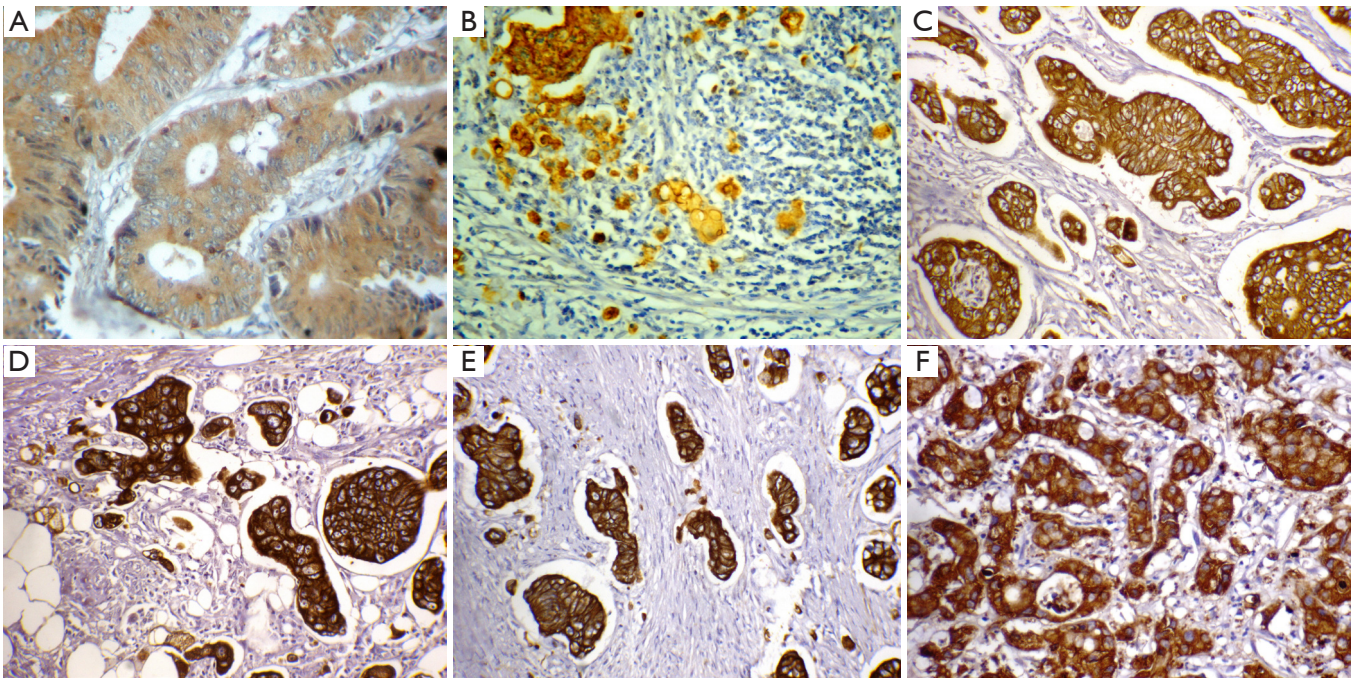

Figure 3 c-MET immunohistochemical expression in CRCs with their corresponding metastases. (A,B) c-MET expression in primary CRC and its corresponding lymph node metastasis (LNM); (C,D) c-MET expression in primary CRC and its corresponding peritoneal deposits; (E,F) c-MET expression in primary CRC and its corresponding liver metastasis. (DAB chromogen, haematoxylin counterstain. A, ×400; B-F, ×200).

Fourteen cases (87.5%) positive for c-MET showed concordance result (P=0.032), Kappa=0.448 (*Figure 3E,F*).

Discussion

c-MET is a key driver of oncogenic transformation and is associated with poor clinical outcome in a defined subset of cancers. The poor prognosis of metastatic CRC patients underscores the importance of defining molecular factors responsible for cancer metastasis. Therefore, identification of prognostic factors allows the definition of high risk groups of patients for whom optimal therapy might be necessary (34).

In this study we examine the degree of c-MET expression in adenoma and primary colorectal carcinomas as well as its correlation with clinicopathological parameters. We also analyzed the c-MET expression in primary tumors in relation to c-MET expression in matched metastases, with special focus on regional lymph nodes, peritoneal and liver metastases.

We found that adenomas had a c-MET high expression in 47.8%, while the high expression in carcinomas reached 66.7% with statistically significant differences among the three groups; normal versus adenoma groups, normal versus carcinoma groups and in adenoma versus carcinoma groups. In this study, c-MET expression in matched metastasis and peritoneal dissemination was statistically significant. We found that c-MET overexpression in the corresponding metastatic sites including LNM, peritoneal dissemination and liver metastasis were 86.4%, 71.4%, and 93.8%, respectively. Previous studies were reported that c-MET was overexpressed in the cancer tissue when compared with its expression in corresponding normal tissue (28,35-37). Boon *et al*. (38) stated that along the colon adenoma-carcinoma sequence, c-MET was overexpressed in both lesions without any apparent correlation. Beside that previous studies observed a change in the expression of c-MET from primary tumors to metastases (8,33,39).

Our results has shown that the rate of c-MET expression was significantly increased with the course of cancer development as c-MET is expressed more strongly in adenoma and primary CRC than in normal mucosa and that c-MET expression in metastases is higher than that in the corresponding primary cancer. This progressive increase highlights the oncogenic role of c-MET in colorectal carcinogenesis.

In adenoma cases, our results demonstrated that c-MET overexpression was significantly related to the grade of dysplasia where c-MET overexpression was significantly higher with advanced dysplastic changes. There was no significant relation between c-MET expression and histological type. Previous studies, mentioned that, there was no significant relation between c-MET expression with histological type or grade of dysplasia of adenomas (35,40).

TNM classification is still believed to be a better option in evaluating prognosis. We found that c-MET correlated with TNM stages with a perceptible and progressive significant increase of c-MET expression from stage I to stage IV. Our data are in part corroborated by some data already published where c-MET was indeed demonstrated to be a good marker for predicting the metastatic potential of colorectal tumors (25,36,37,41). Our results coincided with the results of (37) which found that the patients with low c-MET expression had fewer nodal and distant metastases.

According to our results and previous study by Abou-Bakr and Elbasmi (37), c-MET expression can be used in a preoperative staging scheme. There are many potential benefits to include molecular markers in staging of CRC and select the group of patients with worse prognosis and who are at high risk of relapse.

There was no significant correlation between c-MET expression and clinic-pathological variables. This is in accordance with previous studies (25,28,37,42,43). However, Tabuchi *et al*. (42) reported that a significant difference was found between the regional LNM, venous invasion and lymphatic invasion. A trend for low c-MET expression in well differentiated cancers compared to the moderately or poorly differentiated ones was previously observed (35).

The regional lymph node and liver are common sites of metastasis in patients with CRC (44). We found that c-MET expression in metastatic tissues was also higher than that of the primary tumor. However, the difference was not significant. Concordance rate between primary tumors and lymph node metastases was 88.6%, between primary tumors and peritoneal dissemination was 85.7% and between primary tumors and liver metastasis was 87.5%. We conclude that, high concordance rates was found between primary tumors and matched metastases. Concordance rate suggests that primary tumors and their corresponding metastases had the same clone (44). Thus, metastatic cells can express most of the genes existing in their progenitors including c-MET. The difference may be due to their expression being influenced by local microenvironments of liver and lymph node.

Some previous studies have analyzed c-MET protein expression in primary CRC and metastases. Few studies showed that c-MET protein expression tended to be decreased in distant metastases compared to their corresponding primary tumors (28,45). Other studies including this one observed that c-MET expression tended to be increased in distant metastases compared to their corresponding primary tumors (8,25,33,39). Further investigation of c-MET activation in primary tumors and their corresponding metastases is needed to determine the importance of c-MET in the metastasis of CRC.

Our study is being one of the first studies to examine c-MET expression in the peritoneal deposits with correlation with their primary CRC. Our results showed that positive protein expression of c-MET in peritoneal deposits was statistically higher than corresponding primary colon. Previous studies have found that local peritoneal involvement is a strong predictor of adverse outcome in stage II and stage III disease and tumor perforation into the peritoneal cavity is a well-established adverse prognostic factor in CRC (46-48).

c-MET may serve as a biomarker for targeted therapy. Several molecules targeting c-MET have been tested in early phase clinical trials (49,50). Most of them are small kinase inhibitors, while others are biological antagonists and monoclonal antibodies targeting either the ligand or the receptor. Combination therapy with MET tyrosine kinase inhibitors and standard chemotherapeutic agents is one treatment modality that targets the HGF/MET pathway (51,52).

In conclusion, our findings suggest that c-MET appears to be an important prognostic factor for patients with CRC. Additional studies of c-MET activation and signal transduction will increase our knowledge of the role of c-MET in CRC metastasis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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