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BRIEF ARTICLE

Preoperative carcinoembryonic antibody is predictive of distant metastasis in pathologically T1 colorectal cancer after radical surgery

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Abstract

AIM: To identify the predictors of distant metastasis in pathologically T1 (pT1) colorectal cancer (CRC) after radical resection.

METHODS: Variables including age, gender, preoperative carcinoembryonic antibody (CEA) level, tumor location, tumor size, lymph node status, and histological grade were recorded. Patients with and without metastasis were compared with regard to age, gender, CEA level and pathologic tumor characteristics using the independent *t* test or χ^2 test, as appropriate. Risk factors were determined by logistic regression analysis.

RESULTS: Metastasis occurred in 6 (3.8%) of the 159 patients during a median follow-up of 67.0 (46.5%) mo. The rates of distant metastasis in patients with pT1 cancer of the colon and rectum were 6.7% and 2.9%, respectively ($P < 0.001$). The rates of distant metastasis between male and female patients with T1 CRC were 6.25% and 1.27%, respectively ($P < 0.001$). The most frequent site of distant metastasis was the liver. Age ($P = 0.522$), gender ($P = 0.980$), tumor location ($P = 0.330$), tumor size ($P = 0.786$), histological grade ($P = 0.509$), and high serum CEA level ($P = 0.262$) were not prognostic factors for lymph node metastasis. Univariate analysis revealed that age ($P = 0.231$), gender ($P = 0.137$), tumor location ($P = 0.386$), and tumor size ($P = 0.514$) were not risk factors for distant metastasis after radical resection for T1 colorectal cancer. Postoperative metastasis was only significantly correlated with high preoperative serum CEA level ($P = 0.001$). Using multivariate logistic regression analysis, high preoperative serum CEA level ($P = 0.004$; odds ratio 15.341; 95%CI 2.371-99.275) was an independent predictor for postoperative distant metastasis.

CONCLUSION: The preoperative increased serum CEA level is a predictive risk factor for distant metastasis in CRC patients after radical resection. Adjuvant chemotherapy may be necessary in such patients, even if they have pT1 colorectal cancer.

Key words: Colorectal cancer; Risk factor; Metastasis; Pathologically T1; Carcinoembryonic antigen

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common ma-

lignancies and a leading cause of cancer-related deaths in Europe and the United States[1-3]. Similarly, it is the fifth leading cause of cancer deaths in China and the incidence of CRC is rapidly increasing[4,5].

The standard surgical treatment for CRC is radical resection. Recent advances in diagnostic methods have led to an increase in the detection of T1 CRC[6,7]. Local excision has been substituted for radical resection in some patients with early CRC. However, local excision may result in a higher rate of local recurrence than radical resection in patients with T1 CRC. Local excision leaves metastatic lymph nodes in 8%-15% of pathologically T1 (pT1) CRC patients without definitively retrieving regional lymph nodes[8], resulting in a recurrence rate of 4.1%-39%[9]. However, the recurrence rate has been reported to be 1.3%-2.8% after radical resection of early CRC[6,10]. To minimize recurrence, radical surgery has been performed in China for the treatment of most patients with pT1 CRC.

Previous studies have focused on evaluating the risk factors for lymph node metastasis[10-13], and there is little evidence with regard to the risk factors for postoperative distant metastasis in patients with pT1 CRC. The aim of the present study was to identify the predictive risk factors that may suggest postoperative distant metastasis in patients with pT1 CRC after radical resection.

MATERIALS AND METHODS

One hundred fifty-nine patients with pT1 CRC who had undergone radical resection with lymph node dissection between January 2005 and June 2011 were enrolled. All patients were followed up until December 2011. The study was performed after approval by the Ethics Committee at the Second Military Medical University in Shanghai, China. None of these patients had received preoperative radiotherapy or neoadjuvant chemotherapy. Patients with pT1 CRC who were treated by endoscopic mucosal resection or transanal resection were excluded. Other exclusion criteria were recurrent CRC or cancer associated with familial adenomatous polyposis and inflammatory bowel disease.

Preoperative investigations included colonoscopy, chest X-rays, ultrasonography, computed tomography (CT) of the liver, and blood tests for carcinoembryonic antigen (CEA). A 3-mL peripheral blood sample from each patient was obtained. Serum CEA levels were determined using an enzyme immunoassay test kit (Beckman Coulter, Inc., Fullerton, CA, United States) with the upper limit of 5 ng/mL being defined as normal according to the kit manufacturer.

We established a 5- to 10-year follow-up period which included serum CEA measurements every 3 mo for the first 2 years and every 6 mo for the next 3 years, hepatic imaging (ultrasonography or CT) and chest X-rays every 3 mo, pelvic CT for rectal cancer every 6 mo, and colonoscopy every year.

Continuous variables were presented as means (standard deviation) and dichotomous variables were presented as number and percentage values. Patients with and without metastasis were compared with regard to age, gender, and clinicopathologic characteristics using the independent *t* test or χ^2 test, as appropriate. Logistic regression analysis was used to identify risk factors for distant metastasis. Variables significant at $P < 0.10$ by univariate analysis were subjected to stepwise logistic regression analysis to identify independent risk factors ($P < 0.05$) for distant metastasis. All analysis were performed with SPSS version 17 statistical software package (SPSS, Inc., Chicago, IL, United States).

RESULTS

Demographic data of the 159 patients with pT1 CRC are shown in Table 1. Distant metastasis occurred in 6 (3.8%) of the 159 patients during a median follow-up of 67.0 (46.5%) mo. The rates of distant metastasis in patients with pT1 cancer of the colon and rectum were 6.7% and 2.9%, respectively ($P < 0.001$). The recurrence rates among male and female patients with pT1 CRC were 6.25% and 1.27%, respectively ($P < 0.001$). The most frequent site of metastasis was the liver in pT1 CRC. Preoperative serum CEA level was higher in patients with distant metastasis than in patients without distant metastasis (11.35 ng/mL *vs* 3.25 ng/mL). Comparisons of patients with and without distant metastasis are shown in Table 1. The distant metastasis negative and positive groups were similar with regard to patient demographics and clinicopathologic features.

Based on univariate analysis of the correlation between lymph node metastasis (LNM) and clinicopathologic features, we found that age ($P = 0.522$), gender ($P = 0.980$), tumor location ($P = 0.330$), tumor size ($P = 0.786$), histological grade ($P = 0.509$), and high serum CEA level ($P = 0.262$) were not predictive factors for LNM (Table 2).

Univariate analysis revealed that age ($P = 0.231$), gender ($P = 0.137$), tumor location ($P = 0.386$), and tumor size ($P = 0.514$) were not risk factors for distant metastasis after radical resection for pT1 CRC (Table 2). The patients with unfavorable histological grade [odds ratio (OR) 1.365] were more likely to have metastasis, although the difference did not reach statistical significance ($P = 0.086$). Postoperative metastasis was only significantly correlated with a high serum CEA level ($P = 0.001$, Table 2). Using multivariate logistic regression analysis, high serum CEA level (OR 15.341, 95%CI 2.371-99.275, $P = 0.004$) was an independent predictor for postoperative distant metastasis.

Details of patients with distant metastasis are shown in Table 3. All distant metastases were found less than 3 years after surgery. Two of the six patients died due to the metastases, and the remaining patients are still alive after hepatic resection.

Table 1 Characteristics of 159 patients *n* (%)

Characteristics	With T1 colorectal cancer	Without metastasis (*n* = 153)	With metastasis (*n* = 6)	*P* value
Age, yr, mean ± SD	60.7 ± 11.7	60.48 ± 11.83	66.33 ± 7.012	0.231
Gender				0.099
Male	80 (50.3)	75	5	
Female	79 (49.7)	78	1	
Primary site				0.647
Cecum	3 (1.9)	3	0	
Ascending colon	9 (5.7)	8	1	
Transverse colon	6 (3.8)	6	0	
Descending colon	6 (3.8)	5	1	
Sigmoid colon	21 (13.2)	20	1	
Rectosigmoid	8 (5.0)	8	0	
Rectum	104 (65.4)	101	3	
Anus canal	2 (1.3)	2	0	
Pathology				0.919
Well differentiated	11 (6.9)	11	0	
Moderately differentiated	83 (52.2)	79	4	
Poorly differentiated	2 (1.3)	2	0	
Mucinous	4 (2.5)	4	0	
Localized canceration	59 (37.1)	57	2	
Lymphnode metastasis				0.611
N0	146 (91.8)	141	5	
N1	11 (6.9)	10	1	
N2	2 (1.3)	2	0	
CEA, ng/mL, mean ± SD	3.60 ± 4.01	3.29 ± 3.50	11.35 ± 7.87	0.054

CEA: Carcinoembryonic antibody.

Table 2 Risk factors for lymph node metastasis and distant metastasis in T1 colorectal cancer

Parameter	Odds ratio (95%CI)	*P* value
Lymph node metastasis		
Age	1.015 (0.970, 1.062)	0.522
Gender	0.986 (0.329, 2.954)	0.980
Location	0.518 (0.138, 1.943)	0.330
Tumor size	0.859 (0.287, 2.574)	0.786
Histological grade	0.929 (0.748, 1.155)	0.509
CEA	0.445 (0.115, 1.805)	0.262
Distant metastasis		
Age	1.050 (0.969, 1.138)	0.231
Gender	0.192 (0.022, 1.685)	0.137
Location	0.485 (0.095, 2.491)	0.386
Tumor size	0.563 (0.100, 3.163)	0.514
Histological grade	1.365 (0.957, 1.945)	0.086
LNM	2.154 (0.234, 19.850)	0.498
CEA (preoperation)	18.400 (3.106, 109.006)	0.001

CEA: Carcinoembryonic antibody; LNM: Lymph node metastasis.

DISCUSSION

Patients with pT1 CRC have a favorable prognosis, however, some patients develop recurrence including local recurrence and distant metastasis after radical resection[14,15]. Total recurrence rates have been reported to be as low as 0%-4% and as high as 17%-31% in T1 CRC[16]. The rate of distant metastasis in the present study was 3.8% which was consistent with a previous report.

Various factors such as serum CEA level, histological grade, and LNM for distant metastasis in CRC have been identified in previous reports[17-20], but most of these reports included pT2-T4 patients, and there is a paucity of evidence on the risk factors for distant metastasis in pT1 CRC[21-25]. Following univariate analysis of our data, we found that preoperative serum CEA level (OR 18.400, 95%CI 3.106-109.006, $P = 0.001$) and histological grade (OR 1.365, 95%CI 0.957-1.945, $P = 0.086$) were risk factors for predicting postoperative distant metastasis in patients with pT1 CRC.

Previous studies have reported that the LNM rate is up to 21% for T1-T2 CRC[21,22]. LNM is considered a risk factor for distant metastasis after radical resection for CRC[22]. It is noteworthy that LNM did not reach statistical significance in our series, with a higher OR in univariate analysis (OR 2.154, 95%CI 0.234-19.850, $P = 0.498$). Although our results did not show the same conclusion as previous reports, it is difficult to confidently exclude a correlation between LNM and distant metastasis in T1 CRC, because most patients (5/6, 83.3%) had less than 12 lymph nodes investigated (mean 6.2 lymph nodes).

CEA has been proved to be important in the assessment of prognosis of advanced CRC. Koca *et al*[11] conducted a study on 221 individuals, comprised of 69 (31.2%) patients with clinical stage Ⅱ and 152 (68.8%) with clinical stage Ⅲ, to evaluate potential predictors of recurrence and survival. They found that high serum CEA level was one of the risk factors for recurrence. Kim *et al*[26] also found that elevation of serum CEA was an independent factor for pulmonary metastasis after curative resection in 105 patients with CRC. In multivariate analysis of our data, we found that preoperative serum CEA level was an independent risk factor (OR 15.341, 95%CI 2.371-99.275, $P = 0.004$) in the prediction of postoperative distant metastasis in patients with pT1 CRC. Adjuvant chemotherapy might be necessary for such patients. Regular surveillance after radical resection in CRC patients should be performed, even if they have pT1 CRC, especially in patients with an increased serum CEA level. To our knowledge, this is the first study demonstrating a predictive role for serum CEA level in distant metastasis after radical resection in patients with pT1 CRC.

Interestingly, in our study, with a median follow-up period of 67.0 mo, the rates of distant metastasis in patients with T1 cancer of the colon and rectum were 6.7% and 2.9%, respectively ($P < 0.001$). The rates of distant metastasis in male and female patients with T1 CRC were 6.25% and 1.27%, respectively ($P < 0.001$). It is necessary to accumulate evidence in further studies to confirm these differences, because there is a limit to the number of cases seen in a single institution.

On the basis of our study of 159 consecutive patients with pT1 CRC, we propose that the increased preoperative serum CEA level is the independent risk factor for distant metastasis after radical resection. Adjuvant chemotherapy and regular surveillance after radical resection

Table 3 Details of distant metastasis patients

No.	Age (yr)	Gender	Location	CEA (ng/mL)	Histological grade	LNM	DFS	Recurrent site	Prognosis
1	62	Male	Ascending colon	13.66	Moderately differentiated	0/3	8	Liver and spleen	Diseased
2	61	Male	Descending colon	24.00	Localized canceration	0/15	23	Liver	Survived
3	68	Male	Rectum	15.00	Moderately differentiated	1/1	10	Liver	Survived
4	63	Female	Sigmoid colon	7.91	Moderately differentiated	0/10	30	Liver and lung	Diseased
5	80	Male	Rectum	5.20	Localized canceration	0/2	11	Liver	Survived

CEA: Carcinoembryonic antibody; LNM: Lymph node metastasis; DFS: Disease-free survival.

for such patients should be performed.

COMMENTS

Background

Colorectal cancer (CRC) is one of the most common malignancies and a leading cause of cancer-related deaths. Previous studies have focused on evaluating the risk factors for lymph node metastasis, and there is little evidence with regard to the risk factors for postoperative distant metastasis in patients with pathologically T1 (pT1) CRC.

Research frontiers

Patients with pT1 CRC have a favorable prognosis, but some patients develop recurrence including local recurrence and distant metastasis after radical resection. In this study, the authors demonstrate that the preoperative carcinoembryonic antibody (CEA) level could be predictive of distant metastasis in pT1 CRC after radical surgery.

Innovations and breakthroughs

The authors described the relationship between preoperative CEA levels and distant metastasis in pT1 CRC after surgery. This is the first study to demonstrate a predictive role for serum CEA level in distant metastasis after radical resection in patients with pT1 CRC.

Applications

Preoperative CEA level could be predictive of distant metastasis in pT1 CRC patients after radical surgery. This study suggests that adjuvant chemotherapy might be necessary for such patients.

Terminology

Preoperative serum CEA level is a risk factor in the prediction of postoperative distant metastasis in patients with pT1 CRC.

Peer review

The authors present an interesting study on risk factors for the occurrence of distant metastasis in early pT1 colorectal carcinomas. The manuscript is well structured and the cited literature is comprehensive and up-to-date. This is a clinically very interesting topic. Their results are very valuable.

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