



## Extracapsular invasion as a risk factor for disease recurrence in colorectal cancer

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**Supported by** Grants-in-Aid from the Japanese Ministry of Education, Culture, Sports, Science, and Technology

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Received: November 4, 2010 Revised: November 25, 2010

Accepted: December 2, 2010

Published online: April 21, 2011

**CONCLUSION:** Our results suggest that ECI at metastatic nodes can identify which cases are at high risk of short-term disease recurrence in colorectal cancer.

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**Key words:** Extracapsular invasion; Lymph node; Metastasis; Colorectal cancer; Risk factor; Adjuvant therapy

**Peer reviewer:** Dr. Vui Heng Chong, Gastroenterology and Hepatology Unit, Department of Medicine, Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan BA 1710, Brunei Darussalam

Fujii T, Tabe Y, Yajima R, Yamaguchi S, Tsutsumi S, Asao T, Kuwano H. Extracapsular invasion as a risk factor for disease recurrence in colorectal cancer. *World J Gastroenterol* 2011; 17(15): 2003-2006 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i15/2003.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i15.2003>

### Abstract

**AIM:** To evaluate the presence of extracapsular invasion (ECI) in positive nodes as a predictor of disease recurrence disease in colorectal cancer.

**METHODS:** Two hundred and twenty-eight consecutive patients who underwent colorectal resection were identified for inclusion in this study, of which 46 had positive lymph nodes. Among 46 cases with stage III colorectal cancer, 16 had ECI at positive nodes and 8 had disease recurrence. The clinical and pathological features of these cases were reviewed.

**RESULTS:** In the univariate analysis, the number of positive lymph nodes and depth of tumor invasion were significantly associated with the presence of ECI at positive nodes. Multivariate analysis demonstrated that only ECI was a predictor of recurrence. The recurrence-free interval differed significantly among patients with ECI at positive nodes.

### INTRODUCTION

The role of systemic adjuvant chemotherapy in colorectal cancer patients with lymph node involvement has been established in a large number of clinical trials<sup>[1-3]</sup>. Lymph node status is one of the most important prognostic factors for colorectal carcinoma. However, patients with TNM stage III colorectal cancer are a heterogeneous group. Some patients with stage III colorectal cancer have good prognoses, similar to that of patients with stage II disease, whereas others develop disease recurrence. It is of utmost importance to develop markers that can predict which patients are at high risk for disease recurrence.

Previous studies have demonstrated and confirmed that the presence of extracapsular invasion (ECI) at metastatic lymph nodes is significantly related to prognosis in various types of carcinoma including colorectal cancer<sup>[4-11]</sup>. We have also recently demonstrated that ECI at metastatic nodes in breast and colorectal cancer was strongly associated with

further regional nodes metastasis<sup>[12]</sup>. The purpose of this study was to investigate the correlation between the presence of ECI in positive lymph nodes and disease recurrence in cases of colorectal cancer undergoing curative operation. It will be advantageous to be able to tailor therapy individually, using ECI as an indicator of the risk of recurrence.

## MATERIALS AND METHODS

Two hundred and twenty-eight consecutive patients who underwent colorectal resection in the Department of General Surgical Science, Graduate School of Medicine, Gunma University, from January 2007 to December 2009 were identified for inclusion in this study. Patients with recurrence or metastasis at operation, neo-adjuvant chemotherapy, radiation, or incomplete clinical information were excluded. Of the eligible cases, 46 (20.2%) with positive lymph nodes, identified as TNM stage III colorectal, were analyzed in this study. The clinical features of these cases were reviewed according to the presence or not of ECI at positive lymph nodes, and statistical analysis was performed. ECI was defined as extracapsular growth of tumor cells, invasion into perinodal fat or extranodal location of tumor cells<sup>[12]</sup>. Informed consent was obtained from all patients.

Age, sex, primary tumor size, location, depth of tumor invasion, histological type, lymphovascular invasion at the primary tumor site, number of metastatic lymph nodes, ECI at positive lymph nodes, administration of adjuvant therapy and serum tumor markers (carcinoembryonic antigen) were tested as possible predictors of disease recurrence. Recurrence-free interval was defined as the interval from surgery to the time disease recurrence was diagnosed. The overall median follow-up period was 1.7 years and none of the patients died of surgical complications. Fisher's exact test, the Chi-squared test, and the Student t-test were used to compare the 2 groups. Multivariate analysis was performed with logistic regression analysis to select covariates (primary tumor size and ECI at positive lymph nodes). The recurrence-free interval was calculated by the Kaplan-Meier method. The log-rank test was used to evaluate differences between recurrence-free intervals. Differences were considered to be significant at  $P < 0.05$ .

## RESULTS

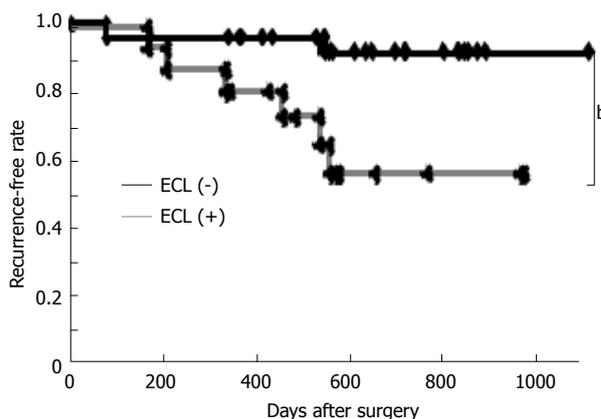
Table 1 summarizes the characteristics of the patients who underwent colorectal resection with TNM stage III colorectal cancer. The series consisted of 16 cases with ECI at positive nodes and 30 with no ECI at positive nodes. Table 1 also summarizes the results of the univariate analysis conducted to determine the relationship between the clinicopathologic variables and the presence of ECI at positive nodes. The number of positive lymph nodes and the depth of tumor invasion were significantly associated with the presence of ECI at positive nodes.

The 46 cases with metastatic lymph nodes were divided into 2 groups based on the presence of disease recurrence. Among 46 cases with stage III colorectal cancer, 8 (17.4%) had disease recurrence. Table 2 summarizes the results of

**Table 1** Patients characteristics and clinicopathological features associated with the presence of extracapsular invasion at lymph node metastases

	ECI	Positive <i>n</i> = 16	Negative <i>n</i> = 30	<i>P</i> value
Age (yr)		65.3 ± 16.1	66.5 ± 13.8	0.798
Sex				
Male		7	21	0.082
Female		9	9	
Location				
Colon		13	20	0.295
Rectum		3	10	
Histological type				
Tub		15	28	0.957
Muc		1	2	
pT category				
T 1,2		1	10	0.040
T 3,4		15	20	
Tumor size (mm)		47.3 ± 15.1	40.4 ± 21.2	0.270
Number of positive LNs		3.63 ± 2.29	1.70 ± 1.27	0.001
Lymphovascular invasion		16	29	0.460
CEA ≥ 3.0		3	3	0.041
Adjuvant treatment	13	0.720	23	0.720

LN: Lymph node; ECI: Extracapsular invasion; CEA: Carcinoembryonic antigen.



**Figure 1** Impact of the presence of extracapsular invasion at positive nodes on postoperative recurrence-free interval. Recurrence-free interval by Kaplan-Meier curves differed significantly among patients with and without extracapsular invasion at positive nodes. <sup>b</sup> $P < 0.01$ .

the univariate analysis conducted to determine the relationship between the clinicopathologic variables and disease recurrence. In the univariate analysis ECI at positive nodes and the depth of tumor invasion were the factors significantly associated with disease recurrence. Among those, multivariate analysis demonstrated that only ECI was a predictor of the recurrence ( $P = 0.016$ ). Time to tumor recurrence by Kaplan-Meier curves was significantly shorter among patients with ECI at positive nodes (Figure 1).

## DISCUSSION

The key observations made in this study can be summarized as follows: (1) the presence of ECI at positive nodes

Table 2 Patient characteristics and clinicopathological features associated with recurrent disease

Recurrent disease	Positive 8	Negative 38	P value
Age (yr)	68.0 ± 17.2	65.7 ± 14.0	0.780
Sex			
Male	3	25	0.278
Female	5	13	
Location			
Colon	6	27	0.795
Rectum	2	11	
Histological type			
Tub	7	36	0.451
Muc	1	2	
PT category			
T 1, 2	0	11	< 0.001
T 3, 4	8	27	
Tumor size (mm)	44.9 ± 11.6	42.5 ± 20.8	0.679
Number of positive LNs	2.38 ± 1.41	2.37 ± 2.02	0.906
ECI	6	10	0.009
Lymphovascular invasion	8	37	0.643
CEA ≥ 3.0	3	3	0.093
Adjuvant treatment	5	31	0.473

ECI: Extracapsular invasion; CEA: Carcinoembryonic antigen.

was significantly associated with the number of positive lymph nodes and depth of tumor invasion; (2) multivariate analysis demonstrated that only ECI was a predictor of recurrence; and (3) the recurrence-free interval by Kaplan-Meier curves was significantly shorter among patients with ECI at positive nodes. These findings suggest that the presence of ECI at positive lymph nodes is a strong predictor for short-term recurrence in cases with colorectal cancer undergoing curative surgery.

The surgical stage remains the most accurate predictor of survival for colorectal cancer<sup>[13]</sup>. Pathologic prognostic factors of primary tumor invasion and regional node involvement predict the risk of relapse of cases with colorectal cancer undergoing curative operation. In the current study, both the number of positive lymph nodes and the depth of tumor invasion were significantly associated with the presence of ECI at positive nodes. Lymph node metastasis is one of the most important prognostic factors in patients with colorectal cancer, and many studies have indicated that the location and number of metastatic nodes affect prognosis<sup>[5,14-16]</sup>. Regarding ECI, previous studies have demonstrated and confirmed that the presence of ECI at metastatic lymph nodes is significantly associated with prognoses in various types of carcinoma including colorectal carcinoma<sup>[4-11]</sup>. The ability of metastatic nodes to recruit degradation factors that permit cancer cells to break through the lymph node capsule is indicative of a very aggressive cancer. We previously demonstrated that the presence of ECI in positive lymph nodes is significantly related to the nodal spread of tumor cells in colorectal and breast cancer patients<sup>[12]</sup>. These studies imply that ECI is a biologic marker of aggressive cancer and essentially support our findings. Tumor cells are thought to invade the lymphovascular vessels, which enables tumor cells to spread metastatic or recurrent disease.

Adjuvant therapy is systemic treatment administered

with the intent of reducing the risk of recurrence. The benefit of adjuvant therapy in patients with lymph node involvement (stage III) has been well established in large prospective randomized trials<sup>[1-3]</sup>. In Japan, the oxaliplatin plus 5-fluorouracil/leucovorin (LV) (FOLFOX) regimen has not been approved for adjuvant therapy for patients with stage III colorectal cancer at this time. In this Japanese population study, oral chemotherapeutic agents, including capecitabine or UFT (tegafur plus uracil) with oral LV, were used for adjuvant therapy for stage III colorectal cancer. Oral chemotherapeutic agents are advantageous because of their ease of administration. However, in the current series, 13 (81.3%) of the 16 cases with ECI in positive nodes had oral adjuvant therapy but 6 of 16 cases (37.5%) had disease recurrence. These results imply that high-risk patients with ECI at positive nodes should receive stronger adjuvant chemotherapy, including FOLFOX with or without monoclonal antibody.

This study has several potential limitations. The major limitation of our study is that it used retrospective methods of data collection. In addition, the number of cases in our study was relatively small and the follow-up periods were relatively short. However, the clinical implications of this data are very important, and these findings serve to emphasize that ECI at metastatic lymph nodes is an important prognostic factor for stage III colorectal carcinoma and will be advantageous in tailoring therapy to the individual case. In patients treated in phase III adjuvant clinical trials, disease-free survival and overall survival have been highly correlated, both within studies and across trials<sup>[17]</sup>; however, in a number of patients, improving the quality of life and the length of recurrence-free intervals may be more important statistical parameters than median overall survival. Additional research is needed to explore this putative association between the presence of ECI and the risk of recurrence.

In conclusion, we have demonstrated that ECI at met-

astatic lymph nodes may predict which cases are at high risk of short-term disease recurrence in colorectal cancer. Thus, it will be possible to tailor therapy individually, using ECI as an indicator of the risk of recurrence. Analyses from large randomized trials or experimental data are warranted to evaluate this relationship between the presence of ECI and disease recurrence.

## ACKNOWLEDGMENTS

The authors would like to thank Saitoh Y, Yano T, Ohno M, Matsui Y, Muraoka S and Sekiguchi M for their secretarial assistance

## COMMENTS

### Background

The authors have demonstrated that extracapsular invasion (ECI) at metastatic nodes in breast and colorectal cancer was strongly associated with further regional nodes metastasis. The purpose of this study was to evaluate the presence of ECI in positive nodes as a predictor of disease recurrence disease in colorectal cancer.

### Research frontiers

Lymph node status is one of the most important prognostic factors for colorectal carcinoma. However, patients with TNM stage III colorectal cancer are a heterogeneous group. It is of utmost importance to develop markers that can predict which patients are at high risk for disease recurrence.

### Innovations and breakthroughs

This study suggests that the presence of ECI at positive lymph nodes is a strong predictor for short-term recurrent-free interval in cases with colorectal cancer undergoing curative operation.

### Applications

It will be possible to tailor therapy individually, using ECI as an indicator of the risk of recurrence.

### Terminology

ECI was defined as extracapsular growth of tumor cells, invasion into perinodal fat or extranodal location of tumor cells.

### Peer review

The key observations made in this study suggest that the presence of ECI at positive lymph nodes is a strong predictor of short-term recurrent-free interval in cases with colorectal cancer undergoing curative operation.

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S- Editor Sun H L- Editor Cant MR E- Editor Ma WH