Size does not determine the grade of malignancy of early invasive colorectal cancer

Takahisa Matsuda, Yutaka Saito, Takahiro Fujii, Toshibo Uraoka, Takeshi Nakajima, Nozomu Kobayashi, Fabian Emura, Akiko Ono, Tadakazu Shimoda, Hiroaki Ikematsu, Kuang-I Fu, Yasushi Sano, Takahiro Fujimori

Abstract
AIM: To clarify the clinicopathological characteristics of small and large early invasive colorectal cancers (EI-CRCs), and to determine whether malignancy grade depends on size.

METHODS: A total of 583 consecutive EI-CRCs treated by endoscopic mucosal resection or surgery at the National Cancer Center Hospital between 1980 and 2004 were enrolled in this study. Lesions were classified into two groups based on size: small (≤10 mm) and large (>10 mm). Clinicopathological features, incidence of lymph node metastasis (LNM) and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

RESULTS: There were 120 (21%) small and 463 (79%) large lesions. Histopathological analysis of the small lesion group revealed submucosal deep cancer (sm: ≥1000 μm) in 90 (75%) cases, LVI in 26 (22%) cases, and PDA in 12 (10%) cases. Similarly, the large lesion group exhibited submucosal deep cancer in 380 (82%) cases, LVI in 125 (27%) cases, and PDA in 79 (17%) cases. The rate of LNM was 11.2% and 12.1% in the small and large lesion groups, respectively.

CONCLUSION: Small EI-CRC demonstrated the same aggressiveness and malignant potential as large cancer.

INTRODUCTION
Colorectal cancer (CRC) is the third most important cause of cancer mortality in Japan, and its incidence is gradually increasing. To reduce CRC mortality, early detection and appropriate treatment are required. In general, small lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size[1-3]. Therefore, lesion size is considered to be indicative of the depth of invasion and presence of lymph node metastasis (LNM). In contrast, flat, and in particular depressed lesions, are considered to have a tendency to invade rapidly the submucosal layer, even when small[4-6]. However, clinicopathological features of small EI-CRCs have still
The significance of differences in proportions was assessed by the \( \chi^2 \) test, Fisher’s exact test and the Wilcoxon matched-pairs signed-ranks test using SPSS statistical software (SPSS for Windows, version 16.0J, Tokyo, Japan). Statistical significance was defined as \( P < 0.05 \).

**RESULTS**

A total of 583 EI-CRCs were retrospectively evaluated, with 120 (21%) small and 463 (79%) large lesions identified (Table 1). The gender ratio (male/female) was 2.4 and 1.7, and the mean age was 61.5 and 62.4 years in the small and large lesion groups, respectively. Mean size of the small and large lesions was 8.3 and 22.1 mm, respectively.

**Macroscopic type, growth type and location**

Macroscopic assessment of small lesions identified 51 cases as sessile (42%), 14 as flat (12%), and 55 as depressed (46%). Similarly, large lesion groups comprised 233 sessile (50%), 64 flat (14%), and 166 depressed (36%) type. PG types were identified in 32% (38/120) and 54% (250/463) of small and large lesions, respectively. In contrast, the prevalence of NPG type in the small lesion group was significantly higher than in the large lesion group (68% vs 46%, \( P < 0.0001 \)). Regarding tumor location, there were 33 (27%) rectal, 56 (47%) distal colon and 31 (26%) proximal colon cancers in the small lesion group. In contrast, there were 213 (46%) rectal, 139 (30%) distal colon and 111 (24%) proximal cancers in the large lesion group. The incidence of rectal cancer in the large lesion group was significantly higher than in the small lesion group (\( P = 0.02 \)).

**LNM**

Among the lesions treated surgically, the incidence of LNM was 11.2% (10/89) and 12.1% (46/381) in small and large lesion groups, respectively (\( P = 0.85 \)) (Table 2).

**Depth of invasion/LVI/PDA**

Histopathological analysis of the small lesion group revealed sm-deep cancer in 90 (75%) cases, LVI in 26 (22%) and PDA in 12 (10%) cases. Similarly, the large lesion group exhibited sm-deep cancer in 380 (82%) cases, LVI in 125 (27%) and PDA in 79 (17%) cases. Therefore, in relation to depth of invasion, LVI and PDA, there were no significant differences between the groups.

**Treatment strategy**

Among the small lesion group, 62 (52%) cases were initially treated with endoscopic mucosal resection (EMR), while 58 (48%) cases were surgically resected. In contrast, among the large lesion group, 133 (29%) cases were initially treated with EMR, while 330 (71%) cases were surgically resected. Among all lesions treated by EMR, there were no differences in the rate of positive and unknown vertical and/or lateral cut margins in the small (18%, 11/62) and large lesion groups (20%, 26/133). Furthermore, among all positive cut margin cases in the small and large lesion groups, there were 11 (100%) and 18 (69%) positive vertical margin cases (Table 3, Figures 1 and 2).
According to the initial treatment, there were 134 (69%) and 336 (87%) sm-deep cancers in the EMR and surgery groups, respectively. Furthermore, there were 33 (17%) and 118 (30%) LVI-positive, and 18 (9%) and 73 (19%) PDA-positive cases in the EMR and surgery groups, respectively. There were 37 (19%) positive cut margin cases, including 29 (78%) positive vertical margins in the EMR group. In contrast, there were no positive cut margin cases in the surgery group. In the EMR group, 82 (42%) patients underwent additional surgery with LN dissection after EMR within 6 mo. The incidence of LNM was 11.0% (9/82) and 12.1% (47/388) in the EMR and surgery groups, respectively. There were 37 (19%) positive cut margin cases, including 29 (78%) positive vertical margins in the EMR group. In contrast, there were no positive cut margin cases in the surgery group. In the EMR group, 82 (42%) patients underwent additional surgery with LN dissection after EMR within 6 mo. The incidence of LNM was 11.0% (9/82) and 12.1% (47/388) in the EMR and surgery groups, respectively (Table 4).

**DISCUSSION**

Several authors have reported a strong association between lesion size and submucosal invasion or risk of LNM when referring to the grade of malignancy of early CRC. Large lesion size has been considered an indicator of deep submucosal invasion and presence of LNM. However, in this large retrospective study, small EI-CRC demonstrated a similar aggressive behavior and malignant potential to those of large lesions, with a similar risk of LNM, LVI and PDA among both groups.

Intramucosal CRC is thought generally to have no potential for LNM. In contrast, it has been reported that LNM occurs in 6%-13% of patients with submucosal invasive CRC[11-13]. Therefore, radical surgery with LN dissection is recommended strongly in these cases. At present, EMR provides an endoscopic cure of early stage CRC when there is no risk of LNM. Advances in endoscopic instruments and techniques have increased the detection rates of early stage CRC and have expanded the indications for EMR[16].

In the past 20 years, many investigators have proposed the following histopathological criteria when considering additional surgery after EMR of submucosal cancers: massive submucosal invasion (> 1000 μm), and/or LVI, and/or PDA[17-22]. Among these factors, LVI and PDA are impossible to predict before resection. At this point, it is crucial to predict the vertical depth of invasion of submucosal cancers prior to EMR. In our center, we use routinely a magnifying colonoscope to decide on the adequate treatment of early stage CRC. Magnifying chromoendoscopy (MCE) is a standardized validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern), in a simple and rapid manner. We have reported previously the efficacy of MCE to diagnose an invasive pattern as a typical finding of sm-deep cancers, and have demonstrated that it provides a good correlation between pit pattern and tumor depth in flat and depressed CRC[21-27].

Many authors have reported that depressed and/or NPG type lesions are considered to have a high malignant potential, compared to the polypoid type lesions of similar.

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**Table 1** Comparison of clinicopathological and endoscopic characteristics for 583 study cases

|               | Small (≤ 10 mm) | Large (> 10 mm) | P value |
|---------------|-----------------|-----------------|---------|
| No. of lesions, n (%) | 120 (21)        | 463 (79)        | < 0.0001|
| Gender (M/F)  | 85/35           | 289/174         | 0.09    |
| Age (yr), mean (range) | 61.5 (39-84)    | 62.4 (30-90)    | 0.86    |

**Table 2** Incidence of LNM and clinicopathological characteristics based on tumor size n (%)

|               | Small (≤ 10 mm) | Large (> 10 mm) | P value |
|---------------|-----------------|-----------------|---------|
| LNM           | 10/89 (11.2)    | 46/381 (12.1)   | 0.85    |
| Depth of invasion |                |                 |         |
| sm-superficial (≤ 1000 μm) | 30 (25)         | 83 (38)         | 0.08    |
| sm-deep (> 1000 μm)      | 90 (75)         | 380 (82)        |         |
| LVI              | 26 (22)         | 125 (27)        | 0.23    |
| PDA              | 12 (10)         | 79 (17)         | 0.06    |

**Table 3** Comparison of treatment strategy and positive rate of cut margin n (%)

|               | Small (≤ 10 mm) | Large (> 10 mm) | P value |
|---------------|-----------------|-----------------|---------|
| Initial treatment |                |                 |         |
| EMR            | 62 (52)         | 133 (29)        | < 0.0001|
| Surgery        | 58 (48)         | 330 (71)        |         |
| Positive rate of cut margin |            |                 |         |
| In EMR cases   | 11 (18)         | 26 (20)         | 0.81    |
| Lateral        | 0 (0)           | 8 (31)          | 0.08    |
| Vertical       | 11 (100)        | 18 (69)         |         |

**Table 4** Comparison of clinicopathological characteristics and incidence of LNM based on the treatment strategy n (%)

|               | EMR (n = 195) | Surgery (n = 388) | P value |
|---------------|---------------|-------------------|---------|
| Depth of invasion |                |                   |         |
| sm-superficial (≤ 1000 μm) | 61 (32)       | 52 (13)           | < 0.0001|
| sm-deep (> 1000 μm)      | 134 (69)      | 336 (87)          |         |
| LVI              | 33 (17)       | 118 (30)          | 0.0006  |
| PDA              | 18 (9)        | 73 (19)           | 0.0006  |
| Positive rate of cut margin |            |                   | < 0.0001|
| Lateral         | 8 (22)        | 0 (0)             |         |
| Vertical        | 29 (78)       | 0 (0)             |         |
| Additional surgical operation |       | 82 (42)          |         |
| LNM             | 9/82 (11.0)   | 47/388 (12.1)     | 0.79    |

1Positive and unknown cut margin.
Kurisu et al. [20] have investigated the development and progression of EI-CRC. In that study, NPG lesions were significantly smaller in size (14.2 mm vs 24.2 mm) but showed deeper infiltration than PG types. They concluded that tumor development and the degree of invasion differed significantly between the two types of carcinoma.

On the other hand, non-polypoid colorectal neoplasms (NP-CRNs) have been reported recently in the United States. Soetikno et al. [31] have reported the prevalence of NP-CRNs in a veterans’ hospital population. The overall prevalence of NP-CRNs and NP-CRNs with in situ or submucosal invasive carcinoma was 9.35% and 0.82%, respectively. They also concluded that NP-CRNs were more likely to contain carcinoma (OR: 9.78) than polypoid lesions, regardless of size. In the present study, small EI-CRCs ≤ 10 mm in diameter showed a significantly higher incidence of NPG type lesions than in the large lesion group (P < 0.0001). However, there was no significant difference in the positive rate of cut margins between the small and large lesion groups (18% vs 20%). This result implies that EMR should not be performed readily for EI-CRCs, from the viewpoint of ‘no-touch isolation’ and EMR complications. Intramucosal lesions (adenoma or intramucosal cancer) are usually well lifted by submucosal injection. In contrast, invasive cancer, especially sm-deep cancer, cannot be lifted because of the presence of submucosal fibrosis or desmoplastic reaction. Uno et al. [32] have reported this phenomenon as the “non-lifting sign”.

In contrast, the rate of EMR as an initial treatment was 33% (195/583) in our study. In particular, it was significantly higher in the small lesion than the large lesion group (52% vs 29%, P < 0.0001). Among the 195 lesions removed by EMR as an initial treatment in both groups, 61 cases (32%) were sm-superficial cancers. On the other hand, there was no significant difference in the positive rate of cut margins between the small and large lesion groups (18% vs 20%). This result implies that EMR should not be performed readily for EI-CRCs, from the viewpoint of ‘no-touch isolation’ and EMR complications. Intramucosal lesions (adenoma or intramucosal cancer) are usually well lifted by submucosal injection. In contrast, invasive cancer, especially sm-deep cancer, cannot be lifted because of the presence of submucosal fibrosis or desmoplastic reaction. Uno et al. [32] have reported this phenomenon as the “non-lifting sign”.

Kobayashi et al. [34] have reported, among 271 colorectal neoplastic lesions, that the non-lifting sign of deeper infiltration had a sensitivity of 61.5%, specificity of 98.4%, and accuracy of 94.8%. In contrast, endoscopic diagnosis had a sensitivity of 84.6%, specificity of 98.8%, and accuracy of 97.4%, with statistically significant differences in terms of sensitivity and accuracy. Furthermore, since submucosal injection varies depending on the expertise of the endoscopist, we consider that an endoscopic diagnosis is much more important and accurate when endoscopic resection is considered as the therapeutic option.

There are some limitations to this study. Firstly, this was a single-center study, and although the number of examined EI-CRCs was adequate, a multicenter analysis should be performed to clarify the clinical importance of small EI-CRCs. In addition, this study was carried out retrospectively between 1980 and 2004. In relation to endoscopic treatment for early CRC, endoscopic submucosal dissection (ESD) technique and Glycerol/Sodium hyaluronate as an injected solution during EMR has made progress recently [35,36]. In particular, ESD provides not only an en bloc large specimen but also...
negative lateral and vertical cut margins.

In conclusion, with regard to the risk of LNM, small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions. Moreover, from the perspective of the concept of no-touch isolation, therapeutic cost, and complications during EMR, special attention must be paid when treating even small early stage lesions, especially NPG type lesions.

COMMENTS

Background
In general, small colorectal lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size.

Research frontiers
The aim of this retrospective study was to clarify the clinicopathological characteristics of small (≤ 10 mm) and large (> 10 mm) EI-CRCs.

Innovations and breakthroughs
A total of 583 EI-CRCs were evaluated retrospectively, with 120 (21%) small and 463 (79%) large lesions identified. With regard to the risk of lymph-node metastasis (LNM), small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions.

Peer review
The authors examined retrospectively a large group of patients with EI-CRCs gathered over 20 years in a national cancer hospital, and demonstrated that small EI-CRCs (≤ 10 mm) had the same aggressiveness and malignant potential as large cancers. Special attention must be paid when treating even small lesions.

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