Prolongation of the period between biopsy and EMR can influence the nonlifting sign in endoscopically resectable colorectal cancers CME

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Background: The nonlifting sign is widely used for evaluating the invasion depth of colorectal tumors, and it is commonly accepted that EMR is contraindicated for colorectal tumors with a nonlifting sign because of the probability of massive submucosal invasion.

Objective: To identify the clinicopathologic factors that affect the nonlifting sign in submucosal invasive colorectal carcinoma (SICC).

Design: Details regarding a history of biopsy, postbiopsy days, tumor location, tumor configuration, tumor size, depth of submucosal invasion, histologic type, adenomatous remnants, and angiolymphatic invasion were studied in relation to the nonlifting sign.

Setting: National Cancer Center, Korea.

Patients: The study involved 76 patients with SICC treated by endoscopic or surgical resection, in whom the tumor was examined for the nonlifting sign from 2001 to 2006.

Results: The nonlifting sign was observed in 15 cases (19.7%). A deep submucosal invasion, a history of biopsy, and the absence of adenomatous remnants were identified as factors affecting the nonlifting sign in univariate and multivariate analyses ($P < .05$). An increase in the number of postbiopsy days was associated with the nonlifting sign in endoscopically resectable SICC, and all 11 sm1 cancer cases with fewer than 21 postbiopsy days showed lifting.

Conclusions: A history of biopsy and the absence of adenomatous remnants, in addition to deep submucosal invasion, were found to influence the nonlifting sign in SICC. It may be best that mechanical stimulation such as forceps biopsies are minimized before EMR, and EMR should be tried as soon as possible if biopsy was performed. (Gastrointest Endosc 2008;67:97-102.)

Endoscopic detection and treatment of early colorectal carcinoma has developed with advances in instruments and techniques.[1] Endoscopic resection of intramucosal carcinomas is accepted as a curative therapy because this carcinoma type carries no risk of lymph node (LN) metastasis.[2,3] However, because LN metastasis occurs in 7% to 15% of submucosal invasive colorectal carcinoma (SICC) cases, endoscopic resection for SICC should be used selectively.[4-7]

Correlations between the depth of submucosal invasion (SM depth) and LN metastasis have been investigated in many previous studies. On the basis of Kudo's classification,[8] sm1 cancers have a low risk of LN metastasis (0%-3% of cases), whereas sm3 cancers have a high risk of LN metastasis (14%-23% of cases).[6,7,9] According to this oncologic rationale, if sm1 cancer is completely removed under endoscopic resection, additional surgical resection may not be required. Therefore, the precise evaluation of SM depth is critical for successful endoscopic resection of SICC.

The nonlifting sign is frequently used for evaluation of SM depth. Nonlifting is defined as when the lesion is not

Abbreviations: ESD, endoscopic submucosal dissection; LN, lymph node; SICC, submucosal invasive colorectal cancer; SM depth, submucosal invasion.

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lifted by saline solution injected into the submucosal layer of the tumor base. Where there is massive tumor infiltration or substantial fibrosis in the submucosa, fluid injection does not separate the tissue, resulting in the nonlifting sign.[10] Ishiguro et al[11] reported that sm3 cancers did not lift in response to submucosal injections and that lesions elevated by injections could be resected endoscopically as if they were either sm1 or sm2 cancers. However, some sm1 or less-invasive cancers may show nonlifting signs. If the decision to resect is based on such nonlifting, then patients may be undergoing unnecessary surgery.

The current study sought to identify clinicopathologic factors that affect nonlifting signs in SICC.

Capsule Summary

What is already known on this topic

- EMR may be contraindicated for colorectal tumors with a nonlifting sign because of the probability of submucosal invasion.

What this study adds to our knowledge

- In a retrospective analysis of 76 submucosal carcinomas, a history of biopsy, the absence of adenomatous remnants, and too-deep submucosal invasion were found to influence the nonlifting sign.

PATIENTS AND METHODS

Between January 2001 and October 2006, a total of 36,382 patients underwent colonoscopic examination in the National Cancer Center, Korea. A total of 215 cases of SICCs were identified during the period. Of these, 76 patients with 76 tumors were included for study. Exclusion criteria were (1) cases that underwent surgery after preoperative chemoradiation therapy (26 cases), (2) cases that underwent surgery without checking for the nonlifting sign because of ulcerated outline or hardness (82 cases), (3) cases that, without checking for the nonlifting sign, underwent surgery because of synchronous advanced colorectal carcinomas (23 cases), and (4) cases diagnosed with a familial adenomatous polyposis (8 cases).

For identifying the nonlifting sign, a mixed saline solution–epinephrine solution was injected into the submucosal base of the tumor with an injector needle (NM-2000U-0423, Olympus Medical Systems, Tokyo, Japan). These mixed solutions were composed of normal saline solution, indigo carmine, and diluted epinephrine (1:1,000,000). Approximately 2 to 3 mL of the saline solution–epinephrine solution was injected at more than 2 sites near the edge of the tumor. Immediately after injection, the extent of lifting was evaluated. If the tumor was not lifted when the mucosal layers around the tumor were lifted, the tumor was defined as being positive for the nonlifting sign.

Clinical data from the colorectal cancer database and clinical charts were reviewed retrospectively. Details regarding a history of biopsy, tumor location, tumor configuration, tumor size, SM depth, histologic type, adenomatous remnants, and angiolymphatic invasion were investigated. For patients with a history of biopsy, the period between the biopsy and nonlifting sign testing (postbiopsy days) was reviewed. The tumor location was classified as colon or rectum. The tumor configuration was classified as either nonpolypoid or polypoid according to the Paris classification.[12] The tumor size was defined as the maximum diameter of the cancerous lesion on a glass slide. The SM depth was evaluated according to Kudo's classification as sm1 (infiltration into the upper third of the submucosal layer), sm2 (middle third), or sm3 (lower third) in surgically resected specimens.[8] For endoscopically resected sessile or flat tumors, the cutoff limit between sm1 and sm2 was 1000 μm of submucosal layer according to the Paris classification,[12] and a submucosal invasion exceeding 2000 μm was defined as sm3. For endoscopically resected pedunculated tumors, the cutoff limit between sm1 and sm2 was the level of the neck, and a submucosal invasion exceeding 3000 μm from the neck was defined as sm3. The method proposed by Kitajima et al[13] was used for the measurement of submucosal invasion depth. The histologic type was classified according to World Health Organization criteria, and the existence of adenomatous remnants was defined as the presence of remnant adenoma elements in the vicinity of carcinoma cells. An angiolymphatic invasion was defined as the presence of cancer cells within endothelial-lined channels.

The χ^2 test and the Fisher exact test were used to estimate relationships between the nonlifting sign and clinicopathologic factors. Multivariate logistic regression analyses were then used to identify factors affecting the nonlifting sign. The *t* test was used to estimate relationships between the nonlifting sign and postbiopsy days. A *P* value less than .05 was considered to indicate a significant difference.

The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

RESULTS

Demographic features of patients and tumors

There were 50 male and 26 female patients with a mean age of 60.6 years (range 33-79 years). Thirty-eight patients underwent endoscopic resection only, 23 patients underwent additional surgical resection after endoscopic resection because of a high risk of LN metastasis, and 15 patients (19.7%) with nonlifting tumors underwent