Editorial

Is lymph node metastasis the only concern in high-risk submucosal colorectal cancer following endoscopic resection?

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Endoscopic resection represents a curative therapy for Tis colorectal cancer (carcinoma *in situ*; intraepithelial or invasion of the lamina propria) as it has no risk of lymph node metastasis (1-3). However, lymph node metastasis occurs in 7-15% of T1 colorectal cancers (invasion of submucosa) (4-10). In order to achieve curative resection of submucosal colorectal cancer, predictors for lymph node metastasis have been evaluated in many studies (7,9-14) and found to be depth of submucosal invasion (1,000 and 3,000 μm for nonpedunculated and pedunculated submucosal colorectal cancers, respectively), lymphovascular invasion, and poorly-differentiated adenocarcinoma (11,15,16). In cases of submucosal colorectal cancer with no risk factors for lymph node metastasis, no further treatments such as surgical resection appear to be necessary following complete endoscopic resection. Conversely, additional surgery has been recommended for high-risk submucosal colorectal cancer (11).

Some patients with high-risk submucosal colorectal cancer, however, hesitate to undergo surgery due to surgery-associated morbidity and mortality. In certain circumstances, endoscopists also struggle with whether to offer surgery as the majority of patients with risk-factors for lymph node metastasis actually have no metastatic spread. Such scenarios seem to be more frequent in rectal cancers compared to colon cancers. Abdominoperineal resection—the standard treatment for low rectal cancer—can leave some patients with permanent stomas (17). Therefore, when taken together with the rate of lymph node metastasis of approximately 10%, careful observation can also be an alternative treatment option in select patients.

Until now, risk of lymph node metastasis has only been a concern in patients with high-risk submucosal colorectal cancer following endoscopic resection. Because rates of lymph node metastasis do not differ between submucosal colon cancer and submucosal rectal cancer (8,11,15), tumor location does not appear to be an important variable in evaluating high-risk submucosal colorectal cancer. However, Ikematsu *et al.*'s recent study (18) in the *Gastroenterology* demonstrated that the risk for local cancer recurrence was significantly higher in patients with high-risk submucosal rectal cancer than in patients with high-risk submucosal colon cancer when treated with endoscopic resection alone. That study reviewed data from 573 patients with submucosal colon cancer and 214 patients with submucosal rectal cancer and who underwent endoscopic or surgical resection at six institutions. This dataset constituted the largest retrospective study population for patients with submucosal colorectal cancer. In total, the number of patients treated with endoscopic resection was 327 and 101 for submucosal colon cancer and submucosal rectal cancer, respectively. Of those patients, 218 and 84 were high-risk for lymph node metastasis, respectively. Patients that refused additional surgery, designated as group B, were 31.7% of high-risk submucosal colon cancer (69 of 218) and 44.0% of high-risk submucosal rectal cancer (37 of 84). The results from this study suggest that patients with high-risk submucosal rectal cancer decline additional surgery more frequently than patients with high-risk submucosal colon cancer (P=0.043, Chi-square test). In group B, rate of local recurrence was higher in submucosal rectal cancer than in submucosal colon cancer (10.8% *vs.* 1.4%, respectively, P<0.01). This serves as an interesting finding as there was no difference in local recurrence rates for patients who underwent surgery or in patients with low-risk submucosal colorectal cancer treated with endoscopic resection alone. This study further demonstrated that disease-free survival for patients with high-risk submucosal rectal cancer was inferior to patients with

high-risk submucosal colon cancer (5-year disease-free survival rates: 77.7% *vs.* 96.5%, respectively, P<0.01). The authors proposed that recurrence rates greater than 10% might be expected when no additional surgery was pursued due to the increased possibility for micrometastasis. Based on these collective findings, it appears important to consider not only risk of lymph node metastasis but also risk of local recurrence when evaluating treatment options for patients with high-risk submucosal rectal cancer following endoscopic resection.

In this study, long-term disease-free survival of patients with low-risk submucosal colorectal cancer following endoscopic resection alone was excellent. All 104 patients with low-risk submucosal colon cancer did not exhibit recurrence during the defined follow-up period (mean: 55.2 months). In the low-risk submucosal rectal cancer group, only one patient (6.3%) had distant metastases—this patient had originally been classed as low-risk for lymph node metastasis, but upon reexamination of the original pathology specimen, additional slices exhibited lymphovascular invasion. Therefore, this patient was actually high-risk for lymph node metastasis, and additional surgery should have been recommended. Evaluation of this patient raises important considerations including: (I) further demonstration that long-term outcomes of low-risk submucosal colorectal cancer are excellent, and (II) presence and impact of pathologic error. A prior retrospective study demonstrated that pathologic errors in cancer diagnosis occur in up to 11.8% of cases (19). Such data underscore the importance of careful evaluation of cancer recurrence following endoscopic resection even in patients with low-risk of lymph node metastasis. In addition, other reports have proposed further risk factors for lymph node metastasis including tumor budding and background adenoma beyond the classic criteria mentioned earlier (7,13,20). Although further research may be necessary, we believe that additional pathologic assessment for tumor budding and background adenoma in patients with low-risk submucosal colorectal cancers may help to better assess risk for lymph node metastasis. In contrast to patients with low-risk submucosal colorectal cancer, seven patients (6.6%) with high-risk submucosal colorectal cancer who underwent endoscopic treatment had recurrence. In addition, 14 patients with high-risk submucosal colorectal cancer (2.6%) had recurrence despite undergoing surgery. Lymph node metastasis was identified in 12.4% of patients (66 of 532) with high-risk submucosal colorectal cancer and who underwent surgery, findings consistent with previous reports (11,15).

In spite of extraordinary conclusion, results of the study should be interpreted with caution given study limitations. First, the en-bloc resection rate was not reported despite including of patients who underwent endoscopic piecemeal mucosal resection. Local recurrence of colorectal tumor occurs more frequently after piecemeal resection than with en-bloc resection (21,22). Second, multivariate analysis for disease-free survival may not have been appropriate, although univariate analysis showed that disease-free survival rate was lower in patients with high-risk submucosal rectal cancer than in patients with high-risk submucosal colon cancer. Tumor location was an independent risk factor for disease-free survival according to the proposed Cox regression hazard model (HR of rectum =6.73, 95% CI, 1.04-43.43). This model included tumor depth (≥2,000 or <2,000 μm), lymphatic invasion, vascular invasion, and tumor differentiation (well-differentiated or moderately-differentiated). However, based on the established risk factors for disease-free survival, tumor depth (≥1,000 or <1,000 μm) and tumor differentiation (well- to moderately-differentiated or poorly-differentiated) should be included in the model. We speculate that the differences in proposed models might be due to fewer patients having either poorly-differentiated adenocarcinoma or submucosal cancer within 1,000 μm of tumor invasion. Third, disease-free survival in this study appears to be analyzed incorrectly. The 3rd table of the article demonstrated no recurrence in patients with low-risk submucosal colon cancer—however, Kaplan-Meier curves for disease-free survival showed that some lesions (perhaps three) had recurrence. In addition, Kaplan-Meier curves for disease-free survival were similar to overall survival curves. It seems, then, that disease-free survival of patients without recurrence of colorectal cancer and who died from other causes were considered as uncensored data. However, in disease-free survival analyses, such patients should be classified as censored data. Therefore, upon reclassification of the data, 5-year disease-free survival of patients with low-risk submucosal colon cancer was 100.0% and not 95.9%. A similar error was also found in Kaplan-Meier curves for disease-free survival in patients from the high-risk endoscopic resection group. Although such errors may not alter the ultimate conclusions, they do question study reliability.

Despite these limitations, this was a strong study that revealed that risk of local recurrence following endoscopic resection was significantly higher in patients with high-risk submucosal rectal cancer than in patients with high-risk submucosal colon cancer. Why local recurrence occurs more frequently in high-risk submucosal rectal cancer as

compared to high-risk submucosal colon cancer remains unanswered, although micrometastasis was suggested as a plausible theory. Whether more extensive cancer excision with sufficient lateral margins improves disease-free survival in high-risk submucosal rectal cancer also remains unclear. Future studies should address these questions. At present, if an endoscopically-resected submucosal rectal cancer has been proven to be a high-risk lesion for lymph node metastasis, additional surgery should be considered to reduce not only distant metastasis but also local recurrence.

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