Editorial

Long-term outcome and surveillance policy after endoscopic therapy for early gastric cancer

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In Japan, nationwide mass screening programs and easy access to endoscopic examinations by experienced gastroenterologists have enabled detection of gastric cancer at very early stages. In recent years, more than half the gastric cancers detected by screening programs are in their early stages, and many of them are amenable to endoscopic resection (ER) [1]. Several techniques for endoscopic mucosal resection (EMR) have been developed, and recent introduction of endoscopic submucosal dissection (ESD) has enabled resection of more extensive lesions beyond the criteria proposed by the Japanese Gastric Cancer Association (JGCA) [2].

Although these endoscopic therapies are now being performed in a large number of institutions throughout Japan, the quality assurance in each institution or comparisons of outcomes among hospitals has not been scrutinized. It should be kept in mind, however, that the conditions for these endoscopic treatments for early gastric cancer compared with surgical operation should be (1) similar or better curative rate, (2) earlier recovery and better quality of life, and (3) cost-effective advantage. Excellent long-term results (5-year survival rate exceeding 95%) after surgical operation for early gastric cancer have been achieved in major institutions in Japan. To be compatible with the first condition, long-term outcome of endoscopic therapy for early gastric cancer with more limited disease extension should theoretically be superior to surgical results. Unfortunately, very few studies have been conducted to verify this premise that is vital for critical evaluation of the indication of ER for early gastric cancer. In this issue of *Gastric Cancer*, two articles that address the subject in part are published by authors from two leading institutions [3,4]. In these institutions, a large number of ERs are routinely performed by highly experienced endoscopists and their surveillance programs after

endoscopic therapy are conducted more rigorously. Thus, we can expect state-of-the-art clinical data on quality assurance after endoscopic therapy for early gastric cancer.

Uedo and colleagues [3] from the Osaka Medical Center for Cancer and Cardiovascular Diseases have analyzed the long-term outcome of early gastric cancer after successful EMR. The subjects enrolled in their study were treated for cancer that fully met the criteria for EMR according to the guidelines established by JGCA: well-differentiated histology, no evidence of submucosal invasion, and smaller size (less than 2 cm) without ulceration [2]. Early gastric cancers fulfilling these criteria are considered to be curable by ER alone because of negligible risk of metastatic spread. Patients with such lesions will benefit most from endoscopic treatment if the conditions mentioned above are met. According to the data of Uedo et al., long-term disease-specific survival rates at 5 or 10 years were both 99%, providing assurance of long-term survival benefit for endoscopic therapy. However, it should be noted that two patients among their subjects died of gastric cancer. One of them actually had a lymphatic invasion that had been misclassified in a completely resected group in their database. This patient, therefore, should have been operated on immediately after endoscopic resection. The other patient had cancer foci in a hyperplastic polyp that had been removed by endoscopy. It is quite unlikely that inadequate polypectomy was the cause of death, because complete resection was confirmed by pathological examination of the resected specimen. Rather, it would be reasonable to assume that a cancer that had developed elsewhere in the stomach may have been responsible for the death, which occurred more than 10 years after resection, because this patient was lost to follow-up. This possibility conveys a very important message in advocating the necessity of continuous follow-up. It is well known that the risk of developing gastric cancer is high in patients with atrophy and

intestinal metaplasia where hyperplastic polyps also develop. Indeed, recent works have shown increased risk of developing gastric cancer in patients with atrophy and intestinal metaplasia [5,6]. The possibility of second or multiple cancer development after ER is another important issue in planning a safe and strict follow-up program. The second report in this issue of *Gastric Cancer*, by Nakajima et al. [4] from the National Cancer Center Hospital (NCCCH), clearly demonstrated that multiple occurrence of early gastric cancer was present in a significant portion (9.2%) of cases and, more importantly, there was a steady increase in metachronous second cancer development during their observation period. The definition of metachronous cancer in their report was arbitrary, and some of the cancers included in “metachronous cancers” already were present at the time of initial therapy. Nevertheless, follow-up endoscopic examinations disclosed second gastric cancers that developed in different sites from the initial lesions at an almost constant rate during the several years of the observation period. Therefore, we should bear in mind that successful endoscopic therapy for early gastric cancer does not imply completion of the therapy, but actually the start of close follow-up for the potential presence of residual or missed cancer foci in other sites, and for early detection of metachronous cancer development as well.

How, then, we should plan a follow-up surveillance policy for patients who have undergone endoscopic therapy? Nakajima's group recommended annual surveillance by endoscopy because more than 96% of the lesions subsequently detected by such a surveillance program could be safely managed by repeat endoscopic therapy. However, we should await further critical data before accepting their proposal. Firstly, as is routinely done by Uedo's group [3], many institutions are performing “second-look” endoscopies within a shorter period (usually within 3 months) after endoscopic therapy to confirm ulcer healing as well as to ascertain that there is no local recurrence. Many of the subjects in the NCCCH study have undergone endoscopic examination within a shorter period at least for the first year after ER. We are not certain, therefore, whether repeat endoscopic follow-up in the first year after ER can be omitted. Secondly, the mean size of the metachronous cancers (about 10 mm) was smaller than that of index lesions (about 15 mm); thus it can be argued that longer intervals might be possible, because the size of the cancer suitable for ER has been extended up to 3 cm at NCCCH [1,4]. In any case, the cost of endoscopic treatment together with surveillance accumulates over time, which might compromise the advantage in terms of medical cost. Therefore, we should also consider other preventive approaches to reduce development of second cancers.

One possibility is eradication therapy for *Helicobacter pylori*. Uemura et al. reported that metachronous development of gastric cancer was significantly reduced in a group of patients who received eradication therapy [7]. A larger retrospective analysis also showed that second-cancer development was reduced to about one-third by eradication therapy [8]. Therefore, we should consider eradication therapy for patients with early gastric cancer treated by endoscopic resection. Although gastric cancer development was reported long after eradication therapy [9–11], and the reversibility of atrophy and intestinal metaplasia with eradication therapy are not certain [12,13], it may be effective at least in halting progression of mucosal atrophy or intestinal metaplasia.

It is well known that virtually no gastric cancer develops in subjects without *H. pylori* infection [6]. Why are we unable to completely suppress the development of gastric cancer after eradication? One of the reasons is our limitation in the diagnosis of very small cancer foci. In Nakajima's series, very small cancers, less than 5 mm in size, are rarely detected during the surveillance examinations that are done more cautiously. These lesions must have evaded detection at routine examinations in many other institutions. The tumors usually grow very slowly and require a long time to become invasive [14]. Therefore, we have to accept this lead-time effect as one of the limitations of late intervention with eradication. A second possibility is that gastric atrophy with intestinal metaplasia often harbors genetic alterations known to be present in gastric cancer [12]. These precancerous lesions may easily transform into cancer with additional mutational events. This has been shown in our mice model of intestinal metaplasia that spontaneously develops differentiated cancer [15]. For that reason, we are not certain how the eradication of *H. pylori* is effective in reducing the development of metachronous gastric cancer. Nevertheless, we should adopt an eradication policy because many of the subjects are elderly and deterrence of cancer development may be reason enough, considering their life expectancy.

Other possible intervention includes nutritional supplementation [16] or medication such as Cox-2 inhibitor with antineoplastic properties [17]. Recently, such cancers have been found to harbor defects in the mismatch repair system, presenting high microsatellite instability (MSI-H) [18,19]. MSI-positive gastric cancers often show silencing of mismatch repair genes such as the *hMLH1* gene by promoter hypermethylation. Identification of such high-risk conditions may be effective in targeting a group of patients requiring a more intensive surveillance program. These patients may be good candidates for a number of drugs currently under development to reverse methylation-induced gene silencing.

Lastly, we should briefly consider safety issues in endoscopic therapies. It seems self-evident that successful endoscopic therapy benefits patients because it is much less invasive, preserves gastric function, and thereby ensures quick recovery. However, this is not always the case. Several related problems include limitations in diagnostic accuracy to determine horizontal and vertical margins of tumor invasion and lack of standardized technical skills to enable safe and reliable resection. Endoscopic therapy is accompanied by considerable risks of re-bleeding, perforation, and incomplete resections resulting in additional endoscopic interventions or surgical operations. In such cases, the advantage of endoscopic therapy would be seriously compromised. Many gastroenterologists are now undertaking to resect lesions exceeding the size limitation recommended by the JGCA. However, the rate of complete, en bloc resection is far from satisfactory for larger lesions. A piecemeal resection will increase the local recurrence rate and preclude precise pathological judgment of complete resection. Moreover, the diagnostic accuracy of vertical extension is still incomplete, with limited sensitivity and specificity even with current high-frequency endoscopic ultrasound examinations [20]. Therefore, we cannot precisely differentiate endoscopically curable lesions from those requiring additional surgery due to vessel invasion and/or positive vertical margin. In the NCCCH series, more than 15% of patients initially treated with ER were subjected to surgical operation because of noncurative ERs [4].

For these reasons, we must admit that endoscopic diagnosis and therapy for early gastric cancer are still evolving and are far from complete. Further refinement and improvement in terms of diagnosis, methods of endoscopic resection, and a training system for technical skills are mandatory for this valuable procedure to fully benefit patients.

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