



Early gastric cancer in super-agers: To treat or not to treat?

Gastric cancer is one of the leading causes of cancer-related mortality worldwide. The incidence is lower in most of the Western countries, like the United States, than in East Asia, where approximately half of the cases occur.¹ However, despite a gradually decreasing incidence, the estimated number of new cases of gastric cancer in the United States in 2016 is still 26,370. Approximately 0.9% of men and women will receive diagnoses of stomach cancer at some point during their lifetime, in comparison with a rate of 0.5% for esophageal cancer.² Unfortunately, only every fourth case is diagnosed at a local stage in most Western countries, and the overall 5-year survival rate is limited to 20% to 30%. Much higher rates of early detection can explain the better overall prognosis in East Asia. It can be expected that future guidelines for gastric cancer screening and surveillance of precancerous conditions could improve the diagnosis of early tumor stages in Western countries.³ In addition, a more thorough inspection of the stomach during endoscopy is required to reduce the substantial risk of missing early lesions.⁴

Endoscopic resection in selected cases of early gastric cancer (EGC) has been widely accepted in Asia and many Western countries.⁵⁻⁷ It offers advantages over open or laparoscopic surgery because of the minimally invasive approach, organ preservation, and a higher postoperative quality of life with a similar efficacy in terms of oncologic aspects. The guidelines of the Japan Gastroenterological Endoscopy Society and the Japanese Gastric Cancer Association provide diagnostic criteria for selecting patients with early tumor stages that are associated with a negligible risk of lymph node metastases.⁸ Comparative studies indicate that the clinical outcomes of endoscopic submucosal dissection (ESD) of early gastric cancer are comparable between absolute and expanded criteria.^{9,10} Further follow-up studies over a longer period are warranted. It remains controversial whether data from Asia can be applied to Western countries. A recent histologic study of a large number of gastrectomy specimens showed higher rates of lymph node metastases in early gastric cancer in patients from the United States than those previously reported in Asia.^{11,12} However, several differences between these studies have to be considered. In the

absence of controlled trials, the decision for the appropriate treatment of gastric cancer requires one to weigh the oncologic risk against the risk of the procedure and the postprocedural quality of life.¹³

In addition to careful selection of patients with EGC, endoscopic treatment requires en bloc resection to provide appropriate specimens for histologic evaluation and to minimize the risk of local tumor recurrence. Recent systematic reviews and meta-analyses have shown that ESD is significantly more effective than EMR in terms of en bloc resection, complete resection, and recurrence rates.^{14,15} The risk of perforation is higher for ESD, but this adverse event is usually recognized during the procedure and can

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be endoscopically managed. There is no difference in overall bleeding rates. The potential harm related to ESD is outweighed by the effectiveness benefit, provided that the procedure is performed by an experienced interventional endoscopist.

For several reasons, ESD of EGC has not yet been widely performed in Western countries.⁷ However, recent studies have demonstrated favorable therapeutic outcomes in specialized centers that are comparable with those achieved in Asian institutions.¹⁶⁻¹⁹ ESD has globally become a major topic in conferences on GI endoscopy, and an increasing number of training courses is offered to interventional endoscopists. In Western countries, the procedure is more frequently performed for colorectal than for gastric lesions because of a higher volume of cases. Operators with appropriate experience in colorectal ESD should also be qualified for gastric ESD, which is considered to be less difficult for most tumor locations.²⁰

The average age of patients undergoing ESD for EGC varies between 60 and 70 years in most of the recent trials.^{10,18-23} The number of patients over that age is increasing, and there is limited evidence about the pros and cons of ESD in patients with early EGC who are older

than 80 years or in super-agers of over 85 years. Curative treatment may have a limited impact on clinical outcomes in these cases. The potential oncologic advantages have to be outweighed against the adverse events of ESD; even minor adverse events can become clinically relevant in elderly patients.

In this context, Sekiguchi et al²³ report on an important retrospective analysis on 108 patients 85 years old and older who were treated by ESD of 149 gastric cancers in the National Cancer Center in Tokyo. Patients with a poor performance status or evidence of other diseases that could determine prognosis regardless of treatment of gastric cancer were excluded. En bloc and curative resection rates of 98% and 73%, respectively, and the procedure-related morbidity rate of 8.8%, are comparable with those in series on patients with a mean age between 60 and 70 years. There were no severe adverse events that required surgical intervention, and no procedure-related deaths were registered. During a mean follow-up period of 40 months, 23 patients died, but only 2 of them died of gastric cancer. Those 2 patients had refused additional surgery, which was indicated because histologic analysis of the resected specimens had shown advanced tumor stages. The 3-year and 5-year overall survival rates were 90% and 72%, respectively. A multivariate analysis identified the prognostic nutritional index (PNI) as the only independent risk factor for poor survival. Based on a PNI cutoff value of 44.6, the 5-year survival rate was significantly higher in patients above than below this value (76% vs 54%; $P < .001$). Comorbidities had no impact on the overall survival. The authors conclude that ESD is feasible for EGC in patients over the age of 84 years who are in a good performance status. However, the prognosis is less favorable in patients with a low PNI, so that the indication for ESD should be critically discussed in these cases.

How do the results of this study compare with those of other trials on endoscopic or surgical treatment of EGC in elderly patients? A recent meta-analysis reported on 9 Asian studies including a total of 30,100 EGC lesions that were treated by ESD.²⁴ These trials provide data for comparison of the clinical outcome between elderly patients and patients below the age of 65 to 80 years according to the definition in each trial. The results showed no significant difference between the elderly and nonelderly groups in terms of en bloc and histologically complete resection rates and procedure-related perforations or bleedings. The only significant difference was registered in terms of postprocedural pneumonias, which were more frequently observed in elderly patients (odds ratio 2.18; $P < .01$). In addition to the study by Sekiguchi et al,²³ only a single recent trial reported on the prognosis of ESD of EGC in super-elderly patients 85 years old and older.^{23,25} This study analyzed the relationship between comorbidities and clinical outcome in a total number of 85 patients. There was no impact of comorbid-

ities on a histologic resection rate of 95%, and no severe adverse events occurred that were related to ESD. However, the frequency of deaths was higher in patients with comorbidities than in those without comorbidities during the follow-up period ($P < .01$). No case of death was related to gastric cancer.

Recent retrospective surgical series indicate that gastrectomy and limited resection are valuable options in elderly patients.^{26,27} Most patients who have undergone surgery seem to have a better survival outcome than do patients who have not been operated on. However, the survival rates were significantly lower in patients with a low performance status, advanced age, male sex, higher tumor stages, and low PNI. A retrospective propensity score matched analysis compared curative distal gastrectomy with best supportive care in 111 patients 85 years old and older with diagnoses of gastric cancer.²⁸ The results demonstrated a significantly higher overall survival in patients who underwent gastrectomy (57 vs 16 months; $P = .0002$).

There is no formal trial that allows a prospective comparison of endoscopic or surgical treatment of EGC with best supportive care. Therefore, the results of interventional trials have to be balanced against the natural course of EGC in elderly patients. There are only a few data on the long-term outcome of patients with EGC who have not undergone surgery. A previous follow-up study revealed a cumulative risk for tumor progression to advanced stages in 63% of 56 patients with EGC.²⁹ The 5-year corrected survival was 63% in patients who had not undergone resection.

In conclusion, the number of elderly patients and even of “super-agers” over 84 years with EGC will increase because of advances in health care, screening, and surveillance programs. In addition, the quality of gastroscopy should improve and should decrease the rate of missed incidental neoplastic or precancerous lesions in the stomach. No treatment of EGC will cause progression to advanced tumor stages and death of gastric cancer in the majority of patients with an estimated life expectancy of more than 3 to 4 years. This potential risk of tumor progression should be balanced against the risk of endoscopic or surgical treatment. The decision cannot be made on the basis of a high level of evidence resulting from a lack of prospective controlled trials. However, the study by Sekiguchi et al²³ and other retrospective series demonstrate that ESD of EGC is safe and effective, even in super-elderly patients with a good performance status and a PNI of more than 45. The clinical outcome seems to be superior to that afforded by best supportive care. This group of patients can even benefit from surgical resection. However, ESD should be preferred if patients meet the standard or extended criteria because of less procedural invasiveness and a higher postoperative quality of life resulting from functional preservation. Additional surgery can still be safely performed in elderly patients if histologic analysis of ESD specimens reveals a noncurative tumor

stage.³⁰ On the other hand, ESD for EGC may not be indicated if geriatric patients do not meet the mentioned criteria. Also, it should be critically discussed whether ESD cannot be performed by experienced endoscopists who can reproduce the results from experts in Asia. Although not shown in trials, high performance skill seems to be even more important in super-agers than in younger patients because of the increased risks in terms of extension of procedural duration and the consequences of severe adverse events.

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Abbreviations: EGC, early gastric cancer; ESD, endoscopic submucosal dissection; PNI, prognostic nutritional index.

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