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Review

Reality of Gastric Cancer in Young Patients: The Importance and Difficulty of the Early Diagnosis, Prevention and Treatment

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Gastric cancer usually arises in middle-aged to older patients, and is rarely found in younger patients. The clinical characteristics, etiology, prognosis, preventive methods and treatment of gastric cancer in young patients have not been fully investigated because of its low prevalence. In this review, we discuss the current understanding and clinical problems associated with gastric cancer in young patients. *Helicobacter pylori (H. pylori)*, which is a major cause of gastric cancer, especially in older populations, is closely associated with gastric cancer in young patients as well as in older patients. Gastric cancer in young patients tends to be diagnosed at an advanced stage with alarm symptoms. However, young patients with advanced gastric cancer tend to have a favorable general condition and organ function, so they can tolerate intensive systematic chemotherapy. Unfortunately, the prognosis of gastric cancer in young patients with an advanced stage is not favorable. We should not take this rare disease lightly, given its poor prognosis if patients are diagnosed at an unresectable stage. The evaluation of the *H. pylori* infection status and performance of *H. pylori* eradication therapy to prevent gastric cancer in young patients as well as the development of more intensive chemotherapy regimens for unresectable gastric cancer in young patients are warranted.

Key words: gastric cancer, young patients, *Helicobacter pylori*

Helicobacter pylori is the major cause of gastric cancer [1,2], which usually occurs in older patients. Some studies have revealed that 2.7-15% of patients with gastric cancer are young age [3-8]. Several studies have reported the clinicopathological features and prognosis of gastric cancer in young patients. Gastric cancer in young patients is reportedly associated with an increased prevalence of women and cases of diffuse type, poorly differentiated lesions, lymph node metastasis, and a poor prognosis due to a diagnosis at an advanced stage [9]. However, since most studies have been retrospective case-control studies with small sample sizes, the clinicopathological features of gastric cancer in young patients remain unclear.

Global gastric cancer incidence and mortality rates have been declining over the last five decades worldwide, due in part to the eradication of *H. pylori* infection, medical screening, and advances in treatment [10]. However, a stable or even slightly increasing trend of gastric cancer in young adults has been reported [11]. Therefore, it is important to discuss the clinical problems of gastric cancer in young patients at present.

In this review, we summarize the current under-

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standing and clinical problems associated with gastric cancer in young patients.

Definition and Clinicopathological Features of Gastric Cancer in Young Patients

The definitions of gastric cancer in young patients have differed among studies. In some studies, gastric cancer in young patients is defined as that manifesting before 40 years old, while in others, the definition generally includes all patients diagnosed before 45 years old. For this reason, the reported clinicopathological features of gastric cancer in young patients are varied. Approximately 10% of gastric cancer patients reportedly fall into the "gastric cancer in young patients" category [12].

Before 40 years old, the incidence of gastric cancer is higher in women than in men, while in those older than 40 years old, the incidence of gastric cancer increases dramatically in men [5, 8, 13-15]. This higher female proportion suggents that sex hormones, especially estrogen, may play an important role in the development of gastric cancer in young patients [16, 17]. In addition, gastric cancer in young patients has a more aggressive growth pattern than that in old patients. The predominance of a poorly differentiated histological type, diffuse macroscopic type, advanced tumor stage, lymphovascular invasion, and high non-curability rate are all poor prognostic factors for gastric cancer in young patients [13, 15, 18-22]. An increased frequency of bone metastases in gastric cancer in young patients may also be associated with estrogen receptor positivity, as has been demonstrated in other cancer types [8, 23].

In general, gastric cancer develops through a cascade of well-defined and recognizable steps — inflammation, atrophy, intestinal metaplasia, dysplasia, and carcinogenesis — and is closely associated with the environment, diet, and gene mutations [24-27]. Genetic factors may be more important in gastric cancer in young patients than in older patients, as younger patients have less exposure to environmental carcinogens [28, 29]. Familial clustering was found in 10% of gastric cancer cases, and epidemiological studies have demonstrated that the risk of gastric cancer in first-degree relatives is increased 2- to 3-fold [30]. Early-onset gastric cancer can arise in such populations. Furthermore, hereditary diffuse gastric cancer (HDGC), Lynch syndrome, juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), familial adenomatous polyposis, and other less common hereditary cancer predisposition syndromes should be discussed as differential diagnoses in cases of gastric cancer in young patients.

The comprehensive molecular analyses of gastric cancer, including The Cancer Genome Atlas (TCGA), suggested 4 molecular subtypes: tumors positive for Epstein- Barr virus (EBV), microsatellite instability (MSI), genomically stable (GS), and chromosomal instability (CIN) [31]. We will discuss the relationship between these subtypes and gastric cancer in young patients. Among these subtypes, GS subtype tumors tend to be related to an early onset and diffuse-type histology. Microsatellite instability-high (MSI-H) tumors are enriched in older patients, while the microsatellite stable/epithelial-mesenchymal transition subtype presents at a significantly younger age, with most patients diagnosed at an advanced stage [32, 33]. Regarding the EBV, a meta-analysis found that the overall prevalence of EBV positivity in gastric cancer was estimated to be 8.7% [34]. EBV has been implicated in gastric carcinogenesis, and its positivity is slightly more frequent in diffuse-type gastric cancers than in intestinal-type gastric cancers [35-37]. A previous study indicated that gastric cancer in young patients was characterized by both EBV positivity as well as enhanced immunostaining of PD-L1, suggesting that such patients may candidates for immunotherapy [38].

Contribution of *H. pylori* Infection to the Pathogenesis of Gastric Cancer in Young Patients

Since the incidence of *H. pylori* infection is lower in heathy young adults than in older individuals, the contribution of *H. pylori* infection to the pathogenesis of gastric cancer in young patients has been considered small. With the spread of *H. pylori* eradication therapy, the morbidity rate of gastric cancer in young patients is decreasing in Japan. *H. pylori* infection usually takes several decades to induce histological changes and subsequent neoplastic transformation. Indeed, it has been reported that gastric cancer in young patients is related to less intestinal metaplasia [39, 40], which suggests that different mechanisms of *H. pylori* can induce carcinogenesis in younger populations.

Table 1 shows studies that reported the incidence of *H. pylori* infection in young patients with gastric cancer.

The incidence ranges from 23.9% to 88% in studies from various countries [6,21,22,38,40-46]. This variation of incidence is due to not only to the regions of the studies but also the number of patients whose *H. pylori* infection status was assessed. Given the low incidence of *H. pylori* infection in the healthy Japanese population [47], the higher incidence of *H. pylori* infection is revealed. This indicates that *H. pylori* infection plays an important role in the development of gastric cancer in young patients as well as older patients [37,48,49].

H. pylori infection is usually related to the pathogenesis of differentiated-type gastric cancer [50,51], while most cases of gastric cancer in young patients are undifferentiated-type gastric cancer. This may seem paradoxical. The inflammation induced by *H. pylori* infection reportedly promotes the development of undifferentiated-type gastric cancer [52]. Hirahashi *et al.* even found a significantly higher incidence of *H. pylori* infection among the young patients than among older patients with intramucosal cancer of poorly differentiated type [49,53]. Observational studies of Japanese adults with nodular gastritis, which is closely related to active inflammation by *H. pylori* infection, have suggested an association with gastric cancer, particularly diffuse type gastric cancer [54,55]. These studies support our hypothesis in this review that *H. pylori* infection can induce active gastritis, and carcinogenesis and promote the rapid progression of undifferentiated-type gastric cancer in young patients.

Table 1 Incidence of *Helicobacter pylori* infection in young patients with gastric cancer

Author (year)	Country	n	Patient age	Incidence (%)
Kokkola (1996) [12]	Finland	50	≤45	72
Chung (2010) [6]	Korea	1,584	31–40	23.9
Nam (2011) [41]	Korea	185	≤40	80.5
Marcos (2013) [42]	Portugal	103	≤45	82
Pisanu (2014) [44]	Italy	20	<50	25
Bautista (2014) [43]	USA	34	<40	88
Zhou F (2016) [21]	China	152	<40	51.1
Lee (2016) [45]	Korea	57	<40	65
Ji (2017) [22]	China	45	<40	75.6
Kono (2019) [46]	Japan	67	<40	81
Moore (2020) [38]	Israel	39	≤45	36

The Prognosis of Gastric Cancer in Young Patients Compared to Older Patients

While some studies have demonstrated poor outcomes of gastric cancer in young patients, others have reported a better prognosis than in older individuals, and some still have described no marked differences in the survival based on age. Table 2 compares the prognosis of gastric cancer in young versus older patients.

Table 2 The prognosis of young patients with gastric cancer compared to older patients

Author (year)	Country	Study design	Subject (age, years old)	Median OS (months)
Nakamura (2011) [18]	Japan	Retrospective	All stage <34 (n=27) vs. ≥34 (n=1,703)	68.5% vs. 83.2% (5-year OS rate)
Liu (2016) [14]	Korea	Retrospective Case-control	All stage ≤45 (n=198) vs. 55–64 (n=1,096)	27.3 vs. 22.9
Rona (2017) [56]	USA	Retrospective Case-control	All stage ≤45 (n=121) vs. >45 (n=121)	11.7 vs. 41
Cormedi (2018) [59]	Brazil	Retrospective Case-control	All stage ≤40 (n=71) vs. 41–65 (n=129)	15 vs. 21
Takesin (2019) [58]	Turkey	Retrospective	All stage ≤40 (n=92) vs. >40 (n=774)	11 vs. 12
Moore (2020) [38]	Israel	Retrospective case-control	All stage ≤45 (n=39) vs. ≧55 (n=35)	69.7 vs. 47.8

OS, overall survival.

The subjects of these studies had disease of all stages, and we excluded the studies including only gastric cancer patients after surgical resection. Although gastric cancer in young patients has been reported to have aggressive clinicopathological factors, most studies reported that the overall survival (OS) of gastric cancer in young patients was comparable to that in older patients. However, Nakamura *et al.* and Rona *et al.* reported that the survival rate of gastric cancer in young patients was worse than that in older patients [18,56]. Kono *et al.* compared the OS in patients in their 20s with that in patients in their 30s, concluding that the former was worse [46]. However, the variation in the OS may be because patients in most studies were not matched based on tumor stage. Gastric cancer in young patients has a better prognosis than that in older patients at an early stage [57,58] but a poor prognosis in the advanced stage [45,46].

The Early Diagnosis, Prevention, and Treatment for Gastric Cancer in Young Patients

Gastric cancer in young patients is most often diagnosed at the advanced stage with organ involvement, suggesting a potentially greater burden of disease, which may lead to the poor long-term survival [8,56,59]. Since a large proportion of cases of gastric cancer in young patients may have no alarm symptoms, gastric cancer is not considered a differential diagnosis in young patients. Indeed, several studies investigated the relationship between symptoms and the disease status of gastric cancer in young patients, finding that the proportion of cases with alarm symptoms was significantly higher in the advanced stage than in the early stage [5,18,51].

The early diagnosis in gastric cancer in young patients may contribute to the long-term survival. However, young populations are not indicated for endoscopic screening in various guidelines, which can delay the investigation and diagnosis and result in a more advanced stage at detection [46,60]. Mass screening endoscopy has been introduced to detect early-stage gastric cancer in Korea and Japan, where gastric cancer is prevalent. However, the screening targets are limited to individuals ≥40 years old because overuse of endoscopy is associated with a low yield rate in young patients and is not cost-effective. Furthermore, young patients tend to avoid promptly visiting the hospital when they have symptoms, which can delay the diagnosis.

Another important issues to consider is how to get young populations to avoid risk factors. A systemic review and meta-analysis showed that the eradication of *H. pylori* in asymptomatic, infected adults led to a reduced incidence of gastric cancer [61,62]. Unfortunately, the system, efficacy, and safety of *H. pylori* eradication for the prevention of gastric cancer in young patients has not been established. To screen for high-risk young patients with gastric cancer, a system for checking the *H. pylori* infection status, and evaluating the family history of gastric cancer in young adults must be established. Of course, the prevention of *H. pylori* infection is more useful to reduce the incidence of gastric cancer in young patients. Since family infection such as the infection from mother to infant is the highest risk of *H. pylori* infection, preventing *H. pylori* infection among the family is an important issue. Checking and eradication of *H. pylori* should be performed before marriage and having infants.

When young patients with gastric cancer are diagnosed at the unresectable stage, they undergo systematic chemotherapy. Young patients who are diagnosed with gastric cancer at an advanced stage tend to have a better performance status than older patients [57,63]. With a favorable general condition and organ function, young patients with advanced gastric cancer experience fewer adverse events than older patients, which can facilitate intensive chemotherapy. The efficacy and tolerance of systematic chemotherapy for gastric cancer in young patients has been reported [64]. Nevertheless, the survival of gastric cancer in young patients at the unresectable stage is not favorable, ranging from 5-6 months for the median OS [5,46]. More intensive anticancer drugs for young patients with unresected gastric cancer are desired to improve the survival.

Conclusion

We reviewed the current understanding and clinical problems associated with gastric cancer in young patients. While difficult, diagnosis is necessary, along with the development of novel preventive methods and intensive treatments for gastric cancer in young patients. Although gastric cancer in young patients has a low prevalence and low mortality, we should treat the clinical issues of gastric cancer in young patients seriously, due to its aggressive nature and miserable prog-

nosis if diagnosed at the unresectable stage.

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