Surgery 165 (2019) 802–807

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Stomach

Effect of age on the clinical outcomes of patients with early gastric cancer with undifferentiated-type histology

Jeung Hui Pyo, MD[a], Hyuk Lee, MD, PhD[b,*], Yang Won Min, MD, PhD[b], Byung-Hoon Min, MD, PhD[b], Jun Haeng Lee, MD, PhD[b], Kyoung-Mee Kim, MD, PhD[c], Heejin Yoo, MS[d], Kyunga Kim, PhD[d], Yoon-Ho Choi, MD, PhD[a], Jae J. Kim, MD, PhD[b], Sung Kim, MD, PhD[e]

[a] Center for Health Promotion, Samsung Medical Center, Seoul, Korea
[b] Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[c] Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[d] Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea
[e] Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Accepted 5 November 2018
Available online 11 December 2018

ABSTRACT

Background: Undifferentiated-type early gastric cancers account for a large proportion of gastric cancers in younger patients. Therefore, the clinical outcomes of endoscopic resection in younger patients are a major concern. We aimed to investigate the influence of age on lymph node metastasis and long-term survival after surgery for undifferentiated-type early gastric cancers.

Methods: We identified 4,236 patients who underwent surgery for undifferentiated-type early gastric cancers. For each T stage, the correlation between age and lymph node metastasis was analyzed using a multivariate logistic regression. Lymph node metastasis rates were compared between younger (<40 years) and older patients (≥40 years) who fulfilled the expanded criteria for endoscopic resection. The Kaplan–Meier method was used to compare long-term survival between younger and older patients.

Results: Younger age groups (20–29 and 30–39 years) had the highest lymph node metastasis rate within each T stage (5.7% and 5.7% for T1a, 26.3% and 24.1% for T1b, respectively). After adjusting for possible covariates, however, age did not have a significant effect on lymph node metastasis in either T stage ($P = .127$ for T1a, $P = .114$ for T1b). Among patients fulfilling the expanded indication for endoscopic resection, younger patients had a slightly higher lymph node metastasis rate compared with older patients (2.7% versus 2.0%), although this difference was not statistically significant. Although younger patients had a significantly better overall survival ($P < .001$), no significant age-related differences were observed in recurrence-free and disease-specific survival ($P = .051$ and $P = .069$)

Conclusion: Endoscopic resection may be feasible in young patients with undifferentiated-type early gastric cancers because these patients share a similar lymph node metastasis rate and long-term survival outcomes with older patients.

Introduction

Endoscopic resection (ER) has been established as a standard treatment for patients with early gastric cancer (EGC), with a negligible risk of lymph node metastasis (LNM).[1,2] Notably, advances in endoscopic technology have expanded the indications for ER for EGC.[1,3] Currently, the indications for endoscopic submucosal dissection (ESD) are generally limited to differentiated-type gastric cancer, whereas ESD is still considered an investigational treatment for EGCs with undifferentiated-type histology (including signet-ring cell carcinoma, poorly differentiated adenocarcinoma, or mucinous carcinoma) because of the increased risk of LNM when compared with that of differentiated-type gastric cancer.[4,5] However, recent studies have reported the technical feasibility and favorable clinical outcomes of ESD for undifferentiated-type EGC, leading to the use of this technique in the clinical field.[6–9]

According to recent reports, the incidence of gastric cancer is increasing among younger patients, who tend to have a worse prognosis when compared with older patients.[10–13] Because

* Corresponding author: Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Irwon-dong, Gangnam-gu, Seoul, 135-710, Republic of Korea.
E-mail address: leehyuk@skku.edu (H. Lee).

https://doi.org/10.1016/j.surg.2018.11.001
0039-6060/

undifferentiated-type tumors comprise a large proportion of gastric cancers in younger patients, the clinical outcomes of ER for these lesions represent a major concern.[14–16] Nevertheless, previous studies of the prognosis of gastric cancer in younger patients have been limited by the inclusion of data from patients with differentiated-type and advanced-stage gastric cancers.

Although we recently analyzed the feasibility of ER for EGC with respect to age, that study focused on patients with differentiated-type EGC.[17] Therefore, in this study, we aimed to investigate the effect of age on the risk of LNM and long-term outcomes among patients with undifferentiated-type EGC. Based on these results, we determined the feasibility of ESD in young patients who met the expanded indication of ESD for undifferentiated-type EGC.

Methods

Study population

Data for this study were obtained from a prospectively maintained database of EGC cases at Samsung Medical Center in Seoul, Korea from 2002 to 2013. Patients with undifferentiated-type EGC who underwent surgical resection were included. The exclusion criteria were as follows: (1) an age younger than 18 years ($n = 0$); (2) history of surgery for gastric cancer ($n = 5$); (3) multiple gastric carcinomas ($n = 149$); or (4) incomplete data ($n = 15$). Of the 8,583 enrolled patients, 4,236 were included in the analysis.

Analysis of clinical outcomes

The primary outcome of this study was the presence of LNM. The secondary outcomes were overall, disease-specific, and recurrence-free survival. Data of clinicopathologic factors, including patient age and sex; tumor location (upper, middle, or lower third of the stomach), macroscopic appearance (elevated [I, IIa, I + IIa, and IIa + IIb], flat [IIb], depressed [IIc and IIc + III], or mixed [consisting of both elevated and depressed type]), ulceration status, size, histology (classified according to the 2010 World Health Organization[18]), and invasion depth; lymphovascular invasion status; surgery type; and number of dissected lymph nodes were obtained. Because of the retrospective nature of the study, the requirement for informed consent was waived.

All patients underwent total or distal gastrectomy combined with D1+ or D2 lymphadenectomy according to the 4th version of the Japanese gastric cancer treatment guidelines.[19] For histology analysis, the resected tumors were fixed in 10% formalin, embedded in paraffin, cut into 5-μm sections, and stained with hematoxylin and eosin. Lymph nodes were bisected along their longitudinal axes. Complete histopathologic examinations were performed by expert pathologists. LNM was identified using hematoxylin and eosin staining. Gastric cancer was staged according to the 7th edition of the American Joint Committee on Cancer criteria.[20] The expanded indication for ESD of undifferentiated-type EGC was an intramucosal and histologically undifferentiated-type tumor (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma), a lack of ulceration, and a tumor size ≤2 cm.[19]

During the first year of follow-up, clinical evaluations, including contrast-enhanced abdominal pelvic computed tomography and esophagogastroduodenoscopy, were performed at 3- and 6-month intervals and annually thereafter. Clinical follow-up data were collected until June 2018. The overall survival duration was calculated from the date of surgery to the date of death. Disease-specific survival was defined as the time from surgery to gastric cancer-related death. Recurrence-free survival was defined as the time interval from the date of surgery to the first relapse or death with evidence of recurrence.

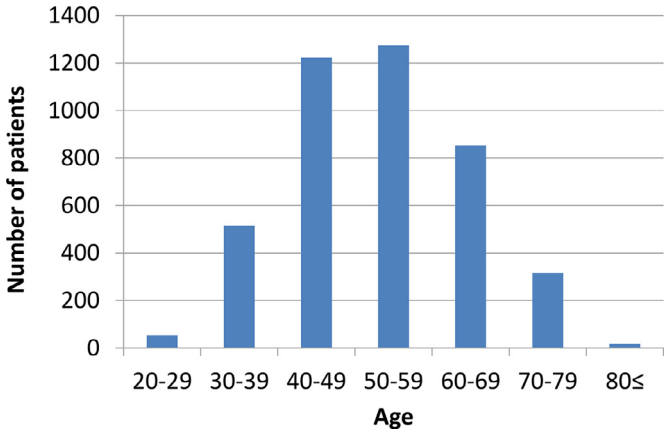


Fig 1. Age histogram for all patients with undifferentiated-type early gastric cancer who underwent surgery.

Statistical analysis

Patients were stratified into 10-year age groups. Those older than 70 years of age were grouped together to ensure a sufficient number of cases in each group. In a T stage-stratified analysis, continuous variables were analyzed using the Student t test, and categorical variables were analyzed using the Pearson χ^2 test or the Fisher exact test. A logistic regression analysis was used to test the associations of potential risk factors with lymph node positivity. In cases of multiple testing, the Bonferroni method was used to correct the P values and 95% confidence intervals. The Kaplan-Meier method and log-rank test were used to compare survival curves among groups. All statistical analyses were executed using SAS v 9.4 (SAS Institute, Inc, Cary, NC, USA).

Results

Clinicopathologic characteristics

The clinicopathologic characteristics of 4,236 eligible patients with undifferentiated-type EGC were compared according to age group (Table 1). Patients were distributed by age as follows: 20–29 years, $n = 54$ (1.3%); 30–39 years, $n = 515$ (12.2%); 40–49 years, $n = 1{,}223$ (28.9%); 50–59 years, $n = 1{,}274$ (30.1%); 60–69 years, $n = 854$ (20.2%;); and 70–90 years, $n = 316$ (7.5%; Fig. 1). Accordingly, 15.8% ($n = 669$) of the patients were considered younger (<40 years). The younger patient groups (20–29 and 30–39 years) exhibited a female predominance or near-equal sex ratio (female-to-male ratios = 2:3 and 1:0, respectively); whereas the older patient group exhibited a male predominance.

In all but one age group, the most common tumor location was the lower third of the stomach. However, equal proportions of tumors were located in the lower and middle third among patients aged 30–39 years. Regarding surgery, 85.0% and 15.0% of patients underwent partial and total gastrectomy, respectively. Depressed type was the most common macroscopic type in all age groups. The highest proportions of submucosal (50.4%) and lymphovascular invasion (21.5%) were observed among the oldest patients (70–90 years), and these patients and those aged 60–69 years had the largest average tumor size of 3.4 cm. Regarding histologic type, the frequency of signet-ring cell carcinoma tended to be higher among younger age groups. In contrast, the frequency of poorly differentiated adenocarcinoma tended to increase with increasing age. Although the median number of examined lymph nodes decreased with increasing age among both patients with stage T1a

Table 1
Baseline characteristics, by age at diagnosis.

	Number (%)	Age at diagnosis, years					
		20–29	30–39	40–49	50–59	60–69	70+
Age at diagnosis, years							
20–29	54 (1.3)						
30–39	515 (12.2)						
40–49	1,223 (28.9)						
50–59	1,274 (30.1)						
60–69	854 (20.2)						
70–90	316 (7.5)						
Sex							
Male	2,289 (54.0)	16 (29.6)	256 (49.7)	627 (51.3)	724 (56.8)	496 (58.1)	170 (53.8)
Female	1,947 (46.0)	38 (70.4)	259 (50.3)	596 (48.7)	550 (43.2)	358 (41.9)	146 (46.2)
Tumor location							
Upper third	387 (9.1)	6 (11.1)	45 (8.7)	107 (8.8)	109 (8.6)	96 (11.2)	24 (7.6)
Middle third	1,859 (43.9)	21 (38.9)	234 (45.4)	558 (45.6)	569 (44.7)	350 (41.0)	127 (40.2)
Lower third	1,990 (47.0)	27 (50.0)	236 (45.8)	558 (45.6)	596 (46.8)	408 (47.8)	165 (52.2)
Tumor macroscopic appearance							
Elevated	173 (4.1)	3 (5.6)	10 (1.9)	34 (2.8)	41 (3.2)	63 (7.4)	22 (7.0)
Flat	699 (16.5)	11 (20.4)	82 (15.9)	190 (15.5)	228 (17.9)	138 (16.2)	50 (15.8)
Depressed	3,097 (73.1)	38 (70.4)	396 (76.7)	938 (65.9)	925 (72.6)	589 (69.0)	211 (66.8)
Mixed	267 (6.3)	2 (3.7)	27 (5.2)	61 (5.0)	80 (6.3)	64 (7.5)	33 (10.4)
Ulcer							
No	3,920 (92.5)	49 (90.7)	472 (91.7)	1,116 (91.3)	1,191 (93.5)	795 (93.5)	297 (94.0)
Yes	316 (7.5)	5 (9.3)	43 (8.4)	107 (8.6)	83 (6.5)	59 (6.9)	19 (6.0)
Tumor size, mean (SD)	3.2 (2.0)	3.0 (1.9)	3.0 (1.8)	3.1 (2.0)	3.1 (2.0)	3.4 (2.1)	3.4 (2.1)
Tumor histology							
Poorly differentiated	2,045 (48.3)	16 (29.6)	184 (35.7)	522 (42.7)	640 (50.2)	494 (57.9)	189 (59.8)
Signet-ring cell carcinoma	2,157 (50.9)	38 (70.4)	330 (64.1)	692 (56.6)	625 (49.1)	348 (40.8)	124 (39.2)
Mucinous carcinoma	34 (0.8)	0 (0)	1 (0.2)	9 (0.7)	9 (0.7)	12 (1.4)	3 (1.0)
Depth of invasion							
Mucosa	2,576 (60.8)	35 (64.8)	353 (68.5)	797 (65.2)	781 (61.3)	453 (53.0)	157 (49.7)
SM1	413 (9.8)	5 (9.3)	48 (9.3)	104 (8.5)	127 (10.0)	95 (11.1)	34 (10.8)
SM2	496 (11.7)	4 (7.4)	53 (10.3)	153 (12.5)	137 (10.8)	114 (13.4)	35 (11.1)
SM3	751 (17.7)	10 (18.5)	61 (11.8)	169 (13.8)	229 (18.0)	192 (22.5)	90 (28.5)
Lymphovascular invasion							
No	3,654 (86.3)	46 (85.2)	470 (91.3)	1,080 (88.3)	1,117 (87.7)	693 (81.2)	248 (78.5)
Yes	582 (13.7)	8 (14.8)	45 (8.7)	143 (11.7)	157 (12.3)	161 (18.9)	68 (21.5)
Surgery type							
Partial	3,599 (85.0)	44 (81.5)	439 (85.2)	1,040 (85.0)	1,101 (88.6)	711 (86.4)	264 (89.2)
Total	637 (15.0)	10 (18.5)	76 (15.0)	183 (15.0)	173 (13.6)	143 (16.7)	52 (16.5)

SD, standard deviation; *SM1*, submucosal invasion <500 μm; *SM2*, submucosal invasion 500–1,000 μm; *SM3*, submucosal invasion ≥1,000 μm.

Table 2
Number of lymph nodes examined by age and stage.

Age group, years	T stage T1a			T stage T1b		
	N	Median LND	25th, 75th percentile	N	Median LND	25th, 75th percentile
20–29	35	42	29, 47	19	42	34, 45
30–39	353	38	31, 47	162	42	33, 53
40–49	797	38	31, 48	426	40	32, 49
50–59	781	39	30, 48	493	41	30, 52
60–69	453	38	28, 49	401	38	29, 49
70–90	157	37	30, 45	159	39	32, 47
P value	.431			.160		

LND, lymph node dissected.

and T1b disease, this difference was not statistically significant (Table 2).

Association between lymph node metastasis and patient age

Of the 4,236 eligible patients in our analysis, 478 (11.3%) had LNMs. The highest frequencies of LNM were observed in younger age groups (20–29 and 30–39 years) within each T stage (respectively, 5.7% and 5.7% for T1a; 26.3% and 24.1% for T1b; Table 3). Accordingly, a logistic regression analysis was performed to evaluate the association between age and LNM (Table 4). The univariate analysis indicated that younger patients (20–29 and 30–39 years) had a higher LNM rate compared with patients aged 50–59 years (reference group), although this difference was not significant ($P = .188$ for T1a; $P = .898$ for T1b). After adjusting for possible covariates, including sex, tumor macroscopic type, location, size, ulceration status, histology, presence of lymphovascular invasion, and number of dissected lymph nodes, age was not a statistically significant factor with regard to either T stage ($P = .127$ for T1a; $P = .114$ for T1b). Among patients with undifferentiated-type EGC who fulfilled the expanded indication for ESD, the LNM rate was slightly higher among younger patients (<40 years) relative to older patients (≥40 years; 2.7% versus 2.0%); however, this difference was not statistically significant (Table 5).

Long-term survival analysis according to patient age

We further investigated the effect of age on survival by comparing the long-term survival outcomes of younger (<40 years) and older (≥40 years) patients (Fig 2). Of note, younger patients had

Table 3
Lymph node positivity with age within T stage groups.

Age group, years	T stage T1a		T stage T1b	
	N	LN-positive	N	LN-positive
20–29	35	2 (5.7)	19	5 (26.3)
30–39	353	20 (5.7)	162	39 (24.1)
40–49	797	35 (4.4)	426	101 (23.7)
50–59	781	27 (3.5)	493	103 (20.9)
60–69	453	23 (5.1)	401	88 (21.9)
70–90	157	1 (0.6)	159	34 (21.4)
P trend	.269		.783	

LN, lymph node.

a significantly higher 10-year overall survival rate (95.9% versus 86.1% for older patients, $P < .001$). However, the recurrence-free and disease-specific survival rates did not differ significantly between the age groups (98.9% versus 97.7%, $P = .051$ and 99.3% versus 98.2%, $P = .069$, respectively).

Discussion

In our earlier investigation of the association between LNM and chronologic age in patients with differentiated-type EGC, we identified ER as a potentially feasible local treatment for young patients.[17] However, the high proportion of histologically undifferentiated-type and aggressive gastric cancers in younger patients and the lack of evidence regarding the effect of age on undifferentiated-type EGC raised concerns about the use of ER to treat young patients who have EGC. Therefore, we sought to investigate the associations of age with clinical outcomes in patients with undifferentiated-type EGC. Of note, we found that younger patients with undifferentiated-type EGC did not face an increased risk of LNM and confirmed this lack of association in a multivariate analysis adjusted for possible covariates. Furthermore, younger patients who met the expanded criteria for ESD of undifferentiated-type EGC did not have a significantly higher LNM rate when compared with older patients. Similarly, younger and older patients did not differ significantly in terms of recurrence-free and disease-specific survival. Accordingly, ESD appears to be feasible in young patients who fulfill the indication for undifferentiated-type EGC.

Although age is an important risk factor for gastric cancer, analyses of the effects of age at diagnosis on patient prognosis have yielded conflicting results. Although the majority of relevant previous studies reported more aggressive clinical behavior and worse prognoses among younger patients with gastric cancer,[21–23] more recent studies suggest that the outcomes of younger patients are not inferior to those of older patients within the same disease stage.[10,24,25] Moreover, Song et al.[26] reported that the prognosis of gastric cancer varied with age, with young patients experiencing a higher postoperative gastric cancer-specific survival rate relative to older patients.

Table 5
LNM in cases that fulfilled the expanded indication for endoscopic resection (undifferentiated, ulceration (–), T1a, tumor size ≤2 cm).

Age group	LNM rate	*P* value
< 40 years	5/184 (2.7%)	.570
≥ 40 years	16/801 (2.0%)	

LNM, lymph node metastasis.

Generally, earlier studies of early-onset gastric cancer also included data from advanced-stage cases.[12,23,27] However, delayed detection, which leads to an advanced stage at presentation, is among the factors contributing to a poor prognosis among young gastric cancer patients.[21,22] Hsieh et al.[14] identified advanced nodal involvement (N3) as the most important indicator of overall survival in young patients. Another study reported that young patients have specific features associated with an increased likelihood of presenting with advanced-stage disease, including higher rates of N2–3 LNM and distant metastasis.[28] To account for this issue, our study only included EGC.

We additionally conducted a subgroup analysis of patients who fulfilled the expanded indication for ESD to evaluate the feasibility of ER in young patients with gastric cancer. Our study findings may accordingly affect the treatment strategies applied to younger patients who have undifferentiated-type EGC, who meet the expanded indication for ER. However, undifferentiated-type histology also worsens prognosis in young patients. Earlier studies usually included both differentiated and undifferentiated-type cancers[12,14,23] or undifferentiated-type cancers obtained from a small number of patients, based on pathologic data of endoscopically resected tissues.[29] These limitations made it difficult to determine the incidence of LNM and the feasibility of an adequate oncologic resection of undifferentiated-type EGC. To our knowledge, therefore, this is the largest study to investigate LNM and long-term outcomes relative to age solely among patients with undifferentiated-type EGC.

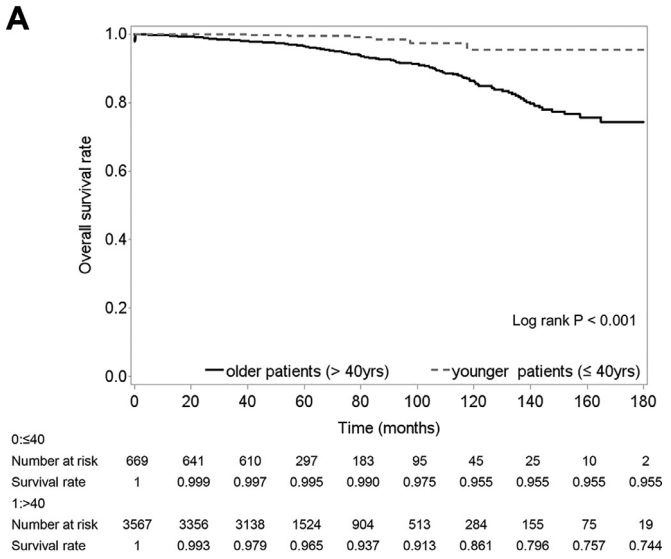
Even among undifferentiated-type EGCs, poorly differentiated adenocarcinoma has less favorable clinicopathologic features for ESD compared with those of signet-ring cell carcinoma.[30] Kang et al.[31] reported that poorly differentiated adenocarcinoma was more likely to have a positive vertical margin and submucosal invasion, whereas signet-ring cell carcinoma was more likely to have a positive lateral margin and mucosal confinement. In our study, we observed a tendency toward an increased frequency of signet-ring cell carcinoma in younger age groups, whereas poorly differentiated adenocarcinoma tended to occur more frequently with increasing age. This histologic difference may account for the prognostic differences among patients who have early-onset gastric cancer. Future studies are needed to clarify the prognostic significance and possible genetic predisposition underlying poorly differentiated adenocarcinoma and signet-ring cell carcinoma.

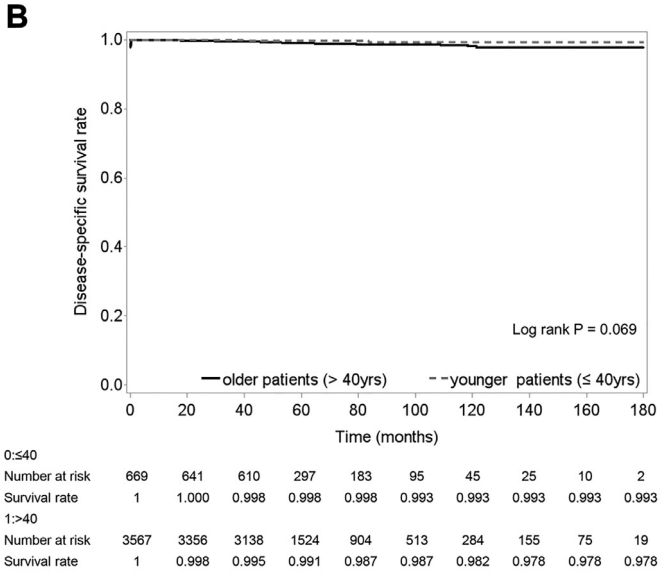
Furthermore, we observed no significant difference in recurrence-free survival with age, consistent with a report by

Table 4
Association of age with lymph node positivity among patients with undifferentiated-type early gastric cancer.

Age group, years	T stage T1a		T stage T1b	
	Unadjusted	Adjusted for covariates	Unadjusted	Adjusted for covariates
20–29 vs 50–59	1.69 (0.24–11.81)	1.45 (0.15–14.02)	1.35 (0.34–5.33)	1.30 (0.28–5.98)
30–39 vs 50–59	1.68 (0.77–3.65)	1.98 (0.88–4.47)	1.20 (0.69–2.09)	1.40 (0.75–2.61)
40–49 vs 50–59	1.28 (0.65–2.51)	1.37 (0.68–2.77)	1.18 (0.78–1.77)	1.14 (0.71–1.81)
50–59 (Ref)	1.00	1.00	1.00	1.00
60–69 vs 50–59	1.49 (0.71–3.15)	1.33 (0.61–2.77)	1.07 (0.70–1.62)	0.84 (0.52–1.35)
70–90 vs 50–59	0.18 (0.01–2.49)	0.18 (0.01–2.55)	1.03 (0.58–1.83)	0.64 (0.33–1.24)
P value	.127		.114	

Ref, reference.





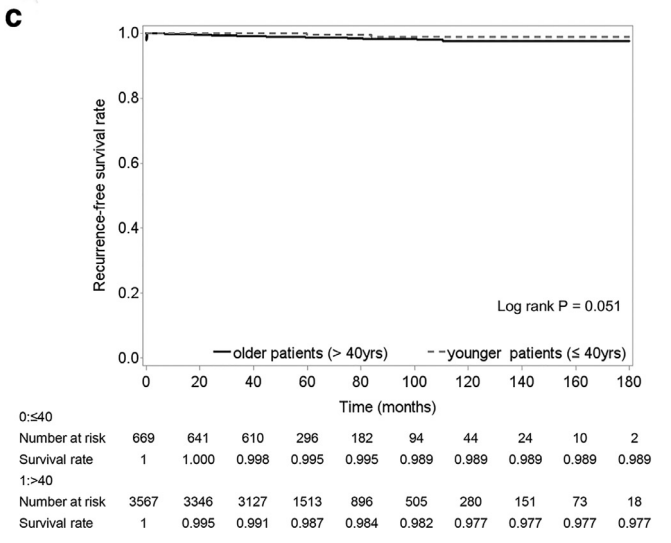


Fig 2. Kaplan–Meier survival curves. (*A*) Overall survival. (*B*) Disease-specific survival. (*C*) Recurrence-free survival in younger (≤40 years) versus older patients (>40 years).

Yang et al.[32] in which the 5-year risk of a metachronous recurrence was lower among younger patients because of the lower prevalence of intestinal metaplasia in that group. However, the effect of age on risk became less important at 7 years, because of the effect of field cancerization. In addition, our observations of increased overall survival among younger patients and the lack of a difference in disease-specific survival between younger and older groups were consistent with previous reports.[12,26]

Our study had some limitations. First, we did not include patients who underwent ER for undifferentiated-type EGC, which may have introduced selection bias. Second, our histologic studies only used conventional hematoxylin and eosin staining, and therefore micrometastases may have been missed. Future studies should use immunohistochemistry and reverse transcription-polymerase chain reaction methods to identify the lymph node micrometastasis status and thus provide an accurate diagnosis and oncological risk reduction.[33]

In conclusion, younger and older patients who have undifferentiated-type EGC had similar LNM rates and long-term survival outcomes. Therefore, ESD may be feasible in these younger patients.

References

1. Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer*. 2007;10:1–11.
2. Pyo JH, Lee H, Min BH, Lee JH, Choi MG, Lee JH, et al. Long-term outcome of endoscopic resection vs surgery for early gastric cancer: A non-inferiority–matched cohort study. *Am J Gastroenterol*. 2016;111:240–249.
3. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. *J Clin Oncol*. 2005;23:4490–4498.
4. Lee JH, Kim JG, Jung HK, Kim JH, Jeong WK, Jeon TJ, et al. Clinical practice guidelines for gastric cancer in Korea: An evidence-based approach. *J Gastric Cancer*. 2014;14:87–104.
5. Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer*. 2009;12:148–152.
6. Bang CS, Baik GH, Shin IS, Kim JB, Suk KT, Yoon JH, et al. Endoscopic submucosal dissection for early gastric cancer with undifferentiated-type histology: A meta-analysis. *World J Gastroenterol*. 2015;21:6032–6043.
7. Kamada K, Tomatsuri N, Yoshida N. Endoscopic submucosal dissection for undifferentiated early gastric cancer as the expanded indication lesion. *Digestion*. 2012;85:111–115.
8. Park JC, Lee YK, Kim SY, Roh Y, Hahn KY, Shin SK, et al. Long-term outcomes of endoscopic submucosal dissection in comparison to surgery in undifferentiated-type intramucosal gastric cancer using propensity score analysis. *Surg Endosc*. 2018;32:2046–2057.
9. Abe S, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Odagaki T, et al. Short- and long-term outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. *Endoscopy*. 2013;45:703–707.
10. Kong X, Wang JL, Chen HM, Fang JY. Comparison of the clinicopathological characteristics of young and elderly patients with gastric carcinoma: A meta analysis. *J Surg Oncol*. 2012;106:346–352.
11. Merchant SJ, Kim J, Choi AH, Sun V, Chao J, Nelson R. A rising trend in the incidence of advanced gastric cancer in young Hispanic men. *Gastric Cancer*. 2017;20:226–234.
12. Wang Z, Xu J, Shi Z, Shen X, Luo T, Bi J, et al. Clinicopathologic characteristics and prognostic of gastric cancer in young patients. *Scand J Gastroenterol*. 2016;51:1043–1049.
13. Anderson WF, Camargo MC, Fraumeni Jr JF, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA*. 2010;303:1723–1728.
14. Hsieh FJ, Wang YC, Hsu JT, Liu KH, Yeh CN. Clinicopathological features and prognostic factors of gastric cancer patients aged 40 years or younger. *J Surg Oncol*. 2012;105:304–309.
15. Isobe T, Hashimoto K, Kizaki J, Miyagi M, Aoyagi K, Koufuji K, et al. Characteristics and prognosis of gastric cancer in young patients. *Oncol Rep*. 2013;30:43–49.
16. Park HJ, Ahn JY, Jung HY, Lim H, Lee JH, Choi KS, et al. Clinical characteristics and outcomes for gastric cancer patients aged 18–30 years. *Gastric Cancer*. 2014;17:649–660.
17. Pyo JH, Lee H, Min YW, Min BH, Lee JH, Kim KM, et al. Young age and risk of lymph node metastasis in differentiated type early gastric cancer. *Ann Surg Oncol*. 2018;25:2713–2719.
18. WHO classification of tumours of the digestive system. Lyon, France: IARC Press; 2010.
19. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer*. 2017;20:1–19.

20. Washington K. 7th edition of the AJCC cancer staging manual: Stomach. *Ann Surg Oncol*. 2010;17:3077–3079.
21. Theuer CP, de Virgilio C, Keese G, French S, Arnell T, Tolmos J, et al. Gastric adenocarcinoma in patients 40 years of age or younger. *Am J Surg*. 1996;172:473–476 discussion 476–7.
22. Saito H, Takaya S, Fukumoto Y, Osaki T, Tatebe S, Ikeguchi M. Clinicopathologic characteristics and prognosis of gastric cancer in young patients. *Yonago Acta Med*. 2012;55:57–61.
23. Takatsu Y, Hiki N, Nunobe S, Ohashi M, Honda M, Yamaguchi T, et al. Clinicopathological features of gastric cancer in young patients. *Gastric Cancer*. 2016;19:472–478.
24. Llanos O, Butte JM, Crovari F, Duarte I, Guzman S. Survival of young patients after gastrectomy for gastric cancer. *World J Surg*. 2006;30:17–20.
25. Al-Refaie WB, Hu CY, Pisters PW, Chang GJ. Gastric adenocarcinoma in young patients: A population-based appraisal. *Ann Surg Oncol*. 2011;18:2800–2807.
26. Song P, Wu L, Jiang B, Liu Z, Cao K, Guan W. Age-specific effects on the prognosis after surgery for gastric cancer: A SEER population-based analysis. *Oncotarget*. 2016;7:48614–48624.
27. Liu S, Feng F, Xu G, Liu Z, Tian Y, Guo M, et al. Clinicopathological features and prognosis of gastric cancer in young patients. *BMC Cancer*. 2016;16:478.
28. Santoro R, Carboni F, Lepiane P, Ettorre GM, Santoro E. Clinicopathological features and prognosis of gastric cancer in young European adults. *Br J Surg*. 2007;94:737–742.
29. Bang CS, Park JM, Baik GH, Park JJ, Joo MK, Jang JY, et al. Therapeutic outcomes of endoscopic resection of early gastric cancer with undifferentiated-type histology: A Korean ESD Registry Database analysis. *Clin Endosc*. 2017;50:569–577.
30. Kim HM, Pak KH, Chung MJ, Cho JH, Hyung WJ, Noh SH, et al. Early gastric cancer of signet ring cell carcinoma is more amenable to endoscopic treatment than is early gastric cancer of poorly differentiated tubular adenocarcinoma in select tumor conditions. *Surg Endosc*. 2011;25:3087–3093.
31. Kang HY, Kim SG, Kim JS, Jung HC, Song IS. Clinical outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. *Surg Endosc*. 2010;24:509–516.
32. Yang HJ, Kim SG, Lim JH, Choi JM, Oh S, Park JY, et al. Surveillance strategy according to age after endoscopic resection of early gastric cancer. *Surg Endosc*. 2018;32:846–854.
33. Arigami T, Uenosono Y, Yanagita S, Nakajo A, Ishigami S, Okumura H, et al. Clinical significance of lymph node micrometastasis in gastric cancer. *Ann Surg Oncol*. 2013;20:515–521.