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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Indications for adjuvant chemotherapy in patients with pT1N1M0 gastric cancer: a single-center experience

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Abstract

Purpose Whether adjuvant chemotherapy (AC) has a survival benefit for all patients with pathological stage pT1N1M0 (Stage IB) gastric cancer (GC) remains controversial.

Methods All patients with surgically resected, histologically confirmed pT1N1M0 GC between January 2011 and December 2017 at the National Cancer Center, China, were retrospectively reviewed.

Results A total of 179 patients with pT1N1M0 were identified. Survival analysis showed that both overall survival (OS) and cause-specific survival (CSS) were significantly different between patients treated with and without AC ($p < 0.01$). Independent risk factors for reduced OS identified in the Cox regression analysis in patients with pT1N1M0 cancer were sex (male sex, hazard ratio [HR] 2.470, 95% confidence interval [CI] 1.294–4.718), examined lymph nodes (EN) (EN ≤ 15, HR 2.402; 95% CI 1.329–4.341), and AC (treated without AC, HR 2.554; 95% CI 1.393–4.681), which were also independent risk factors for reduced CSS. We divided patients with pT1N1M0 into three risk categories (high, moderate, and low) according to two significant prognostic factors (sex and EN) and found that both OS and CSS were significantly different between the three risk groups ($p < 0.05$).

Conclusion An additional survival benefit related to AC is expected for selected pT1N1M0 patients. Male patients with EN ≤ 15 may be particularly appropriate candidates for AC.

Keywords Gastric cancer · T1N1M0 · Adjuvant chemotherapy · Prognosis

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related mortality worldwide (Bray et al. 2018). In Japan and South Korea, early GC (EGC) accounts for more than 60% (Information Committee of Korean Gastric Cancer 2016). The number of EGC cases is increasing in other parts of the world. Stage I GC includes T1N0M0 (stage IA), T1N1M0, and T2N0M0 (stage IB) according to the 8th edition of the AJCC TNM classification (Amin et al. 2017). The 5-years overall survival (OS) rate for stage I patients exceeds 90%. However, nearly 10% of patients experience recurrence within 5 years of curative surgery (Katai et al. 2018). Some studies reported a significant survival difference among patients with T1N1M0, T1N1M0, and T2N0M0 (Gold et al. 2013; Kwon et al. 2016), while others demonstrated no differences in survival between T1N1M0 and T2N0M0 (Aoyama et al. 2014; Lu et al. 2018).

Postoperative adjuvant chemotherapy (AC) has been accepted as a standard treatment for stage II/III GC to decrease the risk of recurrence, according to various GC treatment guidelines based on randomized controlled trials (Noh et al. 2014; Sakuramoto et al. 2007). However, there are limited studies regarding whether stage I GC patients would benefit from postoperative AC. According

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to the Japanese Gastric Cancer Treatment Guidelines 2018 (Japanese Gastric Cancer 2020) and Korean GC guidelines (Guideline Committee of the Korean Gastric Cancer Association and Review 2019), observation alone is recommended for patients with pT1N1M0, while AC is recommended for patients with pT1N1M0 according to the latest NCCN and Chinese Society of Clinical Oncology (CSCO) GC treatment guidelines (Wang et al. 2019a). The Japanese and Korean guidelines are used widely in Eastern Asia, and the NCCN guideline is accepted in the USA. In China, the CSCO guideline is recommended in clinical practice. Thus, there is still no consensus on whether AC is necessary in this subset of patients.

This study aimed to investigate the prognostic factors for patients with pT1N1M0 and to identify patients who have worse survival and would benefit from postoperative AC.

Methods

Patients

A total of 7300 consecutive patients with GC were surgically treated between January 2011 and December 2017, at the Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, China. Of these patients, 179 with pT1N0M0 were enrolled. The inclusion criteria were (1) pathologically confirmed pT1N1M0, and (2) patients with complete clinicopathologic records and at least of 6 months' follow-up. The exclusion criteria were (1) patients diagnosed with other tumor stages, (2) patients with other co-occurring malignancy including other synchronic malignancies at GC diagnosis and other metachronic malignancies during the study period, and (3) patients who refused to complete the chemotherapy because of serious complications, (4) other pathology types such as lymphoma and stromal tumor. Our study was performed in accordance with the Declaration of Helsinki regarding the ethical principles for medical research involving human subjects. All study procedures were approved by the Institutional Review Board of our hospital. All participants signed informed consent forms.

Surgical procedures

All surgical procedures were carried out by highly qualified surgeons. The number of patients who underwent curative gastrectomy with D1, D1+, or D2 lymphadenectomy was 2, 91, and 86, respectively. The extent of systematic lymphadenectomy is defined according to the CSCO guidelines for GC (Wang et al. 2019a). Depending on the location of the primary lesion, distal or proximal gastrectomy was performed. Both laparoscopic and open surgical treatment was included.

Clinicopathologic features

Clinicopathological variables included age, sex, maximum tumor diameter, tumor location, Borrmann type, histological type, and pathological stage (T, N, and M), number of examined lymph nodes, adjuvant chemoradiotherapy, and AC. The TNM stage was defined based on the 8th TNM AJCC/UICC guidelines. The histopathological diagnosis was determined by experienced pathologists.

Adjuvant therapy

In our center, chemotherapy is suggested when patients have pT1N1M0 or < 16 lymph nodes were examined, which is considered a significant risk factor for metastasis. The patient was explained of the fact that there is a lack of scientific evidence supporting the use of AC for T1N1M0 and that, ultimately, the patient must decide whether to receive chemotherapy. The regimens are based on widely accepted studies (Bang et al. 2012; Sasako et al. 2011). After surgery, 124 patients underwent AC. Of them, 70 received the S-1/oxaliplatin (SOX) regimen; nine patients received the single S-1 regimen; 18 patients received the capecitabine/oxaliplatin regimen; 12 patients received the docetaxel, oxaliplatin, and S-1 (DOS) regimen; and 15 patients received capecitabine plus oxaliplatin. The median number of courses of AC was 6 (5–8). Forty-four patients developed grade 3–4 toxicities, with the most common grade 3–4 toxicities being neutropenia and leukopenia, nausea and vomiting, and thrombocytopenia. The toxicity of AC was evaluated according to the World Health Organization standard criteria. A total of 66 patients received postoperative concurrent chemoradiotherapy, the dose of which was the same as that used in a previous study (Macdonald et al. 2001).

Follow up

The patients were assessed every 3 months for the first 2 years after surgery, then every 6 months for 3 years, and yearly thereafter. Survival data were obtained from outpatient clinical visits and telephone interviews. Patients were followed up until death or until the last follow-up (June 2018). OS was defined as the period from the date of surgery until death due to any cause. Cause-specific survival (CSS) was defined as the period from the date of surgery until death due to GC. The median follow-up was 42.0 (range 6–83) months. Fourteen patients (7.7%) were lost to follow-up.

Statistical analysis

Statistical analyses were performed using SPSS 22.0. All continuous variables were assessed using the *t* test. Categorical variables were compared using Fisher's exact or χ^2 tests. Cumulative survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test to evaluate significant differences. Univariate and multivariate analyses of prognostic significance were performed using Cox's proportional hazard model. Factors that were significant in the univariate analysis were subsequently entered into multivariate analysis. A p value < 0.05 was considered to indicate statistical significance.

Results

Clinicopathologic characteristics of the T1N1M0 patients

We compared the clinicopathologic characteristics of T1N1M0 patients treated with and without AC (Table 1). In total, 179 patients with pT1N1M0 were enrolled, 124 treated with AC and 55 without. The two groups were comparable in terms of sex, tumor size, tumor location, histologic type, Borrmann types, T stage, and number of examined lymph nodes. Only age was significantly different between the two groups ($p < 0.001$). There were a significantly higher proportion of younger patients in the AC group.

OS and CSS analyses for T1N1M0 patients

Independent risk factors for reduced OS as identified by Cox regression analyses were sex (male sex, hazard ratio [HR] 2.470, 95% CI 1.294–4.718), examined lymph node (EN) (EN ≤ 15, HR 2.402; 95% CI 1.329–4.341), and AC (without AC, HR 2.554; 95% CI 1.393–4.681) (Table 2). Similarly, both univariate and multivariate analyses for CSS identified sex (male, hazard ratio [HR] 1.495, 95% CI 0.743–3.010), examined lymph node (EN) (EN ≤ 15, HR 2.330; 95% CI 1.211–4.483), and AC (without AC, HR 2.104; 95% CI 1.058–4.185) as significant prognostic factors (Table 3). The absence of AC was an independent risk factor for worse OS and CSS in T1N1M0.

Survival analyses for pT1N1M0

The median OS of the whole study cohort was 32.0 months, with 3- and 5-years survival rates of 87.5% and 82.3% for those treated with and without AC, respectively. For those with stage I GC, the median survival, and 3- and 5-years survival rates for CSS were the same as that of OS in our cohort. Survival analysis showed that both OS and CSS were significantly different between patients treated with and without AC (Fig. 1a, b). The p value was 0.006 and less than 0.007 for OS and CSS, respectively.

Table 1 Clinicopathologic characteristics of the T1N1M0 patients with and without AC

Variables	With AC ($n = 124$), n (%)	Without AC ($n = 55$), n (%)	p
Age, years			**0.000**
< 65	106 (85.5)	23 (41.8)	
≥ 65	18 (14.5)	32 (58.2)	
Sex			0.352
Female	45 (36.3)	24 (43.6)	
Male	79 (63.7)	31 (56.4)	
Primary site			0.359
Cardia	41 (33.1)	10 (18.2)	
Fundus	3 (2.4)	2 (3.6)	
Body	10 (8.1)	8 (14.5)	
Antrum	32 (25.8)	18 (32.7)	
Pylorus	6 (4.8)	3 (5.5)	
Lesser curve	15 (12.1)	7 (12.7)	
Greater curve	9 (7.3)	2 (3.6)	
Overlapping/NOS	8 (6.5)	5 (9.1)	
Tumor size, cm			0.965
≤ 3	83 (66.9)	37 (67.3)	
> 3	41 (33.1)	18 (32.7)	
AJCC 8th pT			0.119
T1a	25 (20.2)	7 (12.7)	
T1b	89 (71.8)	47 (85.5)	
T1 NOS	10 (8.1)	1 (1.8)	
Lymph nodes examined			0.108
1–15	68 (54.8)	23 (41.8)	
> 15	56 (45.2)	32 (58.2)	
Tumor grade			0.277
Well differentiated	7 (5.6)	2 (3.6)	
Moderately differentiated	42 (33.9)	27 (49.1)	
Poorly differentiated	73 (58.9)	25 (45.5)	
Undifferentiated	2 (1.6)	1 (1.8)	
Pathology type			0.399
Intestinal	24 (19.4)	17 (30.9)	
Diffuse	32 (25.8)	13 (23.6)	
Mix	6 (4.8)	2 (3.6)	
Not known	62 (50.0)	23 (41.8)	

AJCC American Joint Committee on Cancer, *NOS* not otherwise specified, *AC* adjuvant chemotherapy

Bold indicate statistically signifcant P values

Analyses to identify candidates for AC among patients with T1N1M0

We tried to stratify patients based on sex and EN, as these had been calculated as significant independent factors in

Table 2 Univariate and of multivariate analysis of OS for T1N1M0 gastric cancer

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years (≥65)	2.342 (1.278–4.291)	0.006	1.495 (0.743–3.010)	0.260
Sex		0.010	2.470 (1.294–4.718)	**0.006**
Female	1.000			
Male	2.019 (1.019–4.001)			
Primary Site		0.695	–	
Cardia	1.000			
Fundus	0.000 (0.000–0.001)	0.973		
Body	0.439 (0.129–1.489)	0.186		
Antrum	0.472 (0.212–1.053)	0.067		
Pylorus	0.680 (0.158–2.932)	0.605		
Lesser curve	0.691 (0.274–1.742)	0.433		
Greater curve	0.823 (0.242–2.796)	0.755		
Overlapping/NOS	0.504 (0.148–1.714)	0.272		
Tumor size, cm		0.744	–	
≤3	1.000			
>3	1.109 (0.595–2.070)			
Lymph nodes examined		0.006	2.402 (1.329–4.341)	**0.004**
1–15	2.246 (1.267–3.982)			
>15	1.000			
Tumor grade		0.858	–	
Well differentiated	1.000			
Moderately differentiated	0.910 (0.208–3.983)	0.900		
Poorly differentiated	1.203 (0.285–5.070)	0.801		
Undifferentiated	0.000 (0.000–0.242)	0.970		
Lauren classification		0.745	–	
Intestinal	1.000			
Diffuse	0.935 (0.379–2.306)	0.884		
Mix	0.000 (0.000–0.001)	0.976		
Not known	1.350 (0.630–2.893)	0.441		
Chemoradiotherapy		0.148	–	
Yes	1.000			
No/not known	1.929 (0.976–3.812)			
Chemotherapy		0.008	2.554 (1.393–4.681)	**0.002**
Yes	1.000			
No/not known	2.234 (1.233–4.047)			

OS overall survival, *NOS* not otherwise specified

Bold indicates statistically signifcant P values

multivariate analyses. They were stratified to four sub-categories (male, EN ≤ 15; male, EN > 15; female, EN ≤ 15; female, EN > 15). Survival analysis showed that there were significant differences in OS and CSS between the four subsets (Fig. 2a, b), but an overlap in survival curves was found between two categories (male, EN > 15) and (female, EN ≤ 15), which had a similar prognosis. We, therefore, combined these two subcategories and re-classified the risk category as follows: high risk (male, EN ≤ 15), moderate risk (male, EN > 15 or female, EN ≤ 15), and low risk (female, EN > 15). The new classifications seem to have an optimal prognostic stratification. There were significant differences in OS and CSS between each category ($p < 0.05$) (Fig. 2c, d).

Discussion

Although the prognosis of T1N1M0 patients is excellent, with a 5-years survival rate exceeding 90% (Kunisaki et al. 2010), some patients develop recurrence. The recurrence rate has been reported to range from 1.4 to 6.4% (Lee et al. 2003; Shiozawa et al. 1994). Once recurrence or metastasis

Table 3 Univariate and of multivariate analysis of CSS for T1N1M0 gastric cancer

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years (≥ 65)	2.342 (1.278–4.291)	0.006	1.495 (0.743–3.010)	0.260
Sex, male	2.109 (1.019–4.001)	0.044	2.184 (1.099–4.340)	**0.026**
Primary Site		0.695	–	
Cardia	1.000			
Fundus	0.000 (0.000)	0.973		
Body	0.439 (0.129–0.1489)	0.186		
Antrum	0.472 (0.212–1.053)	0.067		
Pylorus	0.680 (0.158–2.932)	0.605		
Lesser curve	0.691 (0.274–1.742)	0.433		
Greater curve	0.823 (0.242–2.796)	0.755		
Overlapping/NOS	0.504 (0.148–1.714)	0.272		
Tumor size, > 3 cm	0.901 (0.483–1.682)	0.744	–	
Lymph nodes examined, ≤ 15	2.250 (1.192–4.246)	0.012	2.330 (1.211–4.483)	**0.011**
Tumor grade		0.858	–	
Well differentiated	1.000			
Moderately differentiated	0.910 (0.208–3.983)	0.900		
Poorly differentiated	1.203 (0.285–5.070)	0.801		
Undifferentiated	0.000 (0.000–0.242)	0.970		
Lauren classification		0.745	–	
Intestinal	1.000			
Diffuse	0.935 (0.379–2.306)	0.884		
Mix	0.000 (0.000)	0.976		
Not known	1.350 (0.630–2.893)	0.441		
Chemoradiotherapy, yes	1.929 (0.976–3.812)	0.148	–	
Chemotherapy, no/not known	2.234 (1.233–4.047)	0.008	2.104 (1.058–4.185)	**0.034**

CSS cause specific survival, *AJCC* American Joint Committee on Cancer, *NOS* not otherwise specified
Bold indicates statistically signifcant P values

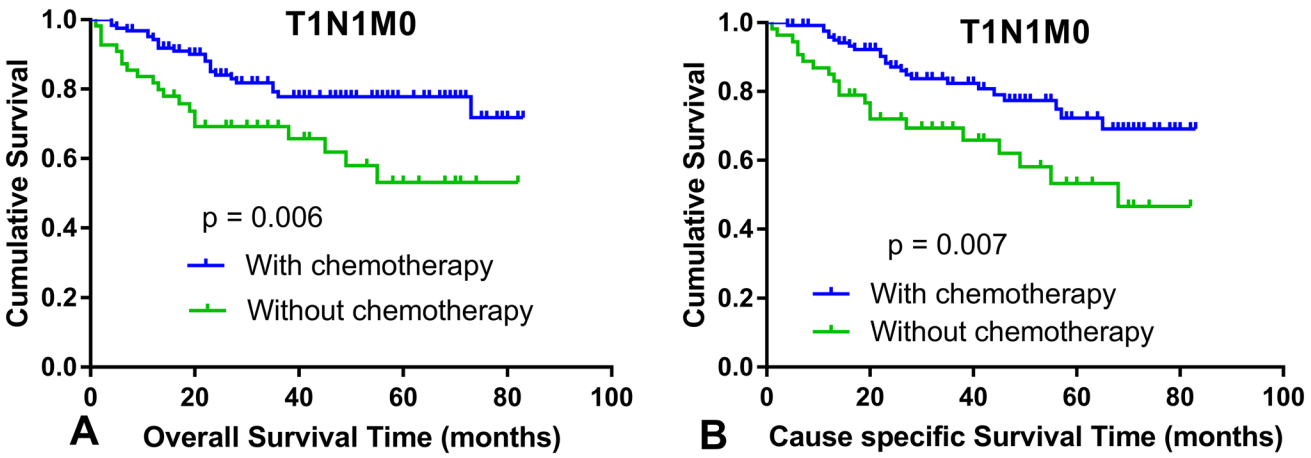

Fig. 1 OS and CSS analyses for T1N1M0 patients treated with and without chemotherapy ($p < 0.01$)

has developed, the prognosis is rarely more than 1 year (Boku et al. 2009; Lee et al. 2003). Lymph node metastasis has been reported to be the strongest prognostic factor in many previous studies (Folli et al. 2001; Lee et al. 2003). Several studies have suggested that AC reduces recurrence and metastasis in T1N1M0 patients (Aoyama et al. 2014; Wang et al. 2019b), while others suggest that AC should not be indicated because of the low frequency of recurrence.

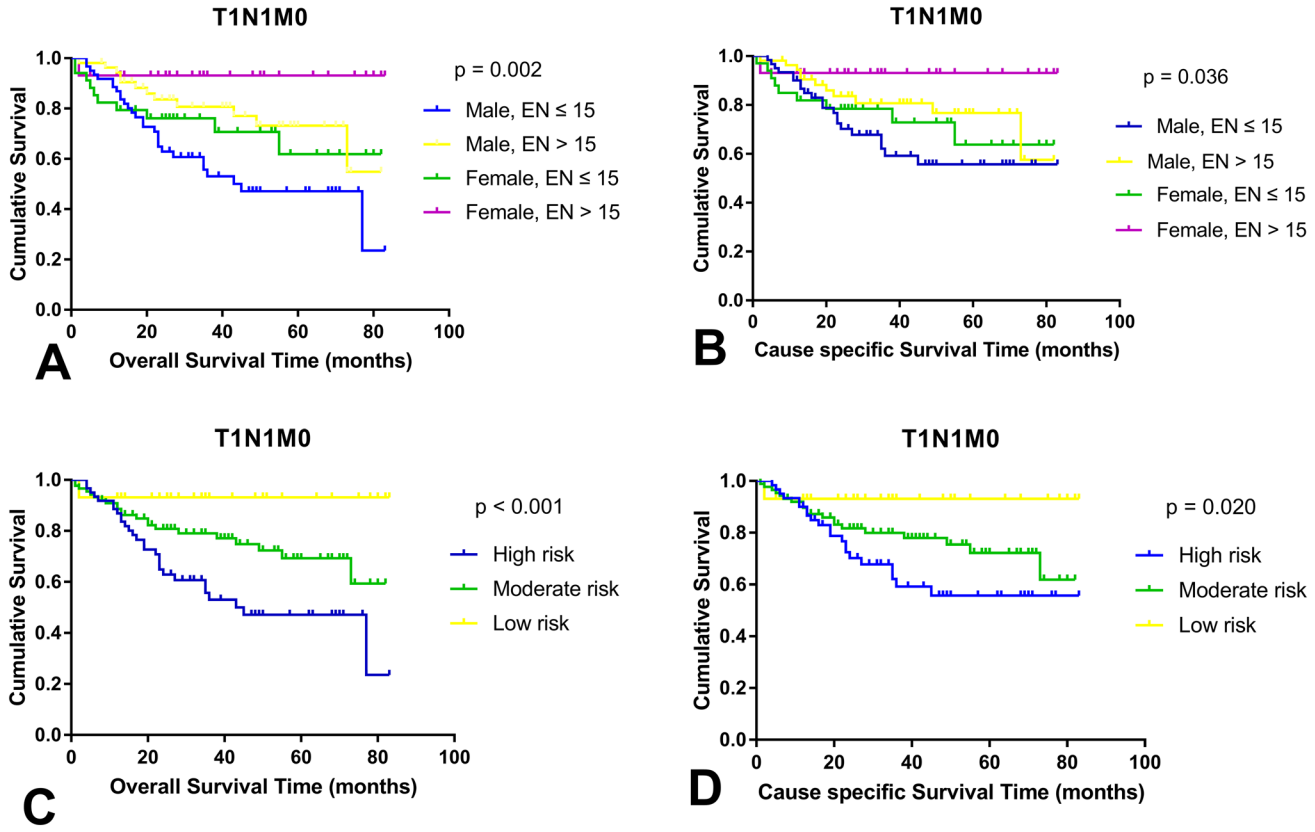

Fig. 2 Patients were stratified to four sub-categories (male, EN ≤ 15; male, EN > 15; female, EN ≤ 15; female, EN > 15). An overlap in survival curves was found between two categories (male, EN > 15) and (female, EN ≤ 15) (**a**, **b**). OS and CSS analyses for T1N1M0 patients with low-risk, moderate-risk, and high-risk ($p < 0.05$) (**c**, **d**)

Moreover, in the latest Japanese Gastric Cancer Treatment Guidelines 2018 (Japanese Gastric Cancer 2020), postoperative AC is not recommended for patients with T1N1M0. Therefore, it is highly necessary to explore the validity of AC for patients with T1N1M0.

In the present study, sex, EN, and treatment without AC were independent risk factors for reduced CSS and OS. Previous studies showed that the number of EN was associated with prognosis. Lymph node count less than 15 increases the possibility of postoperative recurrence and decreases OS (Hsu et al. 2013; Zheng et al. 2016). EN ≤ 15 was an independent risk factor for worse CSS and OS in stage IB GC (Wang et al. 2019b), which is in agreement with our results. Curative surgery plus adequate lymph node dissection reduces the likelihood of recurrence and improves survival in T1N1M0 patients. Moreover, AC might improve OS in T1N1M0 patients (Jabo et al. 2018; Wang et al. 2019b). Lee et al. (2003) suggested that patients with EGC with more than six positive lymph nodes were at high risk and could be candidates for AC. In addition, another study revealed that lymphovascular invasion was an independent prognostic factor in patients with stage IB GC (Kunisaki et al. 2010). Yura et al. (2020) reported that tumor size and N stage were two significant prognostic factors for T1 GC. The fact that sex is associated with survival has been reported in a few studies (Ryu et al. 2019). Aznab et al. discovered that male patients had higher rates of HER2/neu positivity, which could reduce survival (Aznab et al. 2019). Li et al. reported that women were associated with improved OS and CSS based on data from the SEER database (Li et al. 2019b). Another study revealed that the effect of sex on GC prognosis may vary with the patient's racial background (Li et al. 2019a). These studies suggest that sex may affect prognosis. However, more studies are warranted to elucidate the cause.

To further evaluate which specific groups might have a greater survival benefit after treatment with AC, T1N1M0 patients were divided into three subgroups using these two significant prognostic factors (sex and EN). Male patients with EN ≤ 15 had worse survival than the other two groups. Therefore, it may be necessary for these patients who might obtain greater survival benefit to receive AC. Using a similar grouping method as that used in our study, Yura et al. (2020) divided patients with pT1N2-3 GC into three risk categories using N stage and tumor size and found that pT1N2-3 with at least N3a/b or a tumor diameter < 30 mm may be candidates for AC.

However, a few limitations of the present study should be mentioned. First, there is inevitable bias in a retrospective study with only 179 T1N1M0 patients enrolled. Moreover, information regarding recurrence and lymphovascular invasion was unavailable in our study. Further studies are warranted to confirm the results. The biological behavior and molecular mechanism of lymph node metastasis in T1N1M0 need further clarification. Despite the above-mentioned limitations, we are convinced by the survival benefits of AC in T1N1M0 patients with a high risk of recurrence.

Conclusions

The survival time of pT1N1M0 patients is different among various risk categories. Additional survival benefit after treatment with AC was expected for patients with worse survival. Particularly, male patients with EN ≤ 15 may be appropriate candidates for AC. More trials are warranted to explore the effect of AC in patients with T1N1M0.

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Author contributions PJ and XJ contributed equally to this work. PJ was involved in study concept, data analysis, and interpretation, and production of tables and figures, wrote the first draft, and revised it critically in light of comments from other authors and reviewers; XJ was involved in production of high resolution figures and manuscript revision. YT was involved in study conception and design, data interpretation, manuscript revision, and discussion; SM, YL, WK, HL, and FM were involved in data acquisition and literature review; HH, WL and XJ were involved in the manuscript revision and discussion.

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Data availability Some or all data are available from the corresponding author by request.

Code availability (software application or custom code) SPSS 22.0 and Graphpad Prism 7.0 are used for statistical analysis and figures drawing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval This study was approved by the Institutional Review Board of the National Cancer Center Hospital.

Consent to participate Written informed consent was obtained from all patients before their treatment. The data were anonymously analyzed.

Consent for publication All authors approved the final version submitted.

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