



The Relevance of Serosal Exposure Without Nodal Metastasis in Resectional Gastric Cancer

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ABSTRACT

Background. According to 8th AJCC/UICC TNM criteria, stage IIB includes pT1N3M0, pT2N2M0, pT3N1M0, and pT4aN0M0, which includes not only early gastric cancer but also locally advanced cancer. There are currently no data about whether there is any additional impact of serosal exposed cancer without nodal metastasis (pT4aN0) on patients' survival outcomes compared with other subgroups in IIB.

Methods. Patients who underwent radical gastrectomy for gastric cancer patients were enrolled, including 427 patients in stage IIB; 20 (4.68%), 104 (24.35%), 172 (40.28%), and 131 (30.67%) patients were classified as pT1N3a, pT2N2, pT3N1, and pT4aN0, respectively. Clinicopathological characteristics, recurrence pattern, and survival and recurrence rates were analyzed according to the TNM subgroups.

Results. Cancer-specific and relapse-free survival were significantly worse in serosal exposed cancer than in non-serosal exposed cancer in stage IIB ($P = 0.019$ and $P = 0.015$). Recurrence rate was highest in the pT4aN0 subgroup (29.0%) in stage IIB, and peritoneal metastasis was the most common pattern. Survival outcomes of the pT4aN0 subgroup were not significantly different from those of the stage IIIA or pT4aN1 subgroups.

Conclusions. Patients with serosal exposed cancer without nodal metastasis shows worse cancer specific and disease-free survival with higher incidence of peritoneal metastasis than other subgroups in stage IIB. Further surveillance studies, including staging laparoscopy and active adjuvant therapy, are required in this subgroup of patients.

Among various factors, depth of invasion, lymph node metastasis, and distant metastasis are the strongest ones that affect clinical outcomes of gastric cancer patients, and as such, they are used to determine TNM stage.^{1,2} One of the changes from the 7th to 8th American Joint Committee on Cancer (AJCC) TNM criteria was that pN3b was migrated to stage IIIB or IIIC regardless of T stage, indicating the relative importance and impact of extensive node metastasis on patient survival.^{3,4} Additionally, serosal exposed cancer is one of the most important risk factors for peritoneal metastasis, which has a high mortality rate in gastric cancer.⁵ However, no revisions in the clinical stages of serosal exposure were suggested in the 8th AJCC TNM criteria.⁴ Of note, serosal exposed cancer without nodal metastasis (pT4aN0M0) is categorized as stage IIB and is included in a range of diseases from mucosal cancer to serosal exposed cancer: pT1N3aM0, pT2N2M0, pT3N1M0, and pT4aN0M0.⁴ Furthermore, no current data compare the clinical characteristics of serosal exposed cancer with the other IIB subgroups. This area requires significant attention and further investigation to prevent effectively and control the development of peritoneal metastasis. This study was conducted to evaluate the clinical impact of serosal exposed cancer without nodal metastasis on the long-term outcomes of patients with gastric cancer by comparing the recurrence and survival results of pT4aN0M0 with other TNM subgroups.

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MATERIALS AND METHODS

Medical records of 4995 patients who had been diagnosed with gastric adenocarcinoma and had undergone radical gastrectomy at Seoul St. Mary's Hospital between January 1989 and December 2013 were reviewed. Clinical information on the patients was retrospectively collected from the gastric cancer registry of our institution. Patients who had undergone endoscopic resection for gastric cancer or were diagnosed with other malignant disease were excluded. Pathologic stage was classified according to the 8th AJCC TNM criteria.

Operative Techniques

All patients underwent conventional radical gastrectomy according to the Japanese Gastric Cancer Treatment Guidelines. Depending on the clinical stages, the patients with early gastric cancer underwent D1 + lymph node (LN) dissection, and the patients with locally advanced cancer underwent D2 or D2 + (LN) dissection. Billroth I, Billroth II, or Roux-En-Y anastomoses were performed for subtotal gastrectomy, whereas only Roux-en-Y anastomoses were conducted for total gastrectomy.

Regular Follow-Up

Patients were subjected to regular follow-up checks after surgery according to the standard protocol (every 3 and 6 months for advanced and early gastric cancer, respectively, for the first 3 years; every 12 months thereafter), which included the determination of tumor marker levels, abdominal imaging, and endoscopic examination. Positron emission tomography (PET) was performed when the patient showed evidence of cancer recurrence. The mean follow-up period for the enrolled patients was 86.2 ± 71.1 (range, 2.1–298.1) months. Proportion of the patients who were lost to follow-up was 31.5% (1577/4995 patients) for 5 years. Survival rates were repeatedly determined using the registration data of the Korea National Statistical Office and the patients' medical records. This study was approved by the Institutional Review Board of the College of Medicine, Catholic University of Korea (KC17RISI0036). Patient records were anonymized and deidentified before analysis.

Recurrence Sites

The pattern of recurrence was categorized by the site of involvement: locoregional, distant metastasis, peritoneum, or multiple. Locoregional recurrence included remnant stomach, anastomosis site, and perigastric LN. Distant

recurrence was defined as single involvement of organs, such as liver, lung, bone, ovary, or distant LN. Simultaneous involvement of more than two organs was defined as multiple recurrences. Recurrences were diagnosed by imaging study or endoscopic biopsy during the follow-up period.

Statistical Analysis

The χ^2 test or Fisher's exact test was used to evaluate between-group differences in categorical variables. Survival analyses were performed using the Kaplan–Meier method with the log-rank test for univariate analyses; multivariate analyses of survival were performed using a Cox proportional hazards model. All of the statistical analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL), and P value < 0.05 was considered statistically significant.

RESULTS

Among the 4995 eligible patients, 427 (8.54%) were stage IIB, and 428 (8.54%) patients were stage IIIA. Among the patients categorized as stage IIB, 20 (4.68%), 104 (24.35%), 172 (40.28%), and 131 (30.67%) were classified as pT1N3a, pT2N2, pT3N1, and pT4aN0, respectively. The mean age of the population was 58.8 years, and 65.8% were male. The overall survival of the 4995 resectional gastric cancers is shown in Supplemental Figure 1 and is comparable to previous studies.

Comparative analyses among the four subgroups of stage IIB to which pT4aN0 belongs were conducted to identify the clinicopathological characteristics of the pT4aN0 subgroup. There were no significant differences among pT1N3a, pT2N2, and pT3N1. However, the pT4aN0 group had different features with regard to tumor size ($P = 0.001$), tumor differentiation ($P < 0.001$), and Lauren classification ($P < 0.001$). Pathologically, pT4aN0 cancers were larger in size and were more frequently undifferentiated and diffuse type cancers (Supplementary Table 1).

Survival curves of each subgroup in stage IIB are shown in Fig. 1. In terms of overall, cancer-specific, and relapse-free survival, there were no significant differences among the four subgroups ($P = 0.437$, $P = 0.053$, and $P = 0.082$, respectively; Fig. 1). Next, we compared survival outcomes of the pT4aN0 subgroup with the combined the other three subgroups, because the pT4aN0 group had different pathological features. Overall survival was not significantly different between pT4aN0 and the other subgroups ($P = 0.178$; Fig. 2a). However, patients in the pT4aN0

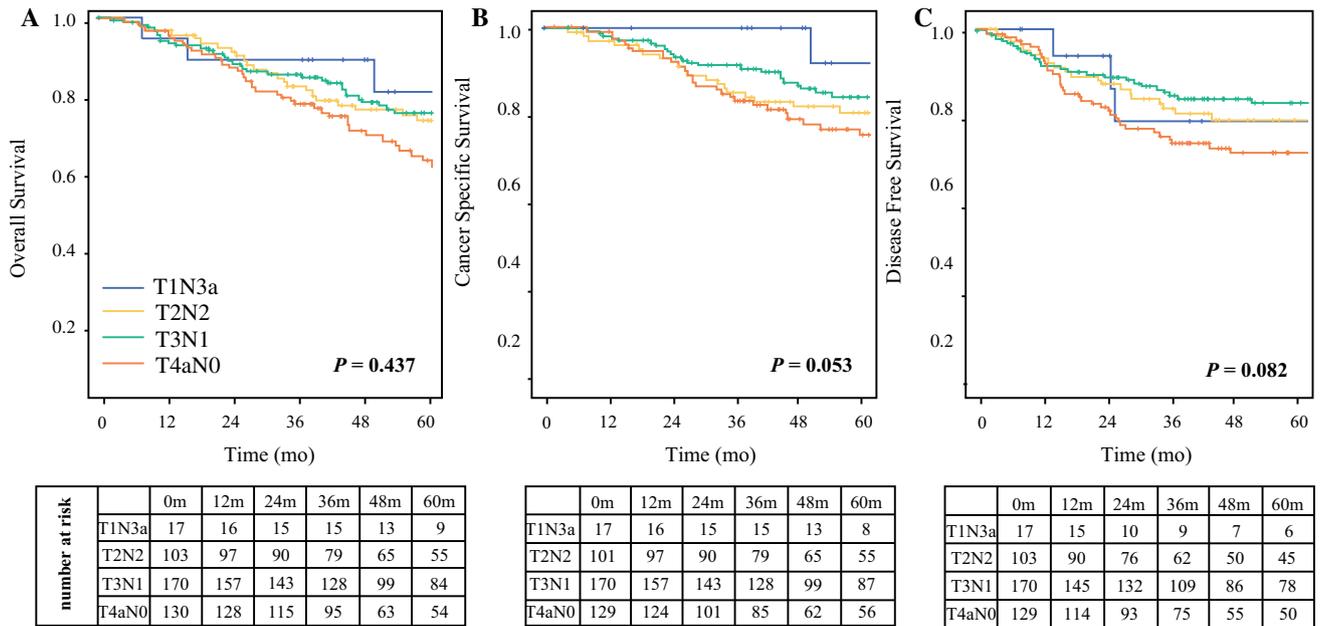


FIG. 1 Survival outcomes among four subgroups of stage IIB. **a** Overall survival ($P = 0.437$). **b** Cancer-specific survival ($P = 0.053$). **c** Relapse free survival ($P = 0.082$)

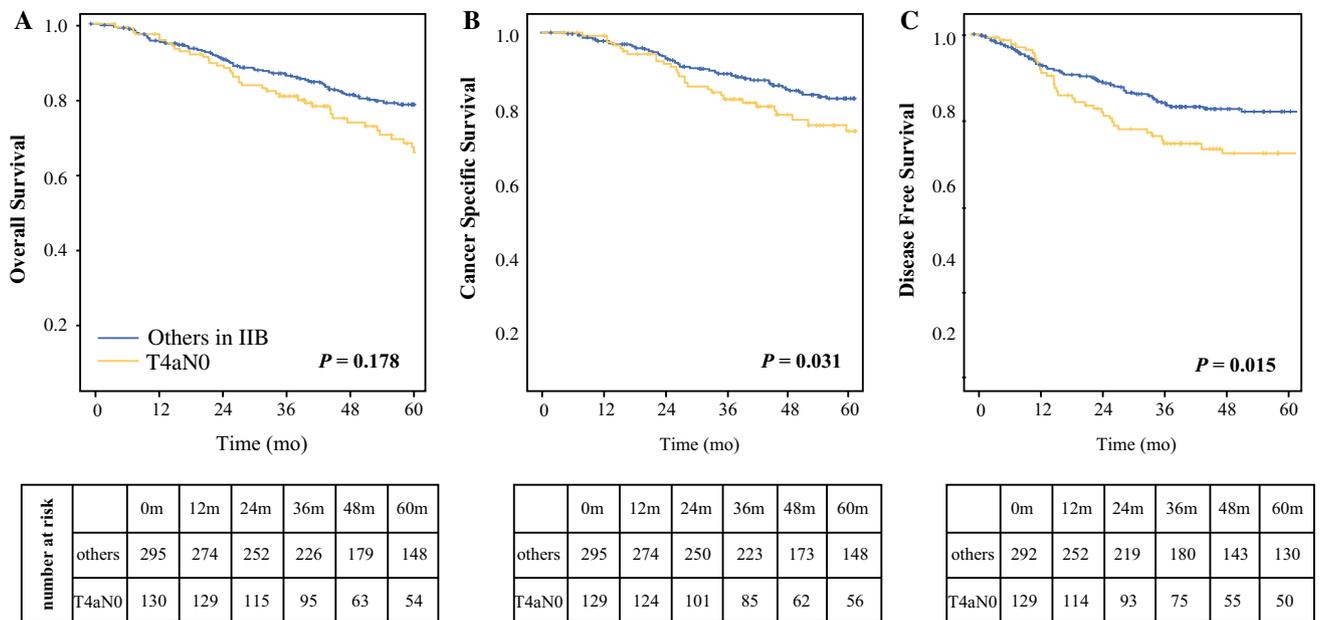


FIG. 2 Survival outcomes between pT4aN0 and the other subgroups in stage IIB. **a** Overall survival ($P = 0.178$). **b** Cancer-specific survival ($P = 0.031$). **c** Relapse-free survival ($P = 0.015$)

group showed a worse prognosis than those in the other groups in terms of cancer-specific survival and relapse-free survival ($P = 0.031$ and $P = 0.015$; Fig. 2b, c).

Table 1 shows the univariate analyses and multivariate analyses for the prognostic factors of patient survival in stage IIB. Serosal exposure was a significantly worse prognostic factor for both cancer-specific survival and

relapse-free survival ($P = 0.011$ and $P = 0.010$, respectively) but had no significant effect on overall survival in multivariate analysis ($P = 0.146$).

The recurrence pattern according to each subgroup of IIB was analyzed (Table 2). The overall recurrence rate was 20.4% (87/427 cases). It was significantly higher in the pT4aN0 group, followed by pT1N3a, pT2N2, and pT3N1 ($P = 0.023$; 29.0%, 20.0%, 18.3%, and 15.7%,

TABLE 1 Univariate and multivariate analysis of prognostic factors for overall survival, cancer-specific survival, and relapse-free survival of stage IIB

	Overall survival			Cancer-specific survival			Relapse-free survival			
	Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	HR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	HR (95% CI)	P
Age	1.02 (1.00–1.03)	0.043	1.03 (1.02–1.05)	< 0.001	1.01 (0.99–1.03)	0.259	1.02 (1.00–1.04)	0.077	1.01 (0.99–1.03)	0.513
Sex	1.03 (0.69–1.53)	0.899			0.85 (0.50–1.42)	0.539			0.84 (0.50–1.37)	0.487
Differentiation	0.92 (0.62–1.35)	0.659			0.97 (0.59–1.61)	0.895			0.86 (0.54–1.40)	0.549
Serosal exposure	1.23 (0.81–1.85)	0.329	1.25 (0.93–1.69)	0.146	1.78 (1.07–2.94)	0.024	1.80 (1.15–2.81)	0.011	1.94 (1.19–3.15)	0.008
Lauren classification	1.07 (0.72–1.61)	0.736			1.32 (0.78–2.27)	0.309			0.92 (0.57–1.52)	0.751
Lymphatic invasion	1.14 (0.75–1.73)	0.553			0.86 (0.51–1.46)	0.562			1.00 (0.60–1.69)	0.991
Vascular invasion	1.13 (0.58–2.22)	0.710	1.74 (1.07–2.82)	0.025	1.94 (1.00–3.78)	0.050	1.99 (1.02–3.89)	0.044	2.45 (1.18–4.52)	0.013
Neural invasion	1.26 (0.85–1.85)	0.245			1.33 (0.82–2.18)	0.248			1.22 (0.76–1.96)	0.407
Chemotherapy	0.63 (0.40–1.98)	0.041			1.16 (0.65–2.15)	0.626			1.35 (0.77–2.50)	0.310

TABLE 2 Recurrence rate and pattern for pathologic stage IIB

	Total (<i>N</i> = 427)	pT1N3a (<i>n</i> = 20)	pT2N2 (<i>n</i> = 104)	pT3N1 (<i>n</i> = 172)	pT4aN0 (<i>n</i> = 131)	<i>P</i> value
Recurrent case (rate, %)	87 (20.4)	3 (15)	19 (18.3)	27 (15.7)	38 (29.0)	0.023
Peritoneum	39 (44.8)	0	2 (10.5)	7 (25.9)	30 (78.9)	0.003
Liver	19 (21.6)	1 (33.3)	7 (40.9)	10 (37.0)	1 (2.6)	0.732
Distant lymph node	7 (7.9)	2 (66.6)	3 (13.6)	1 (3.7)	1 (2.6)	0.534
Lung	3 (3.4)	0	2 (9.1)	1 (3.7)	0	0.662
Bone	2 (2.2)	0	0	1 (3.7)	1 (2.6)	0.778
Locoregional recurrence						
Remnant stomach/anastomosis site	7 (7.9)	0	1 (4.5)	3 (11.1)	3 (7.9)	0.411
Perigastric lymph node	10 (11.4)	0	4 (18.2)	4 (14.8)	2 (5.3)	0.433
Multiple site involvement	25 (28.4)	0	5 (26.3)	8 (29.6)	12 (31.6)	0.523

respectively). The most common pattern of recurrence was peritoneum (45.5%). The most common recurrent sites for each subgroup were distant LN for pT1N3a, liver for pT2N2 and pT3N1, and peritoneal metastasis for pT4aN0. Supplementary Figure 2 shows the cumulative hazard plot for peritoneal metastasis according to serosal exposure, which was statistically significant ($P < 0.001$). In univariate and multivariate analyses for prognostic factors for peritoneal metastasis in stage IIB, serosal exposure was the only significant factor in both analyses ($P < 0.001$ for both, Supplementary Table 2). Noting that the pT4aN0 subgroup showed different outcomes in stage IIB, we further analyzed the survival outcomes of pT4aN0 patients in comparison with those in stage IIIA. There were no significant differences between pT4aN0 and stage IIIA in

terms of overall, cancer-specific, or disease-free survivals (Fig. 3; $P = 0.745$, $P = 0.596$, and $P = 0.593$, respectively). We also compared survival outcomes of serosal exposed cancer patients according to nodal stage. In terms of overall, cancer-specific, and disease-free survivals, there were no significant differences between the pT4aN0 and pT4aN1 subgroups (Supplementary Figure 3; $P = 0.678$, $P = 0.723$, and $P = 0.353$, respectively).

DISCUSSION

Stage IIB includes all grades of depth of tumor invasion, from T1a to T4a, and metastatic lymph nodes, from N0 to N3a.⁴ These heterogeneous subgroups are classified in the same stage according to overall survival. Therefore, there

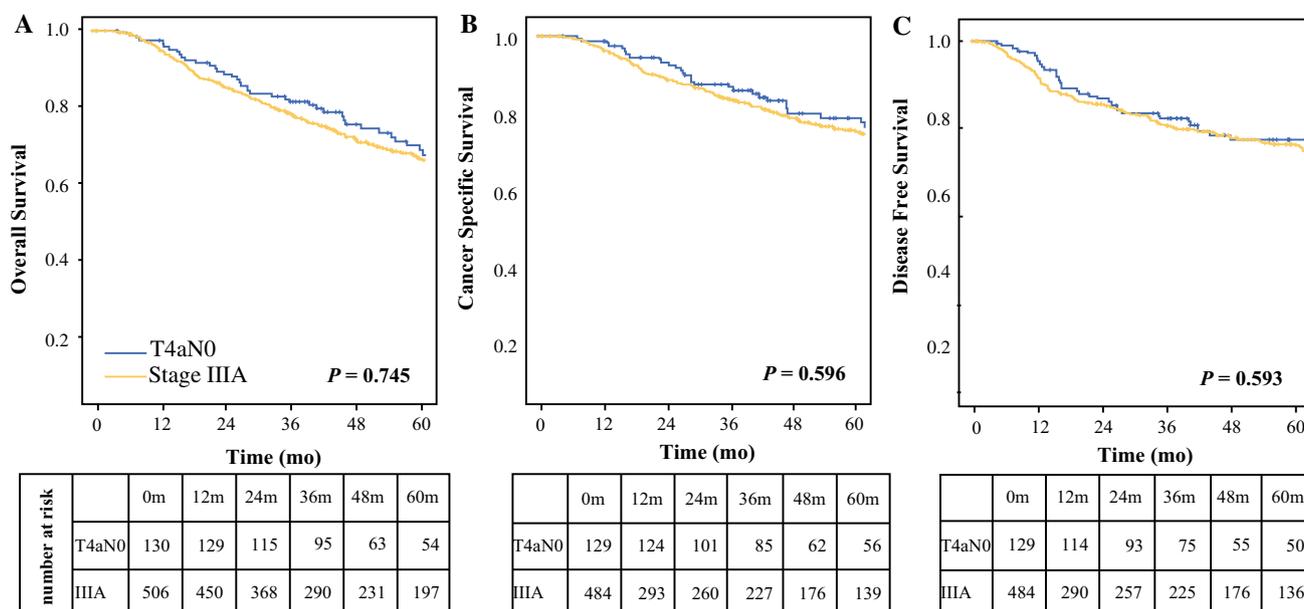


FIG. 3 Survival outcomes between pT4aN0 and stage IIIA. **a** Overall survival ($P = 0.745$). **b** Cancer-specific survival ($P = 0.596$). **c** Relapse-free survival ($P = 0.593$)

could be differences among the subgroups in terms of clinical outcomes such as cancer-specific and relapse-free survival or recurrence patterns.^{6,7} To develop a precise treatment strategy, more detailed and accurate analyses of survival outcome are required. In this context, this study evaluated the differences in recurrence and survival according to subgroup, including pT4aN0.

In our cohort, patients with serosal exposed cancer without nodal metastasis had worse prognoses than patients in other subgroups in stage IIB. Although the overall survival of pT4aN0 and other subgroups in stage IIB were not significantly different, cancer-specific and disease-free survivals were significantly worse in the pT4aN0 subgroup. If a multicenter, large cohort analysis is performed, overall survival may show meaningful differences between pT4aN0 and other subgroups in stage IIB. This is supported by the fact that comparisons between pT4aN0 and stage IIIA showed no statistical differences in terms of overall, cancer-specific, or disease-free survivals.

The recurrence rate of stage IIB was 20.4% in our cohort, which is comparable to the results of the ACT-GC trial or the CLASSIC trial (21.8% and 22%, respectively).^{8,9} However, the recurrence rate of serosal exposed cancer without nodal metastasis was significantly higher than that of others in stage IIB ($P = 0.023$; Table 2). Considering that clinical outcomes of pT4aN0 cancer were as poor as stage IIIA or pT4aN1 in our results, this should draw more attention as a potential treatment window to manage advanced gastric cancers. Furthermore, 30 of 131 (22.9%; Table 2) pT4aN0 subgroup patients were diagnosed with peritoneal metastasis within 5 years.

The clinical course after peritoneal metastasis is quite desperate due to the low efficacy of systemic therapy; thus, the key strategy is accurate and early detection of peritoneal metastasis through regular follow-up surveillance.^{10–12} However, computed tomography (CT) in post-gastrectomy patients lacks accuracy for peritoneal metastasis, because the findings are based only on the morphologic changes in the involved organs, and distorted anatomic structures make image interpretation difficult.^{13–17} Only when the disease advances and develops secondary manifestations, such as ascites, hydronephrosis, or hardened omental mass formation with palpable abdomen, can carcinomatosis be diagnosed.¹⁵ Thus, extra efforts should be made toward the early detection of peritoneal metastasis to provide additional treatment options other than systemic chemotherapy, such as intraperitoneal chemotherapy.^{18,19} More intense surveillance studies, including PET CT, magnetic resonance imaging, or even staging laparoscopy, should be considered, particularly for serosal exposed gastric cancer patients, even in the absence

of nodal metastasis.^{20–23} In addition, further research to improve the efficacy of diagnostic tools and curative strategies should proceed in the future.

This study has a few limitations. First, because this was a retrospective study of 25 years of medical records, there were various types of adjuvant chemotherapy regimens. Second, differences in overall survival were not significant between pT4aN0 and other groups. Nevertheless, this study's strengths included a large cohort of subgroups in the same stage and accurate survival analysis through investigating the reasons for each patient's death. In addition, the recurrence pattern according to each stage or subgroup within a stage has rarely been reported. To the best of our knowledge, this is the first report to demonstrate significantly different recurrence rates and patterns between patients with serosal exposed gastric cancer without nodal metastasis and others in the same stage.

CONCLUSIONS

Patients with serosal exposed gastric cancer without nodal metastasis showed a significantly worse prognosis with a higher incidence of peritoneal metastasis compared with patients in other subgroups of IIB. The survival outcomes of pT4aN0 were not significantly different from those of stage IIIA or pT4aN1 subgroups. Taken together, serosal exposure without nodal metastasis had more detrimental effects on the overall prognosis than previously anticipated in TNM staging. Therefore, clinicians should conduct more careful postoperative management, such as active adjuvant therapy and intense surveillance studies, including staging laparoscopy, on those patients.

AUTHOR CONTRIBUTIONS YJJ, HSS, JHK, CHP, HHL, CHP and HHL conceived and designed the study. YJJ and HSS wrote the manuscript and performed data analysis. JHK was responsible for data collection. HHL reviewed the manuscript and provided feedback. All authors discussed the results and contributed to the final manuscript.

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AVAILABILITY OF DATA AND MATERIAL All data and materials are available upon request.

DISCLOSURE The authors declare that they have no conflict of interest.

ETHICS APPROVAL This study was approved by the Institutional Review Board of the College of Medicine, Catholic University of Korea (KC17RISI0036) in accordance with the Declaration of Helsinki and Good Clinical Practice. All procedures followed were in

accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or and appropriated substitute for it was obtained from all patients included in the study.

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