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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Natural History of Gastric Cancer: Observational Study of Gastric Cancer Patients Not Treated During Follow-Up

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ABSTRACT

Background. Understanding the natural progression of untreated gastric cancer is critical for determining the disease prognosis as well as treatment options and timing. The aim of this study is to analyze the natural history of gastric cancer.

Patients and Methods. We included patients with gastric cancer who had not received any treatment and were staged using endoscopy/endoscopic ultrasonography and computed tomography on at least two follow-up visits during intervals of nontreatment. Tumor volumes were also measured in addition to the staging. Survival of each stage at diagnosis was also analyzed.

Results. A total of 101 patients were included. The mean follow-up period was 35.1 ± 34.4 months. The gastric cancer doubling time was 11.8 months for *T*1 and 6.2 months for *T*4. The progression time from early gastric cancer to advanced gastric cancer was 34 months. It decreased as the stages advanced: from 34 months between tumor-nodes-metastasis stage I and II to 1.8 months between stage III and IV. No variable was identified as a risk factor for cancer progression. The 5-year survival rates of untreated patients were 46.2% in stage I and 0% in stage II, stage III, and stage IV.

Conclusions. The progression and doubling times of gastric cancer shorten as the stages advance. Objective data reported in this study can be a critical factor in determining treatment timing and screening interval.

Keywords Gastric cancer · Natural history · Progression · Doubling time · Survival benefit

Understanding the natural history of untreated gastric cancer is essential for determining prognosis, treatment options, and the timing of treatment in certain circumstances that require treatment delay. Such knowledge is of greater importance in slow-growing cancers that have higher probabilities of early detection because of their relatively long natural courses.[1,2]

Seung-Young Oh and Jeong-Hwan Lee contributed equally and are considered joint first authors.

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Although early gastric cancer (EGC) progresses very slowly,[3,4] it definitely requires treatment. Although surgical treatment of elderly ($\geq$ 80 years) patients with gastric cancer reportedly produces reasonable long-term survival rates,[5] recommending surgery in elderly patients is difficult because of less functional capacities and comorbidities that can affect their postoperative recovery. The most important factors when evaluating the advantages and disadvantages of surgical treatment are life expectancy and the natural history of the cancer. However, there are few studies on the natural history of gastric cancer to date, as the development of less invasive treatment options makes it easier for patients to receive treatment.

The aim of this study is to analyze the progression and doubling times and compare the survival of this disease according to initial clinical tumor-nodes-metastasis (TNM) stages.

PATIENTS AND METHODS

This was a retrospective cohort study which was approved by the institutional review board of Seoul National University Hospital, Seoul, Korea (IRB number: H-1508-038-694).

The inclusion criteria were (1) patients who were diagnosed with histologically confirmed gastric cancer, (2) patients who did not receive any treatment, including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), surgery, or chemotherapy, and (3) patients whose clinical stages were evaluated at least twice using endoscopy or computed tomography (CT) at follow-up visits during periods of nontreatment. Information regarding the duration of untreated time of patients whose treatment has been delayed for more than 5 months was additionally included, since stage progressions are likely to occur over several months in patients with advanced stages and the delayed period of treatment is considered to be equivocal in natural progression. Eighty-six patients were included from 25,810 gastric cancer patients at the SNUH between 1998 and 2014. We also included 15 patients who met the above criteria from the Seoul National University Boramae Medical Center. Data of included patients were retrospectively collected from electronic medical charts. We used International Classification of Disease, Tenth Revision (ICD-10) codes that identified patients with gastric cancer (C16); those with any history of endoscopic treatment, such as EMR or ESD, admission for surgery, or chemotherapy prescription, were excluded. Patients whose clinical stage was assessed only once were also excluded.

Clinical *T*, *N*, and *M* stages determined using endoscopy or endoscopic ultrasonography were reviewed by a gastroenterologist, and those determined using CT were reviewed by radiologists. The radiologist also measured tumor volumes to estimate their doubling times. To obtain as complete a picture of stage progression as possible, we considered the stage at every follow-up visit during the period of nontreatment as well as the stage at the initial diagnosis and final follow-up visit. When the stages determined from endoscopy and CT were different, we classified the disease as the higher stage. As this study started in 2014 and data collection was completed in 2016, the American Joint Committee on Cancer (AJCC) 7th stage was used.

The doubling time of gastric cancer was calculated based on the measured volumes at the initial and final examinations using the equation: doubling time = $T \times \log 2/(\log V_2 - \log V_1)$, where T represents the interval between the two examinations, and V_1 and V_2 represent the tumor volume at the initial and final examination, respectively.[6] Since the distribution of the doubling time was skewed to the right, it was transformed using a logarithm function. The geometric means and their 95% confidence intervals (CIs) were estimated. Analysis of doubling time was performed only on the primary tumor irrespective of lymph node metastasis.

To determine the risk factors of progression from EGC to advanced gastric cancer (AGC), lymph node metastasis, and TNM stage progression, we compared differences in age, sex, comorbidities, and cellular differentiation between patients whose stages had progressed since their initial diagnosis and those whose stages had not.

Because our analysis of the natural history of gastric cancer used data from irregular visits, the progression time between stages could not be precisely determined; That is, we only knew that progression may have occurred between the two visits. This type of survival data is known as "interval-censored." One approach to handle interval censoring is to impute survival time to a time point such as the end, beginning, or midpoint of each interval, then apply a standard survival analysis method such as a Kaplan–Meier curve or Cox proportional hazard model. However, the standard methods may result in overestimation or underestimation of survival and underestimation of error variance, which can lead to a false-positive result.[7] Hence, proper statistical methods should be applied for interval-censored survival data. Survival curves with interval-censored data were estimated using the nonparametric maximum-likelihood estimator (NPMLE) method.[8] We also used the Kaplan–Meier method by imputing the progression time to the visit at which upstaging was detected to enable comparisons with previous studies. Univariable and multivariable analyses of the risk factors of cancer progression were performed using a proportional hazards regression model, with a piecewise constant as the baseline

function.[9] The Kaplan–Meier method and log-rank test were used for the analysis of overall survival. *P*-values less than 0.05 were considered statistically significant.

Statistical analysis was performed using the SAS 9.4 software package (SAS institute Inc., Cary, NC).

RESULTS

Among 25,810 patients with an ICD code of C16 (gastric cancer), 101 were eligible for this study (Supplementary Fig. 1). The patients' mean age was 67.4 ± 12.4 years, and their mean follow-up period was 35.1 ± 34.4 months (Table 1). Ninety-five patients of the 101 patients underwent both endoscopy and CT at initial diagnosis. A total of 93 and 59 of these patients received CT and endoscopy as follow-up, respectively, and 51 patients underwent both. A total of 25 patients had pathologically confirmed malignant cells, but differentiation was not evaluated. The reasons for refusing or delaying treatment were unknown in 50 patients. Of the remaining 51 patients, 35 were not treated because of fear, financial inability, or advanced stage of disease, 9 had medical conditions requiring acute management before gastric cancer treatment, and 7 chose alternative treatments, such as physiotherapy, dietary therapy, herbal medicine, and folk remedy. Although it is very difficult to show when each patient visited for follow-up assessment and performed any tests because intervals between visits would be different for different patients, Supplementary Table 1 and 2 show approximate information. The earlier

TABLE 1 Patient characteristics

	n = 101	
Age (years)	Mean	67.4 ± 12.4
	Median	68.0 [29.0–86.0]
Sex	Male	69 (69.7)
	Female	30 (30.3)
Differentiation	Differentiated type	42 (41.6)
	Well differentiated	8 (7.9)
	Moderated differentiated	34 (33.7)
	Undifferentiated type	34 (33.7)
	Poorly differentiated	16 (15.8)
	Signet ring cell carcinoma	17 (16.8)
	Mucinous adenocarcinoma	1 (0.9)
	Unknown	25 (24.8)
Initial *T* stage	*T*1	33 (32.7)
	*T*2	12 (11.9)
	*T*3	25 (24.8)
	*T*4	27 (26.7)
	Unknown	4 (4.0)
Initial *N* stage	*N*0	46 (45.5)
	N+	49 (48.5)
	Unknown	6 (5.9)
Initial TNM stage	I	36 (35.6)
	II	22 (21.8)
	III	19 (18.8)
	IV	17 (16.8)
	Unknown (or only *T* stage available)	7 (6.9)
Final TNM stage	I	20 (19.8)
	II	15 (14.9)
	III	15 (14.9)
	IV	38 (37.6)
	Unknown (or only *T* stage available)	13 (12.1)
Follow-up period (months)	Mean	35.1 ± 34.4
	Median	20.7 [2.1–172.2]

Data presented as mean ± standard deviation, median [range] or number (%)

the initial stage, the longer the interval between visits, and the more advanced the initial stage, the bigger the proportion of patients who visited within 2, 4, and 6 months after the initial diagnosis.

Doubling Time and Survival Rate

The doubling times (95% CI) of gastric cancer according to *T* stages were as follows: 11.8 (1.1–20.1) months for *T*1, 9.8 (1.1–15.5) months for *T*2, 6.5 (1.0–10.2) months for *T*3, and 6.2 (1.1–10.5) months for *T*4. The doubling times shortened as the stages advanced ($P = 0.03$) (Fig. 1).

Stage Progression Time

The median progression times in *T* stage as determined using the NPMLE method were 34.1 months from *T*1 to *T*2, 9 months from *T*2 to *T*3, and 3.8 months from *T*3 to *T*4. Analysis using the Kaplan–Meier method produced longer durations for stage progression than the NPMLE: 34 months from *T*1 to *T*2, 11 months from *T*2 to *T*3, and 7.5 months from *T*3 to *T*4 (Supplementary Fig. 2).

The median progression times in *N* stage were 34 months from *N*0 to *N*1, 7 months from *N*1 to *N*2, and 11 months from *N*2 to *N*3 when evaluated using the NPMLE method. Similar to *T* stage progression, the progressions according to *N* stage when using the Kaplan–Meier method were relatively longer than those determined using the NPMLE method: 56 months from *N*0 to *N*1, 10.6 months from *N*1 to *N*2, and 11.3 months from *N*2 to *N*3 (Supplementary Fig. 3).

The median progression time in *M* stage was 29 months from *M*0 to *M*1 using the NPMLE method and 30.6 months using the Kaplan–Meier method (Supplementary Fig. 4).

The median progression times in TNM stage were 34 months from stage I to stage II, 19 months from stage II to stage III, and 1.8 months from stage III to stage IV using the NPMLE method. The median survival time for stage progression when using the Kaplan–Meier method was relatively longer compared with when using the NPMLE method: 38.3 months from stage I to stage II, 28 months from stage II to stage III, and 9.6 months from stage III to stage IV (Fig. 2).

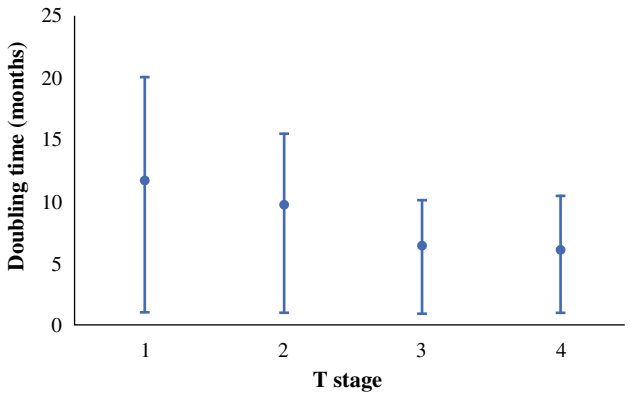

FIG. 1 Doubling time of gastric cancer. As the stages advanced, the doubling times of gastric cancer shortened. The doubling times were 11.8 months for *T*1, 9.8 months for *T*2, 6.5 months for *T*3, and 6.2 months for *T*4. The error bar represents 95% confidence interval

Risk Factors Associated with Cancer Progression

On univariable analysis, the only factor that was significantly predictive of cancer progression from EGC to AGC was male sex ($P = 0.04$); however, this factor was not statistically significant on multivariable analysis. No risk factors were identified for progression from *N*0 to *N*+ or from TNM stage I to higher stages on univariable and multivariable analyses (Table 2).

Overall Survival

The mean survival (95% CI) of untreated patients with gastric cancer according to their TNM stages was 63 (47–78) months for stage I, 25 (16–35) months for stage II, 13 (9–17) months for stage III, and 10 (5–15) months for stage IV ($P < 0.001$). The median survival [range] of untreated patients with gastric cancer was 58.0 [5.9–144.8] months for stage I, 20.2 [4.5–70.5] months for stage II, 12.6 [2.7–33.2] months for stage III, and 6.8 [2.1–35.4] months for stage IV. The 5-year survival rates of untreated patients were respectively 46.2% in stage I and 0% in stage II, stage III, and stage IV (Fig. 3).[10] The 5-year survival rates of untreated patients in our study were 0% across all stages except stage I.

DISCUSSION

Since the first study on the natural history of gastric cancer was conducted in the USA more than 60 years ago,[11] only a few additional studies, mainly case reports or case series, have been published.[12–14] To the best of the authors' knowledge, this study is the first to investigate the natural history of gastric cancer according to stage and to reveal the stage progression time and doubling times of tumors in each stage. Unlike previous studies that only showed durations of their diseases' early stage which was evaluable using endoscopy alone, both TNM staging and distinguishing between EGC and AGC were possible, since about half of the lesions were evaluated using both endoscopy and CT in our study. There are two main reasons why patients underwent examinations multiple times despite not receiving treatment. First, patients who had chosen nonstandard treatment options may have undergone

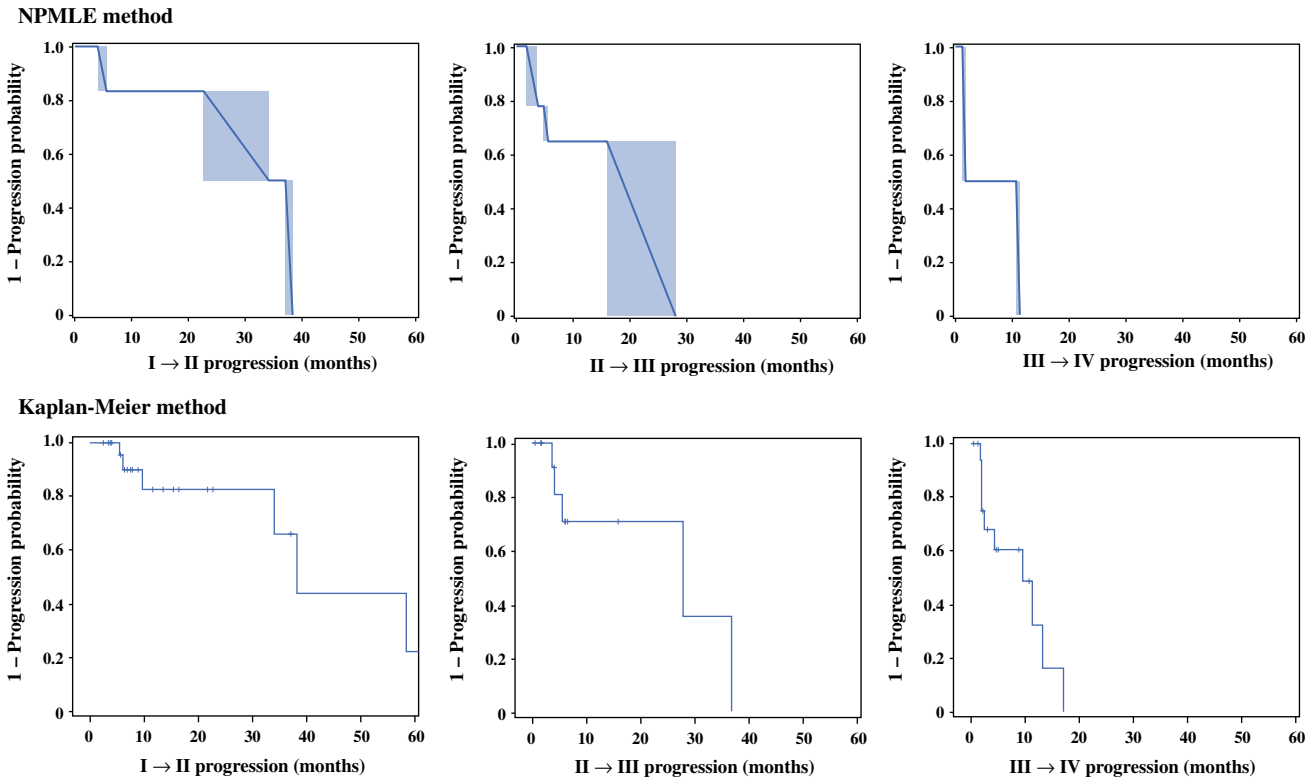

FIG. 2 TNM stage progression time of gastric cancer. As the stages advanced, the median progression times of gastric cancer shortened. The median progression times were 34 months from stage I to II, 19 months from stage II to III, and 1.8 months from stage III to IV using the NPMLE method. Compared with the Kaplan–Meier method, the median survival times for stage progression were shorter with the NPMLE method

TABLE 2 Risk factors associated with EGC to AGC progression, *N*0 to *N*+ progression, and TNM stage I to any higher progression

Type of progression	Risk factors	Univariable		Multivariable	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
EGC to AGC	Age ≥ 75 years (*n* = 38)	1.07 (0.31–3.67)	0.92	2.31 (0.42–12.73)	0.34
	Sex, male (*n* = 71)	5.03 (1.07–23.54)	0.04	2.13 (0.38–11.92)	0.39
	Comorbidity, present (*n* = 38)	2.48 (0.84–7.32)	0.10	2.93 (0.56–15.26)	0.20
	Differentiation, undifferentiated (*n* = 34)	1.06 (0.31–3.59)	0.93	1.97 (0.49–7.92)	0.34
*N*0 to *N*+	Age ≥ 75 years (*n* = 38)	1.10 (0.35–3.48)	0.87	2.63 (0.52–13.36)	0.24
	Sex, male (*n* = 71)	2.56 (0.69–9.59)	0.16	2.67 (0.44–16.11)	0.28
	Comorbidity, present (*n* = 38)	0.41 (0.09–1.95)	0.26	0.36 (0.07–1.96)	0.68
	Differentiation, undifferentiated (*n* = 34)	1.09 (0.30–3.96)	0.90	1.39 (0.30–6.40)	0.24
TNM stage I to higher	Age ≥ 75 years (*n* = 38)	1.04 (0.28–3.89)	0.95	3.28 (0.48–22.47)	0.23
	Sex, male (*n* = 71)	2.96 (0.65–13.42)	0.16	5.42 (0.58–50.67)	0.14
	Comorbidity, present (*n* = 38)	0.42 (0.08–2.12)	0.29	0.33 (0.05–2.07)	0.61
	Differentiation, undifferentiated (*n* = 34)	1.47 (0.37–5.88)	0.59	1.56 (0.29–8.47)	0.24

repeated evaluations to confirm the response to their treatment of choice. Second, the national insurance system of South Korea, which covers 95% of the cost of cancer treatment, may have enabled these examinations for patients of low socioeconomic status even though they could not afford surgery or chemotherapy.

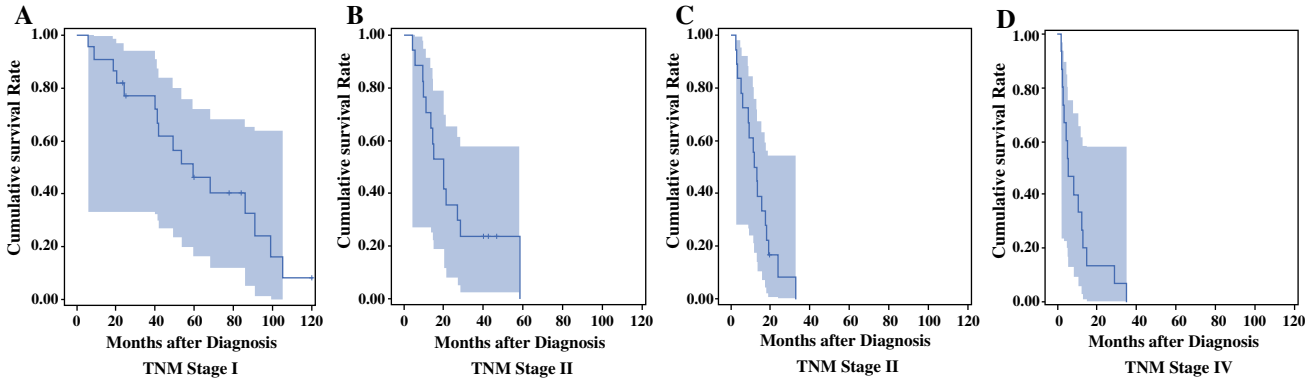

FIG. 3 Overall survival time of gastric cancer according to TNM stage. The 5-year survival rates of untreated patients were 46.2% in stage I and 0% in stage II, stage III, and stage IV. The error bar represents 95% confidence band

Previously, the most thorough study on the natural history of gastric cancer was published in Japan in 2000.[12] This study included 51 patients diagnosed with EGC using endoscopy and biopsy; however, they did not undergo surgery. Twenty of these 51 patients maintained their EGC status over 6–137 months of follow-up with a mean duration of 44 months. The cumulative 5-year risk of progressing to an advanced stage was 63.0%. Another study conducted by Fujisaki et al.[13] found that intramucosal cancer progresses to AGC over 6 years.

A possible explanation for the shorter duration of EGC among our patients, 34 months, compared with the 44 months observed in Tsukuma et al.'s study,[12] is the difference in the statistical method used when analyzing stage progression time. It is impossible to pinpoint the exact time at which the cancer stage changes. Additionally, constant interval examinations or follow-up are not always possible, making studies of the natural history of cancer difficult to plan. Indeed, patients with gastric cancer who were included in our study had not received follow-up at regular intervals. For this reason, we used the NPMLE method to analyze the duration of EGC, which is appropriate for our type of data. The time of progression determined using the Kaplan–Meier method is considered the time of detection of such progression. In contrast, the NPMLE method that we used assumes that the time of progression lies at some point between the follow-up visits at which EGC was last confirmed and AGC was first confirmed. Therefore, the calculated duration of EGC is shorter when using the NPMLE method than when using the Kaplan–Meier method. Considering that the cancer stage at the time of examination is not the actual date of progression to that particular stage, the NPMLE method reflects the unclear progression point of cancer data more reliably than the Kaplan–Meier method. Additionally, the NPMLE method can yield more accurate results when follow-up is performed at constant intervals; therefore, higher-quality data can be obtained if follow-up visits of nontreated cancer patients occur more regularly in future studies. However, it is difficult to apply the NPMLE method for analysis of durations of more than two stages because, while the speed of cancer progression is exponential as the stage advances (as confirmed in our study), the NPMLE method is based on the assumption that the speed of progression between each of the intervals is constant.

Several factors which are known to worsen the prognosis of gastric cancer[15–17] were not identified as significant risk factors for stage progression in our study. The reason why even undifferentiated cancer, which can be expected to have a significant impact on the natural history of gastric cancer, was not a significant risk factor for stage progression in our study is probably because of the lack of relevant data in 25% of the patients. However, the most important reason might be that the sample size of this study was insufficient to verify the impact of each risk factor. To generalize the results of this study is unreasonable, and a further prospective study with large scale will be needed for accurate verification.

According to the results of survival analysis, even in EGC, which progresses very slowly, radical gastrectomy can provide excellent survival benefit. Considering that the median progression times were 34 months in our study and 44 months in a previous Japanese study, the 2-year interval between screening endoscopies recommended in the Korean national health screening system seems appropriate.

Despite producing meaningful results, this study has limitations inherent to researching the natural history of cancer. First, there was a lack of information concerning the reasons for omitting or delaying treatment. Although low socioeconomic status and underlying comorbidities can affect the natural history of gastric cancer, it was impossible to adjust for these variables because data were unavailable for 50% (50/101) of the patients in our study. Additionally, the lack of data regarding the causes of death in untreated patients with gastric cancer may contribute to

the underestimation of the survival rate reported in our study. Second, it is difficult to compare survival directly between the treated and nontreated patients, because the stage used for survival analysis was the final pathologic stage in the treated patients and the clinical stage in the nontreated patients. Although, this cannot be overcome because of the characteristics of the research itself, our results can be employed as a reference on the importance of treatment in gastric cancer.

In summary, the mean doubling time of gastric cancer accelerated from 11.8 months in patients with *T*1 to 6.2 months in those with *T*4. The median progression times of gastric cancer were 34 months from stage *T*1 to *T*2, 34 months from stage *N*0 to *N*1, 29 months from stage *M*0 to *M*1, and 34 months from TNM stage I to II. These results can be a critical factor for deciding when to (re)start treatment in patients who need to discontinue or delay treatment for gastric cancer and provide references for determining the screening interval for a normal population. These results also suggest the importance of surgical treatment by showing the significant survival benefit after radical gastrectomy for gastric cancer.

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DISCLOSURE None.

REFERENCES

1. Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg*. 2010;34(1):28–35.
2. Albertsen PC. Observational studies and the natural history of screen-detected prostate cancer. *Curr Opin Urol*. 2015;25(3): 232–237.
3. Everett SM, Axon AT. Early gastric cancer: disease or pseudo-disease? *Lancet*. 1998;351(9112):1350–1352.
4. Stael von Holstein C, Eriksson S, Huldt B, Hammar E. Endoscopic screening during 17 years for gastric stump carcinoma A prospective clinical trial. *Scand J Gastroenterol*. 1991;26(10): 1020–1026.
5. Yang JY, Lee HJ, Kim TH, et al. Short- and long-term outcomes after gastrectomy in elderly gastric cancer patients. *Ann Surg Oncol*. 2017;24(2):469–477.
6. Ryu EB, Chang JM, Seo M, Kim SA, Lim JH, Moon WK. Tumour volume doubling time of molecular breast cancer subtypes assessed by serial breast ultrasound. *Eur Radiol* 2014;24(9): 2227–2235.
7. Rucker G, Messerer D. Remission duration: an example of interval-censored observations. *Stat Med.* 1988;7(11):1139–1145.
8. Wellner JA, Zhan YH. A hybrid algorithm for computation of the nonparametric maximum likelihood estimator from censored data. *J Am Stat Assoc*. 1997;92(439):945–959.
9. Friedman M. Piecewise exponential models for survival-data with covariates. *Ann Stat*. 1982;10(1):101–113.
10. Ahn HS, Lee HJ, Hahn S, et al. Evaluation of the seventh American Joint Committee on Cancer/International Union Against Cancer Classification of gastric adenocarcinoma in comparison with the sixth classification. *Cancer*. 2010;116(24): 5592–5598.
11. Meiselas LE. Observations on the natural history of gastric cancer. *Am J Med Sci*. 1953;226(4):383–386.
12. Tsukuma H, Oshima A, Narahara H, Morii T. Natural history of early gastric cancer: a non-concurrent, long term, follow up study. *Gut*. 2000;47(5):618–621.
13. Fujisaki J, Nakajima T, Hirasawa T, et al. Natural history of gastric cancer-a case followed up for eight years: early to advanced gastric cancer. *Clin J Gastroenterol*. 2012;5(5):351–354.
14. Sato Y, Fujino T, Kasagawa A, et al. Twelve-year natural history of a gastric adenocarcinoma of fundic gland type. *Clin J Gastroenterol*. 2016;9(6):345–351.
15. Han DS, Suh YS, Kong SH, et al. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. *J Clin Oncol.* 2012;30(31):3834–3840.
16. Takizawa K, Ono H, Kakushima N, et al. Risk of lymph node metastases from intramucosal gastric cancer in relation to histological types: how to manage the mixed histological type for endoscopic submucosal dissection. *Gastric Cancer*. 2013;16(4):531–536.
17. Oh SY, Lee KG, Suh YS, et al. Lymph node metastasis in mucosal gastric cancer: reappraisal of expanded indication of endoscopic submucosal dissection. *Ann Surg* 2017;265(1): 137–142.