Original Article
Middle East Journal of Cancer; October 2022; 13(4): 657-664

Prognosis of Gastric Cancer Patients with a Large Tumor Size

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Please cite this article as: Kim HG, Gang DY, Lee JH, Kim DY. Prognosis of gastric cancer patients with a large tumor size. Middle East J Cancer. 2022;13(4):657-64. doi: 10.30476/mejc.2022.89113.1506.

Abstract

Background: We evaluated the predictive factors associated with survival for gastric cancer patients with large tumor size (≥10 cm).

Method: In this retrospective study, we investigated 279 gastric cancer patients with large-sized tumors, treated at the Chonnam National University Hospital, Gwangju, Korea. We analyzed the clinicopathological features and predictive factors associated with survival in these gastric cancer patients with large tumors. Survival was calculated using the Kaplan-Meier method and the relative prognostic importance of the parameters was investigated through Cox's proportional hazards model.

Results: The recurrence rates were significantly different between the large and small tumor groups (76.3% and 36.6%, respectively; $P < 0.001$). Multivariate analysis showed that the presence of serosal invasion, nodal involvement, the extent of lymph node dissection, the presence of peritoneal dissemination, and curability had prognostic effects in gastric cancer patients with large-sized tumors. The 5-year survival rate was lower in patients with tumors ≥10 cm compared with those with smaller tumors (23.6% versus 57.0%, respectively; $P < 0.0001$). The 5-year survival rate was higher in patients with large tumor size who underwent curative resection (39.1%) than those who did not (10.0%) ($P < 0.0001$).

Conclusion: The long-term survival of gastric cancer patients with large-sized tumors is related to curative resection. Thus, curative resection is of significance for predicting survival.

Keywords: Stomach neoplasms, Tumor size, Prognosis, Survival

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Introduction

Although the incidence of gastric cancer is declining, it remains as one of the leading causes of death from malignant tumors worldwide. Advanced gastric cancer patients have an unfavorable prognosis.[1] In addition, many studies have demonstrated that the depth of tumor invasion and lymph node metastasis are the most important prognostic factors in gastric cancer.[2, 3]

Received: November 25, 2020; Accepted: April 20, 2022

Tumor size may be another valuable prognostic factor and may be clinically useful since it can easily be measured intraoperatively. However, there has been only a relatively small number of reports regarding the follow-up of patients with large-sized gastric cancer. Furthermore, the prognostic value of tumor size in gastric cancer patients remains controversial. In the present study, we analyzed the clinicopathological features of gastric cancer patients with large-sized tumors (≥10 cm) and evaluated the predictive factors associated with survival.

Materials and Methods

This registry-based retrospective study was conducted on 3299 patients with gastric cancer treated at the Department of Surgery, Chonnam National University Hospital between 2005 and 2015, 279 of whom had large-sized tumors (≥10 cm). We analyzed the clinicopathological features and predictive factors associated with survival in these gastric cancer patients with large tumors.

Data regarding patients' age, gender, tumor size, tumor location, macroscopic appearance, depth of invasion, extent of lymph node invasion and dissection, histological type, hepatic metastasis, peritoneal dissemination, stage at initial diagnosis, operative type, recurrence pattern, and curability were obtained from the patients' electronic medical records.

Tumor size was measured according to the Japanese Classification of Gastric Cancer.[4] The dissected stomach specimen was fixed on a flat board and the maximum tumor diameter was determined. The cut-off value for tumor size was defined as the test size with which the highest Wald chi-square value was obtained in this work. Based on this result and the 90th percentile value, we set the cut-off point for tumor size at 10 cm. Using this value, the patients were divided into two groups: the small size group (tumor size < 10 cm) and the large size group (tumor size ≥ 10 cm). The Institutional Review Board of Chonnam National University Hospital approved the current study (approval number: CNUH-2020-324).

The survival rates of the patients were

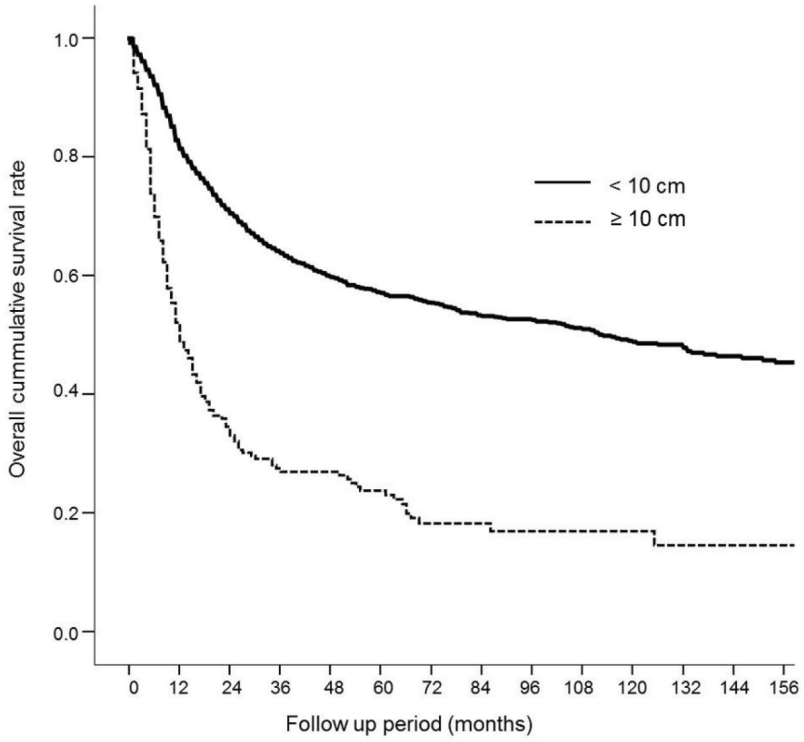

Figure 1. The 5-year survival rate was significantly lower in patients with tumors ≥ 10 cm in size compared with those with smaller tumor sizes (23.6% versus 57.0%, respectively; $P < 0.0001$).

Table 1. Clinicopathologic findings according to tumor size of gastric cancer

Variables	≥ 10 cm (n = 279) (%)	< 10 cm (n = 3020) (%)	*P* value
Age (mean, years)	56.3 ± 0.71	56.9 ± 0.21	NS
Gender			NS
Male	186 (66.7)	2007 (66.5)	
Female	93 (33.3)	1013 (33.5)	
Tumor size (mean, cm)	11.6 ± 0.17	3.9 ± 0.4	< 0.001
Depth of invasion			< 0.001
T1, T2	16 (5.7)	1445 (47.8)	
T3, T4	263 (94.3)	1575 (52.2)	
Borrmann type			< 0.001
I	14 (5.0)	109 (3.6)	
II	19 (6.8)	414 (13.7)	
III	144 (51.6)	1354 (44.7)	
IV	97 (34.8)	151 (5.0)	
Histologic type			< 0.001
Differentiated	63 (22.6)	1279 (42.4)	
Undifferentiated	216 (77.4)	1741 (57.6)	
Extent of lymph node dissection			0.002
< D2	156 (55.9)	1363 (45.1)	
≥ D2	123 (44.1)	1657 (54.9)	
Lymph node metastasis			< 0.001
N (-)	38 (13.6)	1618 (53.6)	
N (+)	241 (86.4)	1402 (46.4)	
Operative type			< 0.001
Total	104 (37.3)	587 (19.4)	
Others	175 (62.7)	2433 (80.6)	
Hepatic metastasis			< 0.001
H (-)	256 (91.8)	2920 (96.7)	
H (+)	23 (8.2)	100 (3.3)	
Peritoneal dissemination			< 0.001
P (-)	179 (64.2)	2779 (92.0)	
P (+)	100 (35.8)	241 (8.0)	
Stage			< 0.001
I	6 (2.2)	1228 (40.7)	
II	29 (10.4)	528 (17.5)	
III	76 (27.2)	723 (23.9)	
IV1	68 (60.2)	541 (17.9)	
Recurrence	213 (76.3)	1106 (36.6)	< 0.001
Locoregional	26 (12.2)	181 (6.0)	
Liver	73 (34.3)	6 (0.2)	
Peritoneum	102 (47.9)	820 (27.0)	
Others	12 (5.6)	99 (3.3)	
CurabilityNS			
Curative	224 (80.3)	2561 (84.8)	
Non-curative	55 (19.7)	459 (15.2)	

NS: Not significant

calculated using the Kaplan-Meier method and the relative prognostic importance of the parameters was investigated via Cox's proportional hazards model. The chi-squared test was employed to evaluate the statistical significance of differences and *P* values < 0.05 were considered statistically significant.

Results

Table 1 summarizes the clinicopathological findings of 279 gastric cancer patients with large tumors (≥10 cm) and 3020 gastric cancer patients

with tumors < 10 cm. Although there were more males than females in each group, no significant differences in gender ratio between the two groups were found. A depth of invasion greater than T3 was observed more frequently in the stomach removed from patients in the large tumor group (94.3%) compared with the small tumor group (52.2%; $P < 0.001$). Borrmann type IV gastric cancer was observed more frequently in patients with large-sized tumors (34.8% versus 5.0%, respectively; $P < 0.001$). Significant differences were also found between the two groups in histological type, the extent of lymph node dissection, nodal involvement, the type of operation, number of hepatic metastases or peritoneal dissemination, and tumor stage. Recurrence rates were 76.3% in the large tumor group and 36.6% in the small tumor group ($P < 0.001$). The curative resection rate of patients with large-sized tumors was 80.3%, which was lower than that of patients with smaller tumors (84.8%). The clinicopathological variables tested in univariate analysis in patients with large tumors are shown in table 2. The factors influencing the 5-year survival rate were tumor location, depth of invasion, histological type, the presence of hepatic metastasis or peritoneal dissemination, the type of operation, lymph node invasion, the extent of lymph node dissection, and curability. Multivariate analysis depicted that the presence of serosal invasion, nodal involvement, the extent of lymph node dissection, the presence of peritoneal dissemination, and curability had prognostic influence on gastric cancer patients with large-sized tumors (Table 3). The 5-year survival rate was significantly lower in patients with tumors ≥10 cm in size compared with those with tumors smaller than this size (23.6% versus 57.0%, respectively; $P < 0.0001$) (Figure 1). Figure 2 illustrates the survival rates according to curability among patients with large gastric cancer. The 5-year survival rate was higher among patients who underwent curative resection (39.1%) than those who did not (10.0%) ($P < 0.0001$) (Figure 2).

Discussion

Herein, 279 gastric cancer patients with large-sized tumors were examined. Large gastric cancers were characterized according to aggressive clinicopathological features, including an increased incidence of Borrmann type IV patterns, T3/T4 stage, undifferentiated histological type, higher rates of lymph node invasion and distant metastases, low curability, and higher recurrence rates. Consequently, the long-term survival of

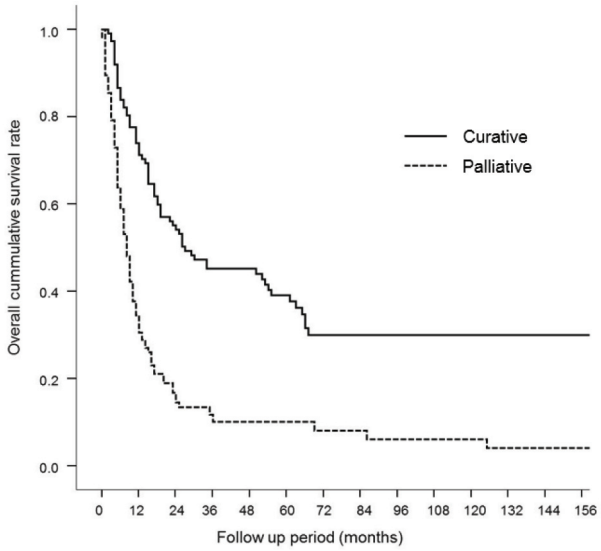

Figure. 2. The 5-year survival rate was higher among patients who underwent curative resection (39.1%) than those who did not (10.0%) ($P < 0.0001$).

Table 2. Univariate analysis of prognostic factors in patients with large gastric cancer

Variables	5-year survival rate (%)	*P* value
Age (year)		0.205
< 65	55.1	
≥ 65	50.1	
Gender		0.100
Male	52.3	
Female	56.9	
Location		0.025
Upper	48.5	
Middle	57.4	
Lower	53.2	
Depth of invasion		< 0.001
T1/T2	82.4	
≥ T3	42.7	
Histologic type		< 0.001
Differentiated	59.8	
Undifferentiated	50.1	
Hepatic metastasis		< 0.001
(-)	55.7	
(+)	12.4	
Peritoneal dissemination		< 0.001
(-)	60.0	
(+)	5.3	
Operative type		< 0.001
Total	43.8	
Partial	56.9	
Lymph node invasion		< 0.001
N (-)	77.8	
N (+)	33.0	
Extent of lymph node dissection		< 0.001
< D2	48.4	
≥ D2	58.2	
Curability		< 0.001
Curative	39.1	
Non-curative	10.0	

gastric cancer patients with large-sized tumors was related to curative resection.

The biology of large gastric cancer was not well described, yet it seemed to represent the late stages of the disease and to be associated with poor prognosis.[5] Whether tumor size is independently correlated with prognosis is controversial. Several studies suggest that tumor size is an independent prognostic factor,[6-9] whereas others show that tumor size does not independently influence survival.[10] It has been reported that tumor size is a simple prognostic indicator of long-term survival in gastric cancer and specifically that patient survival had a stepwise correlation with tumor size (< 4 cm versus 4-10 cm versus ≥10 cm).[11] Some authors have also described tumor size as a significant prognostic factor irrespective of the serosa invasion, but not in early gastric cancer.[12] Furthermore, additional studies have suggested that tumor size is an important prognostic indicator in patients with T3 gastric cancer[13, 14] or pT4a stage advanced gastric cancer.[15] On the contrary, several investigators have concluded that the depth of invasion and tumor location were more important prognostic factors than tumor size.[10] Our previous study implied that there was a significant difference in tumor size between long-

Table 3. Logistic regression analysis of survival for large gastric cancer patients

Variables	Risk ratio	95% CI	*P* value
Serosal invasion (yes versus no)	1.49	1.11-2.02	0.009
Lymph node metastasis (negative versus positive)	3.16	2.65-3.77	< 0.001
Extent of lymph node dissection (< D2 versus ≥ D2)	2.04	1.68-2.48	< 0.001
Peritoneal dissemination (yes versus no)	1.69	1.15-2.49	< 0.001
Curability (curative versus non-curative)	5.52	3.99-7.63	< 0.001

CI: Confidence interval

and short-term survivors of node-positive gastric cancer. Therefore, tumor size emerged as the only independent and significant factor for predicting long-term survival in node-positive gastric cancer patients with curative resection.[16]

Numerous investigators have stated that tumor size was associated with the depth of invasion and lymph node metastasis.[6, 10, 13, 14, 17] Specifically, tumor size was an independent risk factor for lymph node metastasis and patients with large tumors had higher lymph node metastasis rates and a larger proportion of N2 and N3 involvement than those with small tumors. These results were consistent with those of the present study in which nodal involvement was observed more frequently in patients with large-sized tumors compared with those with small-sized tumors (86.4% versus 46.4%, respectively; $P < 0.001$).

A large tumor size is associated with tumor dissemination. It was stated that 22 of 51 tumors larger than 8 cm recurred with peritoneal metastases.[18] Moreover, several authors have reported that patients with advanced large gastric cancer frequently presented with peritoneal metastasis, positive peritoneal cytology, or liver metastasis and there was a high recurrence rate even in patients with curative resection.[19, 20] Consistent with these reports, the present work revealed that peritoneal dissemination occurred more frequently in patients with large gastric cancers than in those with small tumors. Additionally, 76.3% of patients with large gastric tumors exhibited recurrence with the peritoneum being the most frequent site (47.9%) followed by the liver and locoregional recurrence.

It may be reasonable to conclude that the extent of lymph node dissection did not influence the survival of patients with large gastric cancer because of tumor spread.[5] Nevertheless, curability is highly important for achieving long-term survival in gastric cancer patients, even in patients with large-sized tumors. Numerous investigators have found that a considerable proportion of patients with large-sized gastric tumors may not benefit from surgery, if the probability of achieving cure is low.[19] Moreover, some authors have demonstrated that radical gastrectomy offered a low probability of cure in patients with diffuse mixed-type large gastric cancer with serosal invasion.[18] In their series, 82% of tumors > 8 cm in size recurred. However, many investigators have recommended that more than D2 lymph node dissection for curative treatment of advanced gastric cancer.[6] We agree with this recommendation and perform dissection above the D2 lymph node level in patients with large gastric cancer in our institution wherever possible. The present paper indicated that the extent of lymph node dissection has prognostic influence in gastric cancer patients with large-sized tumors. In addition, the survival rate was higher in patients who underwent curative resection than in those who did not in the present study (39.1% versus 10.0%, respectively; $P < 0.0001$).

The reported postoperative mortality rate for gastric cancer patients undergoing resection ranges from 2.0 to 11.9%. Even in Japan, the morbidity of gastrectomy for large gastric cancer is high and associated with operating time, blood loss, pancreatic invasion, and serum CEA level.[21] In our study, the postoperative mortality due to resection in patients with large gastric cancer was acceptable and two postoperative deaths (4.7%) occurred after resection, indicating that resections in patients with large gastric cancer are not associated with an increased postoperative mortality rate.

The retrospective design was the main limitation of our study, which led to losing some patients in the follow-up. Moreover, the data from the Cancer Institute may not be generalized to the entire country. Therefore, further research is required in other provinces employing population-based cancer registries.

Conclusion

In conclusion, the present study exhibited that the survival of gastric cancer patients with large-sized tumors was lower than that of patients with small-sized tumors. Furthermore, the long-term survival of gastric cancer patients with large-sized tumors was related to curative resection. Therefore, curative resection is of great importance for predicting the survival of these patients.

Conflict of Interest

None declared.

References

1. Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, et al. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer.* 1992;70(5):1030-7. doi: 10.1002/1097-0142(19920901)70:5<1030::aid-cncr2820700504>3.0.co;2-c.
2. Bozzetti F, Bonfanti G, Morabito A, Bufalino R, Menotti V, Andreola S, et al. A multifactorial approach for the prognosis of patients with carcinoma of the stomach after curative resection. *Surg Gynecol Obstet.* 1986;162(3):229-34.
3. Yokota T, Ishiyama S, Saito T, Teshima S, Narushima Y, Murata K, et al. Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. *Scand J Gastroenterol.* 2004;39(4):380-4. doi: 10.1080/003 65520310008629.
4. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer*. 2011;14(2):101-12. doi: 10.1007/s10120-011-0041-5.
5. Zhou L, Li W, Cai S, Yang C, Liu Y, Lin Z. Large tumor size is a poor prognostic factor of gastric cancer with signet ring cell: Results from the surveillance, epidemiology, and end results database. *Medicine (Baltimore)*. 2019;98(40):e17367. doi: 10.1097/MD.0000000000017367.
6. Li C, Oh SJ, Kim S, Hyung WJ, Yan M, Zhu ZG, et al. Risk factors of survival and surgical treatment for advanced gastric cancer with large tumor size. *J Gastrointest Surg.* 2009;13(5):881-5. doi: 10.1007/s11605-009-0800-3.
7. Jun KH, Jung H, Baek JM, Chin HM, Park WB. Does tumor size have an impact on gastric cancer? A single institute experience. *Langenbecks Arch Surg.* 2009;394(4):631-5. doi: 10.1007/s00423-008-0417-0.
8. Guo P, Li Y, Zhu Z, Sun Z, Lu C, Wang Z, et al. Prognostic value of tumor size in gastric cancer: an analysis of 2,379 patients. *Tumour Biol.* 2013;34(2):1027-35. doi: 10.1007/s13277-012-0642-6.
9. Del Rio P, Viani L, Bertocchi E, Iapichino G, Luzietti E, Dell'Abate P, et al. The prognostic role of tumor size in patients with gastric cancer. *Ann Ital Chir.* 2017;88:478-84.
10. Yokota T, Ishiyama S, Saito T, Teshima S, Yamada Y, Iwamoto K, et al. Is tumor size a prognostic indicator for gastric carcinoma? *Anticancer Res.* 2002;22(6B):3673-7.
11. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi K. Tumor size as a simple prognostic indicator for gastric carcinoma. *Ann Surg Oncol.* 1997;4(2):137-40. doi: 10.1007/BF02303796.
12. Im WJ, Kim MG, Ha TK, Kwon SJ. Tumor size as a prognostic factor in gastric cancer patient. *J Gastric Cancer.* 2012;12(3):164-72. doi: 10.5230/jgc.2012.12.3.164.
13. Liu X, Xu Y, Long Z, Zhu H, Wang Y. Prognostic significance of tumor size in T3 gastric cancer. *Ann Surg Oncol.* 2009;16(7):1875-82. doi: 10.1245/s10434-009-0449-x.
14. Bilici A, Uygun K, Seker M, Ustaalioglu BB, Aliustaoglu M, Temiz S, et al. The effect of tumor size on overall survival in patients with pT3 gastric cancer: experiences from 3 centers. *Onkologie.* 2010;33(22):676-82. doi: 10.1159/000322215.
15. Liu HG, Liang H, Deng JY, Wang L, Liang YX, Jiao XG. The prognostic analysis of tumor size in T4a stage gastric cancer. *Zhonghua Wai Ke Za Zhi.* 2013;51(3):230-4.
16. Kim DY, Joo JK, Park YK, Ryu SY, Kim YJ, Kim SK. Predictors of long-term survival in node-positive gastric carcinoma patients with curative resection. *Langenbecks Arch Surg.* 2007;392(2):131-4. doi: 10.1007/s00423-006-0114-9.
17. Kim HG, Ghu HD, Yun SK, Ryu SY, Kim DY. Clinicopathological features of female gastric carcinoma patients with curative resection: comparison with male patients. *Chonnam Med J.* 2012;48(2):86-90. doi: 10.4068/cmj.2012.48.2.86.
18. Roviello F, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, et al. Italian Research Group for Gastric Cancer. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg.* 2003;90(9):1113-9. doi: 10.1002/bjs.4164.
19. Kobayashi O, Tsuburaya A, Yoshikawa T, Osaragi T, Murakami H, Yoshida T, et al. The efficacy of

gastrectomy for large gastric cancer. *Int J Clin Oncol.* 2006;11(1):44-50. doi: 10.1007/s10147-005-0535-4.
20. Shiraishi N, Sato K, Yasuda K, Inomata M, Kitano S. Multivariate prognostic study on large gastric cancer. *J Surg Oncol.* 2007;96(1):14-8. doi: 10.1002/jso.20631.
21. Yasuda K, Shiraishi N, Adachi Y, Inomata M, Sato K, Kitano S. Risk factors for complications following resection of large gastric cancer. *Br J Surg.* 2001;88(6):873-7. doi: 10.1046/j.0007-1323.2001.01782.x.