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Clinical and Morphological Indicators of Early Gastric Cancer Recurrence

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Abstract

Background: Despite advancements in diagnostics and the widespread adoption of multimodal therapy for gastric cancer, early recurrence continues to pose a serious clinical challenge. This study aims to identify clinical, morphological, and perioperative factors associated with early recurrence (≤6 months) of gastric cancer after completion of combined treatment and to develop a prognostic model for assessing the risk of recurrence.

Methods and Results: This retrospective study included data from 199 patients who underwent gastrectomy with D2 lymph node dissection in a regional oncology center. A total of 88 patients who completed combined (multimodal) treatment were included in the final statistical analysis. Clinical and tumor-related characteristics, response to treatment, and surgical parameters were evaluated. Patients were divided into two groups based on the presence or absence of recurrence within 6 months. Logistic regression analysis was used to identify independent predictors. Model performance was assessed using ROC analysis.

Among the 88 patients included in the final analysis, disease recurrence was observed in 44 cases (50%). Of these, 21 patients (47.7%) experienced a recurrence within the first six months following completion of combined treatment. The multivariate analysis confirmed that poor tumor differentiation (G3) (OR = 6.084; 95% CI: 1.124–32.917) and the presence of lymphovascular invasion (OR = 9.902; 95% CI: 2.061–47.560) play a significant role in the likelihood of gastric cancer recurrence following the completion of combined treatment. The prognostic model demonstrated good discriminatory ability, with an AUC of 0.852 (95% CI: 0.735–0.969), sensitivity of 85.7%, and specificity of 73.9%.

Conclusion: Lymphovascular invasion and poor tumor differentiation may serve as independent risk factors for recurrence within the first six months following completion of combined treatment for gastric cancer. The developed model may be helpful in stratifying risk and personalizing postoperative surveillance.(**International Journal of Biomedicine. 2025;15(3):500-504.**)

Keywords: gastric cancer • treatment • risk of recurrence • prognostic model

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Introduction

Gastric cancer remains one of the most common and deadly oncological diseases in the Russian Federation, ranking fifth in incidence and third in cancer-related mortality. [1,2] Radical gastrectomy with D2 lymph node dissection is currently a key component in the multimodal treatment strategy for patients with stage IB–III disease. Despite advancements in diagnostics and the widespread adoption of multimodal therapy, early recurrence continues to pose a serious clinical challenge. According to published data, more than 70% of tumor relapses and cancer-related deaths occur within the first two years following surgery.[3]

Recurrence after treatment is typically classified as locoregional, peritoneal, or distant metastatic. The pattern of recurrence is influenced by both the anatomical location and the stage of the primary tumor. Although various studies have examined potential risk factors, a unified system for predicting recurrence has not yet been established.[4] Given the importance of timely detection and the limited number of

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studies specifically focused on early recurrence, identifying reliable clinical and morphological predictors in the first six months after completion of combined treatment remains a pressing task.

This study aims to identify clinical, morphological, and perioperative factors associated with early recurrence (≤6 months) of gastric cancer after completion of combined treatment and to develop a prognostic model for assessing the risk of recurrence.

Materials and Methods

This retrospective study was conducted in the Thoracic and Abdominal Oncology Surgery Departments at the Ulyanovsk Regional Oncological Dispensary. The analysis included data from 199 patients who underwent gastrectomy with D2 lymph node dissection between January 1, 2018, and October 1, 2023.

Inclusion criteria

•Histologically confirmed gastric adenocarcinoma

•Gastrectomy with D2 lymph node dissection, including combined resections when necessary

•Completion of the full perioperative chemotherapy protocol (8 cycles) using the FLOT regimen (docetaxel 50 mg/m², oxaliplatin 85 mg/m², leucovorin 200 mg/m² administered intravenously on day 1, followed by a 24-hour infusion of 5-fluorouracil 2600 mg/m² every 14 days)

•HER2-negative tumor status

Exclusion criteria

•Rare histological subtypes of gastric cancer

•In-hospital postoperative mortality

•Synchronous primary malignant tumors

Based on these criteria, 88 patients were included in the final analysis. During histopathological examination of surgical specimens, the following parameters were assessed: Borrmann macroscopic classification, ypT and ypN status, resection margin involvement, tumor grade, tumor regression according to the Mandard classification, and presence or absence of lymphovascular invasion. Staging was performed according to the 8th edition of the TNM classification (2016).[5]

During the first year after treatment completion, patients were followed up every three months. From the second to the third year, follow-up visits were scheduled every six months, and annually thereafter. At each follow-up, patients underwent laboratory and imaging studies. In cases of suspected recurrence, diagnostic laparoscopy with biopsy of suspicious lesions was performed.

Statistical analysis

All statistical analyses were performed using StatTech v. 4.4.1 (Stattech LLC, Russia). The distribution of continuous variables was assessed using the Shapiro–Wilk test (n<50) or the Kolmogorov–Smirnov test (n≥50). Normally distributed variables were reported as mean ± standard deviation and 95% confidence intervals (CI). Non-normally distributed data were presented as median and interquartile range (Q1–Q3). Categorical variables were described using absolute numbers and percentages. Between-group comparisons of normally distributed continuous variables were performed using Student's t-test. The Mann–Whitney U test was used for nonparametric comparisons. Pearson's chi-square test was applied for analysis of contingency tables; for relative measures, odds ratios (OR) with 95% CI were calculated. Survival analysis was carried out using the Kaplan–Meier method, and differences between groups were evaluated with the log-rank test. Cox proportional hazards regression was used to assess the impact of independent predictors on recurrence risk over time. A P-value of less than 0.05 was considered statistically significant.

Results

Among the 88 patients included in the final analysis, disease recurrence was observed in 44 cases (50%). Of these, 21 patients (47.7%) experienced a recurrence within the first six months following completion of combined treatment.A statistically significant difference between the groups was observed only for obesity (*P*=0.039), suggesting the overall comparability of the cohorts in terms of demographic and comorbid profiles (Table 1).

Table 1.

Clinical characteristics of the study groups depending on the disease recurrence within the first 6 months.

Variable	Category	No Recurrence (n = 67)	Early Recurrence (n = 21)	*P-value*
Sex, n (%)	Female	21 (31.3%)	10 (47.6%)	0,173
	Male	46 (68.7%)	11 (52.4%)	
Age, years (M ± SD)		62.6 ± 7	61.7 ± 8.5	0.617
BMI, M ± SD		25.87 ± 4,15	27.08 ± 5.39	0.283
Charlson comorbidity index, Me [IQR]		4 (4;5)	4 (4;5)	1.000
Obesity, n (%)	No	58 (86.6%)	14 (66.7%)	0.039
	Yes	9 (13.4%)	7 (33.3%)	
Diabetes mellitus, n (%)	No	56 (83.6%)	17 (81.0%)	0.780
	Yes	11 (16.4%)	4 (19%)	
Coronary heart disease, n (%)	No	53 (79.1%)	16 (76.2%)	0.777
	Yes	14 (20.9%)	5 (23.8%)	
Arterial hypertension, n (%)	None	29 (43.3%)	5 (23.8%)	0.424
	Grade I	7 (10.4%)	3 (14.3%)	
	Grade II	19 (28.4%)	7 (33.3%)	
	Grade III	12 (17.9%)	6 (28.6%)	
Chronic heart failure, n (%)	None	44 (65.7%)	16 (76.2%)	0.665
	Class I	14 (20.9%)	3 (14.3%)	
	Class II	9 (13.4%)	2 (9.5%)	
Left ventricular ejection fraction (%), Me [IQR]		63.6 [58;66]	63.7 [62;66]	0.320
Pulmonary artery pressure (mmHg), Me [IQR]		13.8 [12.1;15.5]	13.7 [13.1;14.1]	0.899

Comparative analysis of oncological parameters between the study groups identified the following statistically significant factors: tumor stage, ypT category, lymphovascular invasion, tumor differentiation grade, and tumor regression grade according to the Mandard scale (Table 2).

Table 2.

Oncological characteristics of the study groups.

Variable	Category	No Recurrence (n = 67)	Early Recurrence (n = 21)	*P-value*
Borrmann classification, n (%)	Type 1	2 (3.5%)	2 (7.7%)	<0.001
	Type 2	17 (29.8%)	5 (19.2%)	
	Type 3	34 (59.7%)	12 (46.2%)	
	Type 4	4 (7%)	7 (26.9%)	
Clinical T category (cT), n (%)	2	13 (19.4%)	1 (4.8%)	0.101
	3	48 (71.6%)	15 (71.4%)	
	4a	5 (7.5%)	5 (23.8%)	
	4b	1 (1.5%)	0 (0%)	
Clinical N category (cN), n (%)	0	25 (37.3%)	7 (33.3%)	0.346
	1	31 (46.3%)	10 (47.6%)	
	2	11 (16.4%)	3 (14.3%)	
	3	0 (0%)	1 (4.8%)	
Clinical stage, n (%)	I	25 (37.4%)	2 (9.5%)	0.004
	II	21 (31.3%)	4 (19%)	
	III	21 (31.3%)	15 (71.5%)	
Tumor size (mm), Me [IQR]		54 [41;70]	48 [50;72]	0.763
Retrieved lymph nodes, Me [IQR]		14 [11;19]	12 [10;19]	0.250
ypT category, n (%)	0	6 (9%)	0 (0%)	0.041
	1a	8 (11.8%)	0 (0%)	
	1b	2 (3%)	0 (0%)	
	2	17 (25.4%)	2 (9.5%)	
	3	25 (37.3%)	14 (66.7%)	
	4a	5 (7.5%)	1 (4.8%)	
	4b	4 (6%)	4 (19%)	
ypN category, n (%)	0	36 (53.7%)	7 (33.4%)	0.129
	1	14 (20.9%)	4 (19%)	
	2	12 (17.9%)	4 (19%)	
	3a	4 (6%)	5 (23.8%)	
	3b	1 (1.5%)	1 (4.8%)	
Resection margin status, n (%)	R0	61 (91%)	19 (90.5%)	1.000
	R1	6 (9%)	2 (9.5%)	
Lymphovascular invasion, n (%)	No	52 (77.6%)	8 (38.1%)	<0.001
	Yes	15 (22.4%)	13 (61.9%)	
Tumor differentiation grade, n (%)	G1	26 (38.5%)	0 (0%)	<0.001
	G2	31 (46.6%)	2 (9.5%)	
	G3	10 (14.9%)	19 (90.5%)	
Tumor regression grade (Mandard), n (%)	TRG1	17 (25.4%)	0 (0%)	0.005
	TRG2	12 (17.9%)	0 (0%)	
	TRG3	12 (17.9%)	4 (19%)	
	TRG4	18 (26.9%)	12 (57.2%)	
	TRG5	8 (11.9%)	5 (23.8%)	

Comparative analysis of the main surgical parameters revealed two statistically significant factors: intraoperative blood loss and the need for blood transfusion (Table 3).

Table 3.

The main surgical characteristics of patient groups.

Variable	Category	No Recurrence (n = 67)	Early Recurrence (n = 21)	*P*-value
Operative time, min, Me [IQR]		195 [177.5; 225]	200 [180; 270]	0.453
Intraoperative blood loss, mL, Me [IQR]		300 [200; 400]	300 [200; 800]	0.421
Length of hospital stay, days, Me [IQR]		15 [13; 17]	18 [16; 21]	0.060
Perioperative blood transfusion, n (%)	No	50 (89.6%)	14 (66.7%)	<0.001
	Yes	7 (10.4%)	7 (33.3%)	
Clavien–Dindo complications, n (%)	Grade 0- I	35 (52.3%)	10 (47.6%)	0.437
	Grade II	29 (43.3%)	8 (38.1%)	
	Grade IIIA	1 (1.5%)	2 (9.5%)	
	Grade IIIB	2 (3.0%)	1 (4.8%)	
Combined resections, n (%)	No	11 (19.0%)	3 (11.5%)	0.178
	Yes	47 (81.0%)	23 (88.5%)	

It is noteworthy that no grade 4 complications were observed in the analyzed cohort.

An analysis of overall survival was subsequently performed based on the presence or absence of recurrence within the first six months after curative treatment. Differences in overall survival, assessed using the likelihood ratio test, were statistically significant (*P*=0.006) (Figure 1).

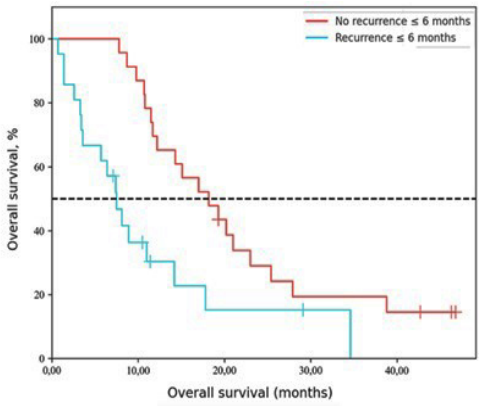

Figure 1. *The overall survival curve depending on the type of relapse.*

Following univariate analysis, a multivariate analysis was performed, and a prognostic model was developed to

estimate the probability of recurrence within the first six months after completion of combined treatment.

The area under the ROC curve (AUC) was 0.852±0.060, with a 95% CI of 0.735 to 0.969, and the model demonstrated statistical significance (P<0.001). The optimal cutoff point of the logistic function (P), corresponding to the highest Youden index, was 0.513. A positive prediction was made when the P-value was equal to or greater than this threshold. The sensitivity and specificity of the model were 85.7% and 73.9%, respectively.

Thus, the multivariate analysis confirmed that poor tumor differentiation (G3) (OR=6.084; 95% CI: 1.124–32.917) and the presence of lymphovascular invasion (OR=9.902; 95% CI: 2.061–47.560) play a significant role in the likelihood of gastric cancer recurrence following the completion of combined treatment (Table 4).

Table 4.

The data of multivariate analysis for the probability of relapse detection within 6 months.

Predictor	Unadjusted		Adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Poor differentiation (G3)	15.200 (3.483 – 66.354)	<0.001	9.902 (2.061 – 47.560)	0.004
Lymphovascular invasion	10.833 (2.418 – 48.521)	0.002	6.084 (1.124 – 32.917)	0.036

Discussion

Advances in modern clinical oncology and surgical techniques have significantly improved survival rates for patients undergoing combined treatment for gastric cancer. However, despite these achievements, several studies report that 50%–70% of patients experience disease recurrence after the completion of therapy, which adversely affects long-term outcomes. A substantial proportion of recurrences occur within the first two years following treatment.

In the present study, 23.9% of patients developed recurrence within six months after completing treatment. Identifying predictors of early recurrence is important for timely diagnosis and initiation of therapy at an earlier stage. A large meta-analysis by Pang et al.[6] demonstrated that patients diagnosed with asymptomatic recurrence after gastrectomy had better survival than those with symptomatic recurrence, underscoring the need for further research into early detection and prediction of relapse.

However, the number of studies focused specifically on early recurrence predictors remains limited. According to both domestic and foreign authors, numerous factors have been proposed to influence recurrence following gastrectomy, including tumor size and location, depth of invasion, and lymph node metastasis.[4] In a large cohort study involving 3,534 patients, pT and pN categories were found to impact the risk of local recurrence significantly.[7,8] In our analysis, no statistical association with pN was confirmed, although a trend was observed for ypT: 66.7% of patients with early recurrence had tumors classified as ypT3. Histological characteristics of the tumor and its response to treatment are currently regarded by many researchers as key factors in early relapse.

In our study, a statistically significant association was found between poor tumor response on the Mandard scale and early recurrence. In univariate analysis, 81% of patients who experienced early recurrence had an unsatisfactory pathological response, suggesting that tumor biology plays a substantial role.

The prognostic significance of treatment response has also been highlighted in other studies. For example, Kang et al.[9] reported that for patients with Mandard Grades 4–5 and ypN0 status, the median survival time was 68.5 and 76.7 months, respectively, whereas those with Mandard Grades 1–2 and ypN3a had median survival times of only 15.6 and 14.5 months. The same authors also emphasized the prognostic value of lymphovascular invasion, which aligns with our findings and those of other studies.[3,10] In our multivariate analysis, lymphovascular invasion was confirmed as an independent predictor (OR = 9.902; 95% CI: 2.061–47.560). While our study did not establish a significant association between lymph node involvement and recurrence risk, Saito et al. previously reported such a link.[11] The lack of association in our cohort may reflect high-quality lymphadenectomy and appropriate selection of surgical candidates.

Jiao et al.[4] suggested that diabetes mellitus may contribute to early recurrence, although other comorbidities showed no significant effect. In our study, no statistically significant associations were found between recurrence and comorbidities. The observed difference in obesity rates may be incidental due to the small sample size; its pathophysiological role remains unclear.

A statistically significant relationship was also found between early recurrence and both length of hospital stay and perioperative blood transfusion, likely reflecting more complex surgical cases. The significantly poorer overall survival observed in patients with early recurrence further highlights the clinical relevance of this problem and the need for effective prediction tools.

One limitation of our study is the relatively small sample size. Further large-scale multicenter studies are necessary to identify additional predictive factors and to confirm the significance of those already established.

Conclusion

Lymphovascular invasion and poor tumor differentiation may serve as independent risk factors for recurrence within the first six months following completion of combined treatment for gastric cancer. The developed model may be helpful in stratifying risk and personalizing postoperative surveillance.

Competing Interests

The authors declare that they have no competing interests.

References

1. Shakhzadova AO, Starinsky VV, Lisichnikova IV. [The state of oncological care for the population of Russia in 2022]. Siberian Oncological Journal. 2023;22(5):5–13. [Article in Russian]. doi: 10.21294/1814-4861-2023-22-5-5-13
2. Malignant neoplasms in Russia in 2022 (morbidity and mortality) / Ed. by A.D. Kaprin et al. Moscow: P.A. Herzen Moscow Oncology Research Institute – branch of the National Medical Research Center of Radiology, Ministry of Health of Russia, 2023. Illustrated. 275 p.[In Russian].
3. Kang WM, Meng QB, Yu JC, Ma ZQ, Li ZT. Factors associated with early recurrence after curative surgery for gastric cancer. World J Gastroenterol. 2015 May 21;21(19):5934-40. doi: 10.3748/wjg.v21.i19.5934. PMID: 26019458; PMCID: PMC4438028.
4. Jiao X, Wang Y, Wang F, Wang X. Recurrence pattern and its predictors for advanced gastric cancer after total gastrectomy. Medicine (Baltimore). 2020 Dec 18;99(51):e23795. doi: 10.1097/MD.0000000000023795. PMID: 33371151; PMCID: PMC7748337.
5. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al.; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016 Jan;11(1):39-51. doi: 10.1016/j.jtho.2015.09.009. PMID: 26762738.
6. Pang HY, Yan MH, Chen LH, Chen XF, Chen ZX, Zhang SR, Sun H. Detection of asymptomatic recurrence following curative surgery improves survival in patients with gastric cancer: A systematic review and meta-analysis. Front Oncol. 2022 Oct 26;12:1011683. doi: 10.3389/fonc.2022.1011683. PMID: 36387075; PMCID: PMC9643694.
7. Wu CW, Lo SS, Shen KH, Hsieh MC, Chen JH, Chiang JH, Lin HJ, Li AF, Lui WY. Incidence and factors associated with recurrence patterns after intended curative surgery for gastric cancer. World J Surg. 2003 Feb;27(2):153-8. doi: 10.1007/s00268-002-6279-7. PMID: 12616428.
8. Lai JF, Kim S, Kim K, Li C, Oh SJ, Hyung WJ, Rha SY, Chung HC, Choi SH, Wang LB, Noh SH. Prediction of recurrence of early gastric cancer after curative resection. Ann Surg Oncol. 2009 Jul;16(7):1896-902. doi: 10.1245/s10434-009-0473-x. Epub 2009 May 12. PMID: 19434457.
9. Kang WZ, Wang BZ, Li DF, Jiang ZC, Xiong JP, Li Y, Jin P, Shao XX, Hu HT, Tian YT. Can Gastric Cancer Patients with High Mandard Score Benefit from Neoadjuvant Chemotherapy? Can J Gastroenterol Hepatol. 2022 Mar 25;2022:8178184. doi: 10.1155/2022/8178184. PMID: 35369117; PMCID: PMC8975703.
10. Lelisho ME, Seid AA, Pandey D. A Case Study on Modeling the Time to Recurrence of Gastric Cancer Patients. J Gastrointest Cancer. 2022 Mar;53(1):218-228. doi: 10.1007/s12029-021-00684-0. Epub 2021 Aug 11. Erratum in: J Gastrointest Cancer. 2022 Mar;53(1):229. doi: 10.1007/s12029-021-00710-1. PMID: 34379265.
11. Saito H, Osaki T, Murakami D, Sakamoto T, Kanaji S, Ohro S, Tatebe S, Tsujitani S, Ikeguchi M. Recurrence in early gastric cancer--presence of micrometastasis in lymph node of node negative early gastric cancer patient with recurrence. Hepatogastroenterology. 2007 Mar;54(74):620-4. PMID: 17523336.