

Clinicopathological Prognostic Factors Determining Outcomes of Treatment in Gastric Cancer Surgery

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Abstract. *Background/Aim: The purpose of this study was to examine the impact of clinicopathological prognostic factors on tumor resectability, perioperative complications, and 5-year survival rates in patients with gastric cancer treated surgically. Patients and Methods: A cohort of 834 patients operated on for gastric cancer between 2007 and 2016 was analyzed. Results: Patients over 70 years of age manifested a significantly higher rate of overall complications, systemic complications, surgical complications, perioperative mortality, and a worse 5-year survival. The diffuse type according to the Lauren classification was an independent prognostic factor for perioperative mortality. TNM stage significantly influenced resectability and 5-year survival rates. Furthermore, the presence of distant metastases (M1 stage) significantly increased the rates of overall complications, systemic complications, and perioperative mortality. Conclusion: Although TNM stage was the most important prognostic factor for resectability, perioperative complications and 5-year survival, other clinicopathological prognostic factors, such as age, and Lauren type also significantly affected treatment outcomes in gastric cancer surgery.*

Worldwide, gastric cancer, despite the decline in morbidity and mortality in recent decades, still remains the fifth most common malignant neoplasm and the fourth cause of cancer-related deaths. In 2020, the annual mortality rate was

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768,793 people globally (1, 2). In Poland, the number of cases and deaths from gastric cancer in 2018 was 5,106 and 4,900, respectively. In Poland, gastric cancer remains an important problem in clinical medicine, mainly due to persistent late diagnosis and the associated unfavorable prognosis, with 5-year survival rates among diagnosed patients being 19% in men and 24% in women (3, 4).

Although early diagnosis is crucial for the improvement of prognosis of patients with gastric cancer and the influence of multimodal therapy is particularly important, tumor resectability, perioperative complications, and 5-year survival rates are the most important parameters of effectiveness of the surgical treatment.

Patients with resectable gastric cancer present much better prognoses, with 5-year survival reaching nearly 40%. Therefore, any analysis of the impact of prognostic factors on surgery in patients with gastric cancer should include resectability as one of the most important treatment outcomes (5-9).

There are many prognostic factors affecting gastric cancer resectability, perioperative complications, and 5-year survival. Some studies, present a different effect of the same prognostic factors (10-18).

In the present study, we present our results and the results of others regarding the influence of clinicopathological prognostic factors on resectability, perioperative complications, and 5-year survival of patients with gastric cancer. In multivariate analysis, we analyzed the effect of prognostic factors such as sex, age, tumor location, Lauren type and TNM stage, in accordance with the eighth edition of the TNM staging system of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) (19).

In our previous study we analyzed the prognostic factors affecting the outcomes of patients with gastric cancer resection (5). In this study, the database was expanded by over one hundred gastric cancer patients in stage M1 according to the TNM classification who underwent unresectable surgical procedures such as gastrojejunostomy, by-pass surgery or explorative laparotomy. This allowed for



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an examination of the influence of clinicopathological prognostic factors on tumor resectability. Moreover, adding such patients significantly changed the influence of some prognostic factors on the outcomes of treatment in comparison with resectable gastric cancer cases.

We reached to other interesting conclusions, which may significantly influence the optimization of treatment outcomes of patients operated for gastric cancer.

Patients and Methods

Patient cohort and potential prognostic factors. A database of 834 gastric adenocarcinoma patients who underwent surgical treatment between 2007 and 2016 at the First Department of General Surgery, Jagiellonian University, Collegium Medicum, in Krakow, Poland was collected.

Their clinicopathological features regarded as potential prognostic factors were sex (male/female), age (≤ 70 years/ >70 years), tumor location (upper/middle/lower), Lauren type (intestinal/diffuse/mixed), and TNM stage (T stage/N stage/M stage) (Table I). The primary site of the neoplasm in the upper, middle, or lower third of the stomach was considered as the tumor location. A histologic evaluation of the tumor was carried out by the Lauren classification (20). The TNM stage of gastric cancer was assessed in accordance with the eighth edition of the TNM staging system of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) (19).

Surgical treatment. The decision whether to remove or not the tumor during surgery was based on the obligatory guidelines of gastric cancer surgery, and it was mainly determined by the general condition of the patient, and the stage of the disease. The procedures that involved resection of the tumor included total/subtotal distal/subtotal proximal gastrectomy. In potentially radical stomach resections, lymphadenectomy D2 or D2+ was performed. For the same reason, in order to obtain potential oncological radicality, in some cases segmental pancreatectomy, spleen and/or bowel resections were additionally carried out. Some patients with many comorbidities and distant metastases (M1) – stage IV according to the TNM classification – or those presenting symptoms of obstruction, jaundice, and malnutrition underwent procedures not involving tumor resection, such as gastrojejunostomy, by-pass surgery, or explorative laparotomy (Table II).

To obtain a more homogeneous group of patients, cases treated laparoscopically or endoscopically were excluded. In this study, all the surgical procedures were performed by conventional laparotomy. Multimodal therapy with different chemotherapeutic regimens including fluorouracil alone, cisplatin and fluorouracil, irinotecan and fluorouracil or etoposide, doxorubicin and cisplatin, was applied in some cases of advanced gastric cancer (stage II or higher according to the TNM classification).

Follow-up. Patients had a routine follow-up every 3-6 months after discharge or in shorter intervals whenever clinically justified. The dates of death were collected using data received from the census registry office. All the crucial parameters determining the outcomes of surgical treatment, including resectability, overall complications, systemic complications, surgical complications, relaparotomy, perioperative mortality, as well 5-year survival of the patients included in this study are shown in Table III.

Table I. Potential prognostic factors.

Clinicopathological features	2007-2016 (n=834) n (%)
Sex	
Male	556 (66.7%)
Female	278 (33.3%)
Age, years	
≤ 70	552 (66.2%)
>70	282 (33.8%)
Location	
Upper	262 (31.4%)
Middle	227 (27.3%)
Lower	167 (20.0%)
Other	178 (21.3%)
Lauren type	
Intestinal	370 (44.4%)
Diffuse	357 (42.8%)
Mixed	107 (12.8%)
T stage (eight edition AJCC/UICC)	
T1a	34 (4.1%)
T1b	42 (5.0%)
T2	133 (15.9%)
T3	188 (22.5%)
T4a	134 (16.1%)
T4b	303 (36.4%)
N stage (eight edition AJCC/UICC)	
N0	113 (13.5%)
N1	116 (13.9%)
N2	140 (16.8%)
N3a	102 (12.2%)
N3b	363 (43.6%)
M stage (eight edition AJCC/UICC)	
M0	445 (53.4%)
M1	389 (46.6%)

For all patients, multivariate analysis of the clinicopathological prognostic factors affecting the treatment outcomes was performed (Table IV, Table V, Table VI, Table VII, Table VIII, Table IX, and Table X).

Statistical methods. In order to establish the relationships between prognostic factors and the results of surgical treatment, a logistic regression model was used, which allowed to generate a model of the relationship of a binary dependent variable and at least one or more predictor (prognostic factors). $p < 0.05$ was considered statistically significant in a two-tailed analysis. The analyses were performed with the statistical package STATISTICA v. 13 (StatSoft Polska, Krakow, Poland) and StatsDirect v. 3.3.4 (StatsDirect Ltd, Wirral, UK).

Results

Potential prognostic factors - clinicopathological features. In this study, the majority of the patients were male: 556 (66.7%) out of 834 patients. The proportion of patients older than 70 years was 33.8%. The upper third part of the stomach (31.4%) was the most common location of the tumor. According to the

Table II. *Type of surgery.*

Surgical procedure	2007-2016 (n=834) n (%)
Resectable	731 (87.7%)
Subtotal distal gastrectomy	145 (17.4%)
Subtotal proximal gastrectomy	45 (5.4%)
Total gastrectomy	541 (64.9%)
Unresectable	103 (12.3%)
Gastro/Jejunostomy	15 (1.8%)
By-pass surgery	32 (3.8%)
Explorative laparotomy	56 (6.7%)

Table III. *Outcomes of treatment.*

Parameter	2007-2016 (n=834) n (%)
Resectability	731 (87.7%)
Overall complications	157 (18.8%)
Systemic complications	96 (11.5%)
Surgical complications	84 (10.1%)
Relaparotomy	35 (4.1%)
Perioperative mortality	29 (3.5%)
5-year survival	289 (34.7%)

Lauren classification, the incidence of intestinal, diffuse, and mixed type gastric cancer was 44.4%, 42.8%, and 12.8%, respectively. The rates of patients with T stage, N stage, M stage according to the eighth edition of TNM (AJCC/UICC) are presented in Table I, and the proportion of patients with distant metastases (M1 stage) was 46.6%.

The outcomes of treatment. Resectability, perioperative complications, and 5-year survival rates are presented in Table III. The proportion of resectable to unresectable cases was 731 (87.7%) to 103 (12.3%), respectively. Generally, the overall incidence of complications was 18.8%, and the percentage of systemic and surgical complications was 11.5% and 10.1%, respectively. The rates of relaparotomy and perioperative mortality were 4.1% and 3.5%, respectively. The 5-year survival rate was 34.7%.

Multivariate analysis. A logistic regression model was used to identify the prognostic factors affecting resectability, overall complications, systemic complications, surgical complications, relaparotomy, perioperative mortality, and 5-year survival (Table IV, Table V, Table VI, Table VII, Table VIII, Table IX, and Table X).

Multivariate analysis showed that patients over 70 years of age had a significantly higher rate of overall complications (OR=2.41, 95%CI=1.63-3.56, $p<0.0001$), systemic

Table IV. *The logistic regression model for resectability.*

Prognostic factors	OR	95%CI	Coefficient	p-Value
(Intercept)	n/a		2.33	0.0001
Sex Male	0.76	(0.50-1.16)	-0.27	0.207
Age >70 years	1.00	(0.65-1.56)	0	0.9872
Location				
Upper	0.78	(0.48-1.27)	-0.24	0.325
Middle	0.71	(0.44-1.13)	-0.34	0.146
Lower	1.08	(0.69-1.69)	0.08	0.7409
Lauren type				
Diffuse	1.35	(0.75-2.42)	0.30	0.3158
Intestinal	0.70	(0.42-1.17)	-0.35	0.1777
Mixed	0.66	(0.42-1.03)	-0.42	0.0691
T stage	2.42	(1.58-3.73)	0.89	0.0001
N stage	1.78	(1.24-2.58)	0.58	0.002
M stage	2.29	(1.41-3.71)	0.83	0.0008

OR: Odds ratio; CI: confidence interval.

Table V. *The logistic regression model for overall complications.*

Prognostic factors	OR	95%CI	Coefficient	p-Value
(Intercept)	n/a		-2.53	0.0001
Sex Male	1.01	(1.00-1.03)	0.01	0.1133
Age >70 years	2.41	(1.63-3.56)	0.88	0.0001
Location				
Upper	0.24	(0.04-1.30)	-1.44	0.0969
Middle	0.90	(0.37-2.20)	-0.11	0.8127
Lower	1.01	(0.39-2.61)	0.01	0.9844
Lauren type				
Diffuse	0.59	(0.24-1.48)	-0.52	0.2617
Intestinal	0.51	(0.20-1.29)	-0.67	0.1552
Mixed	0.27	(0.04-1.90)	-1.32	0.1877
T stage	0.52	(0.07-3.71)	-0.65	0.5157
N stage	0.23	(0.03-1.62)	-1.48	0.1388
M stage	2.03	(1.42-2.91)	0.71	0.0001

OR: Odds ratio; CI: confidence interval.

complications (OR=1.61, 95% CI=1.04-2.50, $p=0.0344$), surgical complications (OR=2.34, 95%CI=1.30-4.21, $p=0.0044$), perioperative mortality (OR=2.48, 95%CI=1.51-4.09, $p=0.00041$), and a worse 5-year survival (OR=1.87, 95%CI=1.05-3.31, $p<0.0326$) (Table V, Table VI, Table VII, Table IX, and Table X).

The diffuse type according to the Lauren classification was characterized as an independent prognostic factor for higher perioperative mortality (OR=1.88, 95%CI=1.12-3.13, $p=0.0162$) (Table IX). The logistic regression model showed that stage T and stage N significantly influenced resectability (OR=2.42, 95%CI=1.58-3.73, $p=0.0001$ – stage T; OR=1.78, 95%CI=1.24-2.58, $p=0.002$ – stage N) and 5-year survival (OR=3.12, 95%CI=1.87-5.21, $p<0.0001$ – stage T; OR=1.97, 95%CI=1.38-2.81, $p<0.0002$ – stage N) (Table IV and Table

Table VI. The logistic regression model for systemic complications.

Prognostic factors	OR	95%CI	Coefficient	p-Value
(Intercept)	n/a		-2.35	0.0001
Sex Male	1.01	(0.99-1.02)	0.01	0.5817
Age >70 years	1.61	(1.04-2.50)	0.47	0.0344
Location				
Upper	0.43	(0.18-1.04)	-0.85	0.0598
Middle	0.63	(0.30-1.34)	-0.46	0.2323
Lower	0.27	(0.05-1.50)	-1.33	0.1326
Lauren type				
Diffuse	0.2	(0.08-0.50)	0.06	0.652
Intestinal	0.16	(0.06-0.41)	0.08	0.325
Mixed	0.2	(0.06-0.70)	0.16	0.121
T stage	1.03	(0.67-1.58)	0.03	0.9042
N stage	0.45	(0.04-5.45)	-0.79	0.5317
M stage	1.97	(1.38-2.81)	0.68	0.0002

OR: Odds ratio; CI: confidence interval.

Table VII. The logistic regression model for surgical complications.

Prognostic factors	OR	95%CI	Coefficient	p-Value
(Intercept)	n/a		-2.75	0.0001
Sex Male	1.02	(0.74-2.01)	0.20	0.4451
Age >70 years	2.34	(1.30-4.21)	0.85	0.0044
Location				
Upper	1.01	(0.37-2.76)	0.01	0.9868
Middle	0.69	(0.34-1.40)	-0.38	0.3005
Lower	1.05	(0.44-2.51)	0.05	0.9048
Lauren type				
Diffuse	1.09	(0.43-2.76)	0.09	0.8573
Intestinal	0.54	(0.22-1.35)	-0.62	0.1887
Mixed	0.39	(0.14-1.07)	-0.94	0.0678
T stage	1.09	(0.95-1.49)	0.18	0.1274
N stage	1.07	(0.92-1.48)	0.15	0.2042
M stage	0.87	(0.46-1.65)	0.13	0.6804

OR: Odds ratio; CI: confidence interval.

X). In multivariate analysis, stage M was an independent prognostic factor of resectability (OR=2.29, 95%CI=1.41-3.71, $p<0.0008$), overall complications (OR=2.03, 95%CI=1.42-2.91, $p<0.0001$), systemic complications (OR=1.97, 95%CI=1.38-2.81, $p=0.0002$), perioperative mortality (OR=2.51, 95%CI=1.23-5.10, $p=0.0111$), and 5-year survival (OR=2.45, 95%CI=1.57-3.84, $p<0.0001$) (Table IV, Table V, Table VI, Table IX and Table X).

Discussion

Sex. Generally, it has been observed that gastric cancer is twice as common in men than in women (2, 21). However, Lou *et al.* reported that the sex difference is not significant below 45

Table VIII. The logistic regression model for relaparotomy.

Prognostic factors	OR	95%CI	Coefficient	p-Value
(Intercept)	n/a		-2.38	0.0082
Sex Male	0.74	(0.29-1.84)	-0.31	0.5127
Age >70 years	0.99	(0.96-1.01)	-0.01	0.2897
Location				
Upper	0.75	(0.26-2.20)	-0.28	0.6033
Middle	0.60	(0.21-1.75)	-0.51	0.3534
Lower	1.11	(0.52-2.36)	0.11	0.781
Lauren type				
Diffuse	0.55	(0.15-2.00)	-0.59	0.3679
Intestinal	0.61	(0.20-1.87)	-0.50	0.3859
Mixed	0.92	(0.40-2.15)	-0.08	0.8514
T stage	0.69	(0.34-1.40)	-0.38	0.3014
N stage	0.93	(0.43-2.02)	-0.07	0.8586
M stage	0.61	(0.09-4.35)	-0.49	0.6235

OR: Odds ratio; CI: confidence interval.

Table IX. The logistic regression model for perioperative mortality.

Prognostic factors	OR	95%CI	Coefficient	p-Value
(Intercept)	n/a		-6.32	0.0001
Sex Male	0.67	(0.24-1.84)	-0.40	0.4342
Age >70 years	2.48	(1.51-4.09)	0.91	0.00041
Location				
Upper	0.46	(0.06-3.26)	-0.78	0.4367
Middle	0.21	(0.03-1.57)	-1.56	0.1283
Lower	0.89	(0.33-2.39)	-0.11	0.8231
Lauren type				
Diffuse	1.88	(1.12-3.13)	0.63	0.0162
Intestinal	0.16	(0.06-0.41)	0.84	0.445
Mixed	0.2	(0.06-0.70)	0.60	0.127
T stage	1.03	(0.67-1.58)	0.03	0.9042
N stage	0.45	(0.04-5.45)	-0.79	0.5317
M stage	2.51	(1.23-5.10)	0.92	0.0111

OR: Odds ratio; CI: confidence interval.

years of age. A greater sex difference was observed in patients of older age and the difference was the largest in the age range of 65-69 years with a male to female ratio of 2.74 (21).

In the resectable and unresectable cases of patients with gastric cancer presented in our studies, sex did not turn out to be a statistically significant prognostic factor affecting resectability, overall complications, systemic complications, surgical complications, relaparotomy, as well perioperative mortality and 5-year survival (5). These conclusions are similar to those reported by Tan *et al.* and Ashieri *et al.*, where sex was not considered to be an independent prognostic factor of survival (9, 12).

As opposed to this conclusion, in the study performed by Li *et al.*, factors such as being a white female or Asian male

Table X. The logistic regression model for 5-year survival.

Prognostic factors	OR	95%CI	Coefficient	p-Value
(Intercept)	n/a		-2.35	0.0001
Sex Male	1.01	(0.99-1.02)	0.01	0.5817
Age >70 years	1.87	(1.05-3.31)	0.62	0.0326
Location				
Upper	0.83	(0.55-1.25)	-0.19	0.3623
Middle	0.94	(0.28-3.13)	-0.06	0.9189
Lower	0.91	(0.30-2.77)	-0.09	0.8685
Lauren type				
Diffuse	0.69	(0.42-1.15)	-0.37	0.155
Intestinal	0.16	(0.06-0.41)	0.08	0.325
Mixed	0.2	(0.06-0.70)	0.16	0.121
T stage	3.12	(1.87-5.21)	1.14	0.0001
N stage	1.97	(1.38-2.81)	0.68	0.0002
M stage	2.45	(1.57-3.84)	0.90	0.0001

OR: Odds ratio; CI: confidence interval.

were observed to be independent prognostic factors of better survival in gastric cancer, without sex-related survival in the black race (11). The study of Park *et al.* revealed that male sex was a risk factor of a poor 5-year survival for patients with resectable stage I gastric cancer according to the TNM classification (22). De Marco *et al.* analyzed a large database of patients with gastric cancer (28,366 cases), and even though sex was not a significant prognostic factor of curative resection (OR=1.15, 95%CI=0.97-1.36, $p=0.10$), women had a greater chance of long-term survival compared to men (OR=1.62, 95% CI=1.33-1.97, $p<0.001$) (23).

Age. Our last study, which was concentrated on resectable cases of gastric cancer, allowed to observe that even an age >70 years was not an independent prognostic factor affecting overall complications, systemic complications, surgical complications, relaparotomy, perioperative mortality, as well 5-year survival for patients (5). In another report from our group, no differences in complications and perioperative mortality rates were observed, except for a higher incidence of cardiopulmonary complications in older patients undergoing gastric cancer resection (6.6% vs. 12.3%); the median survival of patients was not significantly longer in younger (30.8 months) than older (24.1 months) ($p=0.056$) (11). However, this analysis compared the younger (≤ 40 years) and older (>40 years) population of patients with gastric cancer, therefore the age threshold affecting the outcomes of treatment was significantly low (24).

De Marco *et al.* reported that age did not have any significant influence on curative resections and long-term survival in patients with gastric cancer (23). In contrast to these conclusions, Park *et al.* and Yu *et al.* showed that older age was a prognostic factor for worse 5-year survival even

for patients after gastric cancer resection with stage I according to the TNM classification (22, 25). Hsu *et al.* performed a retrospective review of the cohort of patients with gastric cancer who underwent curative resection and found that older age was associated with a higher overall perioperative complications rate ($p=0.035$) and perioperative mortality rate ($p=0.015$). The overall survival rate of the older group was lower than that of the younger group ($p<0.001$). Nevertheless, the cumulative incidence of deaths related to gastric cancer was comparable in the two groups (26).

Nakamura *et al.* suggested that younger age is a prognostic factor of a better prognosis for early gastric cancer, in contrast to advanced gastric cancer, in which younger patients are predisposed to develop a more advanced stage of TNM and have a poorer survival (27). Saito *et al.* reported that elderly patients usually undergo fewer radical resections such as extended lymph node excision or multi-organ resections and show a poorer prognosis (28). Ueno *et al.* recommend that in elderly patients with gastric cancer, limited surgery instead of extensive surgery should be considered, depending on the patient's general condition and co-morbidities, because postoperative complications are an important prognostic factor for survival in these patients (29).

Oya *et al.* analyzed the prognostic factors affecting mortality, complications, and survival in gastric cancer patients of 80 years of age and older. The differences in survival between the two groups (non-surgery group *versus* surgery group) were significantly better for the surgery group in stage I ($p=0.025$) and stage II/III ($p<0.001$) according to the TNM classification. The survival difference was not statistically significant between the surgery group and the non-surgery group, in stage IV ($p=0.05$). Oya *et al.* concluded that older age is not a contraindication for resection of gastric cancer. However, in elderly patients, before any surgery, comorbidities, the degree of tumor spread, and the expected quality of life must be considered (30).

In the present study, when we included the cases of resectable and unresectable gastric cancer, age >70 became an independent prognostic factor which affected overall complications ($p<0.0001$), systemic complications ($p=0.0344$), surgical complications ($p=0.0044$), perioperative mortality ($p=0.00041$), and 5-year survival ($p<0.0326$). The conclusion of our studies regarding the influence of age on the outcomes of treatment of patients with gastric cancer is similar to the reports from Oya *et al.* In elderly gastric cancer patients with stage IV according to the TNM classification – presence of distant metastasis (M1) – not all cases are candidate to operation. In elderly gastric cancer patients, surgical treatment should be performed if it is a curative resection and the patient is in relatively good health. The other indication is gastrojejunostomy, with by-pass surgery used as an emergency procedure, performed in the presence of obstruction, jaundice or malnutrition (5, 18, 24).

Tumor location. Tumor location depends on geographical sphere and race; for example, in some reports from Asia, gastric cancer is still mainly situated in the lower or middle third part of the stomach (9, 31). Nevertheless, worldwide, mainly due to an inappropriate diet, or obesity and reflux disease, in patients with gastric cancer the incidence of tumors situated in the upper third of the stomach has increased within the last decades (8, 14, 17, 32, 33). In line with general world trends, in our database including only resectable cases (31.9%), the dominant tumor location was the upper third of the stomach, as in the case of all surgically treated patients with gastric cancer (31.4%) (5).

According to some studies in patients with gastric cancer, tumor location is not an independent prognostic factor significantly affecting survival (9, 23, 34-37). ZeLong *et al.* reported that tumor location within the stomach does not affect the lymph node metastases and overall survival for resectable gastric cancer (36). De Marco *et al.* concluded that a location in the upper third of the stomach did not have any statistical significance for curative resection (OR=1.41, 95%CI=0.93-2.14, $p=0.10$) (23).

Contrary to the above findings, most of the reports, including a large meta-analysis by Petrelli *et al.* involving 50 studies and 128,268 patients with gastric cancer, showed that a location in the upper third part of the stomach was connected with an increased risk of tumor-related death and poorer 5-year survival rate (15, 33, 38-40).

In our last study, patients that underwent gastric cancer resection manifested better 5-year survival rates, when the tumor was located in the middle third part of the stomach (OR=1.57, 95%CI=0.73-3.37, $p=0.0239$). However, the location was not a prognostic factor that influenced overall complications, systemic and surgical complications, relaparotomy, as well perioperative mortality (5). In the present study, comprising resectable and unresectable gastric cancer patients, a location in the middle third part of the stomach was not an independent prognostic factor significantly affecting the 5-year survival rates ($p=0.9189$). In conclusion, in stage IV disease according to the TNM classification, the location of the tumor in the stomach becomes less relevant for patients operated for gastric cancer.

Lauren types and tumor staging. In our last study, including resectable gastric cancer patients, the Lauren type was not an independent prognostic factor affecting short-term and long-term outcomes of treatment (5). In some studies, similar conclusions can be found, especially after curative gastric cancer resection (9, 41-43). Nevertheless, most reports have shown that patients with intestinal type gastric cancer present significantly better survival rates than those with diffuse type and mixed type (44-47). In the present study, the addition of more than a hundred unresectable gastric cancer cases to the analyzed database, revealed that the diffuse Lauren type was

characterized by a statistically significant higher perioperative mortality rate as compared to the intestinal type and mixed type ($p=0.0162$).

Fonseca *et al.* showed that the diffuse type of advanced gastric cancer was characterized by a higher mortality (OR=1.201, 95%CI=1.054-1.368, $p=0.0056$) and patients with the intestinal type receiving chemotherapy manifested a higher overall survival (OR=0.65, 95%CI=0.49-0.87, $p=0.024$) (46). Tang *et al.* reviewed over 20,000 patients with gastric cancer and concluded that the diffuse type had an overall poorer prognosis as compared to the intestinal type. However, in the patients with stage T1 according to the TNM classification, the diffuse type had a comparable survival rate to the intestinal type (48).

Generally, the diagnostics and treatment of early tumor stages according to TNM classification plays a crucial role in the survival of patients with gastric cancer (7, 9, 12, 30, 34, 35, 40, 49).

What is interesting here, is that in our previous observations, we concluded that in resectable gastric cancer patients, the TNM stage was not an independent prognostic factor influencing overall complications, systemic complications, surgical complications, and relaparotomy (5). Therefore, even for patients with stage IV gastric cancer, resection could be a relatively safe surgical procedure (5, 18).

In the present study, relevantly more gastric cancer cases manifested stage IV disease due to the addition of cases with unresectable surgical procedures, therefore the patients' general prognosis was significantly poorer. As opposed to only resectable gastric cancer cases, in the present study, stage M1 according the TNM classification, was an independent prognostic factor affecting overall complications ($p<0.0001$), systemic complications ($p=0.0002$), and also perioperative mortality ($p=0.0111$). The tumor staging according to the TNM classification in all patients operated for gastric cancer, significantly affected resectability and 5-year-survival rates.

Study limitations. This study has some limitations. First, it has a retrospective, single-center character. Second, only basic clinicopathological features (sex, age, tumor location, Lauren type, and TNM stage) were used to analyze the prognostic factors determining the outcome of treatments, whereas other parameters such as comorbidities, BMI, ASA physical status, lymph node dissection or splenectomy were not included. Thus, the number of prognostic factors used to determine the outcomes of treatment in gastric cancer patients is limited.

Summary. In comparison with a previous study that included patients with gastric cancer resection exclusively, the present analysis also included unresectable cases (5). The present group of patients manifested more advanced stages according to the

TNM classification – more stages of M1. This resulted in quite a significant change in the influence of clinicopathological prognostic factors on the outcomes of treatment.

In gastric cancer patients over 70 years of age, surgery is related with higher rates of overall complications ($p < 0.0001$), systemic complications ($p = 0.0344$), surgical complications ($p = 0.0044$), perioperative mortality ($p = 0.00041$), and a lower 5-year survival rate ($p < 0.0326$) compared the younger group (≤ 70 years). Therefore, in elder patients with gastric cancer, surgical treatment is recommended only when curative resection is possible and the patient is in relatively good health, or in the case where the tumor is unresectable and there is a need for emergency intervention necessitated by symptoms such as obstruction, jaundice, or malnutrition (5, 18, 24).

The inclusion of the unresectable cases resulted in the fact that the presence of the diffuse type according to the Lauren classification significantly increased the proportion of perioperative mortality ($p = 0.0162$), whereas a location in the middle part of the stomach ceased to be an independent factor for a higher 5-year survival rate ($p = 0.9189$) as was in the case of patients with resectable gastric cancer (5).

Moreover, extending the patient database by including unresectable gastric cancer cases allowed for an examination of the influence of prognostic factors on tumor resectability. In fact, as with 5-year survival, T stage ($p = 0.0001$), N stage ($p = 0.0002$), M stage ($p = 0.0008$) according to the TNM classification had a statistically significant influence on resectability.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Piotr Kulig - concept of the study, collection and analysis of patients database, statistical analysis, database results analysis, reviewed articles for the discussion, writing the manuscript. Radosław Pach - collection and analysis of patients database, database results analysis, critical review. Oliwia Majewska - collection and analysis of patients database, statistical analysis, database results analysis, reviewed articles for the discussion. Jan Kulig - concept of the study, and critical review.

References

- 1 Global Cancer Observatory, Stomach Globocan 2020: International Agency for Research on Cancer, World Health Organization. Available at: <https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf> [Last accessed on Sept 30, 2022]
- 2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68(6): 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492
- 3 Wojciechowska U, Czaderny K, Ciuba A, Olasek P and Didkowska J: Krajowy Rejestr Nowotworów, Warszawa 2018: 24-75. Available at: http://onkologia.org.pl/wp-content/uploads/Nowotwory_2016.pdf [Last accessed on September 30, 2022]
- 4 Wojciechowska U, Didkowska J, Michałek I, Olasek P and Ciuba A: Nowotwory złośliwe w Polsce w 2018 roku. Krajowy Rejestr Nowotworów, Warszawa 2020: 72-73. Available at: http://onkologia.org.pl/wp-content/uploads/Nowotwory_2018.pdf [Last accessed on September 30, 2022]
- 5 Kulig P, Nowakowski P, Sierżęga M, Pach R, Majewska O, Markiewicz A, Kołodziejczyk P, Kulig J and Richter P: Analysis of prognostic factors affecting short-term and long-term outcomes of gastric cancer resection. *Anticancer Res* 41(7): 3523-3534, 2021. PMID: 34230148. DOI: 10.21873/anticancer.15140
- 6 Herbreteau E, Jooste V, Hamza S, Lepage C, Faivre J and Bouvier AM: Trends in the management of gastric cancer over a 32-year period: a French population-based study. *Gastric Cancer* 18(1): 129-137, 2015. PMID: 24488016. DOI: 10.1007/s10120-014-0342-6
- 7 Kim JH, Chin HM and Jun KH: Surgical outcomes and survival after gastrectomy in octogenarians with gastric cancer. *J Surg Res* 198(1): 80-86, 2015. PMID: 26095423. DOI: 10.1016/j.jss.2015.05.046
- 8 Kulig P, Sierżęga M, Pach R, Kołodziejczyk P, Kulig J and Polish Gastric Cancer Study Group: Differences in prognosis of Siewert II and III oesophagogastric junction cancers are determined by the baseline tumour staging but not its anatomical location. *Eur J Surg Oncol* 42(8): 1215-1221, 2016. PMID: 27241921. DOI: 10.1016/j.ejso.2016.04.061
- 9 Tan YE, Wang PL, Yin SC, Zhang C, Hou WB and Xu HM: Thirty-year trends in clinicopathologic characteristics and prognosis after gastrectomy for gastric cancer: A single institution in Northern China. *J Cancer* 11(5): 1056-1062, 2020. PMID: 31956352. DOI: 10.7150/jca.36927
- 10 Milano AF: 20-year comparative survival and mortality of cancer of the stomach by age, sex, race, stage, grade, cohort entry time-period, disease duration & selected ICD-O-3 oncologic phenotypes: a systematic review of 157,258 cases for diagnosis years 1973-2014: (SEER*Stat 8.3.4). *J Insur Med* 48(1): 5-23, 2019. PMID: 31609640. DOI: 10.17849/inms-48-1-1-19.1
- 11 Li H, Wang C, Wei Z, Chen W, Guo Z, He Y and Zhang C: Differences in the prognosis of gastric cancer patients of different sexes and races and the molecular mechanisms involved. *Int J Oncol* 55(5): 1049-1068, 2019. PMID: 31793655. DOI: 10.3892/ijo.2019.4885
- 12 Alshehri A, Alanezi H and Kim BS: Prognosis factors of advanced gastric cancer according to sex and age. *World J Clin Cases* 8(9): 1608-1619, 2020. PMID: 32432139. DOI: 10.12998/wjcc.v8.i9.1608
- 13 Shibata C, Ogawa H, Nakano T, Koyama K, Yamamoto K, Nagao M, Takeyama D, Takami K, Yasumoto A, Sase T, Kimura SI, Sawada K and Katayose Y: Influence of age on postoperative complications especially pneumonia after gastrectomy for gastric cancer. *BMC Surg* 19(1): 106, 2019. PMID: 31395044. DOI: 10.1186/s12893-019-0573-x
- 14 Honda M, Wong SL, Healy MA, Nakajima T, Watanabe M, Fukuma S, Fukuhara S and Ayanian JZ: Long-term trends in primary sites of gastric adenocarcinoma in Japan and the United

- States. *J Cancer* 8(11): 1935-1942, 2017. PMID: 28819392. DOI: 10.7150/jca.19174
- 15 Petrelli F, Ghidini M, Barni S, Steccanella F, Sgroi G, Passalacqua R and Tomasello G: Prognostic role of primary tumor location in non-metastatic gastric cancer: a systematic review and meta-analysis of 50 studies. *Ann Surg Oncol* 24(9): 2655-2668, 2017. PMID: 28299508. DOI: 10.1245/s10434-017-5832-4
 - 16 Qiu MZ, Cai MY, Zhang DS, Wang ZQ, Wang DS, Li YH and Xu RH: Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med* 11: 58, 2013. PMID: 23497313. DOI: 10.1186/1479-5876-11-58
 - 17 Anderson WF, Camargo MC, Fraumeni JF Jr, Correa P, Rosenberg PS and Rabkin CS: Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA* 303(17): 1723-1728, 2010. PMID: 20442388. DOI: 10.1001/jama.2010.496
 - 18 Kulig P, Sierzega M, Kowalczyk T, Kolodziejczyk P and Kulig J: Non-curative gastrectomy for metastatic gastric cancer: rationale and long-term outcome in multicenter settings. *Eur J Surg Oncol* 38(6): 490-496, 2012. PMID: 22381671. DOI: 10.1016/j.ejso.2012.01.013
 - 19 Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR and Winchester DP: The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 67(2): 93-99, 2017. PMID: 28094848. DOI: 10.3322/caac.21388
 - 20 Lauren P: The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 64: 31-49, 1965. PMID: 14320675. DOI: 10.1111/apm.1965.64.1.31
 - 21 Lou L, Wang L, Zhang Y, Chen G, Lin L, Jin X, Huang Y and Chen J: Sex difference in incidence of gastric cancer: an international comparative study based on the Global Burden of Disease Study 2017. *BMJ Open* 10(1): e033323, 2020. PMID: 31988231. DOI: 10.1136/bmjopen-2019-033323
 - 22 Park JH, Ryu MH, Kim HJ, Ryoo BY, Yoo C, Park I, Park YS, Oh ST, Yook JH, Kim BS and Kang YK: Risk factors for selection of patients at high risk of recurrence or death after complete surgical resection in stage I gastric cancer. *Gastric Cancer* 19(1): 226-233, 2016. PMID: 25614467. DOI: 10.1007/s10120-015-0464-5
 - 23 De Marco MO, Tustum F, Brunaldi VO, Resende RH, Matsubayashi CO, Baba ER, Chaves DM, Bernardo WM and de Moura EGH: Prognostic factors for ESD of early gastric cancers: a systematic review and meta-analysis. *Endosc Int Open* 8(9): E1144-E1155, 2020. PMID: 32904802. DOI: 10.1055/a-1201-3089
 - 24 Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Jedrys J, Szczepanik AM and Polish Gastric Cancer Study Group: Clinicopathological profile and long-term outcome in young adults with gastric cancer: multicenter evaluation of 214 patients. *Langenbecks Arch Surg* 393(1): 37-43, 2008. PMID: 17618451. DOI: 10.1007/s00423-007-0208-z
 - 25 Yu B, Park JY, Park KB, Kwon OK, Lee SS and Chung HY: Prognostic factors in stage IB gastric cancer after surgical resection. *J Gastric Cancer* 20(3): 328-336, 2020. PMID: 33024588. DOI: 10.5230/jgc.2020.20.e30
 - 26 Hsu JT, Liu MS, Wang F, Chang CJ, Hwang TL, Jan YY and Yeh TS: Standard radical gastrectomy in octogenarians and nonagenarians with gastric cancer: are short-term surgical results and long-term survival substantial? *J Gastrointest Surg* 16(4): 728-737, 2012. PMID: 22350724. DOI: 10.1007/s11605-012-1835-4
 - 27 Nakamura T, Yao T, Niho Y and Tsuneyoshi M: A clinicopathological study in young patients with gastric carcinoma. *J Surg Oncol* 71(4): 214-219, 1999. PMID: 10440758. DOI: 10.1002/(sici)1096-9098(199908)71:4<214::aid-jso2>3.0.co;2-d
 - 28 Saito H, Osaki T, Murakami D, Sakamoto T, Kanaji S, Tatebe S, Tsujitani S and Ikeguchi M: Effect of age on prognosis in patients with gastric cancer. *ANZ J Surg* 76(6): 458-461, 2006. PMID: 16768768. DOI: 10.1111/j.1445-2197.2006.03756.x
 - 29 Ueno D, Matsumoto H, Kubota H, Higashida M, Akiyama T, Shiotani A and Hirai T: Prognostic factors for gastrectomy in elderly patients with gastric cancer. *World J Surg Oncol* 15(1): 59, 2017. PMID: 28284210. DOI: 10.1186/s12957-017-1131-6
 - 30 Oya H, Komatsu Y, Shimizu D, Koike S, Tagami K and Kodera Y: Curative surgery for gastric cancer of the elderly in a Japanese regional hospital. *Hepatogastroenterology* 60(127): 1673-1680, 2013. PMID: 24624449.
 - 31 Eom BW, Jung KW, Won YJ, Yang H and Kim YW: Trends in gastric cancer incidence according to the clinicopathological characteristics in Korea, 1999-2014. *Cancer Res Treat* 50(4): 1343-1350, 2018. PMID: 29361823. DOI: 10.4143/crt.2017.464
 - 32 Asplund J, Kauppila JH, Mattsson F and Lagergren J: Survival trends in gastric adenocarcinoma: a population-based study in Sweden. *Ann Surg Oncol* 25(9): 2693-2702, 2018. PMID: 29987609. DOI: 10.1245/s10434-018-6627-y
 - 33 Abdi E, Latifi-Navid S, Zahri S, Yazdanbod A and Pourfarzi F: Risk factors predisposing to cardia gastric adenocarcinoma: Insights and new perspectives. *Cancer Med* 8(13): 6114-6126, 2019. PMID: 31448582. DOI: 10.1002/cam4.2497
 - 34 Zhao L, Huang H, Zhao D, Wang C, Tian Y, Yuan X, Ma F, Ren H, Zhao Y, Aimaiti S, Zhang S, Zhou H, Wang T, Wang N, Sun Y, Bai X and Chen Y: Clinicopathological characteristics and prognosis of proximal and distal gastric cancer during 1997-2017 in China National Cancer Center. *J Oncol* 2019: 9784039, 2019. PMID: 31312217. DOI: 10.1155/2019/9784039
 - 35 Lee J, Hong Y, Choi Y, Lim H and Lee S: Prognosis of proximal upper-third gastric cancer excluding tumors originating in the esophagogastric junction. *Korean Journal of Clinical Oncology* 15(2): 93-99, 2020. DOI: 10.14216/kjco.19017
 - 36 ZeLong Y, ZhenYu C, JianHai L, MingHua Z, KeCheng Z and ChunXi W: Influence of tumor location on lymph node metastasis and survival for early gastric cancer: a population-based study. *J Gastrointest Surg* 24(9): 1978-1986, 2020. PMID: 31463650. DOI: 10.1007/s11605-019-04367-x
 - 37 Pai SM, Huang KH, Chen MH, Fang WL, Chao Y, Lo SS, Li AF, Wu CW and Shyr YM: Cardia gastric cancer is associated with increased PIK3CA amplifications and HER2 expression than noncardia gastric cancer according to lauren classification. *Front Oncol* 11: 632609, 2021. PMID: 34168977. DOI: 10.3389/fonc.2021.632609
 - 38 Matsuda T, Ohashi M, Tsujiura M, Ida S, Kumagai K, Nunobe S, Sano T and Hiki N: Shorter survival of patients with upper-third gastric cancer preoperatively diagnosed as stage IA compared with those with middle to lower lesions. *Ann Surg Oncol* 27(1): 276-283, 2020. PMID: 31502022. DOI: 10.1245/s10434-019-07782-1
 - 39 Yu X, Hu F, Li C, Yao Q, Zhang H and Xue Y: Clinicopathologic characteristics and prognosis of proximal and distal gastric cancer.

- Onco Targets Ther *11*: 1037-1044, 2018. PMID: 29520154. DOI: 10.2147/OTT.S157378
- 40 Haist T, Pritzer H, Pauthner M, Fisseler-Eckhoff A and Lorenz D: Prognostic risk factors of early gastric cancer—a western experience. *Langenbecks Arch Surg* *401*(5): 667-676, 2016. PMID: 27074726. DOI: 10.1007/s00423-016-1395-2
- 41 An JY, Baik YH, Choi MG, Noh JH, Sohn TS, Bae JM and Kim S: The prognosis of gastric cardia cancer after R0 resection. *Am J Surg* *199*(6): 725-729, 2010. PMID: 19837398. DOI: 10.1016/j.amjsurg.2009.04.012
- 42 Bilici A, Seker M, Ustaalioglu BB, Kefeli U, Yildirim E, Yavuzer D, Aydin FM, Salepci T, Oncel M and Gumus M: Prognostic significance of perineural invasion in patients with gastric cancer who underwent curative resection. *Ann Surg Oncol* *17*(8): 2037-2044, 2010. PMID: 20333555. DOI: 10.1245/s10434-010-1027-y
- 43 Atmaca A, Werner D, Pauligk C, Steinmetz K, Wirtz R, Altmannsberger HM, Jäger E and Al-Batran SE: The prognostic impact of epidermal growth factor receptor in patients with metastatic gastric cancer. *BMC Cancer* *12*: 524, 2012. PMID: 23153332. DOI: 10.1186/1471-2407-12-524
- 44 Shimoda Y, Fujikawa H, Komori K, Watanabe H, Kano K, Yamada T, Shiozawa M, Morinaga S, Katsumata K, Tsuchida A, Ogata T and Oshima T: Prognostic factors for gastric cancer patients with one stage IV factor who underwent conversion surgery. *Anticancer Res* *41*(2): 1005-1012, 2021. PMID: 33517308. DOI: 10.21873/anticancer.14855
- 45 Qiu M, Zhou Y, Zhang X, Wang Z, Wang F, Shao J, Lu J, Jin Y, Wei X, Zhang D, Wang F, Li Y, Yang D and Xu R: Lauren classification combined with HER2 status is a better prognostic factor in Chinese gastric cancer patients. *BMC Cancer* *14*: 823, 2014. PMID: 25380654. DOI: 10.1186/1471-2407-14-823
- 46 Jiménez Fonseca P, Carmona-Bayonas A, Hernández R, Custodio A, Cano JM, Lacalle A, Echavarría I, Macías I, Mangas M, Visa L, Buxo E, Álvarez Manceño F, Viudez A, Pericay C, Azkarate A, Ramchandani A, López C, Martínez de Castro E, Fernández Montes A, Longo F, Sánchez Bayona R, Limón ML, Diaz-Serrano A, Martín Carnicero A, Arias D, Cerdà P, Rivera F, Vieitez JM, Sánchez Cánovas M, Garrido M and Gallego J: Lauren subtypes of advanced gastric cancer influence survival and response to chemotherapy: real-world data from the AGAMENON National Cancer Registry. *Br J Cancer* *117*(6): 775-782, 2017. PMID: 28765618. DOI: 10.1038/bjc.2017.245
- 47 Chen YC, Fang WL, Wang RF, Liu CA, Yang MH, Lo SS, Wu CW, Li AF, Shyr YM and Huang KH: Clinicopathological variation of Lauren classification in gastric cancer. *Pathol Oncol Res* *22*(1): 197-202, 2016. PMID: 26502923. DOI: 10.1007/s12253-015-9996-6
- 48 Tang D, Ni M, Zhu H, Cao J, Zhou L, Shen S, Peng C, Lv Y, Xu G, Wang L and Zou X: Differential prognostic implications of gastric adenocarcinoma based on Lauren's classification: a Surveillance, Epidemiology, and End Results (SEER)-based cohort study. *Ann Transl Med* *9*(8): 646, 2021. PMID: 33987344. DOI: 10.21037/atm-20-7953
- 49 Yaprak G, Tataroglu D, Dogan B and Pekiurek M: Prognostic factors for survival in patients with gastric cancer: Single-centre experience. *North Clin Istanbul* *7*(2): 146-152, 2019. PMID: 32259036. DOI: 10.14744/nci.2019.73549

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