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PATTERNS OF DEVELOPMENT OF PATHOMORPHOLOGICAL TUMOR REGRESS AFTER NEOADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER: EXPERIENCE OF THE NATIONAL RESEARCH ONCOLOGY CENTER

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Abstract

Background: Gastric cancer remains one of the leading causes of cancer-related mortality worldwide. Perioperative neoadjuvant polychemotherapy (NAPCT) using the FLOT regimen has improved long-term outcomes; however, the prognostic value of pathological tumor regression grade (TRG) and its association with clinicopathological factors is not yet fully elucidated.

Objective: To evaluate the association between tumor regression grade (TRG) assessed by the Mandard system, clinicopathological characteristics, and overall (OS) and relapse-free survival (RFS) in patients with locally advanced gastric cancer treated with NAPCT using the FLOT regimen.

Materials and methods: A single-center retrospective cohort study was conducted, including 74 patients with stage II–III gastric adenocarcinoma treated with perioperative FLOT chemotherapy followed by surgery between 2020 and 2024. TRG was evaluated using the Mandard classification. Correlations were calculated using Spearman's coefficient. Survival was analyzed by Kaplan–Meier method with log-rank test and univariate Cox regression. Statistical significance was set at $p<0.05$.

Results: TRG was assessed in 70 resection specimens: TRG1 — 9 (12.9%), TRG2 — 2 (2.9%), TRG3 — 23 (32.9%), TRG4 — 10 (14.3%), TRG5 — 26 (37.1%). A clinically significant response (TRG1–2) was observed in 16% of patients. TRG showed significant correlation with ypT ($\rho=0.51$; $p<0.001$), ypN ($\rho=0.36$; $p=0.0037$), and the number of metastatic lymph nodes ($\rho=0.36$; $p=0.0025$). The presence of signet ring cells was associated with higher tumor grade ($\rho=0.308$; $p=0.008$) and ypT ($\rho=0.324$; $p=0.007$), but not with TRG. In univariate analysis, OS was significantly associated with ypN ($\rho=–0.24$; $p=0.048$) and the number of metastatic lymph nodes ($\rho=–0.28$; $p=0.021$). Median OS and RFS were not reached. Kaplan–Meier analysis demonstrated significantly better OS and RFS in responders (TRG1–2) compared to non-responders (log-rank $\chi^2=7.9$; $p=0.005$ and $\chi^2=10.86$; $p=0.001$, respectively).

Conclusions: A strong pathological response after FLOT-based NAPCT is associated with improved survival; however, residual lymph node metastasis (ypN and number of involved nodes) remains the dominant prognostic factor. TRG should be interpreted in the context of nodal status. Further prospective multicenter studies with standardized pathological assessment are warranted to validate the independent prognostic role of TRG.

Keywords: *tumor regression grade, gastric cancer, neoadjuvant chemotherapy.*

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Резюме

ЗАКОНОМЕРНОСТИ РАЗВИТИЯ ПАТОМОРФОЛОГИЧЕСКОГО РЕГРЕССА ОПУХОЛИ ПОСЛЕ ПРОВЕДЕНИЯ НЕОАДЪЮВАНТНОЙ ХИМИОТЕРАПИИ ПРИ РАКЕ ЖЕЛУДКА: ОПЫТ НАЦИОНАЛЬНОГО НАУЧНОГО ОНКОЛОГИЧЕСКОГО ЦЕНТРА

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Введение. Рак желудка остаётся одной из ведущих причин онкологической смертности в мире. Периоперационная неоадъювантная полихимиотерапия (НАПХТ) по схеме FLOT улучшает отдалённые результаты лечения, однако прогностическая значимость степени патоморфологического регресса опухоли (tumor regression grade, TRG) и её связь с клинико-патологическими характеристиками остаются недостаточно изученными.

Цель исследования. Оценить взаимосвязь степени патоморфологического регресса по системе Mandard с клинико-патологическими параметрами, а также с показателями общей (ОВ) и безрецидивной выживаемости (БРВ) у пациентов с местнораспространённым раком желудка, получивших НАПХТ по схеме FLOT.

Материалы и методы. Проведено одноцентровое ретроспективное когортное исследование, включающее 74 пациента с аденокарциномой желудка II–III стадии, получивших лечение по схеме FLOT и последующую хирургическую резекцию (2020–2024 гг.). Степень регресса оценивали по системе Mandard. Корреляции рассчитывали с использованием коэффициента Спирмена. Выживаемость оценивали методом Каплана–Майера с применением лог-рангового теста и однофакторного анализа регрессии Кокса. Статистическая значимость принималась при $p<0,05$.

Результаты. TRG оценён у 70 пациентов: TRG1 — 9 (12,9%), TRG2 — 2 (2,9%), TRG3 — 23 (32,9%), TRG4 — 10 (14,3%), TRG5 — 26 (37,1%). Клинически значимый регресс (TRG1–2) наблюдался у 16% пациентов. Степень регресса достоверно коррелировала с остаточной стадией (ypT; $\rho=0,51$; $p<0,001$), статусом лимфоузлов (ypN; $\rho=0,36$; $p=0,0037$) и числом метастатически поражённых лимфоузлов ($\rho=0,36$; $p=0,0025$). Наличие перстневидноклеточного компонента ассоциировалось с более высоким грейдом опухоли ($\rho=0,308$; $p=0,008$) и большей стадией (ypT; $\rho=0,324$; $p=0,007$), однако не влияло на TRG. В однофакторном анализе на ОВ статистически значимо влияли ypN ($\rho=–0,24$; $p=0,048$) и число поражённых лимфоузлов ($\rho=–0,28$; $p=0,021$). Медианы ОВ и БРВ не были достигнуты. По данным анализа Каплана–Майера, пациенты с выраженным ответом (TRG1–2) имели лучшую ОВ и БРВ (лог-ранг $\chi^2=7,9$; $p=0,005$ и $\chi^2=10,86$; $p=0,001$ соответственно).

Выводы. Выраженный патоморфологический ответ после НАПХТ по схеме FLOT ассоциирован с улучшением выживаемости, однако ключевым прогностическим фактором остаётся остаточное лимфогенное метастазирование (ypN и число поражённых лимфоузлов). Оценку TRG целесообразно проводить в контексте узлового статуса. Для верификации независимой прогностической роли TRG необходимы проспективные многоцентровые исследования с унифицированным морфологическим подходом.

Ключевые слова: *патоморфологический регресс опухоли, рак желудка, неоадъювантная химиотерапия.*

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Түйіндеме

АСҚАЗАН ЫРЫҒЫНА НЕОАДЮВАНТТЫ ХИМИТЕРАПИЯДАН КЕЙІН ПАТОМОРФОЛОГИЯЛЫҚ ІСІКТЕРДІҢ РЕГРЕССІНІҢ ДАМУ ПЕРЕКШІЛЕРІ: ҰЛТТЫҚ ЗЕРТТЕУ ОНКОЛОГИЯ ОРТАЛЫҒЫНЫҢ ТӘЖІРИБЕСІ

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Кіріспе: Асқазан қатерлі ісігі дүниежүзі бойынша онкологиялық өлім-жітімнің негізгі себептерінің бірі болып саналады. FLOT сызбасы бойынша жүргізілетін периоперациялық неоадъювантты полихимиотерапия (НАХТ) ұзақ мерзімді нәтижелерді жақсартатыны дәлелденгенімен, ісіктің патоморфологиялық регрессия дәрежесінің (tumor regression grade, TRG) болжау маңыздылығы мен оның клиникалық-патологиялық көрсеткіштермен байланысы әлі толық зерттелмеген.

Зерттеу мақсаты: FLOT сызбасы бойынша НАХТ алған, жергілікті таралған асқазан аденокарциномасы бар науқастарда Mandard жүйесімен бағаланған TRG мен клиникалық-патологиялық сипаттамалардың, жалпы өмір сүру ұзақтығы (ӨСҰ) мен рецидивсіз өмір сүру ұзақтығының (РӨСҰ) арасындағы байланысты зерттеу.

Материалдар мен әдістер: 2020–2024 жылдар аралығында FLOT схемасы бойынша НАХТ және хирургиялық ем алған II–III кезеңдегі асқазан аденокарциномасы бар 74 науқастың қатысуымен бір орталықта ретроспективті когорттық зерттеу жүргізілді және TRG Mandard жүйесі бойынша бағаланды. Корреляциялық талдау Спирмен коэффициентімен, ал өмір сүру көрсеткіштері Каплан–Майер әдісі мен log-rank тестімен және бірфакторлы Кокс регрессиясымен есептелді. Статистикалық маңыздылық деңгейі – p<0,05.

Нәтижелер: TRG 70 резекцияланған препаратта анықталды: TRG1 — 9 (12,9%), TRG2 — 2 (2,9%), TRG3 — 23 (32,9%), TRG4 — 10 (14,3%), TRG5 — 26 (37,1%). Клиникалық маңызы бар регрессия (TRG1–2) 16% науқаста байқалды. TRG ypT (ρ=0,51; p<0,001), ypN (ρ=0,36; p=0,0037) және метастаздалған лимфа түйіндерінің саны (ρ=0,36; p=0,0025) сияқты көрсеткіштермен сенімді байланыс көрсетті. Сақинажасушалы асқазан қатерлі ісігінің жоғары дәрежелену (ρ=0,308; p=0,008) және ypT (ρ=0,324; p=0,007) көрсеткішімен байланысты болды, бірақ TRG-мен байланысты болмады. Бірфакторлы талдауда ypN (ρ=–0,24; p=0,048) және метастаздалған лимфа түйіндерінің саны (ρ=–0,28; p=0,021) жалпы өмір сүруге маңызды әсер етті. ӨСҰ және РӨСҰ медианаларына қол жеткен жоқ. Каплан–Майер әдісі бойынша жақсы жауап берген науқастарда (TRG1–2) өмір сүру ұзақтығы айтарлықтай жоғары болды (log-rank χ^2=7,9; p=0,005 және χ^2=10,86; p=0,001).

Қорытындылар: FLOT схемасы бойынша НАХТ-тан кейінгі айқын патоморфологиялық жауап өмір сүру болжамының жақсаруы-мен байланысты, алайда негізгі болжаушы фактор ретінде қалдық лимфогенді метастаз (ypN және зақымданған лимфа түйіндерінің саны) қала береді. TRG көрсеткішін лимфа түйіндерінің жағдайын ескере отырып бағалаған жөн. TRG-ның тәуелсіз болжау мәнін растау үшін морфологиялық үйлестірілген бағалау және көпорталықты проспективті зерттеулер қажет.

Түйінді сөздер: *ісіктің патоморфологиялық регрессиясы, асқазан қатерлі ісігі, неоадъювантты химиотерапия*

Дәйексөз үшін:

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Introduction

Gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide, despite a general decline in overall incidence over recent decades. According to GLOBOCAN 2022 data, GC ranks fifth in incidence and fourth in mortality, claiming approximately one million lives annually [1]. The majority of patients are diagnosed at advanced stages, when radical treatment is associated with a high risk of recurrence and metastasis, necessitating the implementation of comprehensive therapeutic approaches.

Neoadjuvant (perioperative) polychemotherapy (NAPCT) has become an essential component in the treatment of locally advanced gastric cancer. The results of the MAGIC trial demonstrated that the addition of the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil) to surgical treatment significantly improved five-year survival (36% vs. 23%) compared to surgery alone [2]. The subsequent FLOT4 study showed the superiority of the FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) over ECF/ECX both in terms of R0 resection rates (85% vs. 74%) and median overall survival (50 months vs. 35 months), establishing it as the new standard of care [3, 4, 5, 6].

An important parameter for assessing the effectiveness of neoadjuvant therapy is pathological tumor regression (Tumor Regression Grade, TRG), which reflects the amount of residual tumor mass [7]. In the studies by Becker et al. [8] and Wang et al. [9], TRG demonstrated a significant correlation with overall survival and several clinicopathological parameters (tumor stage, lymph node involvement, vascular invasion), and was identified as an independent prognostic factor [4, 10, 11, 12].

Considering the accumulating evidence supporting the prognostic significance of TRG and the effectiveness of contemporary chemotherapy regimens, further clarification of predictive markers remains essential for optimizing individualized treatment strategies.

This study seeks to evaluate the association between the extent of pathological tumor regression, clinicopathological features, and survival outcomes in patients with locally advanced gastric cancer treated with neoadjuvant chemotherapy.

Materials and methods

Patient Selection

A single-center retrospective cohort study was conducted. The inclusion criteria were as follows: patients aged 18 to 80 years; patients who received neoadjuvant polychemotherapy (NAPCT) followed by surgical resection; histologically confirmed stage II–III gastric adenocarcinoma; availability of pathological tumor regression grade (TRG) assessment, complete clinicopathological data, and follow-up information. Exclusion criteria included: patients with concurrent or metastatic malignancies of other origins; those with unresectable or metastatic gastric cancer; and patients with severe hepatic or renal impairment or other significant comorbidities. A total of 74 patients who underwent NAPCT and curative surgery between 2020 and 2024 at the National Cancer Research Center were included in the study. All patients received the FLOT regimen as neoadjuvant therapy. The investigated parameters and overall characteristics of the study cohort are presented in Table 1.

Table 1.

General characteristics of the sample.

Parameter		Abs. (%), n=74 / Me (25, 75%)
Sex	Male Female	53 (71,6) 21 (28,4)
Age, year		58,5 (52, 64)
BMI, kg/m²		25,95 (22,8, 28,3)
cT	2 3 4	3 (4) 59 (79,7) 12 (16,3)
cN0	0 1	16 (21,7) 58 (78,3)
Clinical stage	II III	14 (19) 60 (81)
Histological grade	1 2 3	1 (1,3) 15 (20,7) 58 (78,3)
Tumor localization	Upper third Middle third Lower third	35 (47,2) 25 (34,8) 14 (18,9)
Completion of NACT courses (4 courses)	Yes No	64 (86,5) 10 (13,5)
Type of surgery	Total gastrectomy Distal gastrectomy Extended volume Liver biopsy Peritoneal biopsy Gastrostomy Gastroenteroanastomosis	55 (74,4) 11 (14,9) 3 (4,1) 2 (3,7) 1 (1,3) 1 (1,3) 1 (1,3)
Postoperative complications (Clavien–Dindo)	I-II III-IV	2 (2,7) 4 (5,4)
Duration of the postoperative period, days		11 (9, 12)
Surgical margin status	R0 R+	61 (82,4) 8 (10,8)
TRG according to Mandard	1 2 3 4 5 No data	9 (12) 2 (3,5) 23 (31) 10 (13,2) 26 (35) 4 (5,3)
Presence of response to NACT (TRG 1-2)	Yes No No data	5 (6,9) 58 (78,4) 11 (14,6)
ypT	0 1 2 3 4 No data	3 (4) 6 (8,1) 11 (14,5) 33 (44,6) 16 (21,7) 5 (7,1)
ypN	0 1 2 3 No data	28 (37,8) 14 (18,9) 14 (18,9) 13 (17,3) 5 (7,1)
Number of lymph nodes examined		15 (11, 19)

Pathological Tumor Regression Grade Assessment

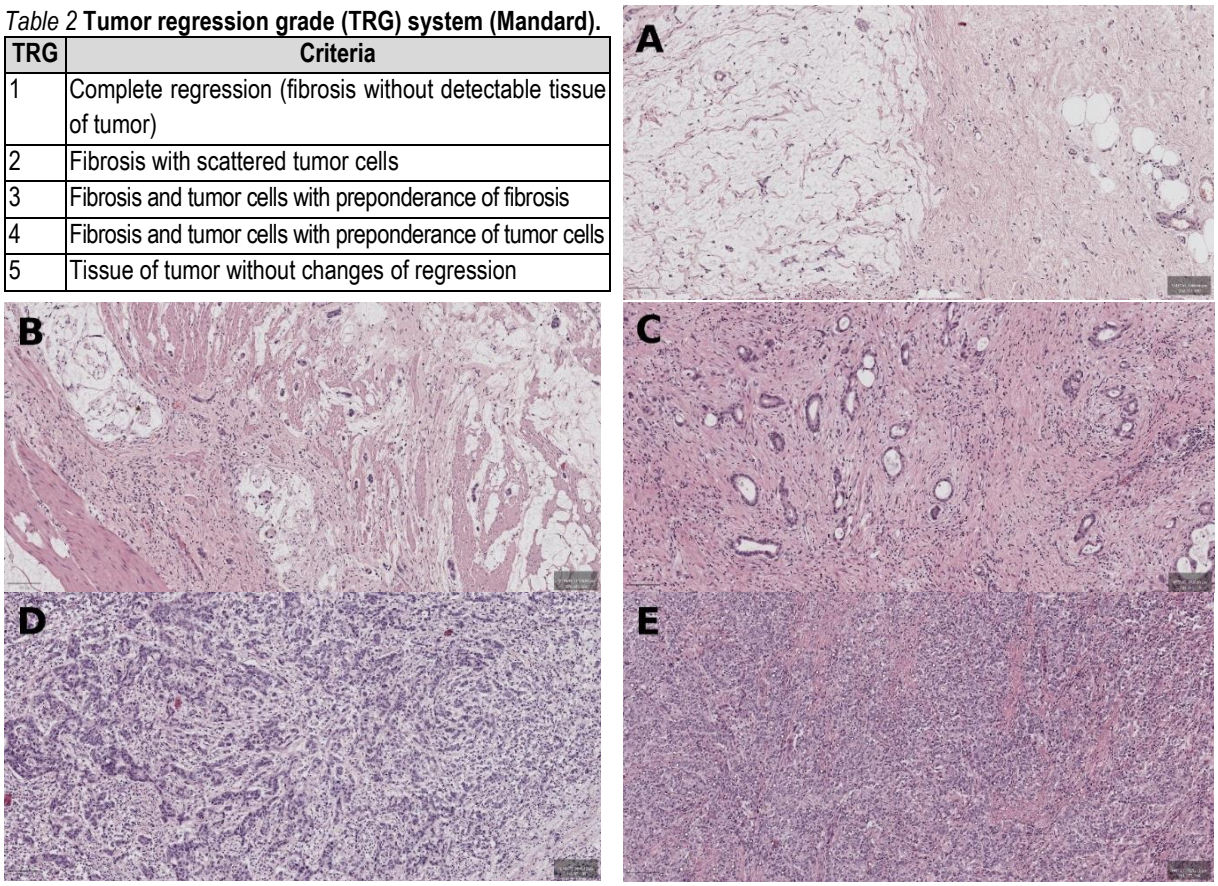
Gastric resection specimens were processed in accordance with the protocols of the College of American Pathologists. During gross examination, all macroscopically identifiable tumor tissue or tumor bed was measured, serially sectioned at 0.5 cm intervals, and embedded in paraffin blocks. Tissue sections were stained with hematoxylin and eosin. Tumor staging (TNM classification) was performed according to the guidelines of the Union for International Cancer Control (UICC, 2019). Pathological tumor regression grade (TRG) following NAPCT was assessed using the Mandard scoring system, which is widely applied to gastrointestinal malignancies, including gastric cancer. This system classifies tumor response into five grades based on the ratio of residual tumor cells to fibrotic tissue in the post-treatment specimen. The criteria for TRG according to the Mandard system are presented in Table 2 and Figure 1.

Statistical Analysis

Associations between TRG and pathological features were evaluated using the chi-square test or Fisher's exact test where appropriate. Survival analysis was performed using the Kaplan–Meier method, log-rank tests, and Cox proportional hazards regression. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using Statistica 14 software (TIBCO Software).

Table 2 **Tumor regression grade (TRG) system (Mandard).**

TRG	Criteria
1	Complete regression (fibrosis without detectable tissue of tumor)
2	Fibrosis with scattered tumor cells
3	Fibrosis and tumor cells with preponderance of fibrosis
4	Fibrosis and tumor cells with preponderance of tumor cells
5	Tissue of tumor without changes of regression



Picture 1. Examples of pathomorphological regression of gastric tumors according to the Mandard system. Hematoxylin and eosin staining, magnification 100x. A – TRG 1, B – TRG 2, C – TRG 3, D – TRG 4, E – TRG 5.

Results

Assessment of Pathological Tumor Regression Grade

A total of 70 surgical specimens from patients with gastric cancer were evaluated using the Mandard tumor regression grading system. Pathological regression grade 1 was observed in 9 patients, grade 2 in 2 patients, grade 3 in 23 patients, grade 4 in 10 patients, and grade 5 in 26 patients. The majority of patients (n = 59) did not achieve a clinically significant pathological tumor response.

Statistical analysis revealed the following associations:

- There was a moderate positive correlation between the Mandard tumor regression grade and residual T stage (ypT) ($\rho = 0.51$; $p < 0.001$). A higher residual T stage following neoadjuvant therapy was associated with a poorer pathological response.

- A weak but statistically significant positive correlation was found between tumor regression grade and residual nodal status (ypN) ($\rho = 0.36$; $p = 0.0037$), indicating that a poorer pathological response was associated with a higher likelihood of metastatic lymph node involvement.

- Tumor regression grade also significantly correlated with the number of metastatic lymph nodes ($\rho = 0.36$; $p = 0.0025$); patients with poorer tumor regression had a greater number of affected lymph nodes.

- No statistically significant correlations were found between tumor regression grade and other clinical or

pathological variables (e.g., age, BMI, laboratory parameters, total number of lymph nodes removed) ($p > 0.05$).

Correlation Analysis Involving Signet Ring Cells

Additional correlation analyses were performed to assess the relationship between the presence of signet ring cells and various clinicopathological characteristics:

- A moderate positive correlation was observed between tumor histological grade and the presence of signet ring cells ($\rho = 0.308$; $p = 0.008$).
- No statistically significant correlation was found between the presence of signet ring cells and the tumor regression grade according to Mandard ($\rho = –0.097$; $p = 0.426$).
- A moderate positive correlation was identified between the presence of signet ring cells and residual T stage (ypT) ($\rho = 0.324$; $p = 0.007$), indicating a larger residual tumor size in tumors containing signet ring cells.
- No correlation was found between the presence of signet ring cells and resection margin status (R status) ($\rho = –0.009$; $p = 0.942$).

Survival Analysis

Overall Survival (OS)

In the univariate Spearman correlation analysis, the following variables demonstrated a statistically significant inverse association with overall survival duration:

- Residual nodal status (ypN): $\rho = –0.24$; $p = 0.048$
- Number of metastatic lymph nodes:
$\rho = –0.28$;
$p = 0.021$

No significant correlations were observed between overall survival and either the Mandard tumor regression grade or residual T stage (ypT) ($p > 0.05$).

In the Kaplan–Meier survival analysis stratified by pathological tumor regression grade (TRG) according to the Mandard system, patients in the regression group (TRG 1–2; n = 11) had significantly better overall survival compared to those without significant regression (TRG 3–5; n = 59). The log-rank test revealed a significant difference between survival curves ($\chi^2 = 7.9$; $p = 0.005$) (Figure 2). The median OS was not reached in either group during the observation period; however, the probability of survival at 60 months remained higher in the TRG 1–2 group than in the TRG 3–5 group. These findings support the prognostic value of a marked pathological response to NAPCT.

Relapse-Free Survival (RFS)

In the Kaplan–Meier analysis of relapse-free survival stratified by TRG (Mandard), patients in the regression group (TRG 1–2; n = 11) also demonstrated significantly better RFS compared to those without regression (TRG 3–5; n = 59). The log-rank test confirmed a significant difference between the survival curves ($\chi^2 = 10.86$; $p = 0.001$) (Figure 2). The median RFS was not reached in either group; the 75th percentile for the entire cohort was approximately 13 months. These results underscore the prognostic importance of a pronounced pathological response in terms of disease control.

None of the assessed variables (ypT, ypN, number of metastatic lymph nodes) showed a statistically significant correlation with RFS duration ($p > 0.05$).

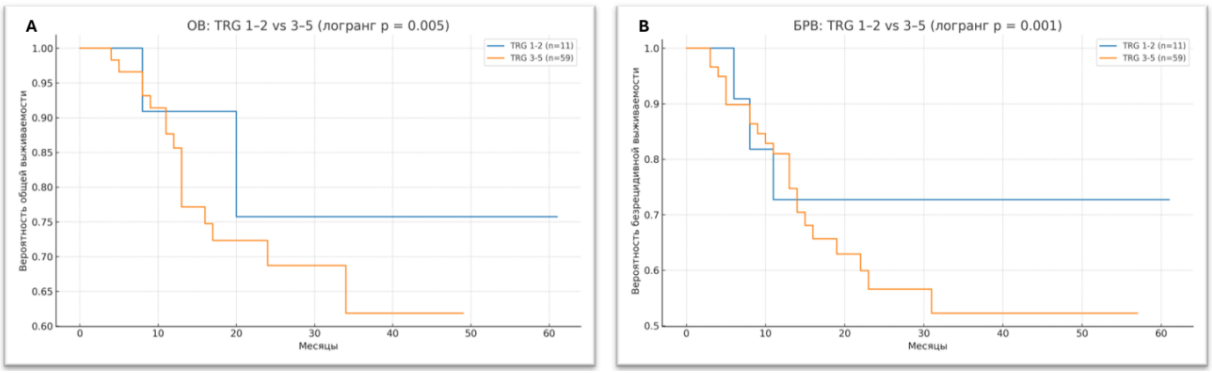


Figure 2. Kaplan-Meier curves for OS (A) and RFS (B) for groups of patients with TRG 1-2 and TRG 3-5.

Discussion

A combined approach incorporating perioperative neoadjuvant polychemotherapy (NAPCT)—in our study, exclusively the FLOT regimen—is currently recognized as the standard of care for locally advanced gastric cancer. Its primary objective is to reduce tumor burden, increase the rate of R0 resections, and thereby improve long-term outcomes. However, the question of which morphological and clinicopathological parameters truly reflect treatment efficacy and prognosis remains a matter of ongoing debate.

In our cohort, a clinically significant pathological response (TRG 1–2 according to Mandard) was achieved in only 16% of patients, which is consistent with data from major studies such as FLOT4, where the proportion of major responses did not exceed one-third of cases [3]. Nevertheless, Kaplan–Meier curves stratified by regression status (TRG 1–2 vs. TRG 3–5) demonstrated statistically significant differences in both overall and relapse-free survival (log-rank $p = 0.005$ and $p = 0.001$, respectively), supporting the clinical relevance of a pronounced pathological response.

The moderate-to-weak but statistically significant collinearity of TRG with ypT and ypN observed in our analysis aligns with the literature, where inclusion of these variables in multivariate models has been shown to attenuate the prognostic value of TRG [13]. In several studies [9, 14], both TRG and ypT lost significance in multivariate analysis, whereas in others, both remained independent predictors [15]; some reports found only one of these variables significant [16]. Such discrepancies are likely due to differences in study design, sample size,

follow-up duration, and variability in pathological assessment protocols.

Our data confirms the predominant prognostic value of lymphatic metastasis: residual nodal status (ypN) and the absolute number of metastatic lymph nodes were strongly associated with overall survival, whereas TRG and ypT, when assessed in isolation, were not. This finding is in line with numerous publications identifying nodal status as a principal risk factor for poor outcomes following NAPCT and surgery [4].

Regarding histological phenotype, the presence of signet ring cells was associated with higher tumor grade and greater residual T stage but showed no correlation with TRG. The literature presents conflicting results on the prognostic implications of signet ring cell carcinoma: some authors associate it with poorer chemotherapy response [17, 18], while others report no such correlation [7]. Our findings support the interpretation that this phenotype is linked to more aggressive tumor behavior but does not necessarily indicate chemoresistance.

Limitations. The retrospective design, single-center setting, and relatively small sample size limit the statistical power of our study, particularly in subgroup analyses of TRG 1–2. Additionally, short follow-up duration for a subset of patients and a limited number of outcome events precluded the calculation of median survival, potentially reducing the sensitivity for detecting prognostic associations. Finally, the subjectivity of TRG assessment and preanalytical variability in specimen processing may affect the reproducibility of the results [19].

Clinical Implications. Our data highlights the need for a comprehensive interpretation of pathological tumor response: although TRG is important, its prognostic impact is modulated by residual nodal status. In the context of postoperative management and surveillance, greater emphasis should be placed on ypN and the number of metastatic lymph nodes, which should be incorporated into multifactorial prognostic models. Looking forward, there is a need to develop integrated scoring systems combining TRG, ypT/ypN, lymphovascular invasion, and molecular markers.

Future Directions. Prospective multicenter studies with standardized protocols for pathological assessment and adequate follow-up are required to validate our findings. The inclusion of quantitative morphometric and digital image analysis techniques (including AI-based tools) may reduce the subjectivity of TRG evaluation and improve the reproducibility of prognostic models.

Conclusion

In patients with locally advanced gastric cancer treated with FLOT-based NAPCT, a marked pathological response (TRG 1–2) is associated with improved overall and relapse-free survival. However, residual lymphatic metastasis (ypN and the number of metastatic lymph nodes) remains the most decisive prognostic factor. TRG correlates with ypT and ypN but does not demonstrate independent prognostic value in isolation; the same applies to tumor grade and signet ring cell phenotype. Accurate risk stratification requires multifactorial models that incorporate nodal status. Prospective multicenter trials with standardized pathological evaluation are needed to confirm the independent prognostic value of TRG and to refine the definition of clinically meaningful tumor regression.

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