

Gastric cancer patients' survival with neoadjuvant chemotherapy versus direct surgery

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Abstract

Background: Despite these theoretical advantages, there is still a lack of evidence to answer whether NeoAdjuvant Chemotherapy (NAC) can further improve the survival of Locally Advanced Gastric Cancer (LAGC) patients on the basis of Adjuvant Chemotherapy (AC) following curative gastrectomy. The present research assessed the 36-month survival of gastric cancer patients treated in our center with and without NAC and over-all 36-month survival.

Methods: The present research assessed the 36-month survival of gastric cancer patients treated in our center with and without NAC and over-all 36-month survival. 79 patients entered this study, of whom 64 received NAC and 15 underwent direct surgery.

Results: Generally, the three-year survival rate in the groups was statistically different based on the Wilcoxon test (P 0.004). NAC was effective in increasing survival in the groups with lymph o vascular invasion, higher stage and all pathologic groups. However, age, type of surgery (TG vs DG), number of positive lymph nodes, and positive margin after surgery were not effective in interfering with survival in both groups. Neoadjuvant chemotherapy can positively increase OS and DFS in locally advanced gastric cancer. NAC was effective in increasing survival in the groups with lymph o vascular invasion, higher stage and all pathologic groups.

Conclusion: Considering the similar results in previous studies, larger prospective studies with accurate information can effectively achieve definitive results. However, age, type of surgery (TG vs DG), number of positive lymph nodes, positive margin after surgery were not effective interfering with survival in both groups.

Keywords: Gastric cancer, Survival, Chemotherapy.

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Despite its decreasing prevalence, gastric cancer (GC) remains among the most prevalent and fatal tumors globally (1). According to GLOBOCAN 2018, it is the third major cancer mortality cause globally, following lung and colorectal malignancy. It accounts for almost one-fifth of oncological fatalities. Also, it is the sixth most prevalent cancer, accounting for 5.7% of all new cases. Each year, almost one million new incidences of this cancer are diagnosed globally (1). Males are more likely to develop gastric cancer; it affects men 2.2 times more than women in developed countries, while in developing countries, the ratio is 1.83 (2). GC is the most prevalent cause of death among Iranians of both genders, and most patients are diagnosed at advanced stages, with a five-year survival of below 25% (3). Thus, even among medical professionals, there is a common belief that this diagnosis indicates hopelessness (4). According to either national or regional reports, gastric cancer is attributed to the highest rate among Iranian males. In both Iranian males and females, the death rate is significantly higher than in other neoplasms. However, it is associated with decreased cancer morbidity and death in most parts of the world. The explanation for this discrepancy is connected to late-stage diagnosis (5).

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Most gastric cancer patients present in advanced stages, and surgery is the primary treatment, but not enough. Various preoperative therapies have been proposed; however, the exact regimen of chemotherapy or radiochemotherapy is still unclear (6). Adjuvant treatment alone puts patients at risk of not getting any curative-intent chemotherapy due to the possible morbidity of gastrectomy and the postoperative challenges of physical and nutritional recovery. This has been demonstrated in high rates of failure of patients to start or complete postoperative adjuvant therapies (7). The only curative alternative for gastric cancer is surgery, and the over-all survival (OS) at early-stage is up to 90% (8). Since most GC cases are diagnosed at advanced stages, despite aggressive treatment, the prognosis is unfavorable and even with curative resection and lymphadenectomy, there is high rates of local recurrence and distant metastasis (9). Although effective adjuvant therapy is essential for the outcome improvement of advanced gastric cancer cases (10-12), it may not be possible for all due to the challenges of recovery after surgery (7, 13). The effect of neoadjuvant chemotherapy (NAC) has been proven in well-designed, multicenter, and randomized clinical trials (14-18).

Neoadjuvant fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) are efficient in locally advanced gastric cancer, providing a chance for surgery with curative outcome in cases with a fatal prognosis (14). Xu et al. (18) demonstrated that NAC could improve the prognosis of overall and disease-free survival in locally advanced GC cases. According to the JCOG0210 study, Japanese scholars conducted a phase III study (JCOG0501) confirming the superiority of NAC. The short-term results of JCOG0501 showed that NAC and then D2 gastrectomy were safe and did not increase surgical morbidity or mortality for type 4 and large type 3 GC (19). Many trials have investigated NAC for gastric cancer, but the definite result is unknown (15, 16, 18, 20, 21). In recent decades, the efficacy of curative gastrectomy followed by adjuvant chemotherapy (AC) in enhancing overall survival (OS) and disease-free survival (DFS) when compared to surgery alone has been firmly established (4, 5). Following the influential MAGIC trial, multimodal therapeutic approaches, such as neoadjuvant chemotherapy (NAC) and perioperative chemotherapy (PEC), have emerged as adjuncts to conventional AC after curative gastrectomy, presenting promising avenues for extending the survival of patients with Locally Advanced Gastric Cancer (LAGC) (6, 7, 8). However, recommendations for multimodal therapy vary across regions, and a consensus on the optimal strategy and

sequence remains elusive. In Europe, the standard approach entails PEC alongside curative gastrectomy, predicated on findings from the MAGIC trial (6), while in North America, adjuvant chemoradiotherapy post-surgery is favored, informed by outcomes from the INT0116 trial (9, 10). Conversely, AC following surgery in Asia is customary, informed by research such as the CLASSIC (4) and ACTS-GC trials (5). Factors such as a substantial tumor burden, metastatic lymph nodes, and systemic micrometastasis pose challenges to achieving curative resection. Consequently, NAC has been explored to reduce tumor size, diminish metastatic lymph nodes, and mitigate micrometastases, thereby enhancing the likelihood of successful curative resection for LAGC (6, 11, 12). Despite the theoretical benefits, the question of whether NAC can further augment the survival outcomes of LAGC patients in conjunction with AC post-curative gastrectomy remains unanswered due to a dearth of conclusive evidence. Moreover, there are concerns that NAC may heighten the risk of postoperative complications and adverse events during AC when compared to the strategy of upfront surgery followed by AC. Unlike in Europe and North America, NAC appears limited in Asian clinical practices (22). This paper aimed to compare Survival of gastric cancer patients with neoadjuvant chemotherapy versus direct surgery. The present research assessed the 36-month survival of gastric cancer patients treated in our center with and without NAC and over-all 36-month survival. This paper is organized as follows: the next section provides the methods and materials including exclusion criterion, the DS (surgery + AC) and NAC (NAC + surgery + AC) groups. Then, the obtained results are described in the next section such NAC effect in Distal gastrectomy versus Total gastrectomy. Finally, discussion and conclusion are presented at the end of the paper.

Methods

Code of ethics: The research was found to be in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran with the code of IR.SUMS.REC.1400.648. According to the cancer registry database of Faghihi Hospital of Shiraz University of Medical Sciences, gastric cancer cases admitted and underwent surgery from April 2018 to October 2019 were selected and followed-up for 36 months, and their data were analyzed. The inclusion criteria were: patients aged under 80 and above 18 at their initial gastroscopy, pathologically proven gastric adenocarcinoma before any treatment,

pretreatment CT in the hospital, no peritoneal seeding due to pre-surgery laparoscopic evaluation, complete recovery after the surgery, the ability to start oral feeding with more than 1500 kcal per day, and provided consent for the treatment. The exclusion criterion was: patients with a change in treatment regimen or with no gastrectomy and AC. Demographic information, contact information (phone/address), pathology file number, disease diagnosis date, histology and endoscopy results, tumor differentiation rate, and chemotherapy regimen used as treatment, NAC, number of NAC sessions, type of surgery, and the definitive pathology report was extracted from patients' documents.

Based on whether they received NAC, all cases were grouped into the DS (surgery + AC) and NAC (NAC + surgery + AC) groups. The NAC's existence or absence was the difference between the two groups. The Ethics Committee of Shiraz University of Medical Sciences approved this research. An informed consent form was taken from all patients. Charlson Comorbidity Index was used to evaluate concurrent diseases; the general condition of cases was also evaluated with Eastern Cooperative Oncology Group Performance Status Scale. NAC was performed with Fluorouracil /Leucovorin/ Oxaliplatin/ Docetaxel for four cycles. All cases were examined for hematological indicators, including liver function, electrolyte, blood routine, DIC and tumor markers, and renal function, before each cycle of NAC. The same surgical team did all surgeries. Based on site of tumor, distal gastrectomy (Billroth I stomach-duodenal anastomosis, Billroth II stomach-jejunal anastomosis, or Roux-en-Y stomach-jejunal anastomosis) or total gastrectomy (Roux-en-Y esophagus-jejunal anastomosis) was done. Outpatient visits and phone calls were used to follow-up on the patients. Physical examination, hematological testing, and abdominopelvic sonography were the most common

outpatient follow-up procedures. If needed, multidetector computed tomography (MDCT), gastroscopy, and magnetic resonance imaging (MRI) were performed. For the first two years after surgery, a phone call was made every three months. Later, phone follow-up was maintained every six months. The death date and the malignancy relapse were noted. The length of survival was calculated from the first diagnosis date of stomach cancer to the death date. The time from the gastrectomy date to the gastric cancer recurrence was defined as DFS. The statistical analysis was done with SPSS v25 (IBM Corp., Chicago, IL, USA); also, the survival data analysis was performed by the Kaplan-Meier method. Descriptive statistics were percentages, frequencies, ranges, median, means, and standard deviations (SD). The significance was considered at $p < 0.05$ for multivariate analyses.

Results

The total number of participants was 79, of which 64 were in the NAC group and 15 were in the DS group. In the NAC group, the average age was 58.7, the youngest was 22, and the oldest was 79; in the DS group, they were 63.26, 51, and 70, respectively. An insignificant difference was detected between the groups with a t-test. In the NAC group, 31.3% were women and 68.8% were men, and in DS group 26.7% were women and 73.3% were men. According to the ECOG scale, in the NAC group, 85.9% were grade 0, 7.8% were grade 1, and 6.3% were grade 2; in contrast, in the DS group, 80% were grade 0, and 20% were grade 1. Between the groups, the difference was insignificant according to the chi-square test ($P=0.25$). According to the CCI scale (table 1), no significant difference was detected between the 2 groups according to the chi-square test ($P=0.423$).

Table 1. CCI scale in NAC and DS group

		CHARLSON * VAR00006 Crosstabulation			Total
		NEO			
		NO	YES		
CHARLSON	0.0	Count	0	13	13
		% within VAR00006	0.0%	20.3%	16.5%
	1.0	Count	2	11	13
		% within VAR00006	13.3%	17.2%	16.5%
	2.0	Count	6	20	26
		% within VAR00006	40.0%	31.3%	32.9%
	3.0	Count	4	7	11
		% within VAR00006	26.7%	10.9%	13.9%

CHARLSON * VAR00006 Crosstabulation				
		NEO		Total
		NO	YES	
4.0	Count	1	7	8
	% within VAR00006	6.7%	10.9%	10.1%
5.0	Count	1	3	4
	% within VAR00006	6.7%	4.7%	5.1%
6.0	Count	1	3	4
	% within VAR00006	6.7%	4.7%	5.1%
Total	Count	15	64	79
	% within VAR00006	100.0%	100.0%	100.0%

NAC: neoadjuvant chemotherapy

The three-year survival in the DS group was 20%, and the mean 3-year survival was 15.6 with a DFS of 8.5 months, while the three-year survival in the NAC group was 57%, and the mean 3-years survival was 26.9 with a DFS of 14.22 months. The three-year survival in the 2 groups was statistically different based on the Wilcoxon test (P=0.004)

(figure 1 and 2). Among 64 patients who received NAC, 16 (25%) had a positive margin. Of the 15 patients who underwent DS, 4 (26.7%) had a positive margin, and in general, NAC did not have a statistically significant impact on reducing the positive margin (P=0.894> 0.05) (table 2).

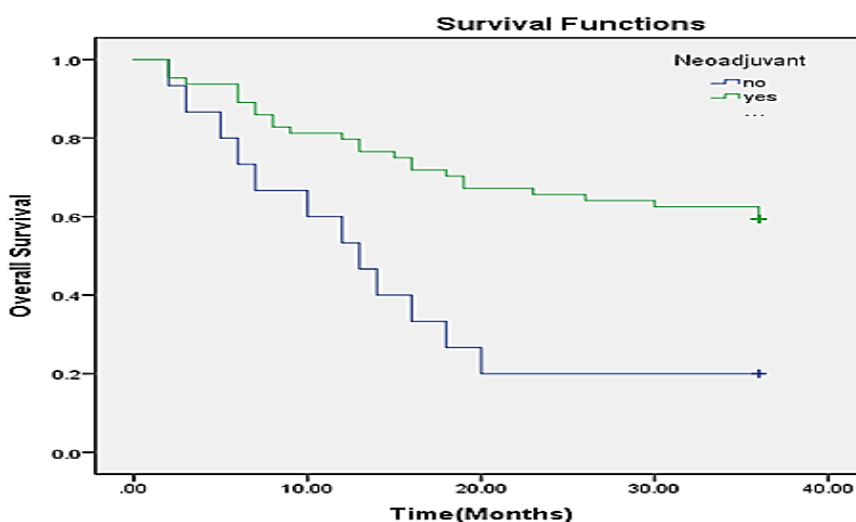


Figure 1. Survival in both groups

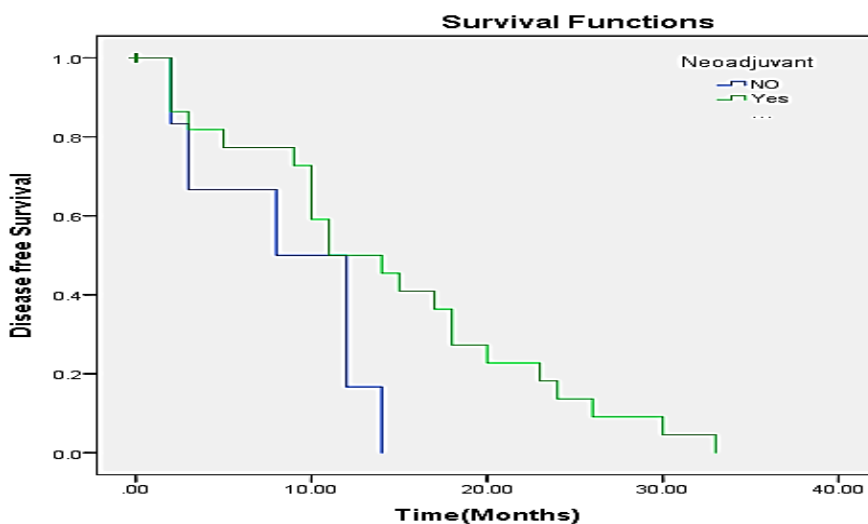


Figure 2. DFS in both groups

Table 2. Positive margin in both groups

		NEO * margin			
		R0	R1	Total	
NEO	-	Count	11	4	15
		% within NEO	73.3%	26.7%	100.0%
	+	% within R	18.6%	20.0%	19.0%
		Count	48	16	64
	Total	% within NEO	74.7%	25.3%	100.0%
		% within R	100.0%	100.0%	100.0%

In the positive margin group, the overall survival was significantly lower than the overall survival rate of each group. In the DS group with a positive margin, the survival rate for the first year was 25% (1 of 4) and 0 for the second year; also, only 1 of 4 was poorly differentiated, with a mean survival time of 9.5 months. In the NAC group, the survival rate was 44% for the first year, 19% for the second year, and zero for the third year; further, 82% were poorly differentiated, with a mean survival time of 12.06 months. Based on the independent t-test, an insignificant difference was observed in the average number of LND resected (18 in the DS group and 16 in the NAC group) ($P=0.262$). According to the lymph node-based comparison, the average survival time for n0, n1, n3a, and n3b was 30.26, 31.75, 24.75, 17.51, and 9 months ($P=0.001$), respectively. In the NAC group, the three-year survival for n0, n1, n3a, and n3b was 65%, 60%, 60%, 47%, and 0%, respectively. Also, in the DS group, the three-year survival for n0, n1, n3a, and n3b was 33%, 100%, 0%, 0%, and 0%, respectively. The comparison based on the Wilcoxon test

showed no statistical difference in survival considering the involved lymph node in the NAC and DS groups ($P=0.067$). In comparing the mean survival in two age groups (under and above 50) in the DS and NAC groups, the mean survival time of cases under 50 years old with NAC was 26.64 months. In contrast, the mean survival time of cases above 50 years old in the NAC group was calculated to be 27.06 months.

The mean survival time of cases above 50 years old in the DS group was 15.6 months. With $P=0.04$, no significant survival rate difference was observed in the age groups. The average survival rate for the poorly, moderately, and well-differentiated pathology groups was 24.48, 20.83, and 29.05 months, respectively. The three-year survival rate for the poorly, moderately, and well-differentiated pathology groups was 51%, 32%, and 65%, respectively. Based on the chi-square test, no statistical difference was observed concerning pathological differentiation ($P=0.147$). According to table 3, the 3-year survival in different pathology groups is as follows:

Table 3. Comparison of the three-year survival of different pathologies in both groups

Second-order Controls	First-order Controls	Interval Start Time	Number Entering Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval
neo	No	0	3	3.000	0	0.00	1.00	1.00

Second-order Controls	First-order Controls	Interval Start Time	Number Entering Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	
Biopsy well diff		12	3	3.000	2	0.67	0.33	0.33	
		24	1	1.000	0	0.00	1.00	0.33	
		36	1	0.500	0	0.00	1.00	0.33	
		0	17	17.000	1	0.06	0.94	0.94	
	Yes	12	16	16.000	3	0.19	0.81	0.76	
		24	13	13.000	1	0.08	0.92	0.71	
		36	12	6.000	0	0.00	1.00	0.71	
Poorly diff	neo	0	6	6.000	1	0.17	0.83	0.83	
		No	12	5	5.000	4	0.80	0.20	0.17
			24	1	1.000	0	0.00	1.00	0.17
			36	1	0.500	0	0.00	1.00	0.17
		Yes	0	35	35.000	8	0.23	0.77	0.77
	12		27	27.000	6	0.22	0.78	0.60	
	Mod diff	neo	24	21	21.000	1	0.05	0.95	0.57
			36	20	10.000	0	0.00	1.00	0.57
			0	6	6.000	5	0.83	0.17	0.17
		No	12	1	1.000	0	0.00	1.00	0.17
24			1	1.000	0	0.00	1.00	0.17	
Yes	neo	36	1	0.500	0	0.00	1.00	0.17	
		0	12	12.000	3	0.25	0.75	0.75	
	12	9	9.000	1	0.11	0.89	0.67		
	24	8	8.000	0	0.00	1.00	0.67		
		36	8	5.000	2	0.40	0.60	0.40	

The three-year survival in the well-differentiated group was 71% in NAC and 33% in DS treatments; in the poorly differentiated group, it was 57% in NAC and 17% in DS treatments; in the moderately differentiated group, it was 40% in NAC and 17% in DS treatments. Based on the type of surgery performed, the patients were also compared between the two groups of distal gastrectomy and total gastrectomy. In the distal gastrectomy group, the overall survival time was 25.88 months, while in the total gastrectomy group, it was 23.95 months, being statistically insignificant (P=4.32). In the distal gastrectomy group, the three-year survival was 55%, while in the total gastrectomy group, it was 46% (figure 3). Nine people in the DS group and 26 in the NAC group underwent distal gastrectomy. In the DS group, the average survival was 16.44 months in distal gastrectomy and 14.33 in total gastrectomy. In the same group, the three-year survival in distal gastrectomy

was 22.7%, while it was 16.7% in total gastrectomy. In the NAC group, the survival was 29.15 and 25.47 in the distal and total gastrectomy, respectively. The three-year survival in the same group was 69.2% and 52.6% for the distal and total gastrectomy, respectively. There was an insignificant difference between the two surgical methods either in general or in each of the DS and NAC groups; however, in both groups, chemotherapy before surgery had a significant effect on survival (table 4). Based on the stage, the survival rate was 33.4 months for stage one, 27.7 months for stage two, 19.42 months for stage three, and 7.25 months for stage four. The three-year survival percentage in stages one, two, three, and four was 65%, 65%, 36%, and zero, respectively (table 5 and 6; figure 4). In the total gastrectomy group, survival was 32.7 months in stage 1, 29.58 in stage 2, 19.1 in stage 3, and 3 in stage 4. In the same group, the three-year survival was 53% in stage 1, 75% in stage 2, 32% in

stage 3, and 0% in stage 4. In the distal gastrectomy group, survival was 34 months in stage 1, 25 in stage 2, 19.85 in stage 3, and 20 in stage 4. Also, the three-year survival was 76% in stage 1, 50% in stage 2, 43% in stage 3, and 43% in stage 4. In the group with NACT, the three-year survival was

62% in stage 1, 75% in stage 2, 46% in stage 3, and 0% in stage 4. In the DS, the three-year survival was 100% in stage 1, 25% in stage 2, 0% in stage 3, and 0% in stage 4, which indicate that NAC was effective in stages 2 and 3 and increased survival (P=0.004) (table 7).

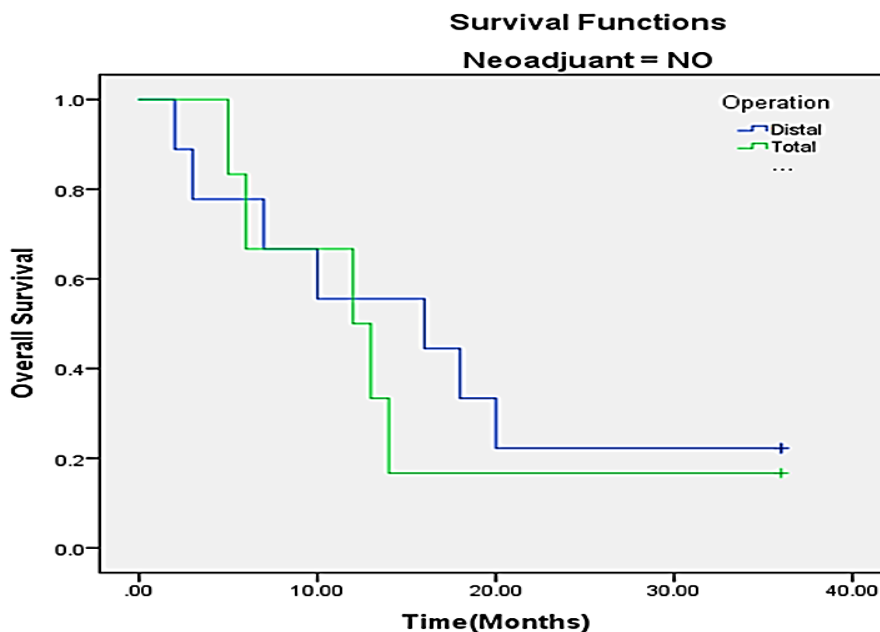


Figure 3. Three years survival in total gastrectomy versus distal gastrectomy

Table 4. NAC effect in distal gastrectomy versus Total gastrectomy

Second-order Controls	First-order Controls	Interval Start Time	Number Entering Interval	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	
Neo	No operation	0	9	4	0.44	0.56	0.56	
		12	5	3	0.60	0.40	0.22	
		24	2	0	0.00	1.00	0.22	
		36	2	0	0.00	1.00	0.22	
	Yes Operation	Distal	0	6	2	0.33	0.67	0.67
			12	4	3	0.75	0.25	0.17
		Total	24	1	0	0.00	1.00	0.17
			36	1	0	0.00	1.00	0.17
			0	26	4	0.15	0.85	0.85
			12	22	3	0.14	0.86	0.73
Yes Operation	Distal	24	19	0	0.00	1.00	0.73	
		36	19	1	0.10	0.90	0.66	
	Total	0	38	8	0.21	0.79	0.79	
		12	30	7	0.23	0.77	0.61	

	24	23	2	0.09	0.91	0.55
	36	21	1	0.09	0.91	0.50

Table 5. Over-all three years survival rate according to stage

STAGE	Means and Medians for Survival Time(os)							
	Estimate	Std. Error	Meana		Estimate	Std. Error	Median	
			95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound			95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
I	33.409	1.455	30.558	36.260
II	27.750	2.574	22.705	32.795
III	19.424	2.328	14.861	23.987	16.000	3.814	8.525	23.475
IV	7.250	4.308	0.000	15.695	2.000	.	.	.
Overall	24.810	1.497	21.876	27.744

a. Estimation is limited to the largest survival time if it is censored.

Table 6. Chi-Square test of survival according to stage

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	26.092	3	0.000

Test of equality of survival distributions for the different levels of VAR00013.

Table 7. Three-year survival in DS versus NAC according to stage

Second-order Controls	First-order Controls	Interval Start Time	Number Entering Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	
Neo	No STAGE	I	0	2	2.000	0	0.00	1.00	1.00
			12	2	2.000	0	0.00	1.00	1.00
			24	2	2.000	0	0.00	1.00	1.00
			36	2	1.000	0	0.00	1.00	1.00
		II	0	4	4.000	1	0.25	0.75	0.75
			12	3	3.000	2	0.67	0.33	0.25
			24	1	1.000	0	0.00	1.00	0.25
			36	1	.500	0	0.00	1.00	0.25
	III	0	7	7.000	4	0.57	0.43	0.43	
		12	3	3.000	3	1.00	0.00	0.00	
		IV	0	2	2.000	1	0.50	0.50	0.50
			12	1	1.000	1	1.00	0.00	0.00
	Yes stage	I	0	20	20.000	0	0.00	1.00	1.00
			12	20	20.000	2	0.10	0.90	0.90
			24	18	18.000	2	0.11	0.89	0.80
			36	16	9.000	2	0.22	0.78	0.62
II		0	16	16.000	1	0.06	0.94	0.94	
		12	15	15.000	3	0.20	0.80	0.75	
		24	12	12.000	0	0.00	1.00	0.75	

	36	12	6.000	0	0.00	1.00	0.75
	0	26	26.000	9	0.35	0.65	0.65
III	12	17	17.000	5	0.29	0.71	0.46
	24	12	12.000	0	0.00	1.00	0.46
	36	12	6.000	0	0.00	1.00	0.46

Based on tumor size, the outcomes were as below: under 2 cm, the average survival was 26.91 months with a three-year survival of 44%; in 2 to 5 cm, the average survival was 27.06 months with a three-year survival of 68%; over 5 cm, the average survival was 21.26 months with a three-year survival of 40% (P=0.229). The average survival in the DS group was 24 months for a tumor size below 2 cm, with a three-year survival of 50%. Also, in 2-5 cm, it was 16.2 months with a three-year survival of 29%, and above 5 cm, it was 12 months with a three-year survival of 0%.

The average survival in the NAC group was as below: for a tumor size below 2 cm, it was 27.18 months with a three-year survival of 43%; for 2-5 cm, it was 31.22 months with a three-year survival of 83%; for above 5 cm, it was 23.58 months with a three-year survival of 50%. Tumor size could not predict survival in the NAC and DS groups. Further, NAC did not increase survival according to tumor size (P=0.229). In the DS group with lymph vascular invasion (LVI), the average survival was 13.28 months with a three-year survival of 14%, while without LVI, the average survival was 17.62 months with a three-year survival of 25%. In the NAC group with LVI, the average survival was 21 months with a three-year survival of 43%, while without LVI, the average survival was 29.83 months with a three-year survival of 63%. LVI was effective in reducing the survival rate (P=0.02), and NAC was effective in increasing the survival rate in patients with LVI (P=0.002) (tables 8 and 9). The average survival for the laparoscopic group was

30.4 months with a three-year survival of 80%, while for open surgery, it was 24 months with a three-year survival of 50% (P=0.105), showing that laparoscopy versus open surgery did not increase survival. Based on tumor location, the outcomes were as follows: for the proximal tumor, the average survival was 24.25 months with a three-year survival of 47%; for the body of stomach tumor, it was 27.94 months with a three-year survival of 53%; for distal tumor, it was 25.26 months with a three-year survival of 58%; for disseminated tumor, it was 15 months with a 3-years survival of 17%. The outcomes based on tumor location in the NAC group were as below: for the proximal tumor, the average survival was 27.73 months with a three-year survival of 59%; for the body of stomach tumor, it was 31.37 months with a three-year survival of 63%; for distal tumor, it was 25.66 months with a three-year survival of 58%; for diffused tumor, it was 16.2 months with a three-year survival of 20%. Further, the following results were obtained in the DS: for the proximal tumor, the average survival was 16.88 months with a three-year survival of 22%; for the body of stomach tumor, it was 9.66 months with a three-year survival of 0%; for the distal tumor, it was 20.5 months with a three-year survival of 50%; for the diffused tumor, it was 12 months with a three-year survival of 0%. No statistical difference was observed between survival according to the tumor site (P=0.202), except for diffused type. NAC could improve survival in either of the 4 groups.

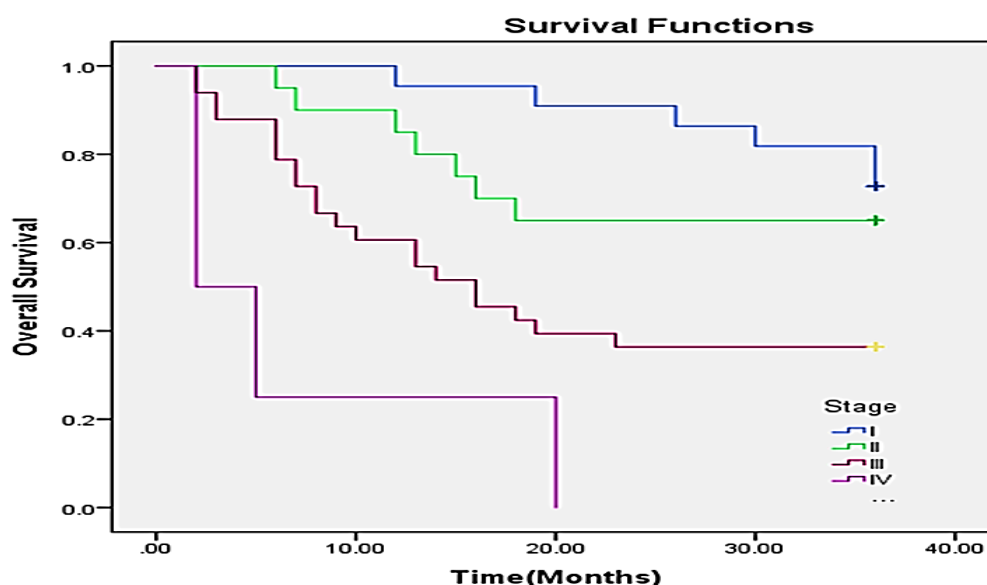


Figure 4. Over-all three years survival rate according to stage

Table 8. Survival of NAC and DS group according to LVI

neo	LVI	Means and Medians for Survival Time							
		Estimate	Std. Error	Mean ^a		Estimate	Std. Error	Median	
				95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound			95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
No	0	17.625	4.209	9.375	25.875	13.000	5.657	1.913	24.087
	1	13.286	3.900	5.641	20.930	12.000	6.547	.000	24.831
	Overall	15.600	2.944	9.831	21.369	13.000	2.576	7.951	18.049
Yes	0	29.837	1.710	26.486	33.189
	1	21.095	3.012	15.192	26.998	19.000	7.629	4.047	33.953
	Overall	26.969	1.601	23.830	30.107
Overall	Overall	24.810	1.497	21.876	27.744

a. Estimation is limited to the largest survival time if it is censored.

Table 9. Chi square test of survival in NAC and DS group according to LVI
 Overall Comparisons^a

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.070	1	0.024

Test of equality of survival distributions for the different levels of LVI.

a. Adjusted for VAR00006.

Discussion

Seventy-nine cases were included in the present research, 15 of whom were in the DS group, and 64 were in the NAC group. The majority of cases in the groups were male. An insignificant difference was detected between the groups regarding the general condition according to the ECOG and CCI scales. In the Kaplan-Meier analysis, according to the survival curve, the OS and DFS of the NAC group were considerably higher compared to the DS group. NAC could downstage tumors, eradicate potential micrometastasis, and enhance prognosis in patients.

Paknazar et al. (17) reported a rate of 1- and 5-year net post-surgery survival as 67.96 (95% CI: 62.35–72.98) and 23.35 (95% CI: 17.94–29.28) in gastric cancer patients in Iran (17). In the present research, in the DS group, the 1-, 2-, and three-year survival was 60 %, 20 %, and 20%, respectively; the mean three-year survival was 15.6 with a DFS of 8.5 months. While the probability of survival in the

NAC group was 81% in the first year, 66% in the second year, and 57% in the third year, showing an overall better survival rate in the NAC group in comparison with Paknazar et al. (17) Faghihi Hospital in the Shiraz University of Medical Science is one of the principal centers of cancer surgery. In Iran, because of no screening program, most patients are referred in high stages, thus having an unfavorable short survival rate after diagnosis. 53.04% of all study patients were females, while 46.96% were males, and their average age was 59.5 years. From 64 cases, 31.3% were women and 68.8% were men in the NAC group, and from 15 cases, 26.7% were women and 73.3% were men in the DS group, similar to Rawla et al. (1)

Gholizade et al. (23) showed that NAC had a positive effect on survival. Also, Xu et al. (18) revealed that the OS and DFS in the NAC group were considerably higher compared to those in the DS group. Similarly, the present study demonstrated that NAC could improve overall and

disease-free survival rates in locally advanced GC. The survival rate in the DS group was 60 % in the first year, 20 % in the second year, and 20% in the third year; the mean three-year survival was 15.6, with a DFS of 8.5 months. While the probability of survival in NAC group was 81% in the first year, 66% in the second year, and 57% in the third year; also, the mean three-year survival was 26.9 with a DFS of 14.22 months. The three-year survival rate in the two groups was statistically different based on the Wilcoxon test ($P=0.004$). Positive margin has been a negative prognostic factor in previous studies. In Akhavan et al. (24) the positive margin was not a negative prognostic factor, but its percentage was higher in the DS group (37%) compared to 18.9% in the NAC group. Even though in the present research, the positive margin percentage in the NAC group was 25 % and in the DS group was 26.6%, with no statistical significance, showing that NAC does not reduce positive margin percentage. In the positive margin group, the average survival time was significantly lower than the mean survival time of each group. In the DS group with a positive margin, the average survival time was 9.5 months, while it was 12.06 in the NAC group. Like Zhao et al. (25) the positive margin was a negative prognostic factor. In the well-differentiated pathology with NAC treatment, the three-year survival was 71%, while it was 33% in the surgical group. In the poorly differentiated pathology, it was 57% in the NAC group, while it was 17% in the DS group. Also, in the moderately differentiated pathology, it was 40% in the NAC group, while it was 17% in the DS group. In all three categories of pathology, the NAC group had a higher three-year survival rate, and, as comparing poorly differentiated GC with well-differentiated GC, well differentiated had higher survival (26). According to various studies, the clinical responses in the better-differentiated group are much greater than in the poorly differentiated group, and the better-differentiated group with locally advanced GC is appropriate for preoperative chemotherapy. More investigation should be done to evaluate the result.

El Halabi et al. (27) showed that age did not affect survival. In the present study, all cases in the surgical group were over 50 years old; however, in the NAC group, the cases were grouped into two, under and equal to 50 and over 50 years old; the survival rate of the groups was analyzed by Will-Coxon method. Similarly, age, as an independent factor, had no effect on survival in the present research. Liu et al. (28) found that despite longer 5-year overall survival rate after DG for distal gastric cancer patients than TG, but the resection type was not an independent prognostic factor.

Only in TNM stage III, TG bring a worse prognosis for distal gastric cancer than DG according to multivariate analyses. As in the present research statistical evaluation, no difference was demonstrated in the survival of both procedures. There was an insignificant difference between the two surgical methods either in general or in each of the DSI and NAC groups; however, in both groups, chemotherapy before surgery had a significant effect on survival. Based on tumor location, the three-year survival was 47% for the proximal tumor, 53% for the stomach tumor, 58% for the distal tumor, and 17% for the disseminated tumor. In the NAC group, it was 59% for the proximal tumor, 63% for the body of stomach tumor, 58% for the distal tumor, and 20% for the disseminated tumor. In the DS group, it was 22% for the proximal tumor, 0% for the stomach tumor, 50% for the distal tumor, and 0% for the disseminated tumor. No statistical difference was observed between survival according to the tumor site ($P=0.202$), except for diffused type. It was concluded that NAC could improve survival in either of the 4 groups. Xue et al. (29) concluded that the 1-year, the 3- and 5-year OS rates of PG patients were lower than those of DG patients in eastern countries. The reasons for shorter survival of PG patients than DG patients have been investigated and are multifactorial. First, it may be because of not having obvious or specific early symptoms in PG patients, and detection is difficult with gastroscopy; even targeted biopsy may have lower accuracy, resulting in not diagnosing some patients until the advanced stage of cancer (29); this shows that factors more than just the site of the tumor may be effective in survival, thus needing more investigation.

According to Bando et al. (30), there were significant differences between all other clinical stages, and the TNM clinical staging system had a better prognosis ability with a satisfactory C-index; thus, it should be regarded as valuable in choosing therapeutic strategies for gastric cancer treatment (30). Based on stage, the survival rate was 33.4 months for stage one, 27.7 for stage two, 19.42 for stage three, and 7.25 for stage four. The three-year survival percentage was 65% in stage one, 65% in stage two, 36% in stage three, and zero in stage four. In the NAC group, the three-year survival was 62% in stage 1, 75% in stage 2, 46% in stage 3, and zero in stage 4. In the DS, the three-year survival was 100% in stage 1, 25% in stage 2, 0% in stage 3, and zero in stage 4 ($P=0.004$). TNM was an independent predicting factor of survival; also, NAC could improve overall survival in stages 2 and 3.

Based on the involved lymph nodes, the average survival time was 30.26 months for n0, 31.75 for n1, 24.75 for n2,

17.51 for n3a, and 9 for n3b ($P=0.001$). In the NAC group with involved lymph nodes, the three-year survival in n0 was 65%, in n1 was 60%, in n2 was 60%, in n3a was 47%, and in n3b was 0%. In the DS group with involved lymph nodes, the three-year survival in n0 was 33%, in n1 was 100%, in n2 was 0%, in n3a was 0%, and in n3b was 0% ($P=0.067$). NAC had a statistical effect in increasing survival according to the number of involved lymph nodes ($P=0.03$). In the present research, the number of positive lymph nodes was considered an independent predictive factor; however, NAC did not improve overall survival in the same number of positive lymph nodes. The lack of difference in survival with an equal number of lymph nodes could be due to the regression of positive lymph nodes caused by NAC. Indeed, there were more positive lymph nodes cleared due to chemotherapy. To begin, the retrieval of at least 16 lymph nodes is the minimum need for their dissection, according to the 8th edition of the AJCC staging manual (20). There is growing evidence showing that an increased number of harvested lymph nodes improves survival significantly (20). For the laparoscopic group, the average survival was 30.4 months, while the three-year survival was 80%. Further, for the open surgery group, the average survival was 24 months, and the three-year survival was 50% ($P=0.105$), indicating that laparoscopy versus open surgery does not increase survival. Similarly, Best et al. (31) demonstrated no difference in short-term or long-term results between laparoscopic and open gastrectomy. The average survival in the surgical group with LVI was 13.28 months with a three-year survival of 14%, while, without LVI, it was 17.62 months with a three-year survival of 25%. In the NAC group with LVI, it was 21 months with a three-year survival of 43%, while, without LVI, it was 29.83 months with a three-year survival of 63%. These results demonstrated LVI as an independent prognostic factor, showing that NAC can improve outcomes and survival in patients. LVI-positive cases have a poorer prognosis than LVI-negative cases, regardless of tumor stage or lymph node metastases, according to Di Mei et al. (32). Further, LVI was found to be an independent prognostic factor for GC cases.

This study provides critical insights into the survival outcomes of gastric cancer patients, emphasizing the significant prognostic role of tumor size. Patients with tumors between 2 to 5 cm exhibited the highest three-year survival rate of 68%, compared to 44% for tumors below 2 cm and 40% for tumors over 5 cm, aligning with recent literature highlighting tumor size as an independent predictor of survival. Additionally, neoadjuvant

chemotherapy (NAC) significantly improved overall and disease-free survival, suggesting its potential as a valuable treatment component, despite no significant interaction with tumor size ($P=0.229$). These findings have important clinical implications, supporting the integration of NAC into treatment protocols and the consideration of tumor size in prognostic assessments. However, the study's limitations, including a small sample size, lack of side effect data, and potential confounding due to tumor size regression after NAC, warrant cautious interpretation. The larger number of patients in the NAC group may have also influenced the results. Future research should focus on larger, prospective studies to validate these findings, investigate NAC side effects, and explore molecular biomarkers for personalized treatment approaches. Such efforts could refine patient selection criteria and enhance multimodal treatment strategies, ultimately improving survival and quality of life for gastric cancer patients.

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