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The Efficacy and Safety of Neo-Adjuvant Therapy for Gastric Cancer: After Surgical Management

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ABSTRACT

Background: Globally, gastric cancer ranks second in terms of the incidence of cancer-related fatalities. Gastric cancer ranks twelfth among all types of cancer in Egypt. Besides, the prevalence increases as age increases, with 55% of cases occurring in individuals aged 50 to 70. Complete resection, partial gastrectomy, or total gastrectomy is determined by the surgical margins, tumor location, stage, and histology. The degree of necessary regional lymphadenectomy has been a subject of contention. Neoadjuvant chemotherapy has the potential to enhance the likelihood of tumor downstaging and augment the rate of curative resection. *Aim of work:* TO identify the function of neoadjuvant chemotherapy in patients with gastric cancer who require surgical treatment.
Patients and methods: This study involves a prospective analysis of sixty patients aged 18-60 diagnosed with gastric adenocarcinoma. These patients underwent neo-adjuvant chemotherapy with a minimum follow-up period of 16 months. The study was conducted at the Upper Gastro-Intestinal Surgeries Unit, Ain Shams University Hospitals. Primary end-points encompass overall survival, R0 resection rate, local recurrence, and pathological complete response rate.
Results: This study comprised patients aged 22-60, with a mean age of 46.67 ± 12.76. The median disease-free survival (DFS) was 6 months, while the mean overall survival (OS) was 26.3 months. The recorded one-year and two-year OS rates were 75.8% and 67.9%, respectively. However, the median OS was not reached.
Conclusion: This research provided support for the utilization of neoadjuvant chemotherapy before undergoing surgical intervention in gastric cancer at various stages. Other studies, on the other hand, cast doubt on its utility and call for a reevaluation of the clinical outcome; these warrant additional research.
Key words: neo-adjuvant, gastric adenocarcinoma, OS, DFS

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INTRODUCTION

Estimating one million new cases per year, gastric cancer ranks fifth among the most frequently reported malignancies globally and is an illness of international significance (1).

Gastric cancer ranks twelfth among all malignancies in Egypt, affecting both

sexes. It accounts for 1.6% of all cancers diagnosed and 2.2% of all cancer-related deaths (2).

Globally, gastric cancer accounted for 784000 fatalities in 2018; as a result of its frequently detected late stage, mortality is high; it is ranked as the third primary cause of cancer-related deaths. Eastern Europe, South America, and the Far East are regions with high incidence and mortality rates of gastric cancer. Males have a twofold excess of females in the incidence of gastric cancer (1).

A consistent decrease in this particular malignancy's incidence and mortality rates has been observed throughout the last century. Nevertheless, despite the general downward trend in gastric cancer incidence rates, clinicians can anticipate a rise in the number of patients diagnosed in the future. This can be attributed to the fact that improved socioeconomic conditions and an aging population have played a role in diminishing the number of cases of Helicobacter pylori, the principal etiological agent of gastric cancer (3).

Comprehensive resection of the tumor is the preferred course of action whenever feasible. However, the degree of resection, which may consist of a partial or total gastrectomy, is determined by factors such as the tumor's stage, surgical margins, placement, and histology. Considerable debate has revolved around the extent to which regional lymphadenectomy is necessary. Compared to limited D1 dissection, which cured 0% of patients with N2 disease, randomized controlled trials demonstrated that extended (D2) lymphadenectomy is safe and can cure 20% of patients (4).

Research has demonstrated that adjuvant chemotherapy and therapeutic gastrectomy with dissection of lymph nodes are tolerable and yield comparable advantages for elderly individuals with non-metastatic GCs, as opposed to non-elderly individuals (5).

Chemotherapy administered before surgery improves the prognosis for curative resection, eradicates early microscopic metastasis, and permits an in vivo evaluation of therapeutic efficacy (6).

Survival rates were significantly improved with the implementation of "FLOT"; consequently, those suffering from localized advanced gastric carcinoma who can tolerate a perioperative three-drug combination regimen are advised to adhere to "FLOT" as the recommended course of care (7).

NACT for individuals diagnosed with gastric cancer in its late stages fails to enhance overall prognoses substantially and may even have adverse effects on survival in the early stages. NACT therapy, on the other hand, led to a higher rate of R0 resection (8).

PATIENTS AND METHODS

The research sample consisted of sixty patients diagnosed with gastric cancer, aged between 22 and 60 years, who underwent neo-adjuvant fluoropyrimidine-based chemotherapy at Ain Shams University Hospitals.

All surgically eligible patients diagnosed with gastric adenocarcinoma, within the age range of 18 to 60 years, were included in our study.

Exclusions from the study encompassed patients below 18 years or above 60 years of age, those deemed unfit for surgery, individuals with psychiatric illnesses, and those with a history of previous upper gastrointestinal surgeries.

Follow-up for all included patients involved CT chest, pelvis-abdomen with contrast, and upper gastrointestinal endoscopy every 3-6 months, guided by history and clinical examination.

RESULTS

The study comprised 60 patients aged 22-60, with a mean age of 46.67 ± 12.65. Of these, 32 were males and 28 were females. Thirty-two patients were above 50 years old, while 28 were below 50 (*table 1*).

Only 8 patients in the study had a family history of malignancy, while the majority had no such history. Twenty-six patients had a medical history of chronic diseases, whereas thirty-four patients had no documented medical history.

In our prospective study, the definitive site of tumors was as follows: 28 patients (46.7%) had cancer in the cardia, 16 patients (26.7%) had cancer in the body, 10 patients (16.7%) had cancer in the pylorus, and only 6 patients (10%) had cancer in the fundus.

In terms of performance status, 42 patients (70%) were classified as "PS I," while 18 patients (30%) were classified as "PS II." Regarding pathology, 40 patients (66.7%) had diffuse adenocarcinoma, and 20 patients (33.3%) had intestinal adenocarcinoma (*table 2*).

Correlating with gross endoscopy appearance, 24 patients exhibited a fungating cauliflower mass, 18 had a raised everted ulcer, 6 had a signet ring ulcer, 6 had a diffuse ulcer, and 6 had a large mass obstructing the

Table 1 - Age and gender percentage of our studied patients

		No. = 60
Age	Mean ± SD	46.67 ± 12.65
	Range	22 – 60
Gender	Female	28 (46.7%)
	Male	32 (53.3%)

Table 2 - Site, performance state, upper GI endoscopy, and biopsy findings in our patients

		No.	%
PS	I	42	70.0%
	II	18	30.0%
Biopsy	Diffuse type adenocarcinoma	40	66.7%
	Intestinal type adenocarcinoma	20	33.3%
Endoscopy	Raised everted ulcer	18	30.0%
	Fungating cauliflower mass	24	40.0%
	Signet ring ulcer	6	10.0%
	Diffuse ulcer	6	10.0%
	Large mass obstructing cardia	6	10.0%
Site	Body	16	26.7%
	Cardia	28	46.7%
	Fundus	6	10.0%
	Pylorus	10	16.7%

cardia. Concerning clinical staging, 7 patients were classified as stage IIA, 7 as stage IIB, 33 as stage III, and 13 as stage IVA. In terms of pathological staging, 24 patients (40%) were classified as stage IIIB, 14 patients (23.3%) as stage IIA, 10 patients (16.7%) as stage IIIA, 8 patients (13.3%) as stage IIB, and only 4 patients (6.7%) as stage IB (*fig. 1*).

Our analysis of neo-adjuvant chemotherapy regimens revealed that patients received a range of 3-8 cycles. Among them, 38 patients (63.3%) received FLOT, 8 patients (13.3%) received XELOX, 6 patients (10%) received DCF, 4 patients (6.7%) received DOX, and another 4 patients (6.7%) received EOX. In the surgical procedures, thirty-two patients (53.3%) underwent total gastrectomy, while twenty-eight patients (46.7%) underwent subtotal gastrectomy. Thirty-eight patients (63.3%) achieved negative margins, whereas twenty-two patients (36.7%) had positive margins. Patients with positive margins underwent concurrent adjuvant chemotherapy and radiotherapy (*table 3*).

The study revealed no complete pathological

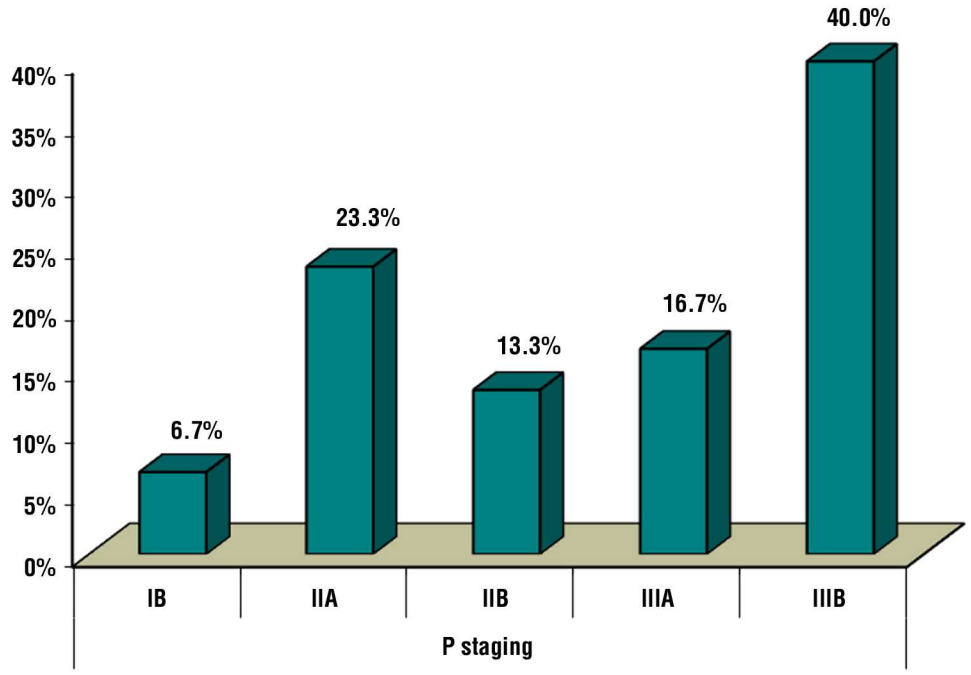

Figure 1 - Percentages of multiple pathological stages included in our patients

Table 3 - Number of NACT cycles, type of NACT, surgeries, grading, pathological staging, and margins post-resection

		No. = 60
Neo-adjuvant	Mean ± SD	4.57 ± 1.78
	No of cycles	3 – 8
Type	FLOT	38 (63.3%)
	XELOX	8 (13.3%)
	EOX	4 (6.7%)
	DOX	4 (6.7%)
	DCF	6 (10.0%)
Surgery	Subtotal gastrectomy	28 (46.7%)
	Total gastrectomy	32 (53.3%)
Grade	II	36 (60.0%)
	III	24 (40.0%)
P staging	IB	4 (6.7%)
	IIA	14 (23.3%)
	IIB	8 (13.3%)
	IIIA	10 (16.7%)
	IIIB	24 (40.0%)
Margin	Negative	38 (63.3%)
	Positive R1	22 (36.7%)

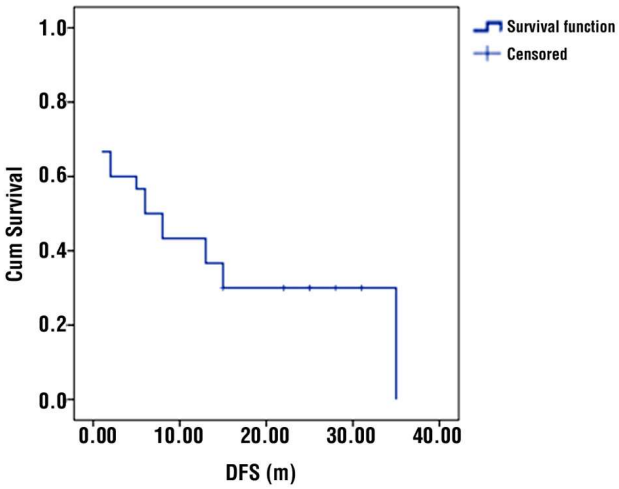

Figure 2 - Kaplan Meier analysis for factors affecting disease-free survival of the studied patients

response. However, partial pathological response was observed in 26 patients (43.3%), with poor response noted in 28 patients and excellent response in 6 patients. Concerning relapse, 44 patients (73.3%) experienced relapse, while 16 patients (26.7%) showed no signs of relapse.

Treatment outcome

Disease-free survival (DFS)

The prospective study revealed a median DFS of 6 months, with a 1-year DFS rate of 43.3% and a 2-year DFS rate of 30% (*tables 4, 5*, and *6* and *fig. 2*).

Overall survival rate (OS)

The mean OS was 26.3 months. Recorded survival rates were 75.8% at 1 year, 67.9% at 2 years, and the median OS was not reached *(tables 7* and *8* and *fig. 3*).

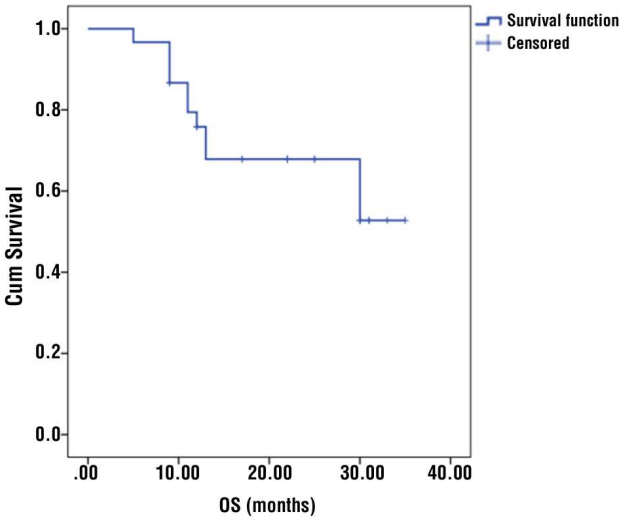

Figure 3 - Kaplan Meier analysis for factors affecting the overall survival of the studied patients

Table 4 - DFS mean survival of our patients

Total No.	DFS (months)		95% CI		Survival at			
	Mean	SE	Lower	Upper	3 months	6 months	12 months	24 months
60	13.933	1.882	10.244	17.622	60.0%	50.0%	43.3%	30.0%

Table 5 - DFS median survival of our patients

Total No.	DFS (months)		95% CI		Survival at			
	Mean	SE	Lower	Upper	3 months	6 months	12 months	24 months
60	6.000	1.452	3.153	8.847	60.0%	50.0%	43.3%	30.0%

Table 6 - Demographics and clinicopathological data with their correlation with DFS

		Total No.	No. of deaths	DFS (months)		95% CI		Log Rank test		
				Mean	SE	Lower	Upper	X^2	P-value	Sig.
Age (yrs)	< 50 yrs	28	18	13.714	2.475	8.864	18.565	0.386	0.534	NS
	> 50 yrs	32	26	12.875	2.489	7.997	17.753			
Gender	Female	28	24	10.071	2.562	5.051	15.092	3.638	0.056	NS
	Male	32	20	15.812	2.248	11.407	20.218			
Medical history	No	34	32	5.000	0.912	3.212	6.788	22.304	0.000	HS
	Yes	26	12	24.077	2.913	18.368	29.786			
SH	No	18	8	20.778	2.910	15.075	26.481	9.275	0.002	HS
	Yes	42	36	10.048	1.979	6.168	13.927			
PS	I	42	32	12.810	2.272	8.356	17.263	0.842	0.359	NS
	II	18	12	14.222	2.553	9.219	19.225			
Biopsy	Diffuse type adenocarcinoma	40	30	13.100	2.399	8.398	17.802	0.375	0.541	NS
	Intestinal type adenocarcinoma	20	14	11.700	1.706	8.356	15.044			
Site	Body	16	16	6.000	2.849	0.416	11.584	6.130	0.013	S
	Cardia	28	20	15.000	2.073	10.938	19.062			
	Fundus	6	4	10.000	5.196	0.000	20.184			
	Pylorus	10	4	15.400	3.718	8.113	22.687			
Surgery	Subtotal gastrectomy	28	22	11.214	2.131	7.037	15.391	0.654	0.419	NS
	Total gastrectomy	32	22	15.562	2.806	10.063	21.062			
Grade	II	36	32	10.944	2.002	7.020	14.869	3.660	0.056	NS
	III	24	12	16.417	2.984	10.567	22.266			
Margin	Negative	38	32	10.947	2.167	6.700	15.195	3.773	0.052	NS
	Positive R1	22	12	15.909	2.494	11.021	20.797			

NS* = non-significant; HS** = highly-significant.

Table 7 - OS mean survival in our patients

Total No.	OS (months)		95% CI		Survival at			
	Mean	SE	Lower	Upper	3 months	6 months	12 months	24 months
60	26.326	1.520	23.347	29.305	96.7%	86.7%	75.8%	67.9%

Table 8 - Demographics and clinicopathological data with their correlation with OS

		Total N	N of events	OS (months)		95% CI		Log Rank test		
				Mean	SE	Lower	Upper	X^2	P-value	Sig.
Age (yrs)	< 50 yrs	28	10	25.971	1.679	22.680	29.263	0.014	0.905	NS
	> 50 yrs	32	12	25.388	2.188	21.100	29.675			
Gender	Female	28	10	26.524	2.016	22.573	30.474	0.328	0.567	NS
	Male	32	12	24.938	1.846	21.319	28.556			
Medical history	No	34	16	21.972	1.884	18.280	25.664	3.792	0.052	NS
	Yes	26	6	29.308	2.040	25.309	33.306			
SH	No	18	4	27.667	2.352	23.057	32.276	3.525	0.060	NS
	Yes	42	18	24.270	1.845	20.654	27.886			
FH	No	52	18	25.733	1.748	22.307	29.158	0.178	0.673	NS
	Yes	8	4	30.000	0.000	30.000	30.000			
PS	I	42	18	24.796	1.892	21.087	28.505	2.593	0.107	NS
	II	18	4	28.111	2.156	23.886	32.336			
Biopsy	Diffuse type adenocarcinoma	40	12	26.813	1.940	23.010	30.615	1.513	0.219	NS
	Intestinal type adenocarcinoma	20	10	23.600	2.334	19.026	28.174			
Site	Body	16	14	12.625	2.172	8.368	16.882	28.179	0.000	HS
	Cardia	28	8	28.143	1.174	25.842	30.444			
	Fundus	6	0	--	--	--	--			
	Pylorus	10	0	--	--	--	--			
Surgery	Subtotal gastrectomy	28	10	27.472	1.694	24.152	30.793	1.75	0.186	NS
	Total gastrectomy	32	12	24.650	2.346	20.052	29.248			
Grade	II	36	10	29.000	1.620	25.826	32.174	1.948	0.163	NS
	III	24	12	21.667	2.347	17.066	26.267			
Margin	Negative	38	14	26.959	1.853	23.327	30.591	0.313	0.576	NS
	Positive R1	22	8	24.273	2.481	19.409	29.136			

NS* = non-significant; HS** = highly-significant.

DISCUSSION

Despite recent modest reductions in cancer-associated morbidity and mortality, gastric cancer (GC) continues to rank as the fourth most prevalent malignancy globally. The far eastern countries of "China, Japan, and Korea" had the highest incidence of early gastric cancer, accounting for over fifty percent of global totals (1).

The cancer stage primarily influences the prognosis of patients with GC. An example is the 5-year survival rate of approximately 25% for patients with advanced stages of GC (preoperative TNM stages III and IV). Even after undergoing macroscopic resection, it is estimated that local recurrence or distant metastases will occur in approximately 60% of GC patients (9).

Multimodality therapy encompasses D1+/D2 gastrectomy and neoadjuvant chemotherapy (NACT) and is widely recognized as the acknowledged standard of care in North America, Europe, and Australasia. D2 gastrectomy with adjuvant therapy is a standard procedure in the majority of Asia, whereas NACT therapy is required for patients with advanced gastric malignancies (10).

In our study, we examined patients aged 22-60 years, with a mean age of 46.67 years. We specifically reviewed PS I and II individuals, as they are candidates for chemotherapy. According to the SEER database, the mean age at diagnosis was 68 years, and 39.6% of all patients fell within our targeted age group (11).

A distinct investigation revealed that 92.6% of patients in the surgery-alone (SA) group achieved favorable surgical outcomes, including D2 lymph node dissection. In contrast, the percentage of patients in the neoadjuvant plus surgery (NACT + S) group was 95.7%. In the neoadjuvant arm, the 2-year survival rate was 72.7% (95%CI: 60.7%-81.7%), while in the surgery-only arm, it was 69.9% (95%CI: 57.7%-79.2%) (12).

Data from a multicenter randomized controlled trial (RCT) conducted by a group from the European Institute of Oncology in Milan were published. The trial aimed to assess the non-inferiority of preoperative neoadjuvant chemotherapy (NACT) with TCF followed by surgery (Arm A) compared to surgery followed by the same chemotherapy regimen (Arm B) concerning clinical outcomes, specifically fatalities and surgery-related morbidity, in patients with gastric cancer (GC). A minimum sample size of 240 patients presenting with locally advanced GC was mandated according to the initial prototype. Preoperative TCF was, in summary, comparable in morbidity and safety to surgery after a TCF regimen. Additionally, the lack of survival outcomes and the early termination of this investigation due to sluggish accrual rendered this study devoid of information regarding the effectiveness of preoperative TCF (13).

Eighty-eight patients with cTNM stage III or IV (M0) gastric cancer were registered in the studies by Biffi et al. and Qu et al. Of the patients, 39 were assigned to the surgical arm, and 39 were randomized to the NACT arm (paclitaxel combined with FOLFOX4). 66% of patients received a clinical response from the NACT division. In contrast with the SA arm, the NACT arm exhibited considerably lower lymph node metastases and a substantially higher R0 resection rate. Furthermore, the R-ACT group exhibited a greater 2-year survival rate than the surgery-only group. The lymph node dissection technique and site of the disease were not specified. Besides, very few samples were collected (14,15).

In our study, the R0 resection rate was achieved in 38 patients (63.3%). Another study conducted by Cunningham et al. (16) included two groups with a total of 503 patients: the first arm received neoadjuvant chemotherapy (NACT) followed by surgery (D2 lymphadenectomy), and the second arm underwent surgery only, with R0 resection rates of 64% and 61%, respectively. Moreover, Ajani et al. (17) reported an R0 resection rate of 72% in their trial. D'Ugo et al. (18) found an R0 resection rate of 82% in a study involving 34 patients, while Tsuburaya et al. (19) reported an R0 resection rate of 82% in a study with 53 patients. Furthermore, Kinoshita et al. (20) studied 55 patients, achieving an R0 resection rate of 80%. Biffi et al. (14), comparing 34 patients receiving NACT followed by surgery to 35 patients undergoing surgery alone, found an R0 resection rate of 85%.

Yachou et al. (21) investigated two groups, comprising 113 patients who received neoadjuvant chemotherapy (NACT) followed by surgery and 111 patients who underwent surgery alone, with R0 resection rates of 84% and 73%, respectively. Iwasaki et al.'s study, involving 36 patients, reported an R0 resection rate of 73%. Katayama et al. (22) studied 53 patients, achieving an R0 resection rate of 84.6%. In a study by Al-Batran et al. (23) involving two groups with different chemotherapy regimens followed by resection surgery (360/356 patients), the R0 resection rates were 78% and 85%, respectively.

In our study, no complete pathological response was observed. Instead, partial pathological response was noted in 26 patients (43.3%), with 28 patients exhibiting a poor response and 6 patients showing an excellent response. Similarly, Ajani et al.'s trial (17) and Kinoshita et al.'s study (20) did not report a complete pathological response. In contrast, D'Ugo et al. (18) found a complete response rate of 3%, and a trial by Biffi et al. (14)

reported a complete response rate of 11%.

Regarding OS, the median OS was not reached in our study. However, the 1-year OS rate was 75.8%, and the 2-year OS rate was 67.9%.

Ajani et al. (17) reported a median OS of 15 months, while Songun et al. (24) stated a median OS of 18 months. D'Ugo et al. (18) found a median OS of 28 months in their study with 34 patients. Tsuburaya et al. (19) reported a 5-year OS of 53%. Moreover, Yachou et al. (21), comparing two groups (113 patients receiving NACT then surgery to 111 patients undergoing surgery alone), found 5-year OS rates of 38% and 24%, respectively. In addition, Iwasaki et al. (25) reported a 3-year OS of 24.5%. Katayama et al. (22) reported a 5-year OS of 55%. Furthermore, Cunningham et al. (16), with two groups totaling 530/533 patients, discussed median OS as 33.9 vs. 34.4 months. Al-Batran et al. (23), in two groups receiving different chemotherapy regimens followed by resection surgery (360/356 patients), reported a median OS of 35 months and 50 months.

Conflicts of interests

There are no conflicts of interest.

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