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Feasibility of Upfront Debulking Surgery versus Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery for Advanced Ovarian Cancer

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Abstract

Background: Inappropriately ovarian cancer cannot be detected until an advanced stage. Radical debulking surgery is considered the cornerstone in the management of advanced ovarian cancer pointing to complete tumor resolution. Unless optimal debulking cannot be achieved, these patients gain little benefit from surgery. Neoadjuvant chemotherapy (NACT) has been recommended as a novel therapeutic modality to a diversity of malignant tumors when the disease is not willing to optimal surgical resection at the time of diagnosis or the patient who unfit for aggressive debulking surgery. **The purpose of this study** is to compare survival in the patient with advanced ovarian cancer (stage III/IV) underwent primary debulking surgery followed by adjuvant chemotherapy (PDS-ACTR) to those who received neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS). **Results:** Neoadjuvant chemotherapy (NACT-IDS) showed significant complete cytoreduction and decreased in surgical morbidity in comparison to primary debulking surgery (PDS-ACTR). NACT-IDS showed significant improvement in progression-free survival (P-value 0.002) and overall survival (P-value 0.03) in comparison to PDS-ACTR. Response to NACT and residual volume were the two independent prognostic factors for overall survival. **Conclusion:** NACT-IDS for advanced ovarian cancer (III/IV) resulted in higher frequency of complete resection with no residual tumor, less post-operative surgical morbidity and

significant increase progression-free survival and overall survival. Both responses to NACT and residual tumor volume were the two independent prognostic factors for survival in ovarian cancer.

Keywords

Advanced Ovarian Cancer, Debulking Surgery, Neoadjuvant Chemotherapy

1. Introduction

The fifth most common cancer among women is ovarian cancer, and approximately, half of the ovarian cancer patients die from the disease instituting it as the fourth most common cause of gynecologic cancer-related death in most industrialized countries [1] [2]. Early staging ovarian cancer confined to the ovary may have few or no symptoms, making its clinical diagnosis and management more difficult and symptoms were most commonly seen with the advanced disease. ≤30% of the patients with apparently early epithelial ovarian cancer might be upstaged after comprehensive surgical staging [3] [4]. Previous reports by Cass *et al.* and Maggioni *et al.* showed that patients with even early ovarian tumor confined to ovary might have pelvic or even Para aortic lymph nodes metastases which making systemic lymphadenectomy improving progression-free survival and disease-free survival [5] [6]. Although advances in diagnosis and management of epithelial ovarian cancer have changed in the last 25 years, the overall survival has not been improved as approximately 65% to 70% of all ovarian cancer continues to be diagnosed with advanced stage (III or IV). Primary optimal debulking surgery has become the standard step in the management of advanced epithelial ovarian cancer [7]. When optimal debulking cannot be achieved, little benefit from debulking surgery will be gained [8]. Neoadjuvant chemotherapy (NACT) has been anticipated as a novel therapeutic modality to a diversity of solid tumors when the disease is not amenable to radical surgical resection at the time of diagnosis or those who are unhealthy for aggressive debulking surgery [9]. NACT has been accepted as a useful approach for the treatment of various advanced cancers [10] [11]. In cases with advanced ovarian cancer, platinum-based chemotherapy regimens have been established to produce highest response rates and a statistically significant survival advantages compared with drug regimens without platinum [12] [13]. Recently, the results of a large phase III trial reported that women with stages IIIC and IV EOC randomized to NACT followed by debulking surgery (NACT-IDS) had the same survival as women undergoing PDS followed by chemotherapy (PDS-CTR) [14].

The purpose is to compare survival in the patient with advanced ovarian cancer (III/IV) underwent primary debulking surgery (PDS-CTR) followed by chemotherapy to those who received neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS).

2. Patients and Method

A noncontrolled interventional randomized prospective study, including patients diagnosed with advanced ovarian cancer (III/IV) in South Egypt Cancer Institute and Oncology department in As suit University hospital from April 2012 to March 2016. Each of the consecutive patients chose a closed envelope containing the number of the assigned group. Ethical approval waived and informed written consent obtained from each patient.

The diagnosis based on radiological studies, Cytology from as cites, histopathology obtained by tumor biopsy and tumor marker (CA125) is set to be more than 200 U/ml. We excluded patients with previous history of chemotherapy or radiotherapy for other malignancy, the patients with a history of organ dysfunction and poor performance status.

Patients in the study divided into two groups:

● ***Neoadjuvant Chemotherapy Arm*** (***NACT-IDS, the group I***)

Four cycles of chemotherapy regimen (TC) paclitaxel (175 mg/m^2, Day 1) and carboplatin (AUC 5, Day 1) were administered every three weeks followed by Interval debulking surgery (complete surgical resection include panhysterectomy, pelvic and para-aortic lymph node dissection, omentectomy, appendectomy and small or large bowel resection unless disease progression occurs followed by another four cycles.

● ***Standard Treatment Arm*** (***PDS-ACTR, group II***)

Primary debulking surgery is performed firstly including panhysterectomy followed by postsurgical chemotherapy (PDS-ACTR) of six to eight cycles of taxanes based regimen (TC), is administered every three weeks

● ***Imaging studies***

All patients included in the study performed imaging for diagnosis and staging at the time of admission. Modalities employed included. Abdominal and transvaginal sonography with color flow mapping (**Figure 1**), post contrast Multidetector CT (MDCT) (**Figure 2**) and MRI with diffusion are reserved for indeterminate cases.

For the sake of follow up; patients in group I Post contrast MDCT is performed after the first four cycles of administration of the chemotherapeutic agents and after finishing the regimen before surgical intervention (**Figure 3**). Afterwards routine follow up was carried out after four weeks from the time of operation to assess the presence of residual disease.

While for Group II; Imaging performed after the operative intervention to assess residual disease if present and to create a new baseline before applying the chemotherapy (**Figure 4**).

For both groups, Follow up was carried out with a routine clinical and radiological assessment where imaging is performed routinely after finishing three consecutive doses of chemotherapy (average every ten weeks). Response evaluation criteria employed with RECIST (response evaluation criteria in solid tumors) version 1.1.

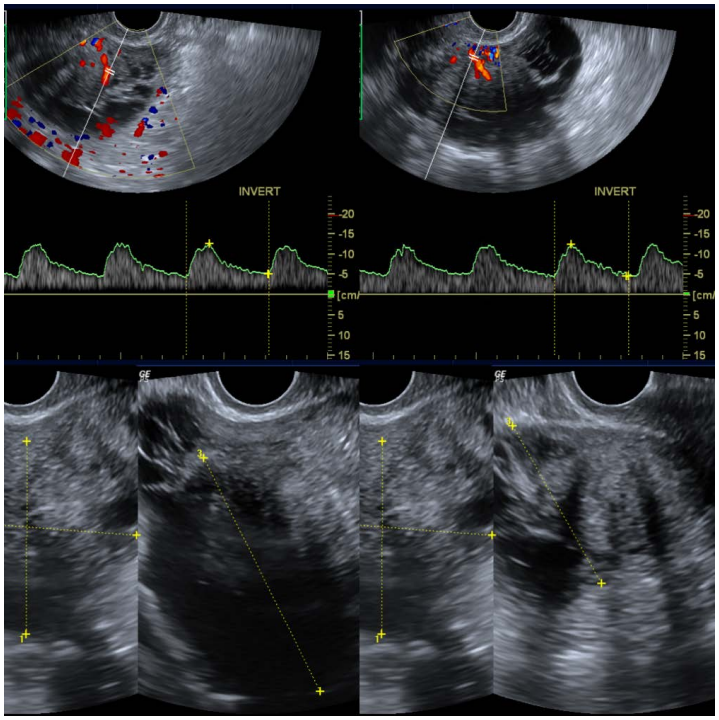

Figure 1. Transvaginal sonoraphy of a malignant featuring right mixed ovarian mass lesion with increased vascularity in color flow mapping.

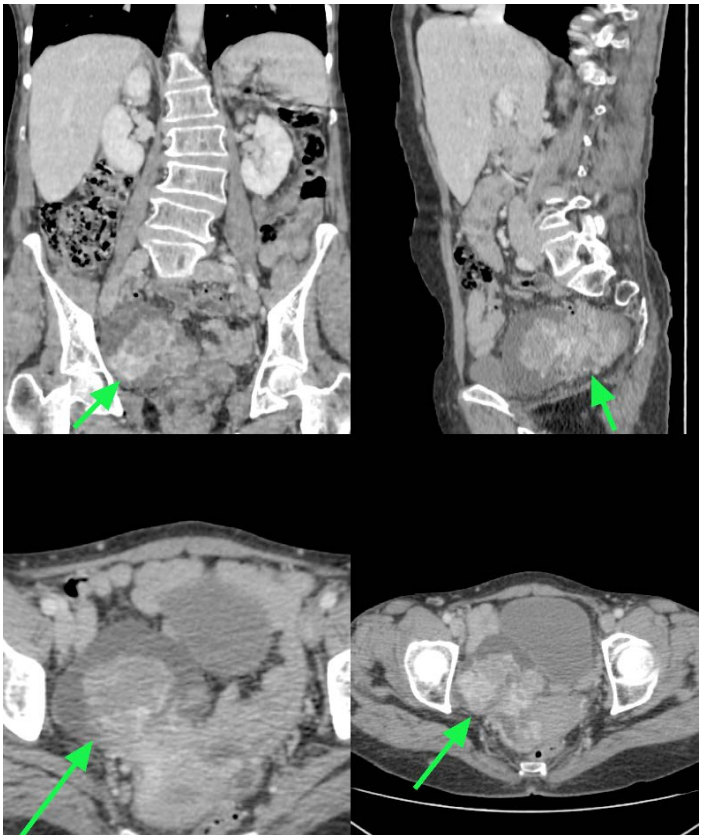

Figure 2. Post contrast MDCT of a malignant featuring right ovarian mass lesion of mixed nature (green arrow) and evident pelvic peritoneal deposites > 2 cm in size.

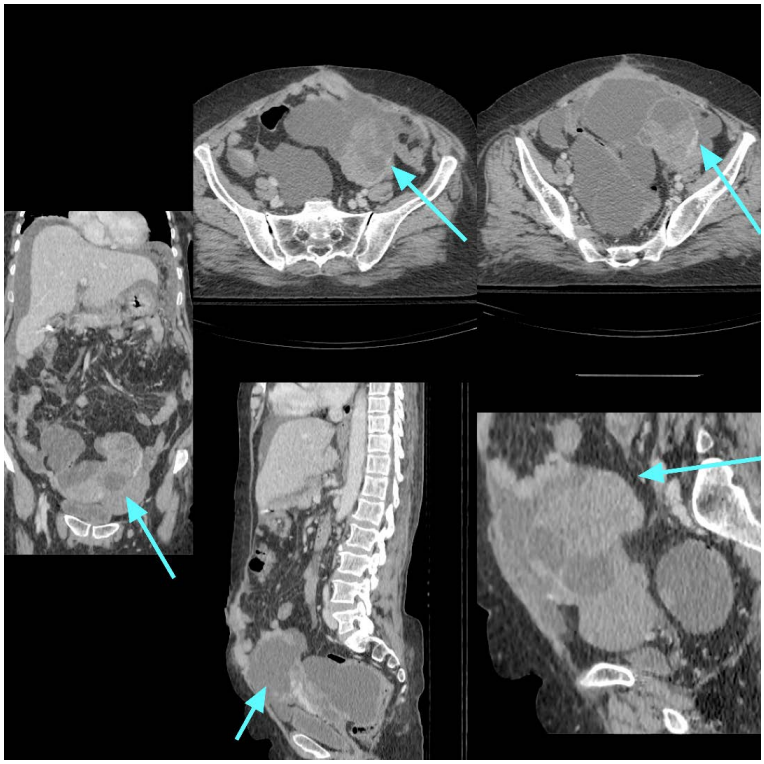

Figure 3. Post contrast MDCT of a malignant featuring left ovarian mass lesion of mixed nature and heterogenous enhancement (blue arrow) and evident peritoneal deposites posterior to anterior abdominal wall.

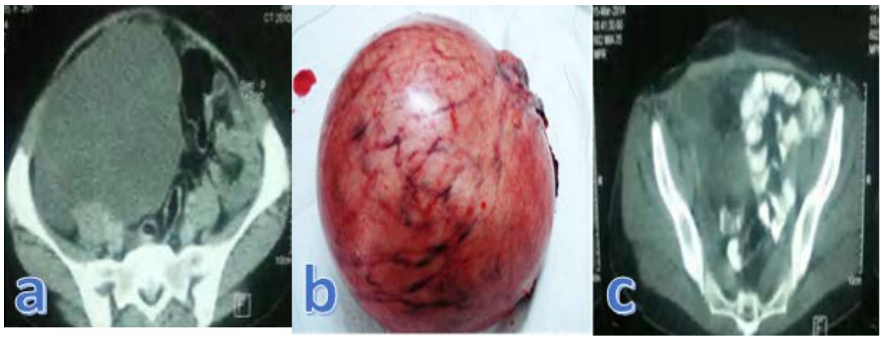

Figure 4. (a) Before chemotherapy: Right large pelviabdominal mass about 6 × 8 cm, mixed solid and cystic components. The lesion extends laterally with no line of separation with right iliopsoas muscle suggestive of infiltration and extends anteriorly with a clear fatty line of separation with the anterior abdominal wall, and the lesion compresses the adjacent bowel loops with multiple pelvic peritoneal deposits; (b) Apostoperative specimen of panhysterectomy of large Rt. ovarian mass; (c) After chemotherapy: Marked significant reduction of the size and extension. No definite infiltrationof the right iliopsoas muscle with complete pacifications of the related bowel loops with any mass effect on it.

• *Statistical Analysis*

Comparisons among groups performed with the t-test and the Fisher's exact test. The test was two sides. The result considered significant at $P < 0.05$. The Kaplan-Meier method is used for survival analysis. Cox regression analysis was used to predict factor affecting survival. SAS software version 6.2 (SAS Institute,

Cary, NC) was used for analysis of the result. Definition of the overall survival as the period from enrollment to the date of death from any cause or last follow-up. Progression-free survival is defined as the interval from enrollment of patients, to the time of disease relapse or progression.

3. Result

● ***Patients characteristics***

Among 130 patients of advanced ovarian carcinoma (III/IV), 66 patients received neoadjuvant chemotherapy (TC) followed by interval debulking surgery (NACT-IDS, the group I)and 64 patients underwent primary debulking surgery followed by postoperative chemotherapy(PDS-ACTR, the group II). No statistical significant difference between the two groups as regard patient's characteristic criteria including age, PS, histopathology, and serum level of CA125 (Table 1).

● ***The result of surgery in both groups***

The rate of complete resection with no residual disease was significantly higher in patients with NACT-IDS group versus PDS-ACTR group (76.9% vs 54%, P = 0.03) (Table 2). Also, the following post-operative morbidity such as;

Table 1. Patient's characteristics comparison between both groups.

Variables		NACT-IDS	PDS-ACTR	P-value
Age	Median	61	63	NS
	Range	42 - 74	39 - 78	
	Total	66	64	
Histopathology	Serous	42 (65%)	40 (63%)	NS
	Mucinous	13 (20%)	12 (19%)	
	Clear	3 (4%)	2 (3%)	
	Endometroid	5 (7%)	6 (9%)	
	Undiffertiated	3 (4%)	4 (6%)	
Figo Stage	IIIB	9 (14%)	12 (19%)	NS
	IIIC	49 (74%)	45 (70%)	
	IV	8 (12%)	7 (11%)	
CA125 level	Normal	6 (9%)	7 (11%)	NS
	<500	38 (58%)	42 (66%)	
	>500	22 (33%)	15 (23%)	

Table 2. Degree of surgical debulking between both groups.

Variables		NACT-IDS (n = 66)	PDS-ACTR (n = 64)	P-value
TBSO/Omentectomy		65 (98%)	59 (92%)	NS
Optimal cytoreduction		50 (76.9%)	32 (54%)	0.03
Suboptimal Cytoreduction	**Total**	15	27	0.002
	<1 cm	8	7	
	1.1 - 2	4	13	0.002
	>2 cm	3	7	

bowel resection, urinary bladder injury, blood loss, deep venous thrombosis (DVT), hospitalization and ICU admission were significantly lower in a group received NACT-IDS (Table 3).

● ***Survival analysis***

The median time of follow up was 36-month range from (8 - 42 month). *The progression-free survival* (PFS) tended to be significantly improved in NACT-IDS group in comparison to whom underwent PDS-ACTR group (mPFS, 20 months vs. 15 months respectively, P value = 0.002 [log rank test], HR: 2.661, 95% CI 1.269 - 5.582) (Figure 5).

There is significant difference in Overall survival between NACT-IDS group and PDS-ACTR group (mOS, 27 months vs. 18 months respectively, P value = 0.04 [log rank test], HR: 2.661, 95% CI 1.269 - 5.582) (Figure 6). Cox regression analysis showed significant factors predicted survival is residual tumor volume in both groups, Cox proportional hazard models demonstrated both macroscopic residuals (>2 cm, P = 0.002) (odds ratio, 1.47; 95% confidence interval (95% CI), (1.23 - 1.77; P = 0.002) and response to neoadjuvant chemotherapy (P = 0.03) (odds ratio, 1.67; 95% confidence interval (95% CI), (1.34 - 2.07; P = 0.03) to be the most statistically significant predictive survival variables (Table 4).

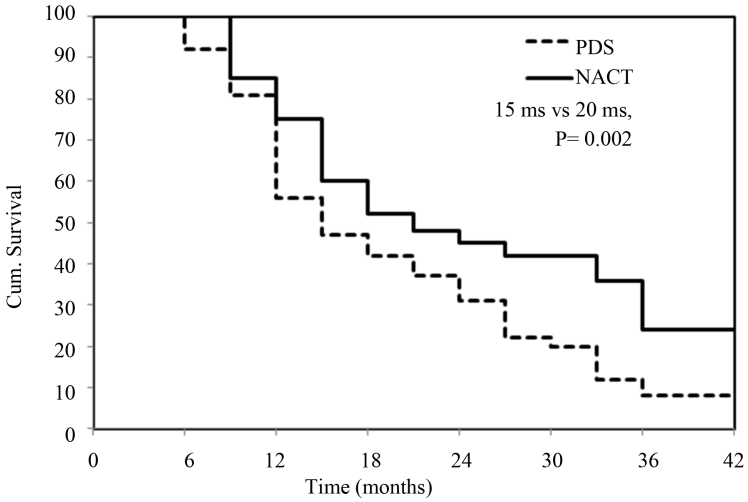

Figure 5. Graphical presentation of progression free survival in NACT and PDS groups.

Table 3. Surgical morbidities between both groups.

Variables	NACT-IDS	PDS-ACTR	P-value
Urinary bladder injury	4	9	0.02
Bowel injury	0	3	0.02
ICU stay	1.9	4.2	0.02
Hospital stay	8.7	15	0.03
DVT	5	12	NS
Blood loss	430	720	0.001
Blood transfusion	1 (500 cc)	4 (500 cc)	0.02

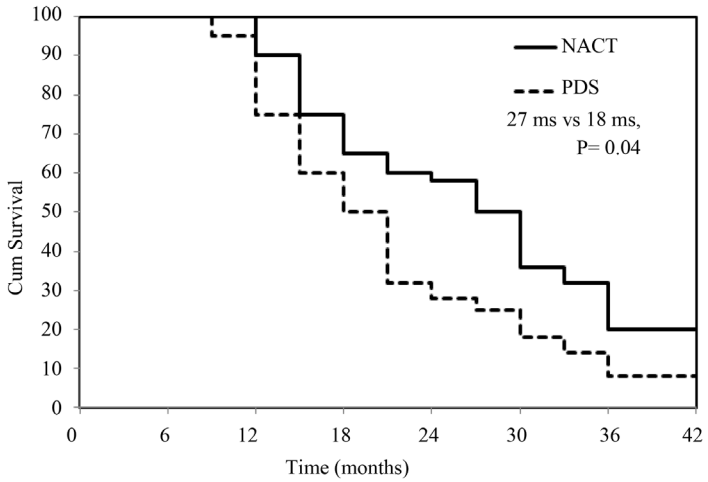

Figure 6. Graphical presentation of overall free survival in NACT and PDS.

Table 4. Multivariate Cox regression analysis of both groups for overall survival.

factor		No. of cases	OCR deaths (%|)	HR	CI (95%)	P-value
Age at diagnosis	50 - 55	32	15 (46.8%)	0.67	0.47 - 0.95	0.06
	56 - 60	40	18 (45%)	0.64	0.73 - 1.02	
	61 - 65	33	21 (63.3%)	0.88	0.64 - 1,12	
	65 - 70	25	19 (76%)	1.03	0.75 - 1.23	
Histology	Serous	82	49 (59.7%)	0.98	0.67 - 1.34	0.76
	Mucinous	25	14 (56%)	1.00	0.65 - 1.23	
	Clear cell	5	3 (60%)	089	0.71 - 1.29	
	Endometroid	11	6 (54%)	0.93	0.68 - 1.34	
	Undifferetiated	7	4 (57%)	097	0.71 - 1.34	
Stage	III	115	79 (68.6%)	1	-	0.01
	IV	15	11 (73.3%)	0.5	0.61 - 0.85	
Grade of differetiation	Well	60	20 (30%)	1	-	0.06
	Moderate	40	25 (62%)	1.34	0.98 - 1.67	
	Poor	30	21 (70%)	1.54	0.87 - 1.87	
Residual tumor	0	82	23 (28%)	1	-	0.002
	≤2cm	32	10 (31.3%)	1.33	1.07 - 1.64	
	>2cm	10	6 (60%)	1.47	1.23 - 1.77	
Response to NACT	Responding	49	30 (61%)	1	-	0.03
	No responding	16	12 (75%)	1.67	1.34 - 2.07	

4. Discussion

Management of ovarian cancer is one of highest confrontation in oncology, but unfortunately 70% of patients presented in advanced stage (III, IV) and approximately half of them die from cancer, making it one of the leading cause of

gynecologic-cancer related death [15]. Primary debulking surgery has become the favored first step in the management of advanced ovarian cancer [7]. Our purpose aims to evaluate the upfront role of neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) in advanced ovarian cancer (III/IV) versus primary debulking surgery followed by chemotherapy (PDS-ACTR). Our results showed that the rate of attaining complete resection with no residual disease was significantly higher in patients with NACT-IDS versus PDS-ACTR ($P = 0.03$). The patient underwent NACT-IDS show less surgical invasiveness and less postoperative morbidity such as; bowel resection, urinary bladder injury, blood loss, deep venous thrombosis (DVT), hospitalization and ICU admission. The previous reports exposed complete resection in NACT-IDS after neoadjuvant chemotherapy ranging from 75% to 90%. Neoadjuvant chemotherapy decreases tumor volume and facilitates surgical procedures especially chemosensitive tumor which had completed or partial clinical response achievement in 76% of patients with less residual volume which had an impact of decrease morbidity and mortality and improving clinical outcome [16]-[23]. Analysis of our data showed significant improvement in both progression-free survival and overall survival in those underwent NACT-IDS compared to PDS-ACTR these results comparable to those published by Kuhn *et al.* [24] [25], Rose *et al.*, and Muggia *et al.* [6] [24] [25] [26], they showed prolonged survival times and significantly better median survival in NACT group than the conventional PDS-ACTR. According to data published by Onnis *et al.* [18] and Surwit *et al.* [24], they described patients treated with NACT-IDS compared with those underwent conventional PDS followed by chemotherapy; They found that overall survival was not upgraded. Analysis of data reported by Schwartz *et al.* [16] and Vergote *et al.* [22] patients treated with NACT followed by PDS still obtained similar survival compared to those undergoing conventional primary surgery. This disagreement might be due to different patient characteristics and dissimilar treatment regimens. Multivariate analysis of previous data suggests the primary goal for best management and excellent outcome of these patients to reach to no residual tumor volume which can achieve by NACT-IDS with less surgical morbidity and better survival (19.20 - 31.32). In our data, show a residual tumor, response to chemotherapy and staging (III) are the most statistically significant predictive variables adversely affecting survival.

5. Conclusion

NACT-IDS for advanced ovarian cancer (III/IV) resulted in higher frequency of complete resection with no residual tumor, less post-operative surgical morbidity and a significant increase in both progression-free and overall survival. Further prospective study with more number of patients is highly recommended.

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