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Role and survival benefits of secondary surgery in ovarian carcinoma patients with isolated lymph node recurrence (ILNR): a comparative study

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ABSTRACT

Objective. Aim of this current study was to assess benefits, role, safety and outcomes of secondary surgery (SS) followed by chemotherapy in comparison with using chemotherapy alone in EOC patient presented with isolated lymph node recurrence (ILNR).
Patients and Methods. This study included 25 EOC patients who presented with ILNR underwent secondary surgery followed by chemotherapy and 35 EOC patients who presented with ILNR and treated with chemotherapy alone. We collected clinical, surgical, pathological and follow-up data and compared between both groups of patients regarding outcome, recurrence and survival rates.
Results. Favorable RFS and OS rates were found to be associated with the type of treatment (SS followed by chemotherapy *versus* chemotherapy alone p = 0.036 and p = 0.049 respectively). Patients who underwent SS followed by chemotherapy had a 75% reduction in recurrence related death risk and an 80% reduction in general death risk after primary diagnosis in comparison with those who received only chemotherapy without SCS.
Conclusions. We concluded that SS in addition to chemotherapy in selected ovarian cancer patients presented with ILNR was associated with a more favorable outcome than using chemotherapy alone.

INTRODUCTION

Epithelial ovarian cancer (EOC) is considered the 4th commonest mortality reason in females worldwide. EOC has a poor prognosis due to late diagnosis [1]. Its management includes surgical excision and platinum-based chemotherapy [2]. Surgical excision of any suspicious or enlarged lymph nodes during surgical management of EOC is needed for cytoreduction and for adequate surgical staging, but performing systematic lymphadenectomy routinely during the primary debulking surgery was not found to improve patients' outcome [3]. Most EOC patients respond well to platinum and taxane combination chemotherapy, but there are many patients with advanced disease found to have recurrence within two years [4].

Primary cytoreduction surgery followed by systemic chemotherapy is the initial management plan for patients with advanced EOC [5].

EOC recurrence primarily involved intraperitoneal (IP) and retroperitoneal LN (RLN) metastases in 13%–37% of cases and isolated para-aortic LN recurrences are diagnosed, in 3–34% of cases [2]. Secondary cytoreductive surgery (SCS) is performed after completion of the primary management and ending the disease-free time [6]. SCS aims at survival prolongation in addition to improvement of patients' quality of life and decreasing cancer related symptoms [7]. It was found that EOC patients who presented with isolated RLN recurrence have favorable survival [8], particularly if it was operable and surgically excised during secondary cytoreduction [9]. But other studies showed that there were no survival benefits from secondary cytoreduction followed by chemotherapy in comparison with chemotherapy alone, in patients with recurrent EOC [10]. LN recurrence is considered a systemic relapse even if localized, which is usually treated by chemotherapy alone. There is lack of sufficient studies regarding comparison between secondary cytoreduction followed by chemotherapy and chemotherapy alone without secondary debulking in patients with EOC recurrence in LN [2]. SCS might be of a benefit in certain patients who presented with isolated lymph node recurrence (ILNR) [11].

Aim of this current study was to assess benefits, role, safety and outcomes of Secondary cytoreductive surgery (SCS) followed by chemotherapy in comparison with using chemotherapy alone in EOC patient presented with isolated lymph node recurrence (ILNR).

PATIENTS AND METHODS

This is a retrospective study which was performed in Zagazig University hospitals, Oncology Units in Departments of Gynecology and Obstetrics and in General surgery.

We selected all EOC patients who presented with ILNR underwent secondary cyto-reductive surgery followed by chemotherapy and EOC patients who presented with ILNR and treated with chemotherapy alone in the period between 2015 and 2020. The study was approved by the local ethics committee of Faculty of Medicine, Zagazig University in compliance with the Helsinki Declaration.

We diagnosed ILNRs during follow-up visits by detailed gynecological examination and measuring serum levels of CA-125 every 3 months for the first 2 years and then every 6 months. In case of a rise in CA-125 levels or clinical suspected recurrence we prescribed PET-TC scan, CT or MRI.

Inclusion criteria of the study were: patients with a past history of EOC who underwent primary successful surgical management, patients with a good performance status, disease free interval (DFI) of at least six months from primary surgical management, clinical and radiological evidence of ILNRs, radiological evidence of resectable disease and absence of ascites.

Exclusion criteria of the study were: patients' age > 75 years, low performance status and presence of peritoneal disease with a sure histopathological diagnosis of recurrence.

Clinical, surgical, pathological and follow-up data were collected. Recording patients' age, presence of co-morbidities, FIGO stage, histopathological subtype, tumor grade, residual tumor after primary surgery, type of used chemotherapy, DFI from the primary surgical treatment, sites and extent of ILNRs, duration of post-operative hospital stay and morbidity, progression free survival (PFS), overall survival (OS) after SCS was performed.

We defined SCS as any surgery performed after the primary treatment completion and after ending the disease free period. PFS rate following patients management was defined as the time from ending the secondary management (whether surgery followed by or chemotherapy alone) until the second recurrence. OS rate following patients management was defined as the time from ending the secondary management (whether surgery followed by or chemotherapy alone) until either death or the date of the last available follow-up.

Management of the group of patients underwent SCS

Median laparotomy, abdominal cavity and complete retroperitoneal exploration were performed. If we found peritoneal recurrence we excluded the patient from the study. Any suspected ILNR were identified and resected. We informed patients underwent surgery about their management, aims, expected results and possible risks. We acquired a signed written consent from included patients.

After surgery, patients were referred to an oncologist for chemotherapy regimen. Patients who did not undergo SCS were only subjected to chemotherapy management. All patients were followed-up until they died or until July 2020. The median follow-up of survivors was 34.5 months (range, 12 to 60 months).

Statistical analyses were performed using SPSS 18.0 software (SPSS, Inc., Chicago, IL). We presented values as median and range. We calculated survival using the Kaplan-Meier method, comparing differences between survival curves was done by using Log Rank test.

RESULTS

Outcome of the included 60 ovarian carcinoma patients who underwent primary surgery then presented later on by ILNRs was assessed.

Median age was 50 years, range (30-68years), FIGO stages were III–IV in 32 (54%) patients, serous carcinoma was found in 30 (50%) patients, lymphadenectomy was performed during the primary surgery in 23 (38.3%) patients, residual tumor after the primary surgery was less than 1 cm in 32 (54%) patients and first-line chemotherapy consisted of paclitaxel-/platinum-based chemotherapy in most patients. Consolidation chemotherapy was given to 48 (80%) patients (**Table 1**).

Management of patients with ILNRs included: chemotherapy alone in 35 (58.3%) and a combina-

Table 1. *Clinicopathological features of all included patients according to presence or absence of secondary cytoreductive surgery (SCS).*

Variable		SCS						P-value
		Absent N = 35		Present N = 25		Total N = 60		
		N	%	N	%	N	%	
Age (years)		50	30 - 68	54	32 - 67	50	30 - 68	0.192
Primary Surgery	Upfront surgery	29	82.9%	21	84.0%	50	83.3%	0.907
	Interval surgery	6	17.1%	4	16.0%	10	16.7%	
Lymphadenectomy	No lymphadenectomy	18	51.4%	19	76.0%	37	61.7%	0.237
	Partial lymphadenectomy	10	28.6%	4	16.0%	14	23.3%	
	Systemic lymphadenectomy	7	20.0%	2	8.0%	9	15.0%	
FIGO stage	I	6	17.1%	5	20.0%	11	18.3%	0.001
	II	11	31.4%	0	0.0%	11	18.3%	
	III	8	22.9%	17	68.0%	25	41.7%	
	IV	10	28.6%	3	12.0%	13	21.7%	
Grade	Low	15	42.9%	10	40.0%	25	41.7%	0.825
	High	20	57.1%	15	60.0%	35	58.3%	
Histology	Serous	14	40.0%	16	64.0%	30	50.0%	0.006
	Mucinous	11	31.4%	5	20.0%	16	26.7%	
	Endometroid	4	11.4%	1	4.0%	5	8.3%	
	Others	6	17.1%	3	12.0%	9	15.0%	
Size of largest ILNRs mm		14	12 -15	18	17 - 20	15	12 - 20	< 0.001
Response to treatment	PD	4	11.4%	2	8.0%	6	10.0%	0.962
	SD	4	11.4%	3	12.0%	7	11.7%	
	PR	5	14.3%	3	12.0%	8	13.3%	
	CR	22	62.9%	17	68.0%	39	65.0%	
Preoperative chemoradiotherapy	Absent	16	45.7%	14	56.0%	30	50.0%	0.432
	Present	19	54.3%	11	44.0%	30	50.0%	
Post-operative chemoradiotherapy	Absent	6	17.1%	6	24.0%	12	20.0%	0.513
	Present	29	82.9%	19	76.0%	48	80.0%	

tion of SCS and chemotherapy in 25 (41.7%) patients. Surgery was performed in 17 patients with recurrence in the pelvic and/or paraaortic lymph nodes, in 3 patients with recurrence in the abdominal lymph nodes, in 3 patients with recurrence in the inguinal lymph nodes, and in 2 patients with recurrence in the pelvic and inguinal lymph nodes. Intra-peritoneal masses were completely removed in 5 (20%) of the 25 patients who underwent SCS and histopathological evaluation revealed only fibrosis and absence of recurrence in the peritoneum. The time to recurrence for the 25 patients who underwent SCS was: 6 months in 1 patient, 6 to 12 months in 6 patients, and longer than 12 months in remaining 18 patients. Among patients who underwent lymphadenectomy, the removed lymph nodes median number was 14 (range 6-28). Histo-pathological examination of surgically excised lymph nodes showed isolated solitary epithelial ovarian cancer recurrence in all patients in about 6 lymph nodes ranged from [3-8].

Median follow-up time after SCS is 34.5 months (range, 12 to 60 months). After ILNR, the second recurrence was usually multiple and distant.

Sites of further recurrences after the follow-up were: Nodal only, Intra-peritoneal, Intra-peritoneal and distant. To date, 30 (50%) are alive (**Figures 1, 2**).

Of the 35 patients who received chemotherapy alone, 22 (62.9%) achieved a complete response and an overall response rate of 67%. 14 (40%) are still alive with no clinical evidence of disease. Of the 25 patients who underwent SCS plus chemotherapy 16 (64%) are still alive with no clinical evidence of disease. Recurrence free survival rate (RFS) was significantly associated with the type of treatment (SCS followed by

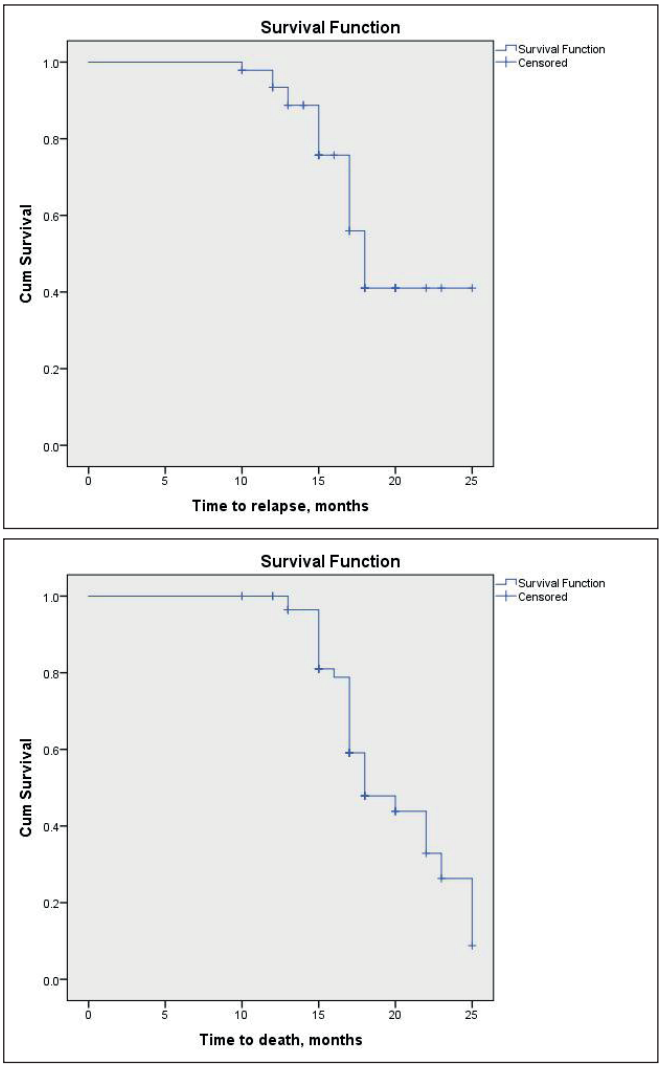

Figure 1. ***(A)*** *Kaplan–Meier survival curves showing recurrence free survival rate (RFS) in all included patients.* ***(B)*** *Kaplan–Meier survival curves showing overall survival rate (OS) in all included patients.*

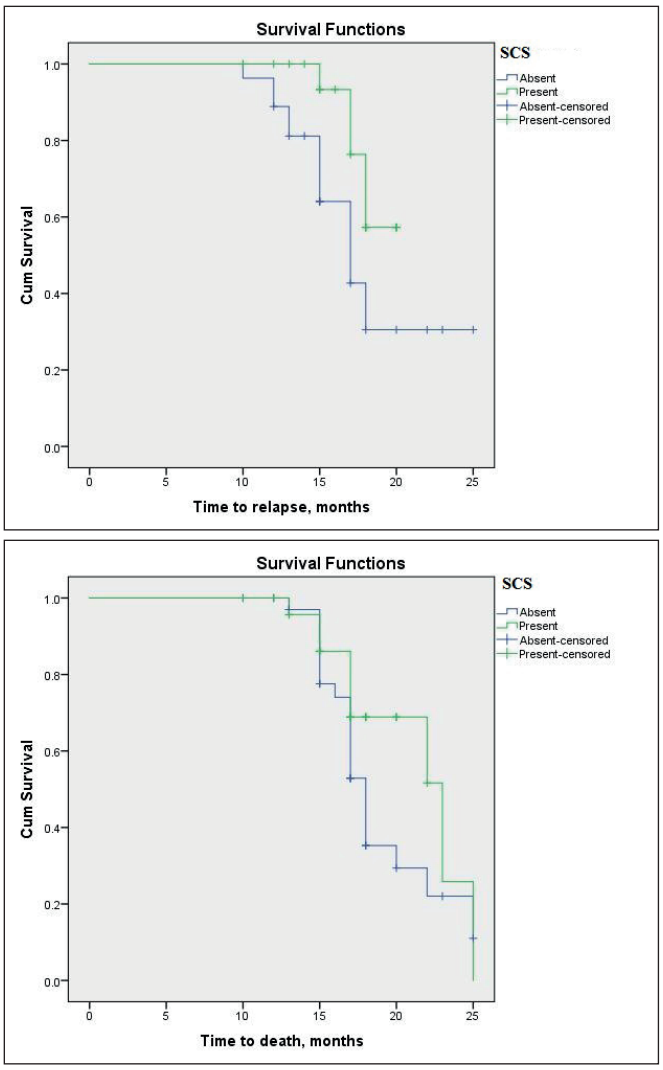

Figure 2. ***(A)*** *Kaplan–Meier survival curves showing comparison of the recurrence free survival rates (RFS) of both included groups of patients.* ***(B)*** *Kaplan–Meier survival curves showing comparison of the overall survival rates (OS) of both included groups of patients.*

chemotherapy *versus* chemotherapy alone p = 0.036) and FIGO stage (p = 0.04), and size of recurrent lymph node (p = 0.044), but not to histological type, lymph node excision during primary surgery, residual tumor after primary surgery, consolidation therapy or grade of the tumor (**Table 2**).

Overall survival was significantly related to the type of treatment (SCS followed by chemotherapy *versus* chemotherapy alone p = 0.049), but not to not to histological type, lymph node excision during primary surgery, FIGO stage, residual tumor after primary surgery, consolidation therapy or grade of the tumor (**Table 3**).

Univariate and multivariate analyses showed that treatment at recurrence was the strongest independent prognostic variable for both RFS and OS rates ($p < 0.001$) (**Tables 4, 5, Figures 1, 2**).

Patients who underwent SCS followed by chemotherapy had a 75% reduction in recurrence related death risk and 80% reduction in general death risk after primary diagnosis in comparison with those who received only chemotherapy without SCS.

DISCUSSION

Benefits and drawbacks of SCS in management of ILNRs in ovarian carcinoma are still important points of research in gynecologic oncology [11].

Berek *et al*. [12] introduced the first published concept of indications of "secondary cytoreduction", and since then many studies assessed such object extensively.

Many studies showed that certain patients who were sensitive to platinum-based chemotherapy, who have high performance status, who have recurrent but resectable disease, patients with serous carcinoma and patients without ascites could benefit of SCS [13-16].

Other studies reported that in cases with multiple sites of recurrence, cases with clear cell morphology, cases with ascites and cases with advanced FIGO stage could not benefit from surgery and have a shorter survival [17].

By contrast, some reports stated that even patients with multiple sites of recurrence surgery are recommended with resection of part of the liver or

Table 2. *Outcome of all included patients according to presence or absence of secondary cytoreductive surgery (SCS).*

Variable		SCS				Total		P-value
		Absent N = 35		Present N = 25				
		N	%	N	%	N	%	
Secondary Recurrence pattern after SCS	Local	8	34.8%	5	50.0%	13	39.4%	0.411
	Distant	15	65.2%	5	50.0%	20	60.6%	
Death	Alive	14	40.0%	16	64.0%	30	50.0%	0.047
	Dead	21	60.0%	9	36.0%	30	50.0%	
Relapse*	Free	12	44.4%	15	75.0%	27	57.4%	**0.036**
	Relapse	15	55.6%	5	25.0%	20	42.6%	

*Calculated from responders.

Table 3. *Survival analysis [OS & RFS] of all included patients according to presence or absence of secondary cytoreductive surgery (SCS).*

PALN	Total N	N of Events	Censored		Survival time in Months				Survival rate%	Sig.
					Mean		Median			
					Estimate ± SE	95% CI	Estimate ± SE	95% CI		
Overall Survival										
Absent	35	21	14	40.0%	18.9 ± 0.8	17.4-20.4	18.0 ± 0.5	17.0-19.0	11.0%	0.049
Present	25	9	16	64.0%	21.1 ± 1.0	19.1-23.1	23.0 ± 2.8	17.5-28.5	0.0%	
Overall	60	30	30	50.0%	19.8 ± 0.6	18.6-21.0	18.0 ± 1.5	15.0-21.0	41.0%	
Relapse-Free Survival										
Absent	27	15	12	44.4%	18.3 ± 1.0	16.2-20.3	17.0 ± 1.0	15.0-19.0	30.5%	**0.036**
Present	20	5	15	75.0%	18.8 ± 0.4	17.9-19.6	NR		57.3%	
Overall	47	20	27	57.4%	19.6 ± 0.8	18.0-21.2	18.0 ± 0.6	16.8-19.2	8.8%	

NR: Not reached; 95% CI: 95% confidence interval; Sig.: significance; SE: standard error.

Table 4. *Univariate and multivariate Cox regression analyses for overall Survival of all included patients according to presence or absence of secondary cytoreductive surgery (SCS).*

Co-variate	Overall Survival			
	Univariate		Multivariate	
	Sig.	HR (95% CI)	Sig.	HR (95% CI)
Age (years)	0.199	1.03 (0.99-1.07)		
Primary surgery	0.978	1.01 (0.41-2.52)		
Lymphadenectomy	**Ref.**			
No	0.458	1.52 (0.50-4.63)		
partial	0.896	1.09 (0.31-3.87)		
systemic	0.076	3.39 (0.88-13.03)		
FIGO stage	**Ref.**			
I	0.998	1.00 (0.30-3.32)	0.959	1.04 (0.25-4.32)
II	0.173	0.47 (0.16-1.39)	0.961	1.04 (0.23-4.66)
III	0.031	0.35 (0.13-0.91)	0.229	0.52 (0.18-1.51)
IV	0.029	2.61 (1.10-6.17)	0.079	2.48 (0.90-6.82)
Size of largest LN mm	0.211	0.91 (0.79-1.05)		
Grade	**Ref.**			
Low	0.506	1.45 (0.48-4.38)		
High	0.264	1.99 (0.59-6.67)		
SCS	0.204	1.66 (0.76-3.63)		
Preoperative chemoradiotherapy	0.002	0.21 (0.08-0.57)	0.003	0.01 (0.00-0.23)
Post-operative chemoradiotherapy	0.037	4.65 (1.10-19.62)	0.205	2.72 (0.58-12.76)
Relapse	0.011	3.37 (1.32-8.63)	0.004	0.01 (0.001-0.26)
Response to treatment	< 0.001	0.54 (0.39-0.75)	0.023	0.59 (0.38-0.93)

HR: hazard ratio; 95% CI: 95% confidence interval; Sig.: significance.

Table 5. *Univariate and multivariate Cox regression analyses for Relapse-free Survival rate of all included patients according to presence or absence of secondary cytoreductive surgery (SCS).*

Co-variate	Relapse-free Survival			
	Univariate		Multivariate	
	Sig.	HR (95% CI)	Sig.	HR (95% CI)
Age (years)	0.87	1.00 (0.95-1.04)		
Primary surgery	0.339	0.49 (0.11-2.12)		
Lymphadenectomy	**Ref.**			
No	0.824	0.86 (0.23-3.25)		
partial	0.948	1.05 (0.25-4.39)		
systemic	0.087	3.79 (0.82-17.40)		
FIGO stage	**Ref.**			
I	0.375	1.89 (0.46-7.70)		
II	0.667	0.75 (0.20-2.83)		
III	0.16	0.41 (0.12-1.42)		
IV	0.04	2.72 (1.05-7.10)		
Size of largest LN mm	0.043	0.83 (0.68-0.99)	0.145	0.86 (0.70-1.05)
Grade	**Ref.**			
Low	0.653	1.43 (0.30-6.72)		
High	0.08	4.11 (0.85-20.00)		
SCS	0.081	4.94 (0.82-29.71)		
Size of largest LN mm	0.062	0.38 (0.14-1.05)		
Preoperative chemoradiotherapy	< 0.001	7.32 (2.43-21.99)	0.001	6.16 (2.02-18.78)
Post-operative chemoradiotherapy	0.108	32.28 (0.46-2240.74)		

HR: hazard ratio, 95% CI: 95% confidence interval; Sig.: significance.

diaphragm and excision of lymph nodes above levels of renal vessels [18].

In the current study when we assessed the role of SCS in ovarian cancer with ILNRs we showed the benefits of surgical excision followed by chemotherapy more than using chemotherapy alone; similarly results of Ferrero *et al*. [11] and T. Levy *et al*. [2].

Moreover, previous publications assessed the outcome of SCS and showed similar results to ours, and they showed the survival advantages of combined surgery followed by chemotherapy *versus* chemotherapy alone [15, 19-22], slightly similar results were showed by Bogani [23], who reported that role of SCS in patients with recurrent ovarian carcinoma might prolong RFS rate but has no benefits on the OS rate. Different results were found by Coleman *et al*. [10] who recently showed that performing SCS followed by chemotherapy has no survival or prognostic importance to patients with recurrent ovarian cancer. These different results might be due to different cohort of studied patheints and different inclusion criteria of them.

There are many theories published by previous studies and could prove our findings; first, rationale of surgical excision of recurrent cancer is supported mathematically using Goldie and Coldman mod-

el which predicts cancer cells drug resistance and it suggests that chemotherapy efficacy is related to tumor cells number: 105 cancer cells are more liable to be curable with chemotherapy and they stated that a malignant nodule of 1 cm contains from 106-107 cancer cells [24], second, surgical excision remove poorly vascularized tumor tissues which was transformed to drug resistant sub-clones [25], third residual tumor cells have high perfusion which will ensure better actions of chemotherapeutic agents, fourth, residual tumor tissues after SCS required small number of cycles of chemotherapy which helps in decreasing drug resistance, finally removing main tumor bulk in SCS with help in restimulation of the host immunity [26]. Recent Meta- and single-study analyses showed that complete SCS which ensured no visible residual disease is associated with marked improvement in survival and outcome in recurrent ovarian cancer patients with platinum-sensitivity; they stated that it was not clear whether these results were solely due to surgical roles or due to tumor cells biology [27].
In ovarian carcinoma patients it was found that extensive debulking surgery might have post-operative morbidity and complication as: peritonitis, infection, infection, hematoma, bowel injury, which subsequently lead to a delay in chemotherapy initiation, but when all surgeries performed by senior surgeons with a good experience in surgical management of advanced ovarian cancers post-operative morbidity markedly decreased and surgery become an alternative safe approach [28].

Points of strengths in our study

Our study has many points of strengths: large number of included patients, long follow-up time, and comparative nature of the study, strict inclusion and exclusion criteria.
Points of weakness in our study were: its retrospective nature in addition to its performed in a single institution.

CONCLUSIONS

As ILNR was found to have slightly less aggressive behavior, we concluded that SCS in addition to chemotherapy in selected patients was safe, feasible, of less post-operative morbidity, in the case it was done by a qualified oncologic surgeon, and associated with a more favorable outcome than using chemotherapy alone.

Recommendation

We recommend performing a comparative and prospective study included huge number of recurrent ovarian cancer patients to prove efficacy of surgery in them.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All the authors shared in surgical techniques, data collection, statistical analysis of data, writing and reviewing the manuscript before publishing.

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None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The study was approved by the local ethics committee of Faculty of Medicine, Zagazig University in compliance with the Helsinki Declaration.

Informed consent

A signed written consent from included patients was acquired.

Data sharing

Data are available under reasonable request to the corresponding author.

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