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Secondary cytoreductive surgery for isolated lymph node recurrence of epithelial ovarian cancer: A multicenter study

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Abstract

Introduction: Chemotherapy is the standard treatment of recurrent epithelial ovarian cancer (EOC), but its use in nodal relapses is still debated. On the other hand, the role of secondary cytoreductive surgery (SCS) remains controversial. Aim of this study is to evaluate feasibility and outcomes of SCS for the specific setting of recurrent ovarian cancer, exclusively relapsing in lymph nodes.
Patients and methods: We conducted a retrospective analysis in five Italian Institutions (University of Torino, INT of Milano, CRO of Aviano, University of Pisa and INT of Napoli) from 2000 to 2012. Patients with EOC who underwent secondary surgery for isolated lymph node recurrence (ILNR) were selected.
Results: Seventy-three patients were identified. At first diagnosis, patients received debulking surgery and platinum-based chemotherapy. The median disease free interval from completion of primary chemotherapy to nodal recurrence was 18 months. Nodal recurrence was para-aortic in 37 patients (50.7%), pelvic in 21 (28.8%), pelvic and para-aortic in 9 (12.3%), pelvic and inguinal in 3 (4.1%) and inguinal in 3 (4.1%). During SCS, in 1 patients nephrectomy was necessary for renal vein injury. No significant postoperative morbidity occurred. Median follow-up is 50 months. After secondary surgery, 32 (43.8%) are alive without disease, 18 (24.6%) are alive with disease and 23 patients (31.5%) are dead of disease. Five-year overall survival from the time of treatment of recurrent disease is 64%.
Conclusions: Secondary surgery for ILNR of ovarian cancer is feasible, safe, with low morbidity and it is associated with a favorable outcome.

Keywords: Epithelial ovarian cancer; Secondary cytoreductive surgery; Isolated lymph node recurrence

Introduction

Epithelial ovarian cancer (EOC) is the first cause of death from gynecological malignancies. Due to the lack of specific symptoms in early disease, more than two thirds of EOC are diagnosed in advanced stage. After radical primary surgery and platinum based chemotherapy, between 25% and 75% of the patients will eventually relapse.[1,2] Nowadays, chemotherapy still is the standard treatment of recurrent ovarian cancer. Cytoreductive surgery, is accepted as the main treatment of primary ovarian cancer, but it is still discussed in recurrent disease. Secondary cytoreductive surgery (SCS) is defined as surgery performed after the completion of the primary treatment and a disease free period. There is no level I evidence to demonstrate a survival advantage associated with secondary cytoreductive surgery in women with recurrent ovarian cancer.[3] Until

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data from ongoing trials will be mature (GOG 213 and AGO-OVAR DESK-TOP 3), the evidence is based almost entirely on retrospective studies, suggesting a benefit of SCS in selected patients with long disease free interval, resectable disease (based on imaging), absence of ascites, a limited number of metastatic sites and a good performance status.[4,5] SCS aims at the prolongation of survival and at the improvement of quality of life and cancer-related symptoms. Pelvis, peritoneum, pleural effusion, liver, lung, lymph nodes and central nervous system are the most frequent sites of recurrence.[6] Among relapses, the frequency of nodal involvement is high, but isolated lymph node recurrence (ILNR) is rare. The range spans between 1% and 6%.[7–9]

ILNR could identify a selected group of patients for whom SCS may be of particular benefit.

The aim of this study is to describe, evaluate and discuss, in the light of the recent literature, feasibility, safety and outcomes of SCS in patient with EOC exclusively relapsed in lymph nodes.

Patients and methods

We conducted a retrospective analysis in five Italian Institutions (University of Torino, National Cancer Institute of Milano, Comprehensive Cancer Centre of Aviano, University of Pisa and National Cancer Institute of Napoli). We selected patients with EOC who underwent secondary cytoreductive surgery for isolated lymph node recurrence in the period between 2000 and 2012. The ILNRs were diagnosed during the scheduled follow-up, including gynecological examination and CA-125 serum measurement every 3 months for the first 2 years and every 6 months thereafter. PET-TC scan, CT or MRI were prescribed in case of clinically suspected recurrence or CA-125 rise.

Inclusion criteria were: history of EOC, good Gynecologic Oncology Group performance status (GOG PS = 0–1), disease free interval (DFI) of at least 6 months from the completion of primary treatments and absence of ascites.

Exclusion criteria were: age >75 years, low Gynecologic Oncology Group performance status (GOG PS = 2), the presence of peritoneal disease and borderline tumor.

Surgical, clinical, pathological and follow-up data were collected. The following characteristics were recorded: age, co-morbidities, FIGO stage, histological type, tumor grade, postoperative residual tumor, type of first line chemotherapy, previous surgery on lymph nodes, DFI from the completion of primary treatment, sites of nodal recurrence, extent of nodal involvement, residual disease after SCS, hospital stay, postoperative morbidity, post-recurrence progression free survival (PFS), overall survival (OS) after SCS and OS from ovarian cancer diagnosis.

During primary surgery, lymphadenectomy was defined systematic when it was extended to pelvic and para-aortic regions, or partial when it was limited to some retroperitoneal regions or to macroscopically enlarged lymph nodes.

During secondary surgery, median laparotomy and thorough exploration of the abdominal cavity were done. If peritoneal recurrence was detected, the patient was not included in the study. Retroperitoneum was completely explored by sight, palpation and, on the basis of pre-operative imaging, ILNR was identified and resected. All lymph nodes, suspected for metastatic disease on the basis of pre-operative imaging or intra-operative exploration and palpation were removed.

Before surgery, the patient was informed by the surgeon about the treatment, its aims, expected advantages and possible risks. A written consent was signed by patient and surgeon and kept in the personal medical file.

The present retrospective study was submitted and approved by the ethics committee of the Mauriziano Hospital of Torino in compliance with the Helsinki Declaration.

DFI was considered to be the period from the end of primary treatment until the diagnosis of ILNR. PFS after SCS was defined as the period of time from the end of secondary treatment (including post surgical treatments when applicable) until the second recurrence. OS after SCS was considered as the period of time from the end of secondary treatments until either death or the date of the last available follow-up. Global overall survival was considered from the diagnosis of ovarian cancer until either death or the date of the last available follow-up.

Statistical analyses were performed using SPSS 18.0 software (SPSS, Inc., Chicago, IL). Values are presented as median. Estimates of survival were calculated using the Kaplan–Meier method. Log Rank test was adopted to compare differences between survival curves.

Results

We identified and included in the study 73 patients with ILNR who underwent secondary cytoreductive surgery. Table 1 shows patients characteristics at primary surgery.

At diagnosis, 67 (91.8%) patients received upfront surgery, according to FIGO surgical staging: median laparotomy, complete adhaesiolsysis, total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of all affected organs (small or large bowel, peritoneum, spleen, pancreas tail, liver etc…).[10] The remaining 6 patients (10%) were submitted to interval surgery following neoadjuvant chemotherapy.

During primary surgery, lymphadenectomy was always performed in cases of early ovarian cancers (FIGO I–II) and, in case of bulky lymph nodes, for advanced tumors.

Among patients who received lymphadenectomy, the median number of removed lymph nodes was 11 (range 5–26).

Five T1–T2 patients had nodal metastases and were classified as FIGO IIIc stage, because of the nodal involvement.

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Table 1
Patients characteristics at primary debulking surgery.

Characteristics	N	%
Patients	73	
Median age: years (range)	54 (29–73)	
Surgery		
-Upfront surgery	67	91.8
-Interval surgery	6	8.2
Lymphadenectomy		
-No lymphadenectomy	31	42.5
-Partial lymphadenectomy	24	32.9
-Systematic lymphadenectomy	18	24.6
Postoperative residual tumor		
-0	57	78.1
-<1 cm	10	13.7
-1–2 cm	4	5.5
->2 cm	2	2.7
Histology		
-Serous	53	72.6
-Endometrioid	11	15.0
-Mucinous	1	1.4
-Mixed	8	11.0
Grading		
-1	4	5.5
-2	5	6.8
-3	64	87.7
FIGO stage		
-I	14	19.2
-II	4	5.5
-III (peritoneal–nodal)	51 (46–5)	69.8
-Iva	4	5.5
First line chemotherapy		
-Carboplatin AUC 6 – Taxol 175 mg/mq, 1:21, 6–9 cycles	52	71.2
-Carboplatin AUC 5 – Caelyx 30 mg/mq, 1:28, 6 cycles	10	13.7
-Carboplatin 5–6 AUC 1:21, 6 cycles	4	5.5
-None	7	9.6

Median DFI from the end of first line chemotherapy was 18 months (range 6–192). Ten patients had the ILNR within 6–12 months, 3 of these patients had received a systematic lymphadenectomy and 7 had a negative preoperative staging for retroperitoneal disease.

Table 2
Patients characteristics at secondary cytoreductive surgery for ILNR.

Characteristics	N	%
Patients	73	
Median DFI: months (range)	18 (6–192)	
ILNR site		
-Para-aortic	37	50.7
-Pelvic	21	28.8
-Para-aortic + pelvic	9	12.3
-Pelvic + inguinal	3	4.1
-Inguinal	3	4.1
N lymph nodes (range)		
-Removed	16 (2–71)	
-Involved	7 (2–21)	
Mean surgical time: min (range)	171 (90–450)	
Median postoperative hospitalization: days (range)	9 (5–10)	

Table 3
Anatomical distribution of the nodal recurrence according to the extent of lymphadenectomy during the primary surgery.

N° of patients	Extent of lymphadenectomy during the primary surgery	Site of nodal relapse
16	No lymphadenectomy	Para-aortic
12	Partial lymphadenectomy	Para-aortic
9	Systematic lymphadenectomy	Para-aortic
8	Partial lymphadenectomy	Pelvic
7	No lymphadenectomy	Pelvic
6	Systematic lymphadenectomy	Pelvic
4	Partial lymphadenectomy	Pelvic + para-aortic
3	No lymphadenectomy	Pelvic + para-aortic
2	Systematic lymphadenectomy	Pelvic + para-aortic
3	No lymphadenectomy	Inguinal
2	No lymphadenectomy	Pelvic + inguinal
1	Systematic lymphadenectomy	Pelvic + inguinal

Data about secondary surgery are reported in Table 2.

Table 3 shows the anatomical distribution of the nodal recurrence according to the extent of lymphadenectomy during the primary surgery.

Eight patients received chemotherapy before secondary cytoreduction, 62 patients received postoperative chemotherapy and 3 patients did not receive second line chemotherapy for concomitant co-morbidities. Radiotherapy was performed neither before nor after secondary surgery in any patient. During secondary cytoreductive surgery, none of the included patients showed macroscopic intraperitoneal disease in addition to nodal involvement. Seventy-two patients underwent complete resection of the macroscopic lymph-node recurrence. One single case was not completely debulked because the lymph nodes were not cleavable from large vessels. The only major intra-operative complication was one case of renal vein injury who required nephrectomy. Eighteen patients needed blood transfusion, 1 patient developed temporary legs lymphedema and 1 patient had temporary atrial fibrillation. Histological examination of removed lymph nodes confirmed epithelial ovarian cancer recurrence in all patients. Median follow-up after secondary cytoreduction is 50 months (range 6–143). During this period, 41 patients had a new recurrence. After ILNR, the second recurrence was usually multiple and extra-nodal (Table 4).

To date, 32 (43.8%) are alive without disease, 18 (24.6%) are alive with disease and 23 patients (31.6%)

Table 4
Follow-up after secondary cytoreductive surgery for ILNR.

Outcome	N	%
Alive without evidence of disease	32	43.8
Alive with disease	18	24.6
Dead of disease	23	31.6
Total recurrences	43	58.9
Sites of further recurrences:		
-Nodal only	3	7.0
-Intraperitoneal	29	67.4
-Intraperitoneal + distant	11	25.6

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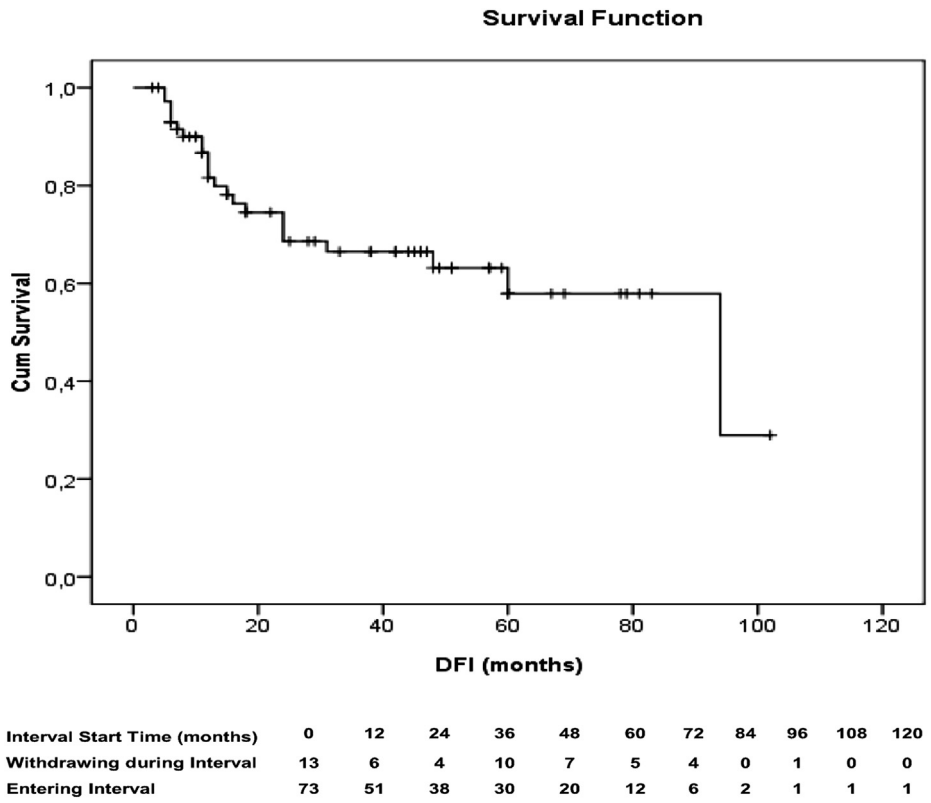

Figure 1. PFS after secondary cytoreduction surgery for ILNR.

are dead of disease. Five-year overall survival from the time of treatment of recurrent disease is 64%. Fifty-three patients (72.6%) had a post-recurrence survival longer than 24 months and 16 patients (21.9%) had a post-recurrence survival longer than 60 months. Figs. 1 and 2 show PFS and OS after secondary cytoreduction for ILNR. No significant differences in survival were found between groups on the basis of: nodal distribution, FIGO stage at the diagnosis, lymphadenectomy at primary surgery, PFS between completion of primary treatments and ILNR (Fig. 3). OS from first diagnosis of EOC is shown in Fig. 4.

Discussion

Clinical significance of EOC involvement of lymph nodes is still unclear even at primary diagnosis. Outcome of FIGO stage IIIC EOC, only because of the lymph node involvement, is more favorable as compared to the prognosis of peritoneal FIGO stage IIIC disease.[8] The clinical impact of systematic lymphadenectomy at primary surgery in advanced EOC is smaller as compared to maximal surgical effort for peritoneal disease.[11] Furthermore, retroperitoneal residual tumor at second-look did not seem to influence overall survival.[12,13] Retroperitoneal lymphadenectomy is mandatory for adequate staging in early ovarian cancer,[14] but its usefulness is still debated in advanced ovarian cancer, showing a minor role as compared to optimal primary radical surgery for intraperitoneal disease.[15–17] The impact of secondary cytoreductive surgery in recurrent ovarian cancer remains one of the hottest topics in international gynecological oncology debates. Since the publication by Berek et al. in 1983, which first introduced the concept of "secondary cytoreduction", indications of surgery for recurrent ovarian cancer have been extensively discussed.[18] Some Authors indicate that selected platinum sensitive patients, with high performance status and apparently resectable recurrent disease, could benefit of secondary cytoreductive surgery.[19–23] The Desktop I study identified three independent predictive factors for a complete resection (AGO score): good performance status (ECOG 0), complete debulking at primary surgery and absence of ascites.[24] On the opposite, a high number of recurrence sites, clear-cell histological type, ascites and advanced FIGO stage are independently associated with shorter survival.[25] In patients with diffuse recurrence, multidisciplinary surgical approach is recommended to ensure extensive liver or diaphragm resections or lymph node excision above the renal vessels.[26] The rationale of surgical removal of recurrent tumor is mathematically supported by the model of Goldie and Coldman, predicting drug resistance in cancer cells and suggesting that the efficacy of chemotherapy is related to the number of tumor cells: 10^5 tumor cells are likely to be curable with chemotherapy, but a neoplastic nodule of 1 cm contains 10^6–10^7cells.[27] Other theoretical benefits are: a) the removal of a poorly vascularized tumor which may be a

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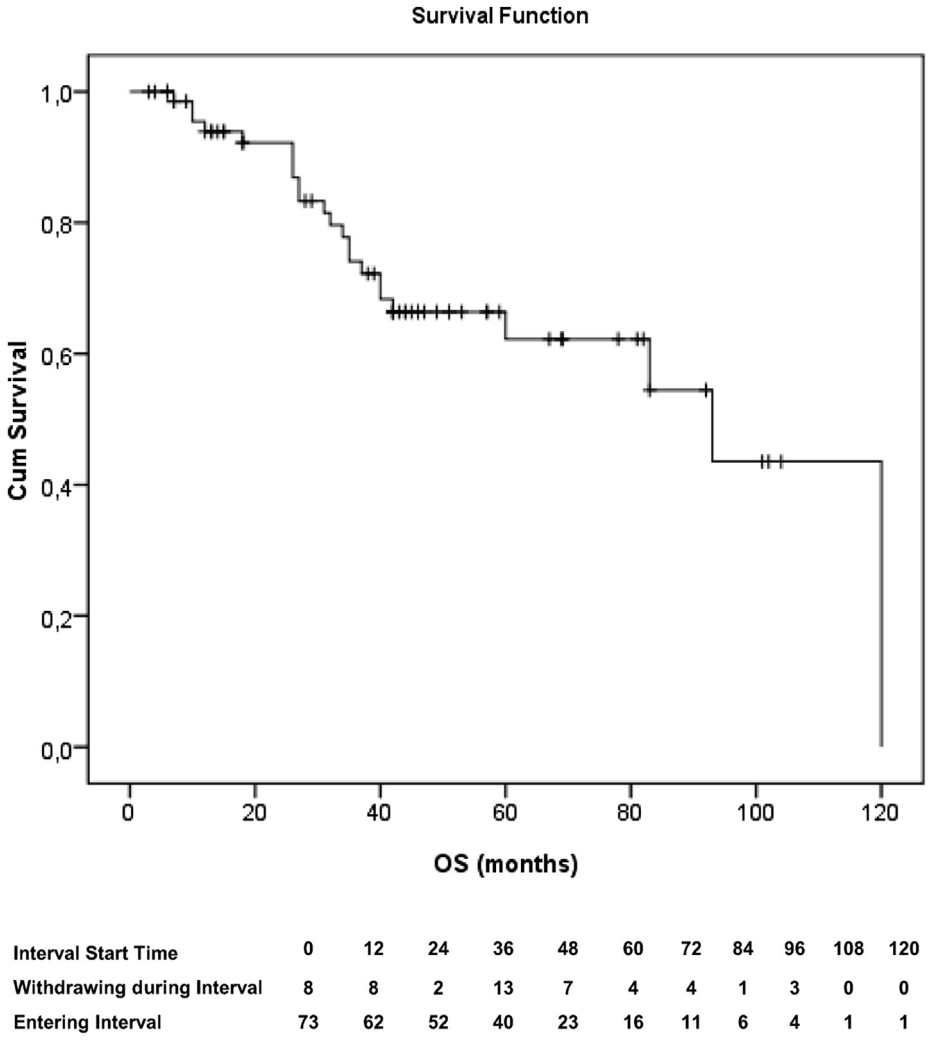

Figure 2. OS after secondary cytoreduction surgery for ILNR.

pharmacologic sanctuary of drug resistance[28]; b) a higher growth fraction in the better perfused small residual tumor masses may favor the action of cytotoxic therapy; c) the smaller number of chemotherapy cycles required by small tumor masses, possibly reducing the probability of drug resistance; d) finally the enhancement of host immune-competence generated by the removal of large tumor bulk.[29] A recent Cochrane review about surgical cytoreduction for recurrent EOC included 9 retrospective and prospective non-randomized studies; no randomized clinical trials (RCT) were found.[5] Meta- and single-study analyses show that complete cytoreduction (no visible residual disease) is associated with significant improvement in overall survival in women with platinum-sensitive recurrent ovarian cancer. In the absence of RCTs evidence, Authors conclude that it is not clear whether this result is solely due to surgical effect or due to tumor biology.

Isolated nodal recurrences from EOC are uncommon, but not exceptional. This specific condition is gaining attention for peculiar clinical characteristics, course of disease and patient management. Since outcome of these patients can be poor with salvage chemotherapy or irradiation of bulky nodes, secondary cytoreduction surgery may be considered. In case of ILNR, the theoretical benefit of removing large tumor volumes, that have a low growth rate and a poor blood supply, is still more relevant, being lymph nodes anatomical structures of the immune system. Furthermore, it seems that retroperitoneal nodal metastases may be more resistant to chemotherapy than other intra-abdominal disease, probably due to some unexplained biological factors, as the diminished blood supply and the consequent lower levels of cytotoxic agents.[29] In the literature, in case of ILNR, multiple approaches have been described: chemotherapy, radiation therapy, surgery, combined therapy and delayed therapy, but no consensus has been reached among Authors. In the study of Blanchard et al., different approaches were offered to 20 patients with isolated nodal recurrence: chemotherapy alone in 8 patients, surgery plus chemotherapy in 5, chemotherapy plus radiation therapy in 2, surgery alone in 2, radiation therapy alone in 2, surgery followed by radiation therapy in 1 patient and delayed therapy in 7 patients without tumor-

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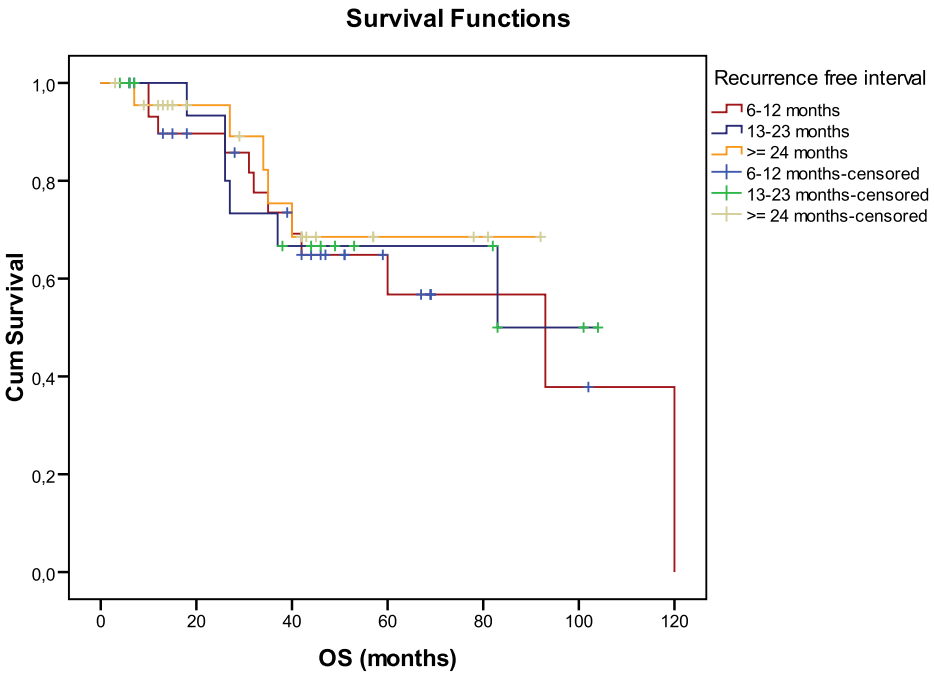
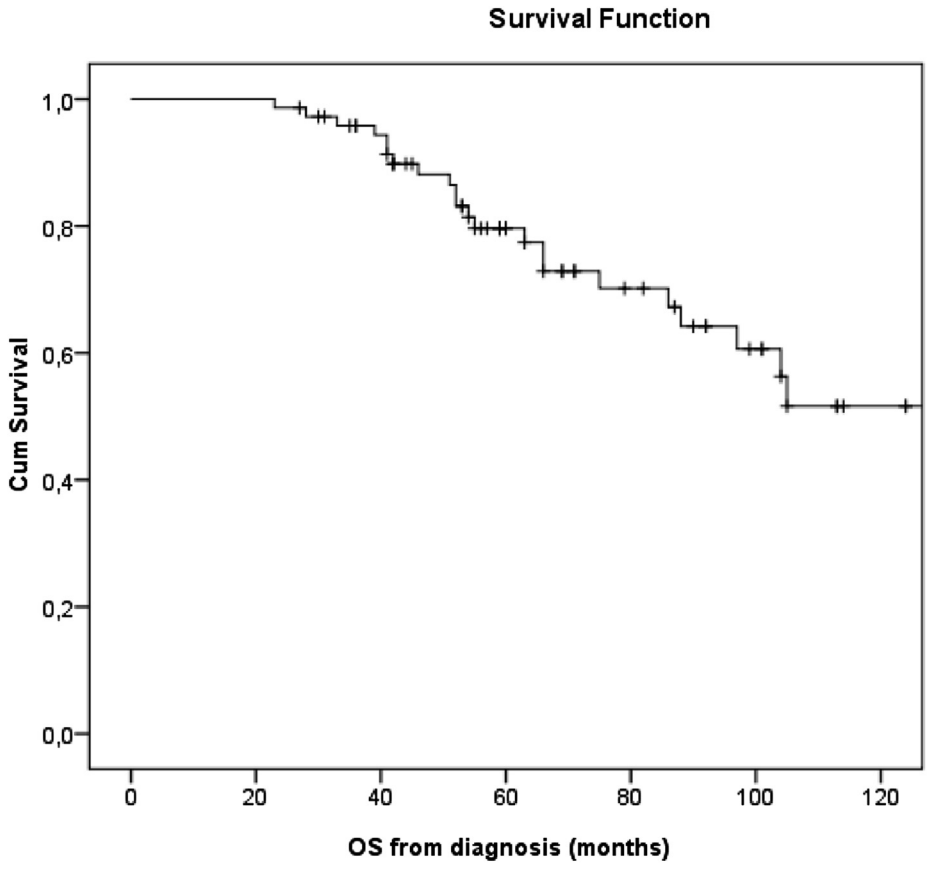


Figure 3. PFS after SCS on the basis of DFI between completion of primary treatments and ILNR.



Interval Start Time	0	12	24	36	48	60	72	84	96	108	120
Withdrawing during Interval	0	0	4	8	10	8	2	4	5	3	6
Entering Interval	73	73	72	66	53	38	27	24	18	10	7

Figure 4. Global OS from the diagnosis of ovarian cancer.

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Table 5
Secondary surgery for ILNR: literature comparison.

Characteristics	Current study	Uzan	Santillan	Fotiu
Patients	73	12	25	21
Mean age: years (range)	54 (29–73)	51 (42–71)	55 (72% < 65)	52 (37–70)
DFI: months (range)	18 (6–192)	21 (6–72)	16 (6–40)	21 (8–156)
Gross peritoneal disease	0	1	2	5
Residual disease	1	0	1	5
Serious complications	1	0	0	1
Pre or post-SCS treatment				
•Chemotherapy	70	9	1	1
•Radiotherapy	0	15	4	4
•Chemotherapy + radiotherapy	0	17	1	3
•None	3	1	2	0
Post-recurrence FU: months	50	50	19	45
Post-recurrence PFS: months	46	44	10	21
Post-recurrence OS: months	(5 years) 64%	(5 years) 71%	37	(5 years) 68%

related symptoms; no difference in results has been observed.[7] Gadducci et al. obtained a significant improvement of survival after recurrence and overall survival in patients with ILNR who underwent secondary surgery plus chemotherapy compared to those treated with chemotherapy alone.[30] Fujiwara et al. reported that local radiation therapy may be an acceptable choice for localized recurrent ovarian cancer, particularly for small masses and lymph-nodes recurrences.[31]

In the present study, complete secondary cytoreduction was achieved in 72 out of 73 patients with isolated lymph node recurrence, demonstrating feasibility and safety of the procedure in accurately selected patients. Seventy patients received platinum based chemotherapy either before or after surgery. Five-year overall survival from the time of treatment of recurrent disease is 64% with a median follow-up of 50 months. These findings are consistent with data reported in previous similar studies (Table 5). Fotiu et al. in 21 patients found a 5-year survival of 68% with a median follow-up of 45 months.[32] Uzan et al. reported a 5-year survival of 71% in 12 patients undergoing secondary cytoreductive surgery for ILNR.[33] Santillan et al. described a series of 25 patients: complete optimal SCS for ILNR was achievable in the majority of the cases and median survival after SCS was 37 months.[34]

Previous evidences show that EOC metastasizing or recurring through lymphatic versus peritoneal path have specific and more indolent course.

In our series, 53 patients (72.6%) had a post-recurrence survival longer than 24 months and 16 patients (21.9%) had a post-recurrence survival longer than 60 months.

PFS in patients with ILNR is significantly longer compared to that usually reported in recurrent EOC, suggesting one more time that nodal recurrence is associated to less aggressive behavior. Patients with ILNR could represent a peculiar group of EOC with specific natural history and behavior who requires a tailored treatment.

The weakness of this study is its retrospective design, but it has some strong points compared to previous studies: large sample size, long follow-up, very strict selection criteria and exclusion of patients with intra-operative finding of peritoneal disease.

In conclusion, ILNR seems to show a less aggressive behavior. Even if the impact of secondary cytoreductive surgery in these patients is not fully understood, lacking a comparison with chemotherapy alone or observation in a randomized trial, in our experience, secondary cytoreductive surgery for isolated lymph nodes recurrence of epithelial ovarian cancer is feasible with low morbidity and is associated with favorable outcomes.

Conflict of interest statement

- **A. Ferrero** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.
- **A. Ditto** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.
- **G. Giorda** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.
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- **L. Fuso** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.
- **E. Panuccio** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.

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- **C. Scaffa** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.
- **F. Raspagliesi** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.
- **P. Sismondi** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.
- **N. Biglia** has no financial and personal relationships with other people or organizations that could inappropriately influence this work.

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