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Salvage lymphadenectomy in recurrent ovarian cancer patients: Analysis of clinical outcome and *BRCA1/2* gene mutational status

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ABSTRACT

Objective: This study is aimed to analyze the clinical outcome of recurrent ovarian cancer patients bearing isolated lymph-node recurrence (ILNR) who underwent salvage lymphadenectomy (SL). The prognostic role of clinicopathological variables and the mutational status of *BRCA1/2* have also been investigated.

Methods: This retrospective, single-institutional study included women with platinum-sensitive lymph node recurrence underwent to SL between June 2008 and June 2018. Univariate and multivariate analysis was performed to evaluate the impact of clinical parameters, and *BRCA1/2* mutational status on post salvage lymphadenectomy progression-free survival (PSL-PFS).

Results: As of June 2019, the median follow-up after SL was 30 months, and the relapse has been documented in 48 (56.5%) patients. In the whole series, the median PSL-PFS was 21 months, and the 3-year PSL-PFS was 36.7%. The median PSL-PFS, according to patients with ILNR (N = 71) versus patients with lymph-nodes and other sites of disease (N = 14), was 27 months versus 12 months, respectively. Univariate analysis of variables conditioning PSL-PFS showed that platinum-free interval (PFI) $\geq$12 months, normal Ca125 serum levels, and number of metastatic lymph-nodes $\leq$3 played a statistically significant favorable role. In multivariate analysis, PFI duration $\geq$12 months and the number of metastatic lymph nodes $\leq$3 were shown to keep their favorable, independent prognostic value on PSL-PFS.

Conclusions: In the context of SL, the patients with long PFI and low metastatic lymph node numbers at ILNR diagnosis have the best outcome. The *BRCA* mutational status seems not associated with clinical variables and PSL-PFS, differently from other sites of disease in ROC patients.

Introduction

Ovarian cancer (OC) is the most lethal gynecological malignancy with the vast majority of patients succumbing within five years from diagnosis; the number of new cases in the USA has been estimated to be 22,530 in 2019, with around 14,000 deaths [1]. The primary clinical challenge in this disease is the management of relapse, which occurs in around 75% of women within two years from diagnosis [2].

Currently, the standard treatment of recurrent ovarian cancer (ROC) is mainly based on medical treatment chosen according to platinum sensitivity; in addition, in the last years, several parameters have been shown to play a major role on clinical outcomes, such as histotype, status of BRCA genes or homologous recombination deficiency (HRD) and pattern of relapse presentation [3–5].

Besides the advances in the medical treatments which have integrated bevacizumab and PARP-inhibitors in the

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chemotherapeutic armamentarium [6], secondary cytoreductive surgery (SCS) has been associated with improved survival in the management of OC relapse: results from a Cochrane meta-analysis [7] and the Phase III randomized DESKTOP study [8] suggest the improvement of progression-free survival (PFS) in selected platinum-sensitive ROC patients if complete tumor eradication is achieved [9].

Moreover, analysis of the CALYPSO trial showed that secondary cytoreduction was associated with improved overall survival (OS) in platinum-sensitive ROC, particularly in patients with favorable prognostic characteristics [10]. On the other hand, the GOG 213 trial showed for platinum sensitive ROC patients, SCS followed by chemotherapy did not result in longer overall survival than chemotherapy alone [11]. Furthermore, if isolated relapse was in the lymph nodes or peritoneum, the survival advantage of SCS was thought to be more evident [12–14].

Lymph node recurrence(s) account for 12% up to 37% of OC relapses, but isolated lymph node relapse (ILNR) is a very rare event (about 5%) [15–24]; indeed, given the low growth rate, the relative less chemosensitivity, and a more indolent behavior compared to parenchymal and peritoneal disease [25–27], lymph node relapses are considered more suitable for selected cases to take advantage of surgical rather than medical treatment [12,22,25]. However, since a prospective, randomized study comparing the two therapeutic approaches would be almost very difficult to achieve due to the rarity of this pattern of disease, we can refer only to the available retrospective, small sample series, thus precluding the possibility to obtain robust data relative to prognostic factors [15–23]. Indeed, it would be clinically relevant to find clinicopathological parameters able to identify patients that would benefit the most from salvage lymphadenectomy (SL) [3–5].

Recent findings have also suggested that assessment of *BRCA* gene status could be helpful in the decision-making approach to surgery versus chemotherapy in platinum-sensitive recurrent disease [28–30]. In this context, a very recent study, which compared isolated lymph node relapse (ILNR) versus extranodal disease in ROC patients, showed that the percentage of *BRCA* mutations does not differ in the two groups [31]; however, the prognostic impact of *BRCA* gene mutation was not investigated in ILNR.

This retrospective study is aimed to analyze the clinical outcome of ROC patients bearing ILNR, and managed by SL; the prognostic role of clinicopathological variables and mutational status of *BRCA1/2* has also been investigated.

Materials and methods

After obtaining the Institutional Review Board (CICOG-04-03-19\8) approval, we performed a retrospective collection and analysis of patients' data who underwent SL for ROC at the Gynecologic Oncology Unit, Catholic University of Rome, Italy. All patients had already provided written informed consent for their data to be collected and analyzed for scientific purposes.

Inclusion criteria were: initial diagnosis of epithelial invasive OC, platinum-free interval (PFI) $\geq$6 months, clinical performance status 0–2 (Eastern Cooperative Oncologic Group-ECOG) at the time of relapse, availability of high quality imaging (i.e. CT scan, PET/CT scan) of recurrent disease in order to preoperatively select patients susceptible to SL.

Exclusion criteria were: the presence of extra-abdominal disease assessed by radiological exams and intra-operative detection of diffuse peritoneal carcinomatosis at the time of SL, evaluated by laparoscopy.

The following data were retrieved from medical records: tumor histology and International Federation of Gynecology and Obstetrics (FIGO) stage at the time of initial diagnosis, data relative to previous treatments, and histopathology reports.

Data about patient features at the time of ILNR were: age, Body Mass Index (BMI), number of previous lines of chemotherapy, duration of median PFI before SL, preoperative CA125 serum levels, sites of ILNR disease; status of BRCA gene was also collected.

As far as operative outcomes are concerned, we planned to collect data on: operative time, estimated blood loss (EBL), type of surgical procedure(s), residual disease at the end of the SL, and hospital length of stay.

No uniform surgical approach of lymphadenectomy was adopted during the study period, and the attending physicians could select to perform metastatic node resection instead of systematic lymphadenectomy. Bulky lymph node resection consisted of the removal of only metastatic lymph nodes, whereas systematic lymphadenectomy consisted of all nodes of the anatomic region. Moreover, selection for minimally invasive approach (MIS) or open approach was based on surgeon preference rather than tumor and/or patient characteristics, and the selection was highly dependent on the individual surgeon's experience with MIS.

Data about intra- and post-operative complications occurring within or after 30 days from surgery were collected, and surgical morbidity was classified according to Clavien-Dindo [32].

Post SL progression-free survival (PSL-PFS) was calculated from the date of SCS to documentation of radiological disease progression or the date last seen. Post SL overall survival (PSL-OS) was calculated from the date of SLS to the death of disease or the date last seen.

Analysis of BRCA gene status

Lymph node FFPE-deriving DNA was obtained using an automatic machine (MagCore HF16 Plus, Diatech Lab-Line, Jesi, Italy). The DNA concentration and quality were evaluated by NanoPhotometer™ (Implen, Munchen, Germany). Samples were stored at −20 °C until use. Quality assessment included total yield and percent dsDNA, fragment analysis. The quality of an adequate quantity of DNA was assessed by determining the F-ratios by QC integrity system is the DNA Fragmentation Quantification Assay (EntroGen, Inc. Woodland Hills, CA). Only DNA meeting following requirements: OD260/280 ratio $\geq$1.7, and with High-quality human genomic DNA F-ratios were processed, as previously reported [33]. Library preparation was performed using Devyser *BRCA* NGS kit (DEVYSER, Hägersten, Sweden), according to the manufacturer's instructions. The reagent kit V2, 500 Cycles PE, on the Illumina MiSeq System (Illumina, San Diego, CA, USA), and Amplicon Suite Software (SmartSeq, Novara, Italy) were used for sequencing pipeline, and NGS results interpretation, respectively. The *BRCA1 and BRCA2* genes reference were: NG_005905.2, NM_007294.3 and NG_012772.3, NM_000059.3. A cut off of 500× minimum coverage was applied to all analyses. The depth of coverage was set on average enough for variant calling at 5% allelic fraction at Q > 30 quality score value. As reference materials, the *BRCA* Somatic Multiplex I FFPE (Horizon), including 16 mutations at the expected 7.5%–100% allelic frequency in genomic FFPE deriving DNA, was used. Somatic BRCA pipeline was followed in keeping with international recommendations [34]. An aliquot of this reference material was mixed (1:1) to a BRCA1/wild DNA in order to stress our NGS pipeline at the lowest allele frequencies.

Statistical analysis

The sample has been described in its clinical and demographic characteristics applying descriptive statistics techniques. Comparisons of categorical data have been performed with Chi-square test or Fisher's exact test. Continuous normal data comparisons have

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been performed with the Wilcoxon test. Survival data have been processed with the Kaplan-Meier method, and the log-rank test has been applied to highlight statistical significance. Analysis of prognostic factors has been performed with Cox's regression model, with stepwise variable selection. Statistical analysis has been performed with R statistical software.

Results

Between June 2008 and June 2018, 293 patients were subjected to secondary cytoreduction, of them 85 were selected to SL according to inclusion criteria. Patient characteristics at the time of primary diagnosis are shown in Table 1: most patients presented FIGO stage III-IV (N = 61, 78.2%), serous histology (N = 68, 85.0%), and grade 3 (N = 73, 94.8%).

At the time of documentation of ILNR at imaging, the median age was 57.5 years (range: 37–78), and the median BMI was 24.4 (range:17.0–35.4) (Table 2).

The median PFI before SL was 15 months (range: 6–175); 33 (40.7%) and 48 (59.2%) patients presented PFI of ≥6–12 months and >12 months, respectively. The median Ca125 level was 44 I.U./ml (range: 5–1355).

The *BRCA1/2* mutational status was available in 80 patients (94.1%): of these, 35 (43.7%) patients were *BRCA* mutated (*BRCA1*: 25, *BRCA2*: 5, *BRCA1/2*: 1, mutated BRCA gene not specified: 4). Of the 35 BRCA mutated patients, 19 (54.3%) had a germline mutation, 12 (34.3%) had a somatic one, and 4 (11.4%) had both a somatic and germinal mutation.

As shown in Table 3, salvage lymphadenectomy was most frequently carried out at the secondary cytoreduction (N = 71, 83.5%), and laparotomy was the most common surgical approach (N = 56, 65.9%). At the time of intraoperative evaluation, 71 patients (83.5%) showed only ILNR, while 14 patients (16.5%) were found to harbor additional disease in anatomical sites other than lymph nodes (LNR + other sites group); however, all patients were deemed as susceptible to achieve complete cytoreduction.

Systematic lymphadenectomy was carried out in 51 patients (60.0%), while bulky lymph node resection was performed in 34 patients (40.0%). Details about the number of lymphadenectomies by site are summarized in Table 3. Zero macroscopic residual disease was achieved in all patients.

The median number of removed lymph nodes was 16 (range: 1–82), and the number of metastatic lymph nodes was 4 (range: 1–50).

Peri-operative outcomes and morbidity

Regarding perioperative outcomes, the median operative time was 275 min (range: 85–1290), and the median EBL was 150 mL (range: 40–1400).

As shown in Supplementary Table 1, in the whole series, 19 intra-operative complications have been documented in 19 patients (22.3%). The proportion of patients experiencing intra-operative complications was statistically significant higher in the group of patients undergoing a laparotomic approach versus the MIS group (28.6% versus 10.3%, p-value: 0.046). Overall, 16 patients experienced 21 early postoperative complications; the proportion of patients experiencing early postoperative complications was not statistically significant between the laparotomic versus MIS approach (19.6% versus 17.2%, p value = 0.52).

Clinical outcomes

Adjuvant platinum-based chemotherapy was administered to all patients; the median time from SL to the onset of adjuvant

Table 1
Patient characteristics at primary diagnosis.

Characteristics	N. (%)
All cases	85[a]
FIGO stage	
I-II	17 (21.8)
III-IV	61 (78.2)
n.a.	*7*
Tumor histology	
High grade serous	68 (85.0)
Clear cells	7 (8.7)
Endometrioid	4 (5.0)
Mucinous	1 (1.2)
n.a.	*5*
Grading	
2	4 (5.2)
3	73 (94.8)
n.a.	*8*
Residual tumor (cm)	
0	67 (90.5)
>0	7 (9.4)
n.a	*11*
Lymphadenectomy at the primary cytoreduction	
No	32 (37.6)
Yes	53 (62.3)
Aortic	*11*
Pelvic	*9*
Aortic + Pelvic	*31*
Inguinal	*2*
Lymph node involvement	
No	22 (45.8)[b]
Yes	26 (54.2)[b]
n.a.	*5*

[a] Percentages calculated on the available data.
[b] Percentages calculated on the 48 patients with histopathological report; *n.a.* = not available.

Table 2
Patient characteristics at the time of salvage lymphadenectomy.

Characteristics	N. (%)
All cases	85[a]
Age, years	
Median (range)	57.5 (37–78)
Body Mass Index, kg/m^2	
Median (range)	24.4 (17.0–35.4)
N. patients with PFI before LNR	
≥6–12 months	33 (40.7)
13–24 months	27 (33.3)
25–36 months	12 (14.8)
>36 months	9 (11.1)
n.a.	4
PFI, months	
Median (range)	15 (6–175)
Site(s) of LNR at imaging before SL	
Aortic	27 (31.8)
Pelvic	28 (32.9)
Hepatoceliac	5 (5.9)
Mesentery	2 (2.3)
Aortic + Pelvic	9 (10.6)
Aortic + Hepatoceliac	5 (5.9)
Aortic + Mesentery	2 (2.3)
Aortic + Pelvic + Hepatoceliac	4 (4.7)
Pelvic + Inguinal	3 (3.5)
N. patients with Ca125 levels (I.U./ml)	
0-35	30 (36.6)
>35	52 (63.4)
n.a.	*3*
Ca125 levels (I.U/ml)	
Median, range	44 (5–1355)
BRCA status	
BRCA wild type	45 (56.2)
BRCA mutated	35 (43.7)
n.a.	*5*

[a] Percentages calculated on the available data.

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Table 3
Surgical details at the time of salvage lymphadenectomy.

Characteristics	N. (%)
All cases	85[a]
SL within cytoreduction	
Secondary	70 (82.3)
Tertiary	15 (17.6)
Type of surgical approach	
Laparotomic	56 (65.9)
MIS	29 (34.1)
Intraoperative findings	
LNR only	71 (83.5)
LNR and other sites of disease	14 (16.5)
Extent of lymphadenectomy	
Systematic	51 (60.0)
Bulky	34 (40.0)
N. of lymphadenectomies by site	
Aortic	53
Pelvic	49
Hepatoceliac	11
Mesentery	3
Inguinal	4
Axillary	1
N. of additional procedures by site	
Peritonectomy	10
Cholecystectomy	4
Radical omentectomy	4
Bowel resection	3
Partial resection of pancreatic tail	2
Splenectomy	1
N. of removed LNs	
Median (range)	16 (1–82)
N. of metastatic LNs	
Median (range)	4 (1–50)

[a] Percentages calculated on the available data, MIS = minimally invasive surgery; LNR = lymph node recurrence; LNs = lymph nodes; *n.a.* = not available.

treatment was 26 days (range: 14–38). PARP-inhibitors were administered to 31 patients (mutated *BRCA1/2*: 22, wild type *BRCA1/2*: 9).

As of June 2019, the median follow-up after SL was 30 months (range: 11–84); relapse of disease was documented in 48 (56.5%) patients; in the ILNR group, relapse of disease was documented in 37 patients (52.1%); of these, 20 patients experienced further ILNR (54.0%), 13 patients had relapse of disease in sites other than lymph node sites (35.1%), and 4 patients (10.8%) showed relapse of disease including both ILNR and other sites of disease (Fig. 1).

Conversely, 11 out of 14 (78.6%) patients with LNR + other sites of disease developed further relapse as ILNR only (N = 4), as only other sites of disease (lung: 1, brain: 2, peritoneal carcinomatosis: 2), and LNR + other sites of disease (N = 2) (Fig. 1).

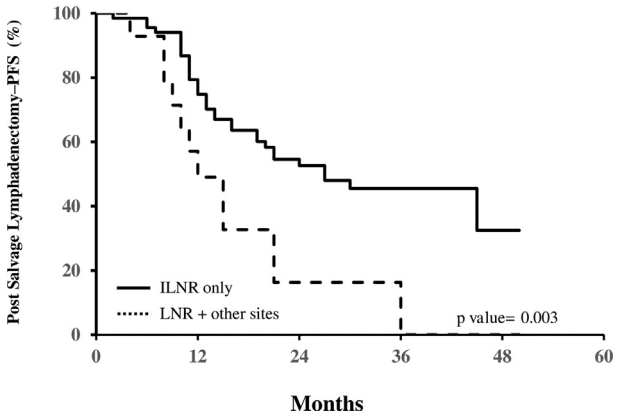

Fig. 2. Post salvage lymphadenectomy progression free survival (PSL-PFS) in ILNR only versus LNR + other sites of disease.

At the time of analysis, 37 patients (43.5%) were alive without disease, while 34 (40.0%) with the disease; there were 14 deaths of disease (16.5%).

In the whole series, the median PSL-PFS was 21 months, and the 3-year PSL-PFS was 36.7%. Fig. 2 shows the PSL-PFS according to patients with ILNR (N = 71) versus patients with LNR + other sites of disease (N = 14): the median PSL-PFS was 27 months versus 12 months, and the 2-year PSL-PFS rate was 52.2% versus 16.3%, respectively (p value = 0.003).

Based on these findings, we decided to focus on the clinical outcome of patients bearing only ILNR disease: univariate analysis of variables conditioning PSL-PFS showed that patients presenting with PFI>12 months, normal Ca125 serum levels, and number of metastatic lymph nodes ≤3 played a statistically significant favorable role (Table 4, Figs. S1, S2 and S3). The surgical approach, tumor histology, and type of salvage lymphadenectomy, as well as *BRCA1/2* mutational status, did not influence the clinical outcome. In the multivariate analysis, PFI duration ≥12 months, and the number of metastatic lymph nodes ≤ three were shown to keep their favorable, independent prognostic value (Table 4).

In the whole series, the median PSL-OS was not reached, and the 3-year PSL-OS was 81.9% (data not shown). There was no difference

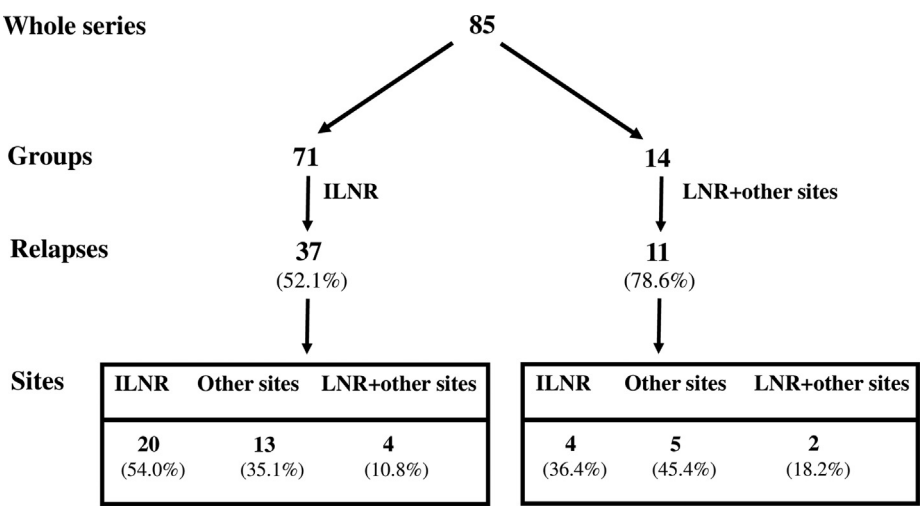

Fig. 1. Flow chart.

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Table 4
Univariate and multivariate analysis of parameters conditioning post salvage lymphadenectomy progression-free survival (PSL-PFS) in ILNR patients (N = 71).

Variable	N. (%)	Univariate		Multivariate	
		HR (95% CI)	p value[a]	HR (95% CI)	p value[a]
Tumor histology					
Non Serous	11 (16.7)	1			
High grade Serous	55 (83.3)	0.677 (0.292–1.574)	0.365		
n.a.	5				
PFI before SL					
6–12 months	27 (40.3)	1		1	
>12 months	40 (59.7)	0.460 (0.233, 0.910)	0.026	0.345 (0.161, 0.740)	0.006
n.a.	*4*				
Ca125 level (I.U.)					
>35	26 (37.7)	1		1	
0-35	43 (62.3)	0.426 (0.198, 0.915)	0.029	0.493 (0.220, 1.106)	0.086
n.a.	*2*				
Type of surgery					
MIS	24 (33.8)	1		–	–
Laparotomic	47 (66.2)	0.829 (0.412, 1.667)	0.598		
Type of SL					
Bulky LNs resection	29 (40.8)	1		–	–
Systematic SL	42 (59.2)	1.017 (0.508, 2.038)	0.962		
N. metastatic LNs					
>3	39 (54.9)	1		1	
1-3	32 (45.1)	0.379 (0.182, 0.788)	0.009	0.363 (0.157, 0.840)	0.018
BRCA status					
Wild-type	36 (53.7)	1			
Mutated	31 (46.3)	0.753 (0.367, 1.543)	0.438	–	–
n.a.	*4*				

[a] Calculated by Cox regression; PFI= Platinum free interval; SL = salvage lymphadenectomy; MIS = minimally invasive surgery; LNs = lymph nodes.

in the PSL-OS between patients bearing ILNR versus LNR + other sites of disease (data not shown).

Discussion

We confirmed in an extensive single-institution study that salvage lymphadenectomy could be considered a therapeutic strategy in selected platinum-sensitive ROC patients with isolated lymph node relapse. Moreover, the use of the models and survival curves generated by our study may be beneficial in counselling patients regarding their options for the management of lymph node ROC (Table 4, Figs. S1, S2 and S3). Indeed, the multivariate analysis showed that the length of PFI $\geq$12 months and the presence of $\leq$3 metastatic lymph nodes maintained their independent favorable prognostic role for PSL-PFS, while the Ca125 serum levels displayed a borderline statistical significance. Despite the data relative to the impact of length of PFI are controversial [17,19,20,22,31], it has to be acknowledged that our findings are sustained by the selection of ILNR only, as well as the adoption of the multivariate approach; in this context, the identification of a new parameter (i.e., the presence of $\leq$3 metastatic lymph nodes) able to predict a better outcome after SL in ROC patients, has been presented for the first time.

Interestingly enough, there was no difference of PSL-PFS according to surgical approach (laparotomy versus MIS), or extent of SL (systematic lymphadenectomy versus bulky node resection); even though a recent study has suggested that systematic lymphadenectomy confers a better PSL-PFS compared to bulky node resection, the limitations inherent in the small sample size should be carefully taken into account [21].

Moreover, the high rate (43.7%) of BRCA mutations in our series could be related to the selected cohort studied in the present manuscript (i.e. PFI >12 months in more than 60% patients). In addition in our experience, we have documented that germline detection rate is around 26% and is also coupled to 6% rate related to only somatic BRCA1/2 mutation detection. Along with this, since we always check for large rearrangements, which account for an additional 2% more detection of genetic alteration. At the end our pipeline is very sensitive and, compared to the solely germline approach, we have found many samples with double mutation where the first (possibly driver) is germline and the second somatic: this is in the nature of the genomic instability linked to BRCA1/2 gene, where the most imbalances are driven by BRCA1/2 deficiency.

As far as clinical outcome is concerned, unexpectedly, the mutational status of BRCA1/2 genes did not show any influence on the clinical outcome either in the whole or in the ILNR group.

In the whole series, the 3-yr PSL-PFS rate was 36.7%, and the median PSL-PFS was 21 months; these figures are in the range of the data present in the literature (Supplementary Table 2); indeed, in the ILNR group the median PSL-PFS is higher (27 months). Recently, the GOG 213 trial showed that in the whole series of ROC patients underwent SCS and in the complete gross resection (CGR) subgroup the median PFS was of 18.9 and 22.4 months, respectively.

Considering the very recent data showing a better outcome in terms of PFS and OS in patients bearing ILNR versus extranodal disease only [31], we were prompted at evaluating whether the surgical documentation of unexpected extranodal recurrence associated with ILNR could have a prognostic impact. Indeed, this specific issue seems to be missing in the literature: this could be ascribed to the fact that the pre-operative imaging failed to identify sites of disease different from ILNR in a range between 8.3% up to 41.4%, but the relatively small sample size of the studies did not allow to carry out robust analysis of this issue [15,16,18,19]. In our series, the rate of patients documented to bear LNR + other sites of disease at the surgical exploration was 16.4%; however, even though complete cytoreduction was achieved in all patients, the PSL-PFS was better in the group of ILNR, versus the group of LNR + other sites of disease. Therefore, we decided to focus only on the group of 71 ILNR in order to better define the most important parameters able to predict the better outcome, as shown by uni- and multivariate analysis.

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Moreover, we showed that *BRCA* mutational status seems not associated with clinical variables and PSL-PFS, differently from other sites of disease in ROC. Alterations of *BRCA* genes or HRD have been associated with better prognosis and a higher sensitivity to cytotoxic drugs [4,28]; in addition, the *BRCA* status has been suggested to play a role in the decision-making approach to treatment(s) in platinum-sensitive ROC overall [29], and in specific settings, such as ROC patients with liver relapse(s) managed through salvage cytoreduction [30].

The lack of the prognostic role of *BRCA1/2* mutation in lymph node OC relapse cannot be explained by the association with clinical and/or pathological features, but it is commonly recognized that lymph node disease usually presents unique features: for instance, in 2014 the FIGO staging Committee acknowledged the data sustaining the better outcome of primary OC patients with metastatic lymph nodes versus the peritoneal disease, and downstaged the former setting to Stage IIIA1, thus identifying its peculiar indolent behavior [35–37].

Very recently, ILNR has been demonstrated to harbor greater $CD3^+$ and $CD8^+$ T cell infiltration compared to extranodal disease [31]; these findings suggest that the more massive presence of cytotoxic T cell population might orient the tumor microenvironment towards better control of disease, which could result in less aggressive clinical behavior. In this conditioned biological context, it is conceivable that the role of *BRCA* mutational status is under further investigation and the data showed in our study should be considered carefully. In this conditioned biological context, the role of BRCA mutational status could hypothetically be modulated; anyway, our data represent just an exploratory analysis, and need to be investigated carefully on a larger series.

Attention has also been focused on the lymphatic metastasis-associated molecular components associated with focal adhesion, epithelial-mesenchymal transition, and angiogenesis in preclinical models [38]; however, the biology of this rare disease remains still unknown.

The molecular characterization of ILNR would be very helpful in clarifying some aspects of this rare pattern of disease in OC natural history, but very few data are available. Earlier flow cytometric data had fuelled the concept that the higher frequency of diploid metastatic lymph nodes in ROC could result in a lower percentage of cells in S-phase, thus sustaining, in principle, worse responsiveness to chemotherapy [25], and highlighting the role of surgical cytoreduction. In this context, thanks to the advancements of MIS, and the expertise of gynecologic oncologic surgeons in high-level centers, secondary salvage lymphadenectomy can be safely afforded, without impairing the oncological outcome [39–41]. Moreover, ILNR in OC often continues to exhibit the same pattern of relapse over time, thus highlighting the persistence of long-lasting lymphocytic features [22].

Given the balance between survival benefit and surgery-related morbidity during the maximum cytoreductive surgical effort, it is essential to establish the optimal selection criteria for identifying appropriate candidates who will benefit from surgery without worsening quality of life [14], as suggested by the LION trial regarding lymphadenectomy in upfront treatment of advanced ovarian cancer [42].

Obviously, the surgeon should be able to prevent and to manage severe vascular complications, and the vascular team should stand ready in case of major need. Finally, the surgeon must recognize the main anatomical anomalies and be able to expose the surgical field optimally to prevent and repair retroperitoneal injuries [18]. In this sense, a preoperative radiological workup is mandatory as well as, in some circumstances, the available intraoperative ultrasound to better localize the lymph node disease [18,43].

The limits of our study are the retrospective nature and the absence of a comparison with platinum sensitive ROC patients subjected to only medical treatment. On the other hand, a strength of our study includes a homogeneous treatment of ROC patients across the time period, in which these cases were submitted to SL with complete tumor eradication.

As many patients undergo complex surgery for SL, information regarding the extent of benefit can be useful for decision-making as well as for referral to expert centers able and willing to perform complex surgery to achieve complete cytoreduction translating in potential clinical benefit. The patients with long PFI and low lymph node numbers at ILNR diagnosis have the best outcome in the context of SL, and the MIS approach could be considered [39,40,44] in order to reduce the rate of intraoperative complications.

Further clinical trials and molecular research should be performed to evaluate the long-term impact of cytoreductive surgery in patients with lymph nodes recurrence.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2020.01.035.

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