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Review

Survival outcomes of ovarian cancer patients treated with secondary cytoreductive surgery for isolated lymph node recurrence: A systematic review of the literature

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ABSTRACT

Background: Isolated lymph node recurrence (ILNR) is present in 12–37% of recurrences in ovarian cancer patients. Although several studies have investigated the impact of secondary cytoreduction in these cases, consensus still lacks concerning their optimal management. The purpose of the present review is to investigate whether secondary cytoreduction benefits patients with ILNR in terms of overall survival (OS) and post-relapse survival (PRS).

Method: The present systematic review was designed using the PRISMA and AMSTAR guidelines and has been registered with PROSPERO (CRD42019122854). We searched Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases from inception until February 2019.

Results: Overall, eight studies where included that recruited a total number of 479 women. Current evidence suggests that ILNR in EOC patients should be clearly distinguished from recurrences in other sites (including peritoneal and parenchymal) as their course seems to be less aggressive. Furthermore, the implementation of secondary cytoreduction as an adjunct to standard chemotherapy should be taken into consideration in this specific group of patients as the PRS may easily reach and even extend beyond 5 years. Prolonged survival (> 110 months) may be seen as a realistic target for a significant number of these patients when systematic lymphadenectomy is performed.

Conclusion: The findings of our review suggest that patients with ILNR should be treated with a combined surgical and chemotherapeutic approach to optimize survival outcomes. However, further studies are needed to reach firm conclusions as current evidence is based in low quality studies.

1. Introduction

Ovarian cancer represents 3.6% of female neoplasms worldwide; according to American Cancer Society the overall survival reaches approximately 45% and only in the United States 22,240 new cases and approximately 14,070 were diagnosed in 2018 [1,2]. Epithelial ovarian cancer (EOC) is the most common histological type of (90% of the cases), and serous carcinoma accounts for the majority of these cases. Complete surgical cytoreduction followed by combined platinum and taxane based chemotherapy has significantly improved the life expectancy of these patients. Targeted therapies against vascular endothelial factor (VEGF) and Poly (ADP-ribose) polymerase (PARP) have also shown promising results and are instituted as complementary therapies [3–5]. However, despite advances in this field, the disease tends to relapse and, to date, the optimal management of these cases remains under investigation as their overall survival rates are expected to be poor.

The role of cytoreductive surgery in recurrent ovarian cancer is under debate the last 20 years. In 2009 Bristow et al. conducted a meta-analysis which was based on a series of forty cohorts that included 2019 patients and they observed that for each 10% of increase of the actual proportion of patients that undergone complete cytoreduction the overall survival of the cohort increased by 3.0 months [6]. A recent phase III randomized controlled trial that was presented recently by the

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gynecologic oncology group (GOG) reported that secondary cytoreductive surgery (SCS) may be performed with safety in patients with platinum sensitive patients but, unfortunately, fails to improve their progression free survival (PFS) and overall survival (OS) rates [7]. The latest evidence suggest that complete cytoreduction is of utmost importance when considering to perform surgery in patients with disease relapse and the procedure should be restricted to platinum sensitive cases, as the limited life expectancy of patients with platinum resistant disease renders the disease meaningless [8].

Isolated lymph node recurrence (ILNR) rates vary in the international literature between 12 and 37%. Current data report that their course is less aggressive compared to disease relapse in other sites resulting in a median post-recurrence survival (PRS) rate of approximately 37 months and an OS rate of 109 months [9]. Given this information, one could assume that these patients should be considered as an optimal subgroup which should be offered SCS. To date however, consensus is still missing in this field. Our systematic review aims to gather all available evidence in this field and evaluate the impact of SCS in PRS and OS rates in EOC patients with ILNR.

2. Materials and methods

The present systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and AMSTAR guidelines and has been registered with PROSPERO (CRD42019122854) [10].

2.1. Information sources and search methods

We searched Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases from inception until January 2019. Snow-balling was also performed by searching the references of articles that were retrieved in full text to minimize the possibility of article losses. Our search strategy included the text words "*lymph node recurrence; cytoreductive; secondary; ILNR; ovarian cancer; lymph node metastasis*" and is schematically presented in the PRISMA flow diagram (Fig. 1).

The selection of studies was conducted in three consecutive stages. After checking for duplicate publications, two authors screened the titles and abstracts of electronically retrieved articles to determine if they were eligible for inclusion. The decision was finalized after retrieving and reviewing the full text of articles that were considered to be relevant to the topic. Any discrepancies that arose among the two authors during these steps were resolved by consensus of all authors.

2.2. Study selection

2.2.1. Types of studies and patients

Eligibility criteria were predetermined. No language restrictions were applied during the electronic search. All articles that were written in Latin alphabet were considered as potentially eligible for inclusion. Articles written in languages that use symbols such as Arabic and Chinese were considered eligible when they could be translated in plain English text using the Google Translate service. All observational studies as well as randomized trials that investigated outcomes of various treatments that were implemented in patients with ILNR were included in the present systematic review, provided that these recurrences were isolated and no other organs were involved in disease relapse. The stage of the disease at primary diagnosis was not considered a criterion for inclusion, neither the extent of the follow-up period; however, differences in baseline characteristics of patients were recorded and tabulated when available. Conference abstracts were also considered as eligible and tabulated. Case reports, experimental animal studies and reviews were not included in the present systematic review.

2.2.2. Investigated outcomes

The primary outcome of the present systematic review was the 5-year OS rate of patients treated for ILNR. Post-recurrence survival DFS and OS were predefined as secondary outcomes, along with the documentation of failure of SCS and potential surgical complications (including severe bleeding (> 500 ml), large vessel injury and injury to other abdominal organs).

2.2.3. Quality and risk of bias assessment

The risk of bias and methodological quality of included cohort studies was explored using the Newcastle-Ottawa Scale (NOS), which evaluates the selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest [11]. The risk of bias and methodological quality of included single arm studies was based on the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (using the fields 1a, 3e, 3h and 4a that are applicable to single arm studies) [12].

3. Results

3.1. Excluded studies

Five articles were excluded from the present systematic review [13–17] as they did not investigate the outcomes of interest. Specifically, two articles investigated the impact of lymphadenectomy in primary staging of advanced EOC cases [13,16], one article focused in patients with neck lymphatic metastasis [15], another one investigated the impact of bulky lymph node resection and systematic lymphadenectomy in patients with recurrent EOC that also had other sites of involvement [17] and the last one investigated the impact of minimally invasive salvage lymphadenectomy for ILNR in patients with gynecological malignancies (including but not limited to EOC) [14].

3.2. Included studies

Overall, ten studies were included in this review that recruited a total number of 436 women [9,18–26]. Of these, 288 women performed either comprehensive lymphadenectomy or isolated bulky lymph node resection as explained in the next section. The methodological characteristics of included studies are briefly presented in Table 1. The results of the risk of bias assessment are presented in Supplemental Table 1 and indicate that the methodology that was used was appropriate in the majority of included studies. Baseline characteristics of included women at primary debulking surgery are presented in Table 2 and briefly denote the heterogeneity in terms of the selected population.

3.3. Case series

3.3.1. Effects on OS and PRS

Uzan et alwere the first to study the outcomes of SCS in EOC patients with ILNR. This study included 12 patients with ILNR that underwent SCS followed by chemotherapy or radiation [18]. The post-recurrence PFS was 44 months (range 8–158), while the 5-year overall survival after SCS was 71% (CI, 41%–91%) and the median-overall survival 114 (range, 43–172) months. Santillan et al. investigated outcomes in a retrospective series of 25 patients who were treated with surgery plus chemotherapy and found that the median PRS was 37 months, while 40% of women had no indication of disease at the time of the last follow-up visit [19]. The median OS in this series was 61 months. Blanchard et al. in a retrospective study of 27 EOC patients with ILNR compared the effects of surgery with adjuvant chemo and chemotherapy alone [20]. The median OS was 68 months, whereas the PRS was 26 months. The 2-year survival rate after ILNR was 50% for patients with early onset recurrence (within 24 months from primary treatment) and 47% for patients with late onset recurrence (> 24

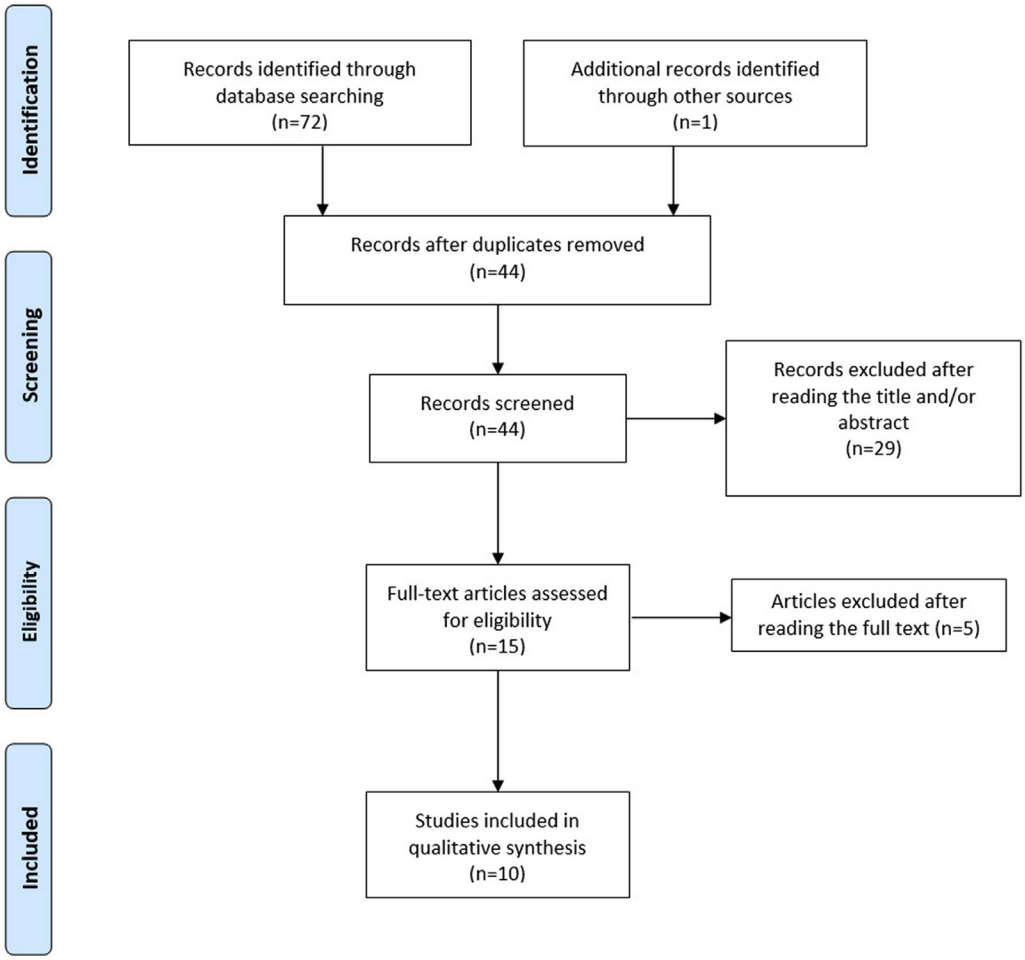

Fig. 1. Search plot diagram.

months from primary treatment). This latter difference was not statistically significant. Prolonged survival (> 110 months) was observed in 30% of included patients. Fotiou et al. presented a series of 21 patients who underwent SCS followed by chemotherapy or radiation [21]. They reported a post-recurrence PFS of 44 months (median 8–158), a PRS of 47 months and a projected 5-year PRS of 68%. The median OS in their series was 66 months. Finally, Ferrero et al. included 73 patients who had SCS for ILNR [25]. Incomplete debulking was noted in one patient. After surgery all patients were treated with adjuvant chemotherapy or radiation. The median follow-up period was 50 months and the 5-year overall survival was 64%. Fifty-three patients (72%) had a PRS longer than 24 months and 16 patients (22%) had a PRS that progressed beyond 60 months.

3.4. Cohort studies

3.4.1. Effects on OS and PRS

Gadducci et al., compared 44 patients with EOC that received chemotherapy to 22 patients that had SCS for ILNR that was followed by chemotherapy [22]. They observed that the median PRS in patients who underwent chemo was significantly better in the latter group (20.8 months vs not reached (> 74.5 months) $p < .001$). Similarly, the median OS was significantly longer in this group (45.4 months vs not reached (> 74.5 months). The authors concluded that women treated with SCS and chemotherapy had decreased odds of disease related death (hazard ratio [HR] = 0.277, $p < .001$) and improved OS.

Petrillo et al. evaluated the impact of anatomic site of relapse in disease progression and sub-stratified 220 patients in three groups according to the anatomic position of the relapse (localize peritoneal, ILNR and localized parenchymal) [24]. They observed that patients with ILNR had significantly better PRS (63 months) compared to patients with localized peritoneal (41 months) or parenchymal relapse (24 months) ($p = .001$). They also reported that complete cytoreduction followed by chemotherapy significantly increased patient survival compared to chemotherapy alone irrespective of the site of recurrence (median PRS for ILNR 78 months vs 30 months $p = .006$).

Tu et al. also observed that cytoreductive surgery followed by chemotherapy was associated with an increased 5-year PRS compared with radiotherapy/chemotherapy and chemotherapy alone (71.8% vs 68.8% vs 40%); however, the result was not statistically significant [23].

Legge et al. also reported that disease progression in INLR patients was less aggressive and they observed that patients subjected to cytoreductive surgery had a more favorable outcome compared to patients that were submitted to chemotherapy alone (PRS not reached vs 31 months); however, the statistical significance was of marginal value ($p = .07$) [9].

Bogani et al. compared the outcomes of complete lymphadenectomy to those of isolated bulky node resection [26]. From 199 patients that were primarily identified 35 were clinically evaluated (including 11 patients that had complete lymphadenectomy and 24 that had bulky node resection). No differences were observed in terms of OS (HR 0.98, 95% CI, 0.37–2.61). However, a significant decrease in post-recurrence disease free survival was noted (HR 0.41, 95% CI, 0.27–0.97) in those submitted to complete lymphadenectomy.

Table 1
Methodological characteristics of included studies.

Year; Author	*Study type*	*Inclusion Criteria*	*Exclusion Criteria*
2018; Bogani	Controlled	• age ≥18 years • advanced stage ovarian cancer at presentation • platinum-sensitive recurrent ovarian cancer • histologically-proven recurrence of invasive epithelial ovarian, primary peritoneal and/or Fallopian tube cancer • recurrence(s) located in the retroperitoneal tissue	• withdrawal of consent • presence of gross peritoneal disease at the time of SCS • positive results of cytological evaluation of peritoneal cavity • performance status not allowing surgical treatment • early stage of disease at primary surgery (FIGO stage I or II)
2013; Ferrero	Single-arm	• history of epithelial ovarian cancer • GOG performance status 0 or 1 • DFI ≥ 6 months • absence of ascites	• age > 75 years • GOG performance status 2 • presence of peritoneal disease • borderline tumor
2013; Petrillo	Controlled	• relapse in a single anatomic site • ≤ 3 nodules • follow-up time after recurrent disease of at least 24 months	• relapse with several nodules • recurrent disease in multiple anatomic sites
2012; Tu	Controlled	• relapse located exclusively in lymph node(s) • initial diagnosis of epithelial ovarian cancer	N/A
2010; Gadducci	Controlled	• clinically or pathologically free of disease after primary surgery • relapse located exclusively in lymph node(s)	N/A
2009; Fotiou	Single-arm	• relapse located exclusively in lymph node(s) • DFI ≥ 6 months • histological verification of relapse • good performance status	N/A
2008; Legge	Single arm	• relapse located exclusively in lymph node(s) • initial diagnosis of epithelial ovarian cancer • at least 12 months follow-up period	N/A
2007; Blanchard	Single-arm	• relapse located exclusively in lymph node(s)	N/A
2007; Santillan	Single-arm	• DFI ≥ 6 months • preoperative diagnosis of ILNR using imaging and/or physical examination and no imaging evidence of peritoneal disease	N/A
2004; Uzan	Single-arm	• epithelial ovarian cancer • relapse located exclusively in lymph node(s) • DFI ≥ 6 months	• history of recurrent disease before the nodal recurrence • PFI < 6 months • non-histologically confirmed recurrence • concomitant recurrences in other site(s) • patients not subjected to surgical treatment

4. Discussion

The findings of this systematic review suggest that ILNR in EOC patients should be clearly distinguished from recurrences in other sites (including peritoneal and parenchymal) as their course seems to be less aggressive. Furthermore, current evidence suggests that the implementation of SCS as an adjunct to standard chemotherapy should be taken into consideration in this specific group of patients as the PRS may easily reach and even extend beyond 5 years. Prolonged survival (> 110 months) may be seen as a realistic target for a significant number of these patients, however, complete cytoreduction is essential to optimize survival outcomes, this is why complete lymphadenectomy is preferable, rather than isolated bulky lymph node removal.

The importance of lymphadenectomy in patients with recurrent EOC that have lymph node involvement has been denoted by Benedetti Panici in 2007 [17]. The authors specifically mentioned that bulky lymph node removal may benefit survival outcomes in this group of patients as the 5-year survival rate of cytoreduced patients was 87%, while non-cytoreducible patients had a median survival of only 23 months. To date, the pathophysiological explanation behind this effect remains unclear. In 2004 Morice et al. observed that lymph node metastases tend to be chemoresistant and this may partially explain the results of this systematic review [27]. An earlier report also suggested that platinum based chemotherapy has a small effect on lymph node tumour deposits [28]. Given this information, one could, assume that lymphadenectomy could improve survival outcomes of patients with ILNR by simply removing the chemoresistant residual disease. The actual pathophysiology behind this possible association remains unclear; however, it is believed that anti-cancer drugs fail to reach metastases due to their small molecular weight which results in their re-absorption in the systemic circulation [29,30]. In a previous animal experimental study Gu et al. showed that organ selective chemoresistance in metastases from human cancer cells may be the result of differential expression of genetic instability [31]. Moreover, patients that relapse following adjuvant chemotherapy overexpress several genes that seem to be associated with lymph node metastases and response to chemotherapy [32,33]. To date, however, the hypothesis of chemoresistance explicitly among patients with ILNR remains untested and, to our knowledge, only one case report of a patient with chemoresistant multiple retroperitoneal lymph node metastases that was effectively treated with complete pelvic and paraortic lymphadenectomy has been published in this field [34]. The role of radiotherapy in this patient group is also poorly explored, although a recent clinical study suggested that it seems to be accompanied by significant antitumor effect with minimal associated toxicity [35].

4.1. Study limitations

The findings of our systematic are based in retrospective cohorts and case series; hence, their level of evidence is graded as 3 and 4. Moreover, the, relatively, small number of included patients renders their results rather inconclusive in the majority of cases. Lastly, the significant heterogeneity in terms of included population, as well as the absence of a control group in the majority of included case series rendered impossible quantitative analysis of outcomes.

Table 2
Baseline characteristics of patients at primary diagnosis.

Year; authors	Patient n	Stage	Histology	Grade	Lymphadenectomy	Residual tumor	DFS (months)
Single arm studies							
2010; Gadducci	69	I: 11 II: 6 III: 46 IV: 6	Serous:52 Endometroid:12 Undifferentiated:3 Clear Cell:1 Mixed:1	1:3 2:13 3:54	Yes:37 No:32	0:22 < 1 cm:11 > 1 cm:36	< 6:4 6–12:21 > 12:44
2013; Petrillo	76	I-II: 10 III-IV: 33	Serous:64 Others:12	1:3 2:15 3:50 N/A: 8	N/A	< 1 cm:48 > 1 cm:28	13
2018; Bogani	24/11¥	III: 30 IV: 5	Serous:27 Other:8	3:27	N/A	R0: 28 > R0: 7	35
Cohort studies							
2004; Uzan	12	I:5 II:1 III:6	Serous:8 Endometrioid:4	N/A	Yes:3 No:9	R0:7 < 2 cm:4 > 2 cm:1	21
2007; Santillan	25	I:2 II:5 III:15 IV:3	Serous:19 Endometrioid:2 Mixed:4	1–2:0 3:25	N/A	E0:16 < 1 cm:5 1–2 cm:0 > 2 cm:2	16
2007; Blanchard	27	I:4 II:5 III:15 IV:3	N/A	N/A	N/A	N/A	26
2008; Legge	60	II: 1 III: 29 IV: 2	Serous:26 Mucinous:1 Endometrioid:2 Undifferentiated:3	1-2: 9 3: 19	No	< 0.5 cm:14 0.5–2 cm:6 > 2 cm:12	17.5
2009; Fotiou	21	I:3 II:3 III:14 IV:1	Serous:16 Other:5	1:0 2:8 3:13	Yes:9 No:41	R0:8 ≤1 cm:7 > 1 ≤ 2 cm:4 > 2 cm:2	21
2012; Tu	38	II: 15 III: 23	Serous:19 Mucinous:1 Endometriod:9 Mixed:9	1:7 2:14 3:17	N/A	N/A	18
2013; Ferrero	73	I:14 II:4 III:51 IV:4	Serous:53 Mucinous:1 Endometrioid:11 Mixed:8	1:4 2:5 3:64	Yes:42 No:31	R0:57 < 1 cm:10 1–2 cm:4 > 2 cm:2	18

4.2. Implications for current clinical practice and future research

Until further evidence becomes available, systematic lymphadenectomy should be considered as a treatment alternative for EOC patients with ILNR resistant to standard chemotherapy. Future randomized studies should be conducted in this field to validate or oppose this theory and help reach firm conclusions in this field. To reach adequate sample size, these should be ideally multicentric and strict criteria should be applied during the preoperative assessment of patients to minimize the possibility of diffuse peritoneal disease. Patient stratification should specifically compare the outcomes of patients subjected to lymphadenectomy and platinum-based chemotherapy to those of patients that complete only platinum-based chemotherapy. Multivariable analysis of variables such as the interval of PFS, extent of disease and primary histology is also essential to help determine factors that seem to increase the odds of secondary relapse, as this usually proves to be lethal with a relatively short median OS.

Ethical approval

This is a systematic review of published evidence. An ethical approval is not required for this type of studies.

Sources of funding

The authors did not receive funding.

Author contribution

Vasilios Pergialiotis and Nikolaos Thomakos: conceived the idea, designed the project, wrote and revised the manuscript; Anastasia Androutsou: tabulated data; Eleni Papoutsi: tabulated data; Ioannis Bellos: wrote the manuscript; Dimitrios Haidopoulos: wrote the manuscript; Alexandros Rodolakis: supervised the project and wrote the manuscript. All authors revised the manuscript and approve its final version.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Research registration unique identifying number (UIN)

This study has been registered in PROSPERO (CRD42019122854). https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=122854.

Guarantor

Vasilios Pergialiotis is the guarantor for the conduct of the present study and had full access to data.

Disclosure

The authors report no conflict of interest.

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

All data that were used to write the present systematic review have been previously presented in original articles published in this field.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.07.026.

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