European Journal of Cancer 195 (2023) 113398

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

Lymph node staging in grade 1–2 endometrioid ovarian carcinoma apparently confined to the ovary: Is it worth?

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ARTICLE INFO

Keywords:
Ovarian cancer
Endometrioid
Early stage
Surgical staging
Lymphadenectomy
Synchronous

ABSTRACT

Objective: The aim of this study was to assess the disease-free survival (DFS) and overall survival (OS) of patients with grade 1–2 endometrioid ovarian carcinoma apparently confined to the ovary, according to surgical staging.
Methods: Multicenter, retrospective, observational cohort study. Patients with endometrioid ovarian carcinoma, surgical procedure performed between May 1985 and December 2019, stage pT1 N0/N1/Nx, grade 1–2 were included. Patients were stratified according to lymphadenectomy (defined as removal of any lymph node versus no lymph node assessment), and subgroup analyses according to tumor grade were performed. Kaplan-Meier curves and cox regression analyses were used to perform survival analyses.
Results: 298 patients were included. 199 (66.8 %) patients underwent lymph node assessment. Of these, 166 (83.4 %) had unilateral/bilateral pelvic and para-aortic/caval lymphadenectomy. Eleven (5.5 %) patients of those who underwent lymph node assessment showed pathologic metastatic lymph nodes (FIGO stage IIIA1). Twenty-seven patients (9.1 %) had synchronous endometrioid endometrial cancer. After a median follow up of 45 months (95 %CI:37.5–52.5), 5-year DFS and OS of the entire cohort were 89.8 % and 96.2 %, respectively. Age $\leq$ 51 years (HR=0.24, 95 %CI:0.06–0.91; p = 0.036) and performance of lymphadenectomy (HR=0.25, 95 %CI: 0.07–0.82; p = 0.022) represented independent protective factors toward risk of death. Patients undergoing lymphadenectomy had better 5-year DFS and OS compared to those not receiving lymphadenectomy, 92.0 % versus 85.6 % (p = 0.016) and 97.7 % versus 92.8 % (p = 0.013), respectively. This result was confirmed after exclusion of node-positive patients. When stratifying according to tumor grade (node-positive excluded), patients

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https://doi.org/10.1016/j.ejca.2023.113398
Received 29 June 2023; Received in revised form 16 October 2023; Accepted 18 October 2023
Available online 20 October 2023

with grade 2 who underwent lymphadenectomy had better 5-year DFS and OS than those without lymphadenectomy (93.0 % versus 83.1 %, p = 0.040 % and 96.5 % versus 90.6 %, p = 0.037, respectively).
Conclusion: Staging lymphadenectomy in grade 2 endometrioid ovarian carcinoma patients was associated with improved DFS and OS. Grade 1 and grade 2 might be considered as two different entities, which could benefit from different approach in terms of surgical staging. Prospective studies, including molecular profiles are needed to confirm the survival drivers in this rare setting.

1. Introduction

About 73.853 early-stage ovarian cancer patients have been estimated in 2018 worldwide [1,2] with a recurrence risk estimated to be 10–15 % at five years [3]. Endometrioid ovarian carcinoma (OC) represents the second most common histology type of epithelial OC after serous, with an incidence of 31 % among early stages [3]. It is associated with endometriosis in 15–30 % of cases [4,5] and may arise from seromucinous or endometrioid borderline tumors [6,7]. Grade is an important prognostic factor for OC, with grade 1 and 2 (G1–2) patients having a better prognosis than grade 3 for all histologies [8]. However, despite serous OC has a clear dichotomy between low and high grade, the same is not clear for endometrioid histology [9,10]. In other words, can G1–2 endometrioid OC be considered as "low grade" or do they have a different behavior, with different clinical implications in terms of retroperitoneal staging? ESMO-ESGO guidelines recommend performing peritoneal and retroperitoneal staging in apparent early-stage OC, regardless of histology or grade, in case this may alter adjuvant treatment [11]. Nevertheless, previous reports questioned the role of lymphadenectomy in grade 1 endometrioid OC in view of the no risk of lymph node metastasis in this sub-group of patients [12,13].

Recently, Swift and colleagues reported a retrospective series of 131 G1–2 early-stage endometrioid OC and found that grade 2 (compared with grade 1) had a significantly higher recurrence rate, while lymph node dissection and adjuvant chemotherapy did not impact the prognosis [14]. With this background, the prognostic role of lymphadenectomy in G1–2 endometrioid OC is still matter of debate [15,16].

The aim of this study was to assess the disease-free survival (DFS) and overall survival (OS) of patients with grade 1 and grade 2 endometrioid OC apparently confined to the ovary, according to surgical staging.

2. Methods

This is a multicenter, retrospective, cohort study. Patients with endometrioid OC, surgical procedure performed between May 1985 and December 2019, stage pT1 N0/N1/Nx, G1–2 were included. Patients with bulky lymph nodes at imaging (>15 mm in short axis) were excluded. Patients were treated in five gynecologic oncology referral centers (in Germany: Ev. Kliniken Essen-Mitte, Essen; in Italy: Policlinico A. Gemelli IRCCS, Rome; San Gerardo Hospital, Monza; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; Regina Elena Hospital, Rome). Patients demographic, clinical, and tumor-related characteristics were extracted from medical records and institutional databases. For patients who did not undergo surgical staging at time of diagnosis, a re-staging with a second operation (during which peritoneal and/or retroperitoneal staging was performed) with midline laparotomy or minimally invasive surgery was performed by a specialized team including at least one board-certified gynecologic oncologist.

Patients with FIGO stage IIIC [17] based on retroperitoneal lymph node metastases only were re-classified into the latest FIGO stage IIIA1 [18] and included. The study protocol was approved by each center's institutional review board.

2.1. Statistical analysis

Statistical analysis was carried out using SPSS 27.0 and R 4.1.2 software. Standard descriptive statistics were used to evaluate the distribution of each variable. Continuous variables were reported as median and categorical variables as frequencies or percentages. The distribution of variables between groups was compared with chi-square test or Fisher's exact test and Mann-Whitney U test or ANOVA test, as appropriate.

DFS was defined as the time in months from the date of OC diagnosis to the date of first recurrence, last follow-up, or death. Overall survival (OS) was calculated as the time in months from the date of OC diagnosis to the date of the last follow-up or death. OS and DFS were estimated by the Kaplan-Meier method [19], and survival curves were compared by the log-rank test [20]. Variables were investigated and included in univariable and multivariable survival Cox regression analyses [21]; Hazard Ratios (HRs) and 95 % confidence intervals were reported.

Patients were stratified according to lymphadenectomy. Complete surgical staging was defined as peritoneal and retroperitoneal staging. Peritoneal staging was defined as complete according to ESGO-ESMO recommendations and included peritoneal washing (or peritoneal fluid cytology), if hysterectomy, bilateral salpingo-oophorectomy, omentectomy and peritoneal biopsy were performed [11]. Retroperitoneal staging included systematic uni/bilateral pelvic and/or para-aortic lymphadenectomy. Fertility sparing surgery was defined as defined as conservation of uterus and at least one tube/ovary. For the Cox regression analysis, fertility sparing surgery was considered as "partial" peritoneal staging. Age was dichotomized according to the median value.

All p-values reported are two-sided and a p-value $\leq$ 0.05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

Two hundred and ninety-eight patients were included in the study period. Characteristics of the patients are listed in Table 1. Most patients were diagnosed with FIGO stage IA (N = 143, 48.0 %), grade 2 (N = 192, 64.4 %), underwent a single staging procedure (N = 197, 66.1 %), and underwent both peritoneal and retroperitoneal surgical staging (N = 166, 56.5 %). One hundred and ninety-nine (66.8 %) patients underwent lymph node assessment (of these, 166–83.4 % - had unilateral/bilateral pelvic and para-aortic/caval lymphadenectomy). Eleven (5.5 %) patients of those undergoing lymph node assessment showed pathologic metastatic lymph nodes (FIGO stage IIIA1). Nine of these (81.8 %) were diagnosed with grade 2 endometrioid ovarian cancer. Adjuvant chemotherapy was administered to 155 (52.2 %) patients, most of them receiving single agent carboplatin (N = 139, 89.7 %). Twenty-six (8.7 %) patients underwent fertility sparing treatment.

3.2. Survival analysis

After a median follow up of 45 months (95 %CI: 37.5–52.5), 5-year DFS and OS of the entire cohort were 89.8 % and 96.2 %, respectively. Twenty-four (8.1 %) patients experienced recurrence (41.7 % G1 and 58.3 % G2) and 13 (4.4 %) died (30.8 % G1 and 69.2 % G2). Of patients with recurrence, 15 (62.5 %) had pelvic/abdominal mass or peritoneal carcinomatosis, 4 (16.7 %) had lymph node recurrence and two (8.3 %) distant disease (in three patients the site of recurrence was unknown).

Table 2 demonstrates the results of Cox univariate and multivariable analysis for risk for recurrence: the only significant variable affecting DFS was the performance of lymphadenectomy at uni- and multivariable analysis (borderline statistical significance at multivariable analysis) (HR=0.39, 95 %CI:0.17–0.86; p = 0.021 and HR=0.44, 95 % CI:0.19–1.02; p = 0.05, respectively). Incomplete peritoneal staging affected DFS at univariable but not at multivariable analysis (p = 0.049 and p = 0.16, respectively). Addition of adjuvant therapy (Supplementary Fig. 1) and the performance of fertility-sparing treatment did not have any impact on risk of recurrence (p = 0.56 and p = 0.72, respectively; Table 2). Similarly, intraoperative cyst rupture did not impact the risk of recurrence (HR=1.24; 95 %CI 0.777–1.979; p = 0.367), when performing analysis of patients with FIGO stage IA-IC1 (result not shown in Table 2).

Table 3 shows the Cox univariable and multivariable analysis for risk of death. Age ≤ 51 years (HR=0.27, 95 %CI:0.07–0.98; p = 0.047) and performance of lymphadenectomy (HR=0.26, 95 %CI:0.08–0.80; p = 0.019) represented independent protective factors toward risk of death.

5-year DFS of patients undergoing any lymphadenectomy versus no lymph node assessment was 92.0 % (95 %CI: 87.1 %−96.9 %) versus 85.6 % (95 %CI: 77.0 %−94.2 %), respectively (p = 0.016) (Fig. 1A). Similarly, patients undergoing lymphadenectomy had better 5-year OS compared to those not receiving lymphadenectomy: 97.7 % (95 %CI: 95.1 %−100.0 %) versus 92.8 % (95 %CI: 85.7 %−99.8 %), respectively (p = 0.013) (Fig. 1B).

The prognostic role of lymphadenectomy in this group of patients was confirmed after excluding women with metastatic lymph nodes at histology (number of N-/Nx patients was 287) (5-year DFS: 93.1 % versus 85.6 %, p = 0.008; 5-year OS: 98.1 % versus 92.8 %, p = 0.009) (Supplementary Fig. 2).

An analysis stratified by tumor grade was then performed (after exclusion of N + patients). The 5-year DFS difference was evident only in grade 2 patients: in this subgroup of patients, those receiving lymphadenectomy had a better 5-year DFS compared with those not receiving lymphadenectomy (94.9 % (95 %CI: 89.8 %−100.0 %) versus 83.1 % (95 %CI: 70.9 %−95.3 %), respectively; p = 0.017) (Fig. 2A). No 5-year DFS difference in grade 1 patients was seen according to lymphadenectomy (p = 0.28). Similarly, within patients with grade 2, those undergoing lymphadenectomy had better 5-year OS than those not undergoing lymphadenectomy (97.1 % (95 %CI: 93.2 %−100.0 %) versus 90.6 % (95 %CI: 79.8 %−100.0 %), respectively; p = 0.021) (Fig. 2B). No 5-year OS difference in grade 1 patients was seen according to lymphadenectomy (p = 0.42).

3.3. Synchronous endometrial cancer

Twenty-seven patients (9.1 %) had synchronous endometrioid endometrial cancer. Endometrial cancers were diagnosed with FIGO stage IA in 23 (85.2 %), IB in three (11.1 %) and II in one (3.7 %) cases. Fourteen (51.8 %) patients had grade 1 and 13 (48.2 %) had grade 2 endometrial cancer. Four (14.8 %) patients with synchronous endometrial and ovarian carcinoma had positive lymph nodes: two were grade 2 and two were grade 1. The only two patients with grade 1 endometrioid ovarian cancer showing metastatic lymph nodes had both a synchronous endometrial cancer (grade 1 in both cases, FIGO stage IA and IB). Synchronous endometrioid endometrial cancer did not represent a risk factor for decreased DFS (HR=0.51; 95 %CI:0.068–3.739; p = 0.503) or OS (HR=1.13; 95 %CI: 0.145–8.761; p = 0.908) (Table 2 and Table 3). The improved 5-year DFS and OS of patients undergoing lymphadenectomy versus those not undergoing lymphadenectomy was confirmed also after excluding patients with synchronous endometrioid endometrial and ovarian cancer (p = 0.015 and p = 0.007, respectively).

Table 1
Patients' characteristics.

	Total (n = 298)	LND no (n = 99)	LND yes (n = 199)	P value
Age (median, IQR)	51.5 (44–60)	56 (47.5–62)	49 (43–58)	**<0.0001**
CA-125 (median, IQR)	66.6 (23.6–224.3)	63.0 (23.7–233.0)	68.0 (23.4–233.0)	0.87
FIGO stage				0.12
IA	143 (48.0 %)	49 (49.5 %)	94 (47.2 %)	
IB	17 (5.7 %)	5 (5.1 %)	12 (6.0 %)	
IC	127 (42.6 %)	45 (45.5 %)	82 (41.2 %)	
IC1	76 (25.5 %)	32 (32.3 %)	44 (22.1 %)	
IC2	35 (11.7 %)	10 (10.1 %)	25 (12.6 %)	
IC3	16 (5.4 %)	3 (3.0 %)	13 (6.5 %)	
IIIA1	11 (3.7 %)[a]	0	11 (5.5 %)	
GRADING				0.84
G1	106 (35.6 %)	36 (36.4 %)	70 (35.2 %)	
G2	192 (64.4 %)	63 (63.6 %)	129 (64.8 %)	
APPROACH TO THE FIRST SURGERY				0.31
Minimally invasive	136 (45.8 %)	49 (50.0 %)	87 (43.7 %)	
Laparotomy	161 (54.2 %)	49 (50.0 %)	112 (56.3 %)	
PERITONEAL STAGING				**<0.0001**
Complete	248 (83.2 %)	77 (77.8 %)	171 (85.9 %)	
Partial	16 (5.4 %)	13 (13.1 %)	3 (1.5 %)	
Fertility Sparing	26 (8.7 %)	9 (9.1 %)	17 (8.5 %)	
Unknown	8 (2.7 %)	0	8 (4.0 %)	
RESTAGING				**0.006**
No	197 (66.1 %)	76 (76.8 %)	121 (60.8 %)	
Yes	101 (33.9 %)	23 (23.2 %)	78 (39.2 %)	
ADJUVANT CHEMOTHERAPY				0.30
No	142 (47.6 %)	52 (52.5 %)	90 (45.2 %)	
Single agent	139 (46.6 %)	44 (44.4 %)	95 (47.7 %)	
Combination	16 (5.4 %)	3 (3.0 %)	13 (6.5 %)	
Unknown	1 (0.3 %)	0	1 (0.5 %)	
SYNCHRONOUS ENDOMETRIAL CANCER				0.089
No	271 (90.9 %)	94 (94.9 %)	177 (88.9 %)	
Yes	27 (9.1 %)	5 (5.1 %)	22 (11.1 %)	

LND: lymphadenectomy; FIGO: International Federation of Gynecology and Obstetrics
[a] 11/199 (5.5 %) patients undergoing lymphadenectomy had positive lymph node(s)

Table 2
Univariate and multivariable Cox regression analysis for risk of recurrence in the entire population.

	UNIVARIATE HR (95 % CI)	MULTIVARIABLE HR (95 % CI)
FIGO stage	P = 0.54	
IA	0.77	
Others	(0.34–1.77)	
	1.00	
LYMPH NODES	P = 0.33	
Positive	2.07	
Negative	(0.48–8.83)	
	1.00	
ADJUVANT CHEMOTHERAPY	P = 0.56	
No	1.00	
Yes	0.77	
	(0.33–1.82)	
GRADING	P = 0.41	
G1	1.00	
G2	0.71	
	(0.31–1.60)	
FSS	P = 0.72	
No	1.00	
Yes	1.25	
	(0.37–4.19)	
AGE	P = 0.15	
≤51 years	0.55	
>51 years	(0.24–1.25)	
	1.00	
LYMPHADENECTOMY	**P = 0.021**	**P = 0.05**
No	1.00	1.00
Yes	0.39	0.44 (0.19–1.02)
	(0.17–0.86)	
SYNCHRONOUS ENDOMETRIAL CANCER	P = 0.50	
No	1.00	
Yes	0.51	
	(0.07–0.74)	
SURGICAL APPROACH TO FIRST	P = 0.37	
SURGERY	1.00	
Laparotomy	0.67	
Minimally invasive	(0.28–1.59)	
PERITONEAL STAGING	**P = 0.049**	P = 0.16
No	1.00	1.00
Yes	0.41	0.52 (0.21–1.30)
	(0.17–0.99)	

Table 3
Univariate and multivariable Cox regression analysis for OS in the entire population.

	UNIVARIATE HR (95 % CI)	MULTIVARIABLE HR (95 % CI)
FIGO stage	P = 0.21	
IA	0.44	
Others	(0.12–1.60)	
	1.00	
ADJUVANT CHEMOTHERAPY	P = 0.51	
No	1.00	
Yes	0.65	
	(0.18–2.33)	
GRADING	P = 0.91	
G1	1.00	
G2	1.07	
	(0.33–3.50)	
FSS	P = 0.38	
No	1.00	
Yes	0.04	
	(0.0–57.31)	
AGE	**P = 0.049**	**P = 0.047**
≤51 years	0.27	0.27 (0.07–0.98)
>51 years	(0.07–0.99)	1.00
	1.00	
LYMPHADENECTOMY	**P = 0.020**	**P = 0.019**
No	1.00	1.00
Yes	0.26	0.26 (0.08–0.80)
	(0.08–0.81)	
SYNCHRONOUS ENDOMETRIAL CANCER	P = 0.91	
No	1.00	
Yes	1.13	
	(0.14–8.76)	
SURGICAL APPROACH TO FIRST	P = 0.15	
SURGERY	1.00	
Laparotomy	0.32	
Minimally invasive	(0.07–1.51)	
PERITONEAL STAGING	P = 0.81	
No	1.00	
Yes	1.20	
	(0.26–5.61)	

4. Discussion

In this retrospective study, grade 1–2 endometrioid OC apparently confined to the ovary showed an overall risk of 5.5 % of lymph node metastases. Lymphadenectomy represented an independent protective factor toward risk of recurrence and death, only in women with grade 2 disease. Age ≤ 51 years was an independent factor for reduced risk of death. No oncological impact of adjuvant therapy and fertility-sparing surgery was seen in the present series.

The prognostic significance of lymphadenectomy in apparent ovary-confined G1–2 endometrioid OC has been previously explored by few studies. In particular, Chen et al. retrospectively analyzed the outcomes of 54 patients with G1–2 endometrioid OC according to different methods of lymph node dissection. They showed that occult lymph node metastasis was found in 2 (3.7 %) cases and that the lymph node dissection did not impact the DFS or OS (despite a trend in a lower risk of recurrence in favor of patients receiving any lymph node assessment, p = 0.059) [16]. Similarly, Swift et al. more recently published the results of a retrospective analysis on 131 G1–2 FIGO stage I endometrioid OC, of whom 41.1 % underwent lymph node assessment, and found no positive lymph nodes. They also did not demonstrate an association between staging lymphadenectomy and risk of recurrence. In their study, the only factor impacting risk of recurrence was the grading (grade 2 when compared with grade 1) [14]. Conversely, in our series we found a higher rate of lymph node metastasis (5.5 %) and we found a significant impact of lymphadenectomy (any lymph node removal) on both DFS and OS. Similarly, we also did not find any adverse survival outcome related with fertility-sparing surgery, however we need to take these results with caution due to low number of patients undergoing fertility-sparing procedures in our and Swift series (8.7 % and 9.2 %, respectively). It is relevant to acknowledge that most patients with metastatic lymph nodes in our series was diagnosed with grade 2 disease (81.8 %): this is in keeping with findings from Heitz et al. [13] (who found no N + case in grade 1 endometrioid ovarian carcinoma), even though grade 2 per se did not impact DFS or OS (differently from Swift study [14]). Moreover, the only two N + patients with grade 1 disease in our series were found to have a synchronous endometrial cancer. We may assume that the removal of occult disease represents the main factor supporting the survival advantage in patients undergoing lymphadenectomy.

More recently, different studies analyzed the molecular classification of endometrioid OC to assess if this could predict clinical outcomes and to compare it with endometrial cancer molecular profile [22–25]. It is known that p53 patients carry the worst prognosis, while loss of mismatch repair protein expression (MMRd) and no specific molecular profile (NSMP) are associated with an intermediate prognosis. The most promising biomarkers to date seem to be progesterone receptor (PR) and CTNNB1, with the latter being the most commonly mutated gene in endometrioid OC [26]. Further research is needed to correlate the prognostic significance of the molecular profiles with known clinic-pathological risk factors. This could help to understand whether the integration of these two systems might aid the clinicians to predict better the risk of lymph node metastasis, recurrences and death and to guide the prescription of adjuvant therapy, thus further tailoring the surgical and medical treatment.

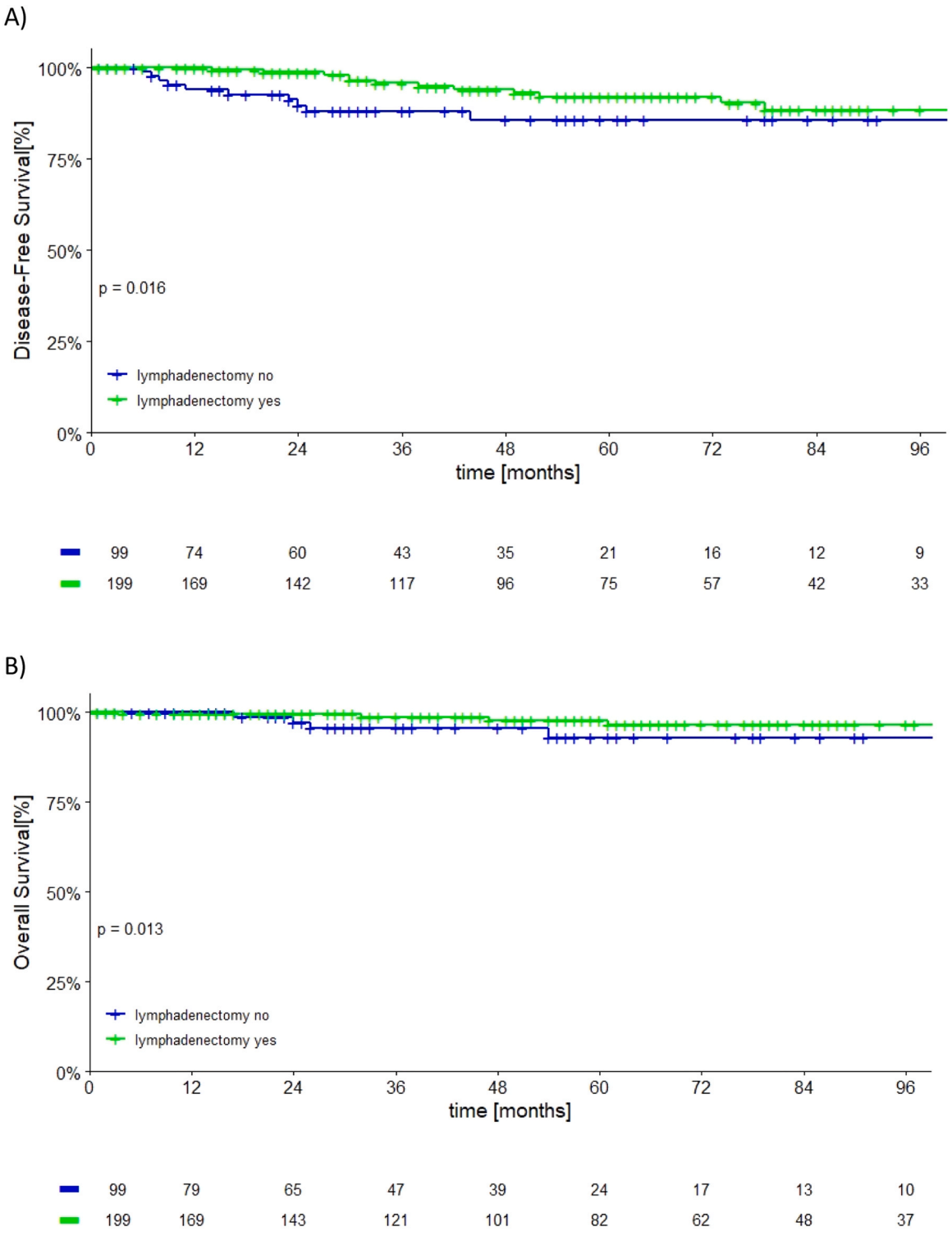

Fig. 1. DFS (A) and OS (B) comparison of patients with (green) and without (blue) lymphadenectomy.

The present study suffers from some limitations such as the retrospective design, the absence of central pathology review, the unknown BRCA status, the lack of information on molecular profile and on the number of lymph nodes retrieved (thus preventing the possibility to correlate the extent of lymphadenectomy with survival). In this context, we may argue that the only two grade 1 cases who had lymph node metastases might be grade 2 carcinomas at a second pathological review. Moreover, the indication for lymphadenectomy was not homogenous. On the other hand, to best of our knowledge this one of the studies with largest sample size in this relatively rare subgroup of patients and the first reporting an association between lymphadenectomy and improved survival.

5. Conclusion

With the limitation of a retrospective uncontrolled study, in which the indication for or against lymphadenectomy was not prospectively defined, our results suggest considering staging lymphadenectomy in

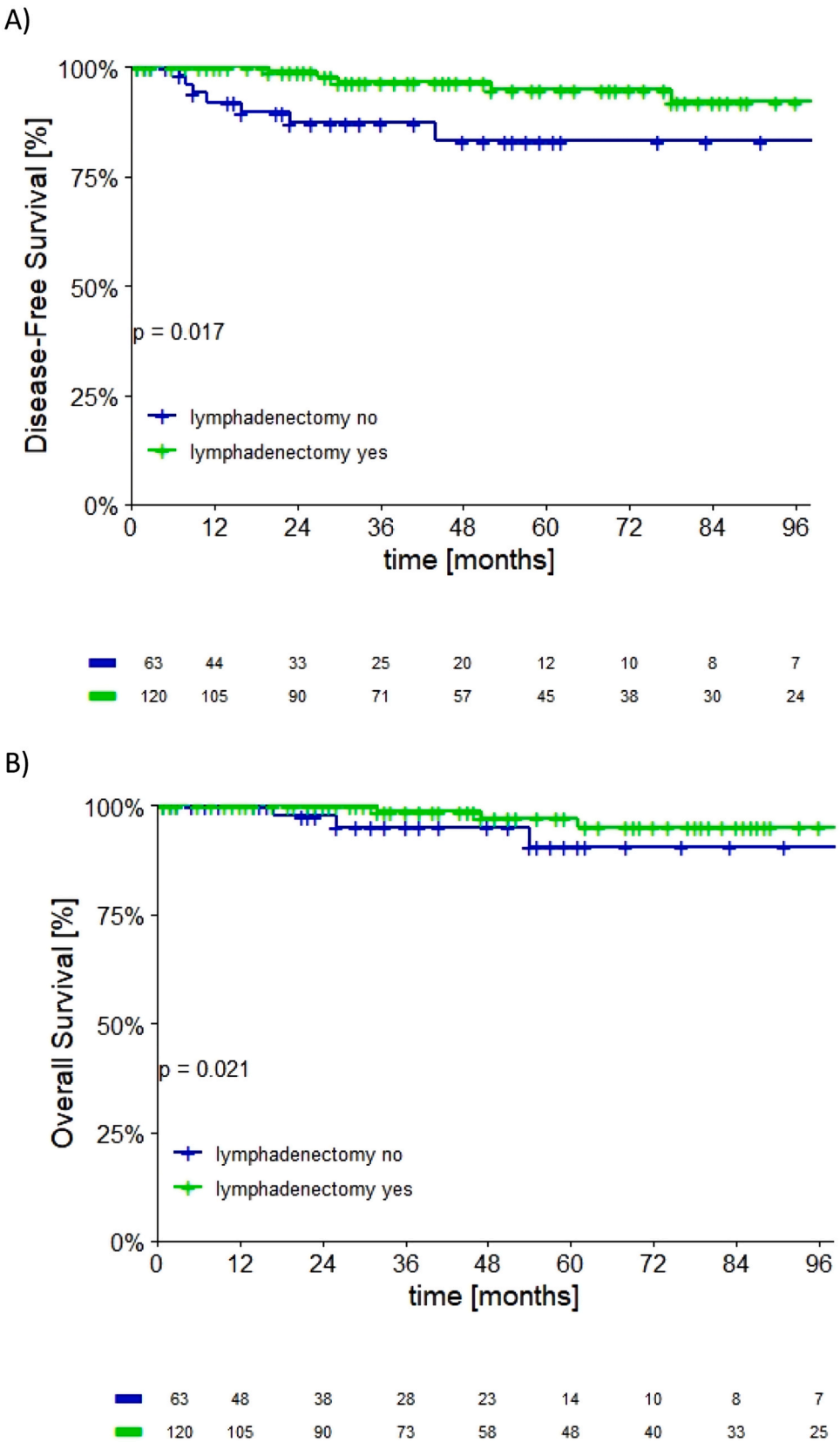

Fig. 2. DFS (A) and OS (B) comparison of patients with (green) and without (blue) lymphadenectomy in the subgroup of patients with node-negative grade 2 endometrioid ovarian cancer.

grade 2 endometrioid OC patients, as it was associated with improved DFS and OS in this subpopulation. Overall, we might consider grade 1 and grade 2 as two different entities, which could benefit from different approach in terms of surgical staging. Prospective studies, including molecular profiles are needed to confirm the survival drivers in this rare setting.

Funding

The present study received no funding.

CRediT authorship contribution statement

CRediT roles: Conceptualization: NB, AF, MI, PH; Data curation: MI; Formal analysis, MI, NB, DG; Investigation RF, PDI, RV, GS; Methodology: MI, RF, AMP, RM, AT, AR, ADB, DF, PDI, RE, BA, TB, MDS, MTP, FH, NC, FF, EV, GS, PH, AF; Project administration: NB, AF, GS; Software: DG; Supervision: AF, PH; Validation: FH, BA, GS; Roles/Writing - original draft: NB, AF; Writing - review & editing: all authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Authors would like to thank the surgical teams and the scrub nurses at their institutions.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113398.

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