Lymphovascular invasion as a criterion for adjuvant chemotherapy for FIGO stage I-IIa clear cell carcinoma, mucinous ,low grade serous and low grade endometrioid ovarian cancer

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RESUME

Background

The aim of this study was to evaluate the impact of lymphovascular space invasion (LVSI) on overall survival (OS) and recurrence-free survival (RFS) in patients managed for stage I-IIa clear cell carcinoma, mucinous, low-grade serous and low-grade endometrioid ovarian cancer

Material and methods

Retrospective multicentre study of the research group FRANCOGYN between January 2001 and December 2018. All patients managed for stage I-IIa clear cell carcinoma, mucinous /low grade serous and endometrioid ovarian cancer and for whom the presence of histological slides for the review of LVSI was available, were included. Patient's characteristics with LVSI (LVSI group) were compared to those without LVSI (No LVSI group). A cox analysis for OS and RFS analysis were performed in all population.

Results

Over the study period, 133 patients were included in the thirteen institutions. Among them, 12 patients had LVSI (9%). LVSI was an independent predictive factor for poorer Overall and recurrence free survivals. LVSI affected OS ($p<0.001$) and RFS ($p=0.0007$),

Conclusion

The presence of LVSI in stage I-IIa clear cell carcinoma, mucinous /low grade serous and endometrioid ovarian cancer has an impact on OS and RFS and should put them at high risk and consider the option of adjuvant chemotherapy

KEYWORDS: Lymphovascular space invasion, Overall survival, Recurrence-free survival, Ovarian cancer, Prognosis.

Introduction

The World Health Organization (WHO) Histological Classification for ovarian tumours separates epithelial ovarian neoplasms into several categories mainly based on the histopathological findings and defines the actual type of tumour. It has, therefore, also an important impact on prognosis and therapy of the patient (1-2). In addition to the frequent tumour forms (serous, endometrioid or high-grade undifferentiated adenocarcinomas), there are rare tumours including carcinosarcomas, mucinous carcinomas, clear cell carcinomas and all low-grade carcinomas (2).

Historically, clinical trials evaluating the efficacy of systemic therapies did not include histological specificities in the inclusion criteria, despite radically different prognoses (3). Most current studies are beginning to distinguish ovarian tumours according to their grade (high grade versus low grade), or even according to their histological subtype (especially clear cell and mucinous cell carcinomas) (4-5). Indeed, different sensitivities to systemic treatments according to histological types, with classically lower efficacy of conventional chemotherapy in non-serous and low-grade tumours, necessitate analysing them separately.

Adjuvant chemotherapy is recommended for all epithelial cancers of the ovary, fallopian tube or primary peritoneum in the early stages (stages I-IIA) with tumours of high histological grade (serous, endometrioid, undifferentiated, carcinosarcoma). (6-7)

It is not possible to make recommendations for mucinous, clear cell carcinoma, low-grade serous carcinoma and low-grade endometrioid carcinoma of the early stages ovary (stage I-IIA). (6-7)

The presence of lymphovascular space invasion (LVSI) appears to be a major prognostic factor in endometrial (8-13), cervical (14-19) and vulvar (20-22) cancers. The presence of LVSI is associated, in the literature, with a greater risk of lymph node and

metastatic dissemination, as well as an earlier risk of relapse and decreased survival. The same assertion remains limited in ovarian cancer. Recent publications suggest that the presence of LVSI is a major prognostic factor in disease progression (23-29), while other studies do not find this association (30,31). The prognostic value of the presence of LVSI in ovarian tumours remains controversial. In fact, the presence of LVSI is not systematically listed in histological reports and is not necessarily one of the key elements facilitating proposals for the management of patients affected by ovarian cancer (32).

Matsuo et al. recently demonstrated that the presence of LVSI was associated with a potential for hematogenic and lymphatic metastatic dissemination directly impacting survival parameters in high- and low-grade epithelial serous ovarian cancers and clear cell ovarian carcinomas (23-25,32). Nevertheless, the impact of the presence of LVSI does not appear to be identical across the different histological subtypes of ovarian cancer.

The objective of this study was to evaluate the impact of the presence of LVSI on overall survival and recurrence-free survival in patients with stage I-IIa clear cell carcinoma, mucinous /low grade serous and endometrioid ovarian cancer.

MATERIALS & METHODS

This was a descriptive, retrospective, multicentre study taking place in 13 French centres: the Regional University Hospital Center (CHRU) of Tours, the University Hospital of Tenon, the University Hospital of Marseille, the Anti-cancer Center of Dijon, the University Hospital Center (CHU) of Lyon Sud, the University Hospital of Lille, the Hospital of La Pitié Salpêtrière, the Centre Hospitalier Intercommunal de Créteil, the CHRU de Rennes, the Hôpital Lariboisière, the CHU Jean Verdier, the Centre Hospitalier Intercommunal de

Poissy/Saint-Germain-en-Laye and the CHU de Strasbourg from 1 January 2001 to 31 December 2018.

Criteria for inclusion

All the patients operated on for stage I-IIa clear cell carcinoma, mucinous /low grade serous and endometrioid ovarian carcinoma with fully staging (omentectomy, pelvic and para aortic lymphadenectomy) and who had undergone LVSI analysis on pathology during the period were included in the study. Histological data were collected from the reports and were centrally reviewed by the histologists of the Rare Malignant Tumours of the Ovary (TMRO) network labelled by the National Cancer Institute (INCa) centres experts TMRG (Tumeurs Malignes Rares Gynécologiques).

The research protocol was approved by the Institutional Review Board of the Collège National des Gynécologues et Obstétriciens Français (CEROG 2016-GYN-1003).

Exclusion criteria included absence of surgical management, conservative surgery or unavailable data concerning LVSI.

Histologists of the Rare Malignant Tumours of the Ovary (TMRO) re examined histopathology slides for hematoxylin and eosin (H&E) stain, of the available cases.

The histotypes of epithelial cancer were defined by the 2014 WHO classification (2).

LVSI was diagnosed when viable tumour nests were observed within endothelial-lined spaces with or without intraluminal red cells or lymphocytes

LVSI were determined to be present (positive) or absent (negative) with no quantification because the extent of LVSI was not shown to impact the survival outcome of EOC (23).

After completion of treatment patients were followed every 3-4 months with a review of clinical symptoms, a physical examination, CA 125 test and imaging according to symptoms. Recurrence was diagnosed when clinical signs of the disease, an increase in the CA125 test result at successive examinations and / or suspicious images during radiological follow-up according to the RECIST criteria were discovered. For each case, data were collected through medical records. The imaging data were collected from the computerized reports of the examinations.

The various statistical analyses were carried out using the R™ software version 3.5.1 (R Stat). Continuous variables were compared using a Mann-Whitney test or a Student's test based on enrolment size. Categorical variables were compared using Fisher's exact test or chi-2 test based on the size of the sample. The statistical significance threshold used was $p < 0.05$.

Overall survival (OS) curves were produced using the Kaplan-Meier method. OS time (in months) was calculated as the time between the initial diagnosis of ovarian cancer and the date of death or last follw-up.

RFS time (in months) was calculated as the time between the initial diagnosis of ovarian cancer and the date of recurrence or last follow-up.

Survival was compared by univariate analysis by log-rank and multivariate analysis by Cox logistic regression. The Hazard Ratios (HRs) are given with 95% confidence intervals.

RESULTS

Characteristics of the study population

Over the study period from January 1st, 2001 to December 31th, 2018, 1765 patients were managed for epithelial ovarian carcinoma in the different centres of the Francogyn group, of which 204 patients met the inlusion criteria but only 133 (7.5%) had histology slides reviewed by Rare Malignant Tumours of the Ovary (TMRO) according to the following distribution: CHRU of Tours (n=29; 21.8%), CHRU of Marseille (n=27; 20.3%), University Hospital of Tenon (n=23; 17.3%), CHRU of Lille (n=13; 9.8%), La Pitié Salpêtrière (n=14; 10.5%), CHU Lyon Sud (n=12; 9%), Dijon Cancer Centre (n=5; 3.7%), Créteil University Hospital (n=6; 4.5%), Lariboisière Hospital (n=1; 0.7%), Jean Verdier University Hospital (n=2; 1.5%), and Poissy/Saint-Germain-en-Laye Intercommunal Hospital (n=1; 0.7%).

Of the 133 patients in the population, 121 (91%) had no LVSI in the histology reports and were included in the (No LVSI) group: absence of LVSI, and 12 (9%) were in the (LVSI) group: presence of LVSI. The demographic characteristics of the patients according to LVSI status are summarised in Table 1.

Table 1: Demographic characteristics of the patients according to lymphovascular space invasion status

	No LVSI (n=121) n(%)	**LVSI (n=12) n(%)**	***p***
Age (median in years, range)	56.2 [18-89]	57.7[30-83]	*0.79*
Age≥65 years	37(31%)	5(42%)	*0.64*
Postmenopausal	74(61%)	6(50%)	*0.65*
Parity (median, range)	1.35 [0-7]	1.58 [0-7]	*0.70*
Nulliparous	40(34%)	4(33%)	*0.59*
Body Mass Index (kg/m^2)	24.5 [15-40]	24.6 [18.2-56.9]	*0.93*
Mutation	5 (11%)	1 (25%)	*0.97*
FIGO stage			*0.21*
Stage Ia et Ib	77 (64%)	5 (42%)	
Stage Ic	34 (28%)	4 (33%)	
Stage IIa	10(8%)	3(25%)	
Normal CA125 at diagnosis	24 (23%)	3 (27%)	*1*
Histology			*0.15*
Low grade serous	18(15%)	1(8%)	
Mucinous	34(28%)	1(8%)	
Low grade endometrioid	35(29%)	7(58%)	
Clear cell carcinoma	25(21%)	1(8%)	
c	9(8%)	2(16%)	

Recurrence	13 (11%)	6 (50%)	***0.001***

LVSI: Lymphovascular space invasion

The median follow-up in our population was 39 months, ranges [1-133]. During the study period, 19 patients (14.3%) relapsed and 10 (7.5%) died. Figure 1 illustrates overall survival and recurrence-free survival according to LVSI status.

There was a significant difference in overall survival between the No LVSI group and the LVSI group ($p<0.0001$). The 5-year overall survival in the No LVSI group was estimated to be 91% while in the LVSI group it was estimated to be 57.1%. There was also a significant difference in recurrence-free survival between the No LVSI and LVSI groups ($p=0.0007$). 5-year recurrence-free survival in the No LVSI group was estimated to be 82.1% while in the LVSI group it was estimated to be 58.3%.

Factors influencing overall survival were analysed in univariate and multivariate cox analysis. These analyses are summarized on table 2.

In multivariate analysis after controlling for the following parameters: age, parity and LVSI, and normal CA125 at diagnosis; the presence of LVSI HR=11.8 [3.10-44.9] $p=0.0003$ remained independent factors affecting overall survival.

Table 2: Factors associated with overall survival (n=133)

Variables	Univariate Analysis		Multivariate analysis	
	HR [CI95%]	***p***	**HR [CI95%]**	***p***
Age	1.03 [0.99-1.07]	*0.13*	-	-
Age≥65	3.76 [1.05-13.5]	***0.04***	2.55 [0.66-9.83]	*0.17*
Postmenopausal	1.68 [0.43-6.53]	*0.45*		
Body Mass Index	0.97 [0.84-1.12]	*0.70*	-	-
Parity	1.37 [0.94-1.99]	***0.10***	1.46 [0.96-2.23]	***0.07***
Ca125	0.99 [0.98-1.0]	*0.60*		
Lymphovascular space invasion	10.1 [2.84-35.7]	***0.0003***	11.8 [3.10-44.9]	***0.0003***
Normal Ca125 at diagnosis	1.31 [0.25-6.75]	*0.74*		
FIGO stage at diagnosis				
Stage Ia	**Reference**			
Stage Ib	3.04 [0.34-27.3]	0.32		
Stage Ic	1.10 [0.26-4.63]	0.89		
Stage IIa	0.73 [0.08-6.36]	*0,78*		
Histology				
Low grade serous	0.22 [0.02-2.56]	*0.23*		
Mucinous	0.00 [0.00-0.00]	*0.99*		

Low grade endometrioid	0.21 [0.02-1.98]	*0.18*
Clear cell carcinoma	0.00 [0.00-1.32]	*0.11*
Mixed	0.20 [0.00-3.47]	*0.27*
Adjuvant chemotherapy	0.80 [0.18-3.61]	*0.78*

Data are presented with HR [CI95%] / CI confident interval

Factors influencing recurrence-free survival were analyzed in univariate and multivariate cox analysis. In multivariate analysis, after controlling for the following parameters: age, parity, LVSI, normal CA125 at diagnosis, and FIGO stage at diagnosis; only age ≥ 65 years HR=4.21 [1.05-16.8], p=0.04 and presence of lymphovascular space invasion HR=13.9 [3.65-52.7] p=0.0001 and FIGO stage other than IA remained significantly associated with recurrence-free survival. Table 3 summarizes these data.

Table 3: Factors associated with recurrence free survival (n=133)

Variables	Analyse univariée		Analyse multivariée	
	HR [IC95%]	***p***	**HR [IC95%]**	***p***
Age	1.02 [0.91-1.05]	*0.18*	-	-
Age≥65	2.63 [1.07-6.49]	***0.03***	4.21 [1.05-16.8]	***0.04***
Postmenopausal	1.45 [0.57-3.68]	*0.43*		
Body mass index	0.98 [0.88-1.08]	*0.66*	-	-
Parity	1.54 [1.16-2.04]	***0.002***	1.23 [0.89-1.71]	*0.20*
Mutation	1.85 [0.35-9.67]	*0.46*	-	-
Ca125	1.00 [1-1.01]	***0.005***		
Lymphovascular space invasion	4.62 [1.73-12.3]	***0.002***	13.9 [3.65-52.7]	***0.0001***
Normal Ca125	0.26 [0.03-1.99]	***0.19***	0.20 [0.02-1.61]	*0.13*
FIGO stage				
Stage Ia	**Reference**			
Stade Ib	5.84 [1.51-22.5]	0.01	8.22 [1.13-59.8]	**0.03**
Stade Ic	0.82 [0.25-2.69]	0.74	1.11 [0.24-5.15]	0.89
Stades IIa	1.42 [0.38-5.26]	*0.60*	0.87 [0.10-7.86]	*0.90*
Histology				
Low grade serous	0.00 [0.00-0.00]	*0.99*		
Mucinous	0.00 [0.00-0.00]	*0.99*		
Low grade endometrioid	0.00 [0.00-0.00]	*0.99*		
Clear cell carcinoma	0.00 [0.00-0.00]	*0.99*		

Mixed	0.00 [0.00-0.00]	*0.99*
Adjuvant Chemotherapy	0.79 [0.27-2.28]	*0.66*

Data are presented with HR [CI95%]

Because of the low number of histological sub types we did not perform sub analysis according to histological subtype

Discussion

Our study demonstrated a relationship between the presence of LVSI and overall and recurrence free survivals in FIGO stages I-IIA clear cell carcinoma, mucinous /low grade serous and endometrioid ovarian cancer. Moreover LVSI was identified as an independent prognosis factor predictive of poorer overall and recurrence free survivals after controlling for the use of postoperative chemotherapy. We also found that LVSI is not frequent in this selected population of early stages and that its incidence increases with increasing FIGO stage.

The presence of LVSI appears to be a major prognostic factor in endometrial (8-13), cervical (14-19) and vulvar (20-22) cancers. Moreover, the presence of LVSI in endometrial and cervical cancers is known to impact prognosis and is used in routine practice for treatment decisions. In EOC, LVSI is not even systematically listed in histological reports probably due to the lack of knowledge of their impact on prognosis in this context.

In the latest recommendations, adjuvant chemotherapy with carboplatin and paclitaxel is recommended for all cancers of the ovary, fallopian tube or primary peritoneum in the early stages (stage I-IIA) with tumours of high histological grade (serous, endometrioid, undifferentiated, carcinosarcoma) (6-7).

Given the small number of early stages (FIGO stages I-IIA) of clear cell carcinoma, mucinous /low grade serous and endometrioid ovarian cancer, there are few Phase III trials that address this situation. Recommendations for adjuvant treatment are therefore mainly derived from meta-analyses, guiding medical treatment.

Ovarian cancer, treated at an early stage, has a relatively good prognosis but remains a serious disease. Seventy to 80% of patients are alive at 5 years, with a relapse rate of 20 to 30% (4-5).

The results of the controlled randomized trials do not allow for a formal conclusion on the benefit of adjuvant chemotherapy. Most trials did not include enough patients at an early stage to draw a conclusion on the place of adjuvant chemotherapy.

The 2 largest trials were published in 2003. These two trials were conducted by European teams whose treatment included a platinum salt but no taxane: the ACTION trial (5) and the ICON-1 trial (4).

In both studies, approximately 450 patients received either adjuvant chemotherapy or were followed up. These trials were stopped for lack of inclusion. A recurrence-free survival advantage in favour of adjuvant chemotherapy was observed in both trials, but only the ICON-1 trial showed gain in overall survival. The risk ratios (HR) for disease-free survival and overall survival are very similar in the ACTION and ICON-1 trials. Updating the 10-year overall survival data from the ICON-1 trial found an improvement in relapse-free survival of 10% (60-70%) and overall survival of 9% (64-73%) for patients receiving chemotherapy.

For a subgroup of patients considered to be at high risk, pre-specified before the updated survival analyses, an even greater improvement was found in overall survival (+18%). High-risk patients were defined according to the following criteria: stage 1B/1C grade 2/3, stage 1 grade 3 or clear cell histological type (33).

High grade tumors (carcinosarcoma, serous and endometrioid) were excluded from our study.

It should be noted, however, that the results of the ICON-1 trial have been criticized because the surgical staging was not optimal.

A meta-analysis (34) showed that adjuvant chemotherapy provided a benefit in terms of overall survival for early stages, mainly when chemotherapy included a platinum salt.

The meta-analysis published in 2009 (35) and updated in 2015 (36), which included 4 randomized clinical trials considered to have a low risk of bias, found statistically significant

results in favour of carrying out platinum-based chemotherapy compared with no postoperative treatment in patients with stage I ovarian cancer. The results are as follows:

- Improved overall survival

5-year overall survival for 1008 patients in 3 studies: HR= 0.71 (95% confidence interval (95% CI): 0.53 - 0.93)

10-year overall survival for 923 patients in 2 studies: HR= 0.76 (95% CI: 0.62 - 0.94;)

- Improved progression-free survival

5-year RFS for 1170 patients in 4 studies: HR = 0.67 (95% CI: 0.53 - 0.84)

10-year RFS for 925 patients in 2 studies: HR = 0.67 (95% CI: 0.53 - 0.83)

Low evidence levels suggest that patients in the high-risk group benefit most from adjuvant chemotherapy. Note that subgroup analyses cannot confirm or exclude a benefit for patients at low risk or for whom optimal surgery has been performed.

In our study considering only I-IIa FIGO stages of the so-called “low risk” epithelial cancer, the presence of LVSI impacted OS and also RFS and was considered as an independent predictive factor of poorer OS and RFS. A localized tumor with LVSI would therefore behave differently with an increased risk of relapse compared to a tumour without LVSI.

In this setting, the administration of postoperative chemotherapy would be beneficial when its use is limited to certain indications acknowledging that LVSI are rare in these histological subtypes.

Our study was retrospective, which may be one of the limitations inherent in this type of study.

The main strength of our study was its multicentre nature, with the different participating centres being experts in the management of ovarian cancer.

Histological data were collected from the reports and were centrally reviewed by the histologists of the Rare Malignant Tumours of the Ovary (TMRO) network labelled by the National Cancer Institute (INCa) centres experts TMRG (tumeurs malignes rares gynécologiques).

LVSI is an Independent factors influencing overall survival and recurrence-free survival in FIGO stages I-IIA clear cell carcinoma, mucinous /low grade serous and endometrioid ovarian cancer. The presence of LVSI in these tumours should put them at high risk and should consider the option of adjuvant chemotherapy

Conflict of interest: none

Ethical approval and consent to participate :

The research protocol was approved by the Institutional Review Board of the Collège National des Gynécologues et Obstétriciens Français (CEROG 2016-GYN-1003).

Informed consent was obtained from the subjects prior to participating in the study.

References

1- Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, Hauptmann S, Sehouli J.

The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Arch Gynecol Obstet 2016 Apr;293(4):695-700.

2- Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO classification of tumours of ovary. In: Robert J. Kurman, Maria Lusia Carcangiu, C. Simon Herrington, et al., editors. WHO classification of tumours of female reproductive organs (4th edition) Switzerland: WHO press; 2014. p. 12

3- de la Motte Rouge T, Ray-Coquard I, You B. .Medical treatment in **ovarian** cancers newly diagnosed: Article drafted from the French Guidelines in oncology entitled "Initial management of patients with epithelial **ovarian cancer**" developed by **FRANCOGYN**, CNGOF, SFOG, GINECO-ARCAGY under the aegis of CNGOF and endorsed by INCa. Gynecol Obstet Fertil Senol. 2019 Feb;47(2):222-237.

4-Colombo, N., Guthrie, D., Chiari, S., Parmar, M., Qian, W., Swart, A.M., Torri, V., Williams, C., Lissoni, A., Bonazzi, C., et al. (2003). International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. J. Natl. Cancer Inst. *95*, 125–132.

5- Trimbos, J.B., Vergote, I., Bolis, G., Vermorken, J.B., Mangioni, C., Madronal, C., Franchi, M., Tateo, S., Zanetta, G., Scarfone, G., et al. (2003). Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. J. Natl. Cancer Inst. *95*, 113–125.

6- Lavoue V, Huchon C, Akladios C, Alfonsi P, Bakrin N, Ballester M,et al. Management of epithelial **cancer** of the ovary, fallopian tube, primary peritoneum. Long text of the joint French clinical practice guidelines issued by **FRANCOGYN**, CNGOF, SFOG, GINECO-ARCAGY, endorsed by INCa. (Part 2: systemic, intraperitoneal treatment, elderly patients, fertility preservation, follow-up).
.J Gynecol Obstet Hum Reprod. 2019 Jun;48(6):379-386.

7- Lavoue V, Huchon C, Akladios C, Alfonsi P, Bakrin N, Ballester M, et al. Management of epithelial **cancer** of the ovary, fallopian tube, and primary peritoneum. Short text of the French Clinical Practice Guidelines issued by **FRANCOGYN**, CNGOF, SFOG, and GINECO-ARCAGY, and endorsed by INCa. Eur J Obstet Gynecol Reprod Biol. 2019 May;236:214-223.

8. Guntupalli SR, Zighelboim I, Kizer NT, Zhang Q, Powell MA, Thaker PH, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor

outcomes in endometrioid endometrial cancer. Gynecol Oncol. 2012 Jan;124(1):31–5.

9. Watanabe Y, Satou T, Nakai H, Etoh T, Dote K, Fujinami N, et al. Evaluation of parametrial spread in endometrial carcinoma. Obstet Gynecol. 2010 Nov;116(5):1027–34.

10. Tsuruchi N, Kaku T, Kamura T, Tsukamoto N, Tsuneyoshi M, Akazawa K, et al. The prognostic significance of lymphovascular space invasion in endometrial cancer when conventional hemotoxylin and eosin staining is compared to immunohistochemical staining. Gynecol Oncol. 1995 Jun;57(3):307–12.

11. O'Brien DJ, Flannelly G, Mooney EE, Foley M. Lymphovascular space involvement in early stage well-differentiated endometrial cancer is associated with increased mortality. BJOG Int J Obstet Gynaecol. 2009 Jun;116(7):991–4.

12. Hachisuga T, Kaku T, Fukuda K, Eguchi F, Emoto M, Kamura T, et al. The grading of lymphovascular space invasion in endometrial carcinoma. Cancer. 1999 Nov 15;86(10):2090–7.

13. Matsuo K, Garcia-Sayre J, Medeiros F, Casabar JK, Machida H, Moeini A, et al. Impact of depth and extent of lymphovascular space invasion on lymph node metastasis and recurrence patterns in endometrial cancer. J Surg Oncol. 2015 Nov;112(6):669–76.

14. Roman LD, Felix JC, Muderspach LI, Varkey T, Burnett AF, Qian D, et al. Influence of quantity of lymph-vascular space invasion on the risk of nodal metastases in women with early-stage squamous cancer of the cervix. Gynecol Oncol. 1998 Mar;68(3):220–5.

15. Chernofsky MR, Felix JC, Muderspach LI, Morrow CP, Ye W, Groshen SG, et al. Influence of quantity of lymph vascular space invasion on time to recurrence in women with early-stage squamous cancer of the cervix. Gynecol Oncol. 2006 Feb;100(2):288–93.

16. Memarzadeh S, Natarajan S, Dandade DP, Ostrzega N, Saber PA, Busuttil A, et al. Lymphovascular and perineural invasion in the parametria: a prognostic factor for early-stage cervical cancer. Obstet Gynecol. 2003 Sep;102(3):612–9.

17. Lim CS, Alexander-Sefre F, Allam M, Singh N, Aleong JC, Al-Rawi H, et al. Clinical value of immunohistochemically detected lymphovascular space invasion in early stage cervical carcinoma. Ann Surg Oncol. 2008 Sep;15(9):2581–8.

18. Morice P, Piovesan P, Rey A, Atallah D, Haie-Meder C, Pautier P, et al. Prognostic value of lymphovascular space invasion determined with hematoxylin-eosin staining in early stage cervical carcinoma: results of a multivariate analysis. Ann Oncol Off J Eur Soc Med Oncol. 2003 Oct;14(10):1511–7.

19. Sakuragi N, Takeda N, Hareyama H, Fujimoto T, Todo Y, Okamoto K, et al. A multivariate analysis of blood vessel and lymph vessel invasion as predictors of ovarian and lymph node metastases in patients with cervical carcinoma. Cancer. 2000 Jun 1;88(11):2578–83.

20. Raspagliesi F, Hanozet F, Ditto A, Solima E, Zanaboni F, Vecchione F, et al. Clinical and pathological prognostic factors in squamous cell carcinoma of the vulva. Gynecol Oncol. 2006 Aug;102(2):333–7.

21. Rouzier R, Preti M, Haddad B, Martin M, Micheletti L, Paniel B-J. Development and validation of a nomogram for predicting outcome of patients with vulvar cancer. Obstet Gynecol. 2006 Mar;107(3):672–7.

22. Cheng X, Zang R, Wu X, Li Z, Cai S, Zhang Z. Recurrence patterns and prognostic factors in Chinese patients with squamous cell carcinoma of the vulva treated with primary surgery. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2009

Jan;19(1):158–62.

23 Matsuo K, Sheridan TB, Yoshino K, Miyake T, Hew KE, Im DD, et al. Significance of lymphovascular space invasion in epithelial ovarian cancer. Cancer Med. 2012 Oct;1(2):156–64.

24. Matsuo K, Yoshino K, Hasegawa K, Murakami R, Ikeda Y, Adachi S, et al. Survival outcome of stage I ovarian clear cell carcinoma with lympho-vascular space invasion. Gynecol Oncol. 2015 Feb;136(2):198–204.

25. Matsuo K, Sheridan TB, Mabuchi S, Yoshino K, Hasegawa K, Studeman KD, et al. Estrogen receptor expression and increased risk of lymphovascular space invasion in high-grade serous ovarian carcinoma. Gynecol Oncol. 2014 Jun;133(3):473–9.

26. Qian X, Xi X, Jin Y. The grading of lymphovascular space invasion in epithelial ovarian carcinoma. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2010 Jul;20(5):895–9.

27. Chen M, Jin Y, Bi Y, Li Y, Shan Y, Pan L. Prognostic significance of lymphovascular space invasion in epithelial ovarian cancer. J Cancer. 2015;6(5):412–9.

28. Li J, Li S, Chen R, Lu X. Increased risk of poor survival in ovarian cancer patients with high expression of SNAI2 and lymphovascular space invasion. Oncotarget. 2017 Feb 7;8(6):9672–85.

29. Masoumi-Moghaddam S, Amini A, Wei A-Q, Robertson G, Morris DL. Sprouty 1 predicts prognosis in human epithelial ovarian cancer. Am J Cancer Res. 2015;5(4):1531–41.

30. Mvunta DH, Miyamoto T, Asaka R, Yamada Y, Ando H, Higuchi S, et al. Overexpression of SIRT1 is Associated With Poor Outcomes in Patients With Ovarian Carcinoma. Appl Immunohistochem Mol Morphol AIMM. 2017 Jul;25(6):415–21.

31. McCluggage WG, Judge MJ, Clarke BA, Davidson B, Gilks CB, Hollema H, et al. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). Mod Pathol Off J U S Can Acad Pathol Inc. 2015 Aug;28(8):1101–22.

32. Matsuo K, Wong K-K, Fotopoulou C, Blake EA, Robertson SE, Pejovic T, et al. Impact of lympho-vascular space invasion on tumor characteristics and survival outcome of women with low-grade serous ovarian carcinoma. J Surg Oncol. 2017 ;

33. Collinson, F., Qian, W., Fossati, R., Lissoni, A., Williams, C., Parmar, M., Ledermann, J., Colombo, N., Swart, A., and ICON1 collaborators (2014). Optimal treatment of early-stage ovarian cancer. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. *25*, 1165–1171.

34. Elit, L., Chambers, A., Fyles, A., Covens, A., Carey, M., and Fung, M.F.K. (2004). Systematic review of adjuvant care for women with Stage I ovarian carcinoma. Cancer *101*, 1926–1935.

35. Winter-Roach, B.A., Kitchener, H.C., and Dickinson, H.O. (2009). Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database Syst. Rev. CD004706.

36. Lawrie, T.A., Winter-Roach, B.A., Heus, P., and Kitchener, H.C. (2015). Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database Syst. Rev. CD004706.

Figure legends

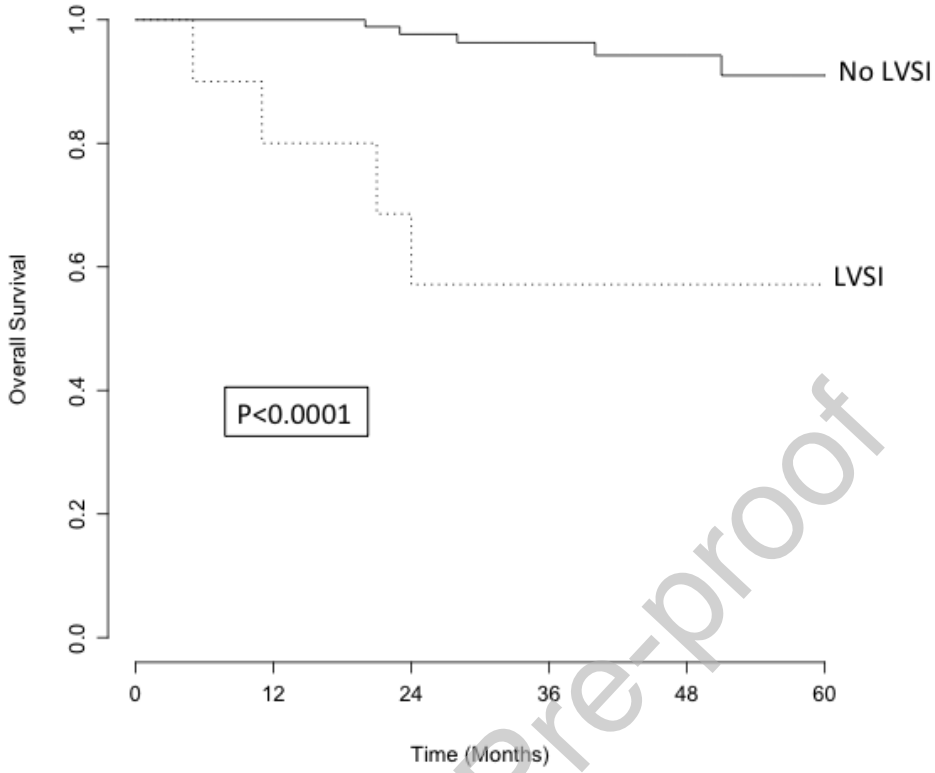

Figure 1 - overall survival according to lymphovascular space invasion status

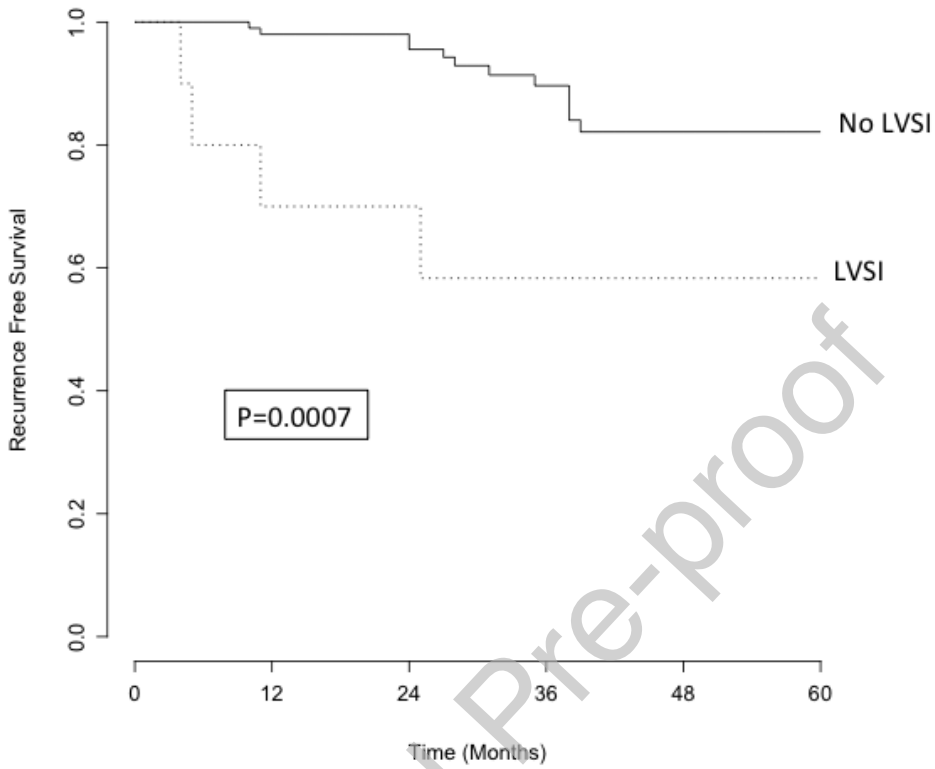

Figure 2 - Recurrence free survival according to lymphovascular space invasion status