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Lymphovascular space invasion and Estrogen Receptor status in high-grade serous ovarian cancer - a multicenter study by the FRANCOGYN group.

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ABSTRACT

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 high-grade serous epithelial ovarian cancer (HGSOC).

Materials and methods

Retrospective multicenter study by the FRANCOGYN research group between January 2001 and December 2018. All patients managed for HGSOC and for whom histological slides for the review of LVSI were available, were included. The characteristics of patients with LVSI (LVSI group) were compared to those without LVSI (No LVSI group). A Cox analysis for OS and RFS analysis was performed in all populations.

Results

Over the study period, 410 patients were included in the thirteen institutions. Among them, 289 patients had LVSI (33.9%). LVSI was an independent predictive factor for poorer Overall and Recurrence-Free Survival. LVSI affected OS ($p<0.001$) and RFS ($p<0.001$), Association of LVSI status and estrogen receptor status (ER) also affected OS and RFS ($p=0.04$; $p=0.04$ respectively).

Conclusion

The presence of LVSI in HGSOC has an impact on OS and RFS and should be routinely included in the pathology examination along with ER status.

KEYWORDS: Lymphovascular Space Invasion, Overall Survival, Recurrence-Free Survival, High-Grade Serous, Prognosis.

Key message

Routine histology examinations should report lymphovascular space invasion status in order to establish appropriate treatment in patients with HGSOC.

INTRODUCTION

Ovarian cancer (OC) ranks seventh in terms of incidence among the different types of women's cancer, with, in 2018, 295,414 new cases and 184,799 cases of specific mortality worldwide ¹. Ovarian cancer remains the 7th lethal female malignancy, with a median age at diagnosis of 63 years. It is mostly diagnosed at an advanced age (International Federation of Gynecology and Obstetrics FIGO stages IIB-IV), which largely explains its poor prognosis. Survival for all types and stages combined is estimated at 40% at 5 years and 32% at 10 years ¹. Epithelial ovarian cancer accounts for 90% of primary OC (2). In 2014, the World Health Organization's histologic classification and grading system modified the grading system into two-tiers, with low- and high-grades ². High-grade serous ovarian carcinoma (HGSOC) represents 70% of EOC and is the most lethal subtype, accounting for about 60% of OC deaths. The identification of prognostic markers associated with disease progression would be useful in the management of ovarian cancer patients and in the choice of treatments to be used.

The presence of Lymphovascular Space Invasion (LVSI) appears to be a major prognostic factor in other female malignancies ³⁻¹³, the presence of LVSI being associated with a greater risk of lymph node involvement and distant metastatic dissemination, as well as an earlier risk of relapse and decreased survival.

Evidence remains limited for OC. In the study by Matsuo *et al.* they found that the presence of LVSI was associated with a potential for lymph node involvement and distant metastatic dissemination directly impacting survival in high- and low-grade epithelial serous ovarian cancers ¹⁴⁻¹⁷. Recent publications suggest that the presence of LVSI is a major prognostic factor in disease progression ¹⁴⁻²⁰, while other studies do not find this association ^{21, 22}. The prognostic value of the presence of LVSI in OC remains controversial. Moreover, LVSI is not systematically listed in histological reports and is not actually considered as a key element to take into account in proposals for OC management ²³.

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 high-grade serous ovarian cancer.

MATERIALS & METHODS

We conducted a retrospective, descriptive, multi-center study. Data from 1,765 women with ovarian cancer collected from January 1, 2001 to December 31, 2018, were reviewed from the FRANCOGYN database pooling data from 13 centers: Tours Regional University Hospital, Tenon University Hospital, the University Hospital of Marseille, the Dijon cancer center, the Lyon Sud University Hospital, the University Hospital of Lille, La Pitié Salpêtrière Hospital, the Centre Hospitalier Intercommunal in Creteil, Rennes University Hospital, Lariboisière Hospital, Jean Verdier University Hospital, the Centre Hospitalier Intercommunal in Poissy/Saint-Germain-en-Laye and Strasbourg University Hospital.

Patients included had been diagnosed with HGSOE.

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

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

LVSI was diagnosed when viable tumor nests were observed within endothelial-lined spaces with or without intraluminal red cells or lymphocytes. Information about LVSI has always been harvested on primary tumor ovaries in both early and advanced stages.

LVSI was 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 EOC²⁴.

The expression of estrogen receptor (ER) and progesterone receptor (PR) in ovarian tissue was measured by immunohistochemistry on paraffin-embedded sections.

After completion of treatment, patients were followed up every 3-4 months with a review of clinical symptoms, a physical examination, CA 125 test and imaging according to symptoms.

Recurrence was diagnosed where there were clinical signs of the disease, an increase in the CA125 test result at successive examinations and / or where suspicious images were discovered during radiological follow-up according to the RECIST criteria. For each case, data were collected through medical records. Histological data were collected from computerized histological reports. The imaging data were collected from the computerized reports of the examinations.

The various statistical analyses were carried out using the RTM 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-square test based on the size of the sample. The statistical significance threshold used was $p < 0.05$.

The factors associated with the presence of LVSI were analyzed by logistic regression on all variables with p-value of < 0.10 in univariate analysis. A bilateral formulation was chosen for all tests. The Odds Ratios (ORs) are given with their 95% confidence interval.

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.

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

RESULTS

Characteristics of the study population

During the study period, 1,765 patients with EOC were treated in the 13 FRANCOGYN research group centers. Among these patients, 410 (23.2%) met the inclusion criteria in the different study centers mentioned according to the following distribution (Flow chart): Tours University Hospital (n=116; 28.3%), Marseille University Hospital (n=52; 12.7%), Lille University Hospital (n=47; 11.5%), Tenon University Hospital (n=40; 9.7%), Hospices Civils de Lyon, n=33 8%, La Pitié-Salpêtrière Hospital in Paris n=28; 6.8%, Rennes University Hospital (n=23; 5.6%), Creteil University Hospital (n=18; 4.4%), Jean Verdier University Hospital (n=18; 4.4%), Lariboisière University Hospital: n=16; 3.9%, Poissy/Saint-Germain-en-Laye Intercommunal Hospital (n=9; 2.2%), Strasbourg University Hospital: n=6; 1.5% and Georges François Leclerc cancer center in Dijon: n=4; 0.9%.

Among the 410 women with HGSOC, 174 patients had LVSI (42.4%). The demographic characteristics of the patients included are summarized in Table 1. The histological characteristics are summarized in table 2.

The 5-year Overall Survival rate in the No LVSI group was 63.6% and 47.7% in the LVSI group ($p=0.02$). The 5-year Recurrence-Free Survival rate in the No LVSI group was 44.7% and 20.6% in the LVSI group ($p=0.009$). Figure 1 illustrates these results.

Table 1: population characteristics

	No LVSI (n=236)	LVSI (n=174)	<i>p</i>
Age (years) median	62.4 [25-94]	60.1 [18-89]	0.05
Parity (median)	1.8 [0-11]	1.7 [0-10]	0.39
Mutation	26 (26%)	19 (21%)	0.86
FIGO stage			<0.0001
Stage I	32 (14%)	7 (4%)	
Stage II	26 (11%)	5 (3%)	
Stage III	137 (59%)	131 (76%)	
Stage IV	37 (16%)	30 (17%)	
Primary debulking surgery	106 (45%)	73 (43%)	0.58
Type of surgery			0.89
Primary debulking surgery	106 (45%)	73 (43%)	
Interval surgery	70 (30%)	51 (29%)	
Surgery after C6	48 (20%)	40(23%)	
Laparoscopic exploration	12 (5%)	10 (6%)	
Residual disease			0.02
R0 (complete surgery)	184 (81%)	117 (69%)	
R1 (optimal surgery)	20 (9%)	21 (12%)	
R2 (sub-optimal surgery)	24 (11%)	32 (19%)	
Recurrence	91 (39%)	88 (51%)	0.02
Bilateral ovarian involvement	142 (64%)	121 (77%)	0.01
Ovarian extracapsular involvement	38 (23%)	84 (64%)	<0.0001
Lymph node involvement	67 (39%)	82 (69%)	<0.0001
Lymph node involvement			
Pelvic	39 (23%)	61 (52%)	<0.0001
Para-aortic	55 (34%)	69 (66%)	<0.0001
Hormone receptor status			0.005
ER positive	30 (33%)	29 (54%)	
HR negative	24 (26%)	3 (6%)	
HR positive	30 (33%)	20 (37%)	
PR positive	7 (8%)	2 (4%)	
ER positive (NA=245)			<0.0001
	73 (69%)	53(90%)	
Immuno-histochemistry markers			
CK7	87 (93%)	52 (98%)	0.29
CK20	3 (4%)	2 (4%)	1
WT1	83 (91%)	33 (92%)	1
Pax8	26(74%)	22(92%)	0.17
P16	25(83%)	10(83%)	1
Estrogen receptor	74 (70%)	53 (90%)	0.006
Progesterone receptor	37 (40%)	22 (39%)	1
P53	52(71%)	36 (80%)	0.39

Data are presented in numbers (%)

ER, estrogen receptors; PR: progesterone receptors; HR: hormone receptors

The impact of estrogen receptor (ER) status was evaluated in this histological subtype. The 5-year Overall Survival rate in the ER- group was 44.4% and 57.8% in the ER+ group (p=0.76).

The 5-year Recurrence-Free Survival rate in the ER- group was 65.9% and 32.7% in the ER+ group (p=0.03).

The difference in survival was evaluated according to the combination of both LVSI and estrogen receptor status (LVSI+/ER+; LVSI+/ER-; LVSI-/ER-; LVSI-/ER+). The 5-year Overall Survival rate for patients in the LVSI-/ER- group was 53.2%, 70.6% in the LVSI-/ER+ group, 0% in the LVSI+ER- group and 36.1% in the LVSI+/ER+ group (p=0.04). The 5-year Recurrence-Free Survival rate for patients in the LVSI-/ER- group was 69.7%, 40.2% in the LVSI-/ER+ group, 53.3% in the LVSI+ER- group and 28.7% in the LVSI+/ER+ group (p=0.04). Figure S2 illustrates these results.

No other immunohistochemical markers could be significantly related to survival of high-grade serous tumors except WT1 (p=0.02) which had an impact on Overall Survival.

We evaluated, in univariate and multivariate analysis, predictive factors of LVSI in HGSOC. Table 2 summarizes these results.

Table 2: Predictive factors of lymphovascular invasion

Variables	Univariate analysis OR [95%CI]	p	multivariate analysis OR [95%CI]	p
Age	0.98 [0.97-1.00]	0.05	-	-
Parity	0.94 [0.81-1.09]	0.40	-	-
Body Mass Index	0.97 [0.94-1.01]	0.14	-	-
Postmenopausal	0.62 [0.37-1.04]	0.07	0.39 [0.15-1.02]	0.05
Mutation	0.77 [0.39-1.52]	0.45	-	-
FIGO stages				<0.001
Early (I and II)	0.22 [0.12-0.43]	<0.001	0.06 [0.007-0.46]	
Advanced (III and IV)	Reference		Reference	-
Estrogen receptor status (+vs-)	3.82 [1.49-9.78]	0.005		
Progesterone receptor status	0.96 [0.49-1.90]	0.91		
Hormone receptor status				
ER+PR-	Reference		Reference	-
ER-PR-	0.13 [0.03-0.47]	0.002	0.08 [0.02-0.40]	0.002
ER+PR+	0.69 [0.32-1.48]	0.33	0.77 [0.34-1.78]	0.54
ER-PR+	0.30 [0.06-1.54]	0.14	0.22 [0.04-1.19]	0.07

Data are presented with OR [95%CI] / ER, estrogen receptor; PR progesterone receptor, CI confidence interval

Factors impacting Overall Survival are shown in table 3. The presences of a gene mutation, LVSI and estrogen receptor status were independent predictive factors of OS.

Table 3: Factors impacting Overall Survival in case of high-grade serous ovarian cancer (n=410)

Variables	Univariate analysis		Multivariate analysis
	HR [95%CI]	p	HR [95%CI]
Age	1.00 [0.99-1.02]	0.57	-

Body Mass Index	0.99 [0.96-1.04]	<i>0.97</i>	-	
Parity	1.04 [0.91-1.18]	<i>0.55</i>	-	
Mutation	0.35 [0.15-0.83]	0.01	0.21 [0.05-0.93]	0.04
Primary debulking surgery	0.42 [0.29-0.62]	<0.001	0.94 [0.29-3.07]	0.96
Residual disease				
R0	Reference		Reference	
R1	2.57 [1.55-4.62]	0.0002	4.07 [0.91-18.3]	<i>0.06</i>
R2	1.72 [1.06-2.72]	0.03	0.98 [0.26-3.57]	<i>0.96</i>
FIGO stage				
Early (I-II) vs. advanced	0.39 [0.22-0.72]	0.002	0.74 [0.07-7.47]	0.79
Lymphovascular space invasion	1.52 [1.06-2.18]	0.02	3.54 [1.08-11.6]	0.03
Estrogen receptor status (+vs-)	0.91 [0.50-1.68]	<i>0.07</i>	0.23 [0.07-0.79]	0.01
LVSI+ER+	1.67 [0.79-3.53]	0.17		
Recurrence	1.76 [1.20-2.62]	0.004	0.80 [0.27-2.40]	<i>0.69</i>

Data are presented with HR [95%CI] / ER, estrogen receptor; PR progesterone receptor, CI confidence interval, HR Hazard Ratio

Factors impacting RFS are shown in table 4. The combined status of both LVSI and estrogen receptor was an independent predictive factor of RFS.

Table 4: Factors impacting Recurrence-Free Survival in the case of high-grade serous ovarian cancer (n=410)

Variables	Univariate analysis		Multivariate analysis	
	HR [95%CI]	<i>p</i>	HR [95%CI]	<i>p</i>
Age	0.99 [0.97-1.00]	0.11	-	-
Body Mass Index	1.01 [0.98-1.04]	0.54	-	-
Parity	0.99 [0.89-1.10]	0.85	-	-
Mutation	1.03 [0.64-1.66]	0.89	-	-
Primary debulking surgery	0.58 [0.43-0.80]	0.0006	0.54 [0.25-1.17]	0.11
Residual disease	1.04 [0.84-1.28]	0.70	-	-
FIGO stage				
Early vs. advanced	0.37 [0.23-0.60]	<0.001	0.99 [0.20-4.99]	0.99
LVSI+ER+	3.19 [1.41-7.18]	0.005	3.23 [1.34-7.82]	0.008
Hormone receptors (+ vs -)	2.43 [1.04-5.65]	0.03		
Lymphovascular space invasion	1.48 [1.10-1.99]	0.009		
Estrogen receptor status (+vs-)	2.01 [1.05-3.87]	0.03		

Data are presented with HR [95%CI] / ER, estrogen receptor; PR progesterone receptor, CI confidence interval, HR Hazard Ratio

Surgical resectability

The presence of LVSI was associated with residual disease after surgery (presence/absence; $p=0.008$). Sub optimal surgery with residual disease R2 was more common in the case of LVSI (19% versus 11%; $p=0.02$)

Predictive factors associated with residual disease (presence/absence) are summarized in table 5.

Table 5: predictive factors of residual disease after surgery in case of high-grade serous ovarian cancer (n=410)

Variables	Univariate analysis		Multivariate analysis	
	OR [95%CI]	<i>p</i>	OR [95%CI]	<i>p</i>
Age	1.01 [0.98-1.03]	0.47	-	-
Body Mass Index	0.99 [0.94-1.03]	0.56	-	-
Parity	0.87 [0.73-1.04]	0.11	-	-
Mutation	0.46 [0.19-1.12]	0.08	0.55 [0.20-1.06]	0.23
Primary debulking surgery	0.42 [0.25-0.69]	<0.001	0.62 [0.36-1.05]	0.07
FIGO stage				
Early vs. advanced	0.11 [0.03-0.36]	<0.001	0.12 [0.03-0.52]	<0.001
LVSI+ER+	1.48 [0.55-3.96]	0.43		
Hormone receptors (+ vs -)	1.31 [0.37-4.69]	0.67		
Lymphovascular space invasion	1.89 [1.19-3.01]	0.006	1.58 [0.97-2.58]	0.06
Estrogen receptor status (+vs-)	1.03 [0.44-2.43]	0.94		

Data are presented with OR [95%CI] / ER, estrogen receptor; PR progesterone receptor, CI confidence interval, HR Hazard Ratio

In case of neoadjuvant chemotherapy

In the subgroup of patients who received neoadjuvant chemotherapy, $n=230$ (56.1% of the whole population), 100 women (43.5%) had tumors with persistent LVSI on the histology examination. In this subgroup, residual disease (presence/absence) was associated with persistent LVSI ($p=0.02$). Sub optimal surgery with residual disease R2 was more common in the case of persistent LVSI (26.9% vs. 17.3%; $p=0.05$)

Discussion

In our population of women with HGSOE, we found that LVSI was an independent predictive factor for poorer Overall and Recurrence-Free Survival ($p < 0.001$ and $p < 0.001$ respectively).

In the literature, the rate of LVSI varies from 17.5% to 83.5% according to the study design. Our rate was 33.9%. HGSOE is the most common histological subtype with its own clinical and biological characteristics²⁵. Chen *et al.* reported a LVSI rate of 67.1% in their population of 492 patients²⁷. Matsuo *et al.* also reported an LVSI rate in stage I HGSOE close to 22.2% in a population of 434 patients¹⁴. In this early stage study, the authors found a significant decrease in 5-year Recurrence-Free Survival compared to other histological subtypes in the case of LVSI (70.9%, $p = 0.01$). In the multivariate analysis, this histological subtype was associated with a higher relapse rate than other histological subtypes (HR=2.47; $p = 0.036$)²². In a study of the HGSOE subtype only, Matsuo *et al.* reported an LVSI rate of 83.5% in a population of 121 patients¹⁷. The presence of LVSI was correlated with decreased Recurrence-Free Survival ($p = 0.001$) and Overall Survival ($p = 0.021$)²⁵. Our data were consistent with these findings.

We also found that positive ER was predictive of the presence of LVSI. The combination of LVSI status and estrogen receptor status (ER) also affected OS and RFS in this study ($p = 0.04$; $p = 0.04$ respectively).

The positive ER or PR is associated with outcomes in OC and is related to cancer subtype (26-30), however the underlying mechanisms are still unknown.

ER and PR mediate the effects of estrogen and progesterone on OC cell proliferation and apoptosis.

In a study in 2014, Matsuo *et al.* were able to demonstrate a relationship between the estrogen receptor (ER) and LVSI in HGSOE in a population of 121 patients. Indeed, the presence of LVSI was correlated with the presence of ER in uni- and multivariate analysis (respectively $p = 0.002$ and $p = 0.039$) with an impact on Recurrence-Free Survival and Overall Survival in the case of LVSI. No significant difference could be shown concerning the impact of ER expression on Overall Survival¹⁷. In our population, ER status was an independent predictive factor associated with the presence of LVSI. We also found an impact from ER expression and the presence of LVSI on Recurrence-Free Survival and on Overall Survival. One could hypothesize as to the role of ER in the development of LVSI and in the potential

hematogenous and lymphatic dissemination of the disease. The study by Sieh *et al.*, which involved 1,742 patients with HGSOE, does not suggest an impact from ER on the survival of patients with this subtype of tumors²⁷. The value of estrogen-blocking treatment could be evaluated in the case of LVSI in other histological subtypes (endometrioid tumors)²⁷. As angiogenesis is favored in neoplastic processes, it also appears useful to be able to discuss an angiogenesis-modulating therapy (anti-VEGF), particularly in the presence of LVSI in patients with ovarian cancer even at an early stage^{31,32}. Chen S *et al.*,³³ in a study including various EOC subtypes, reported an association between ER and PR positivity and peritoneal metastases in HGSOE with no association with lymph nodes metastases. They also reported that 86% of recurrent HGSOE with peritoneal metastases were ER positive.

The role of antiestrogen drugs in OC is not well established but clearly have a place in recurrent disease. Yokoyama *et al.*, reported that hormone therapy may have a place in the treatment of recurrent disease in the case of positive ER³⁴. Moreover, Zheng Feng *et al.* demonstrated in their study that paired primary and recurrent HGSOE exhibit different hormone receptor profiles, implying re-assessment would be necessary for recurrent patients³⁵.

Shen Z *et al.*³⁶, in their meta-analysis of 35 studies on 5,824 patients, found that ER expression was related to neither OS nor time-to-progression in serous (both low- and high-grade) types of OC. However, in the general population, ER expression was found to be a positive predictive factor of OS, but not time-to-progression, suggesting that the role and mechanisms of action of ER in EOC vary across the different subtypes. We probably have to study the outcome of the impact of ER expression in association with LVSI status. The presence of LVSI in our study was significantly related to the FIGO stage, menopausal status and ER status.

The presence of LVSI and expression of ER could also be used to determine lymph node involvement and an indication for lymphadenectomy when imaging is not able in the absence of suspected lymph node involvement on CT to detect 55% of patients with microscopic lymph node involvement. We no longer perform lymphadenectomy in advanced stages after NAC in this indication but we know that lymph node involvement is associated with a worse prognosis.

Conversely, for early stages, LVSI and expression of ER may be used in indicating lymphadenectomy de-escalation during restaging in the absence of imaging or clinical lymph node involvement.

The presence of LVSI is a major prognostic factor that impacts Overall Survival and Recurrence-Free Survival in women with HGSOC. Routine histology examinations should report lymphovascular space invasion status in order to establish appropriate treatment in patients with HGSOC, especially at an early stage.

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Figure legends**Figure 1A': flow chart (supplementary material)****Figure 1 A-** Overall Survival according to lymphovascular space invasion status**B** Recurrence-Free Survival according to lymphovascular space invasion status**Figure 2(supplementary material)****A-** Overall Survival according to combined lymphovascular space invasion status and hormone receptor status**B-** Recurrence-Free Survival according to combined lymphovascular space invasion status and hormone receptor status

