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The prognostic significance of positive peritoneal cytology in endometrial cancer and its correlations with L1-CAM biomarker

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ABSTRACT

Background: The aim of this study was to evaluate the prognostic role of positive peritoneal cytology (PPC) in a cohort of patients with endometrial cancer (EC). The secondary objective was to correlate the PPC and the expression of L1CAM in a group of patients with recurrence endometrial disease.
Methods: All women diagnosed with EC and who performed a peritoneal cytology at "Regina Elena" National Cancer Institute of Rome from 2001 to 2013 were included in the study. Patients were divided into two groups according to positivity at peritoneal cytology. Moreover, patients with a recurrence disease and whose a tissue microarray (TMA) tumor sample was available underwent a L1CAM analysis.
Results: Seven hundred sixty six patients underwent to EC staging in our Institute: 696 (90.8%) with negative and 70 (9.2%) with positive cytology. Five-year recurrence rate was higher in women with PPC (46.9% vs 18.4%, $p = 0 < 0.0001$) and, in particular, distant recurrence (86.7% vs 53.4%, $p = 0.03$). Moreover, we found an interesting pattern of recurrence disease in the group of early stage of EC with NPC and positive L1CAM.
Conclusions: Our results support the data that PPC may be a potential prognostic factor in early EC, due to its significant association with other risk factors and its significant influence on survival. Our findings confirm the need for large studies that point out the role of PPC and new prognostic factors, including biomarkers as L1CAM.

1. Introduction

Despite optimal prognosis of patients with early endometrial cancer (EC), with a 10-year overall survival rate higher than 80%, a substantial number of patients experience recurrence with a poor survival rate, where available prognostic factors are not able to predict this poor clinical outcome [1]. The prognostic value of peritoneal cytology was initially evaluated by Creasman and Rutledge in 1971. Through a cohort of 183 patients, the authors demonstrated worse survival at 4 years for patients with positive cytology as compared to patients with negative cytology. They also showed that the impact of positive cytology on overall survival was maintained even in patients with carcinoma limited to the uterus [2]. Although, a limited number of studies showed that peritoneal positive cytology (PPC) could be an independent risk factor for adverse endometrial cancer outcome, several reports failed to demonstrate a negative correlation between PPC and overall survival (OS) or disease free survival (DFS) in patients with early endometrial cancer [3,4]. Further studies, also evaluated the role of PPC correlated to other adverse prognostic factors such as grade, lymphovascular invasion and myometrial infiltration with conflicting results [5–8]. This uncertainty about the clinical and prognostic value of PPC resulted in the exclusion of peritoneal cytology from the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging criteria for endometrial cancer, even though peritoneal cytology continues to be

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collected at the time of surgery and reported separately [9].

To improve the reliability of risk assessment and to allow personalized therapy against cancer, other various molecular biomarkers have been investigated as possible prognostic factors with promising results. L1 cell adhesion molecule (L1CAM) is a neural cell adhesion molecule that promotes cell proliferation, migration, invasion, and metastasis in cancer cells. Its expression is associated with tumor progression in colorectal, gastric, renal, and breast cancer [10]. Recently, some large retrospective studies have found that its expression is associated with poor disease free and overall survival in stage I endometrial cancer, and poor overall survival among cancers of all stages [11–13]. The aim of this study was to evaluate the prognostic role of PPC in a cohort of patients with endometrial cancer. The secondary objective was to correlate the PPC and the expression of L1CAM in a group of patients with recurrent endometrial disease.

2. Materials and methods

We conducted a retrospective observational study on all women with endometrial cancer treated at the IRCCS “Regina Elena” National Cancer Institute of Rome from 2001 to 2013.

2.1. Study design

All women diagnosed with endometrial cancer and who performed a peritoneal cytology, both endometrioid and non-endometrioid, were included in the study. Before surgery, all patients underwent a clinical and instrumental evaluation, including a collection of medical history, a vaginal-pelvic examination, a chest X-ray, an ultrasound scan and a pelvic magnetic resonance imaging scan.

The surgical treatment consisted of a peritoneal washing, closure of the fallopian tubes, radical abdominal/laparoscopic or robotic hysterectomy, bilateral salpingo-oophorectomy, with or without omentectomy and with or without lymph node dissection. Based on the findings of clinical and instrumental evaluation, all the patients underwent type A or type B1 hysterectomy according to Querleau-Morrow classification [14]. An intraoperative histological examination has been required during surgery and a pelvic lymphadenectomy was performed only when risk factors (myometrial invasion more than 50%, high grading and non-endometrioid histotype) were detected. Para-aortic lymphadenectomy was not routinely performed unless pelvic lymph nodes were confirmed to have metastatic disease on frozen section evaluation in order to determine the field of postoperative radiation [15,16]. After surgery, adjuvant therapy was tailored to the pathological findings at primary operation after a multidisciplinary tumor board (gynecologic oncology, pathology, radiation oncology, medical oncology) discussion. Treatment was based on the results of prospective, randomized clinical trials and, since 2016, in accordance with ESGO-ESMO-ESTRO recommendation [17].

Informed consent for abdominal or minimally invasive surgery (laparoscopic or robotic) was obtained from all patients in accordance with the local and international legislation (declaration of Helsinki) [18]. All the data were collected independently from an internal review board.

Patients were divided into two groups according to positivity at peritoneal cytology. Patient characteristics were recorded, including: age, histology, FIGO stage [9] (≤IB and > IB), grading, number of lymph nodes retrieved, lymph nodes status, administration of adjuvant treatments, median follow up in month, recurrence, 5-year disease free survival (DFS), 5-year cancer specific survival (CSS) and 5-year overall survival (OS).

Patients with recurrence and whose tissue microarray (TMA) tumor sample was available underwent a L1CAM analysis.

2.2. Antibody and immunohistochemistry

The mouse monoclonal antibody anti-L1CAM, clone UMAB48, was purchased from OriGene Tchnologies (Rockville, MD, USA). The formalin fixed paraffin-embedded (FFPE) tissue blocks were collected and cut into 5 µm sections and mounted on Superfrost slides. Antigen retrieval was performed at 96 °C (10 mM/L citrate buffer, pH 6) for 20 min. Sections were incubated with the primary antibody anti-L1CAM (1:30) for 30 min at room temperature. Bond Polymer Refine Detection Kit revealed immunoreaction in accordance with the manufacturer's procedure (Leica Biosystems) in an automated autostainer Bond III Leica Biosystems. Diaminobenzidine was used as chromogenic substrate. Microscope Nikon ECLIPSE 55i with digital camera HESP Technology was used. Scale bars 50 µm. The expression level of L1CAM protein was analyzed by IHC analysis. Optimal cut-off was determined at 20% positive staining for L1CAM.

2.3. Statistical analysis

Descriptive statistics was used to describe the patient characteristics. Continuous variables were compared using the Mann-Whitney test and categorical variables were compared using chi-square test or Fisher exact test, as appropriate. Survival curves were estimated by the Kaplan-Meier product-limit method from the date of surgery until the time of death for any cause (cancer specific survival-CSS, Overall Survival-OS, Disease-free Survival-DFS), relapse (DFS), or last visit (OS, CSS and DFS). The log-rank test was used to assess differences between subgroups. Significance was defined at the $p \leq 0.05$ level.

A multivariate Cox proportional hazard model was developed using stepwise regression (forward selection). Variables testing significant at the univariate analysis were entered into the model, enter limit and remove limit were $P = 0.10$ and $P = 0.15$, respectively. The variables considered at univariate analysis included: age, tumor histology, grading, stage, BMI, peritoneal cytology, lymph nodes, LVSI, FIGO stage and adjuvant treatment. SPSS software (SPSS version 21.0, SPSS Inc., Chicago, Illinois, USA) was used for all statistical evaluations.

3. Results

Seven hundred sixty six patients underwent endometrial cancer staging between 2001 and 2013 at our Institute: 696 (90.8%) with negative and 70 (9.2%) with positive cytology. Median age was 62 years (range, 28–90), 62 (range, 28–90) for PPC and 60 (range 36–85) for negative peritoneal cytology (NPC), $p = 0.61$.

3.1. Patient characteristics

Table 1 shows demographic and clinical characteristics of the whole cohort. When comparing patients with and without PPC, we found that patients with PPC were more frequently diagnosed with high risk factors such as grade III disease (52.9% vs. 23.9%, $p < 0.0001$) and unfavorable histologic types ($p < 0.0001$) as clear cell (10% vs. 3.9%) and serous carcinoma (10% vs. 2.4%). Positive lymph nodes were more frequently detected in patients with PPC (25.6% vs. 9.4%, $p = 0.002$). Similarly, adjuvant therapy was administered more frequently in patients with PPC ($p < 0.0001$): chemotherapy (17.1% vs. 3.9%) and radio/chemotherapy (28.6% vs. 4.4%).

Among the 766 patients, 68 (8.8%) relapsed at one or more sites. The sites of recurrence were pelvis in 22 (32.3%), lymph nodes in 7 (10.3%) and distant in 39 patients (57.4%). Five-year recurrence rate was higher in women with PPC (46.9% vs. 18.4%, $p = 0 < 0.0001$) and, in particular, distant recurrence (86.7% vs. 53.4%, $p = 0.03$) (Table 2).

Subsequently, we considered a five-year recurrence rate in two subgroups of patients according to FIGO classification [9] (≤IB and > IB) (Table 3).

Table 1
Comparison of clinical and pathologic features between endometrial cancer with positive or negative peritoneal cytology.

Characteristics		Negative peritoneal cytology (WP-)	Positive peritoneal cytology (WP+)	p value
Number of patients	766	696 (90.9%)	70 (9.1%)	–
Age	< 50	86 (12.4%)	11 (15.7%)	0.72
	50–70	458 (65.8%)	44 (62.9%)	
	> 70	152 (21.8%)	15 (21.4%)	
Grade	G1	145 (20.8%)	3 (4.2%)	< 0.0001
	G2	385 (55.3%)	30 (42.9%)	
	G3	166 (23.9%)	37 (52.9%)	
Histology	Endometrioid	641 (92.1%)	54 (77.1%)	< 0.0001
	Clear cell	27 (3.9%)	7 (10%)	
	Squamous	11 (1.6%)	2 (2.9%)	
	Serous	17 (2.4%)	7 (10%)	
FIGO Stage	< IB	590 (84.8%)	38 (54.3%)	< 0.0001
	> IB	106 (15.2%)	32 (45.7%)	
Adjuvant treatment	None	435 (62.5%)	17 (24.3%)	< 0.0001
	RT	203 (29.2%)	21 (30%)	
	CT	27 (3.9%)	12 (17.1%)	
	RTCT	31 (4.4%)	20 (28.6%)	
Pelvic Lymph nodes	> 10	192 (27.6%)	36 (51.4%)	0.005
	< 10	73 (10.5%)	3 (4.3%)	
	Positive	25 (9.4%)	10 (25.6%)	0.002
	Negative	240 (90.6%)	29 (74.4%)	

WP: peritoneal cytology; RT: radiotherapy; CT: chemotherapy; RTCT: radio-chemotherapy.

Table 2
Comparison of 5-yr recurrence between endometrial cancer with positive or negative peritoneal cytology.

Type of recurrence	Negative peritoneal cytology (WP-) (245 pts)	Positive Peritoneal cytology (WP+) (32 pts)	p value
All	45 (18.4%)	15 (46.9%)	< 0.0001
Pelvic	16 (35.6%)	0 (0%)	0.03
Lymph nodes	5 (11.0%)	2 (13.3%)	
Distant	24 (53.4%)	13 (86.7%)	

WP: peritoneal cytology.

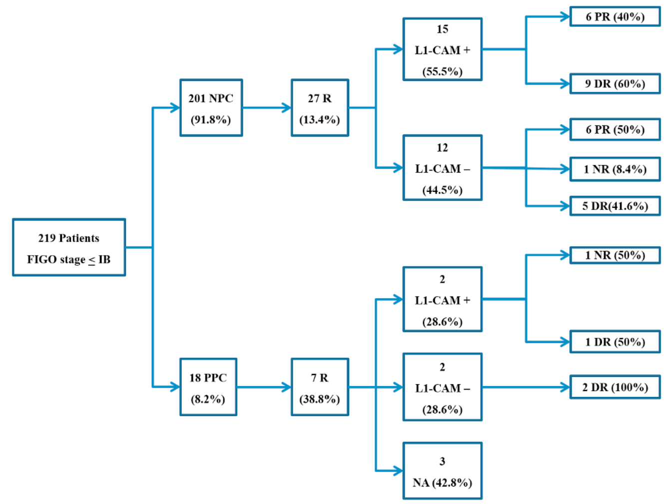
Table 3
Five-year recurrence rate according to peritoneal cytology and FIGO stage in endometrial cancer.

Patients	Recurrence (%)	P value
FIGO Stage ≤ IB		
WP– (201)	27 (13.4%)	P = 0.01
WP+ (18)	7 (38.9%)	
FIGO stage > IB		
WP– (44)	18 (40.9%)	P = 0.29
WP+ (14)	8 (57.1%)	

WP: peritoneal cytology.

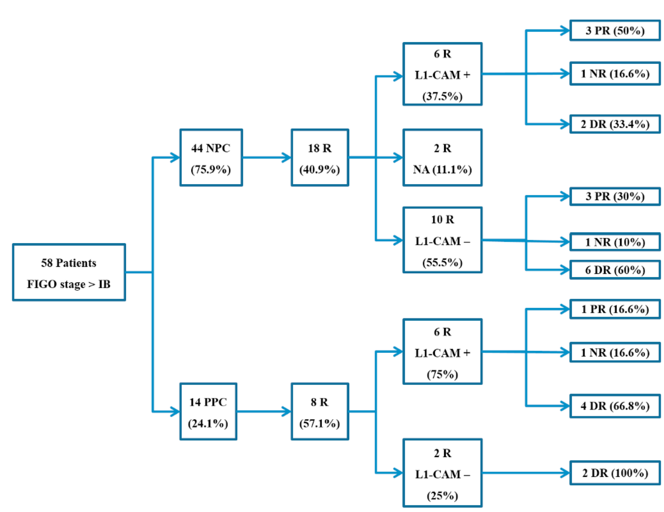
In FIGO stage ≤ IB, we observed a recurrence rate of 38.9% in PPC versus 13.4% in NPC group (p = 0.01). At the five-year follow-up analysis, in the FIGO stage ≤ IB with NPC group, we found 27 women with a recurrence disease, all of them underwent L1CAM analysis. Fifteen out of 27 (55.5%) were L1CAM positive, among which 60% developed distant disease and 40% pelvic recurrence. In the subgroup of L1CAM negative tissues, the overall recurrence rates were 41.6% for distant disease, 8.1% for nodal recurrence and 50% for pelvic recurrence. In the FIGO stage ≤ IB with PPC group, 7 women had a recurrent disease, and 4 of these underwent L1CAM analysis. Two patients were positive for L1CAM, 1 had lymph-node recurrence, and 1 developed distant disease. Both L1CAM negative patients developed distant disease (Fig. 1).

In FIGO stage > IB, we found a recurrence rate of 57.1% in PPC versus 40.9% in NPC group (p = 0.29). At the five-year follow-up analysis, in the FIGO stage > IB with NPC group, we found 18 women with recurrent disease. Sixteen of these underwent L1CAM analysis. Six out of 16 (37.5%) were L1CAM positive. The recurrence rate was 33% for distant disease, 17% for nodal recurrence and 50% for pelvic recurrence in the subgroup of L1CAM positive patients, whereas it was 60% for distant disease, 10% for nodal recurrence 30% for pelvic recurrence in the L1CAM negative cluster. In the FIGO stage > IB with PPC group, we found 8 patients with recurrent disease. All patients underwent L1CAM analysis. Six out of 8 (75%) were L1CAM positive: and with 66% developed distant disease, 17% nodal recurrence and 17% of local disease. All patients belonging to the L1CAM negative subgroup developed distant recurrence (Fig. 2).



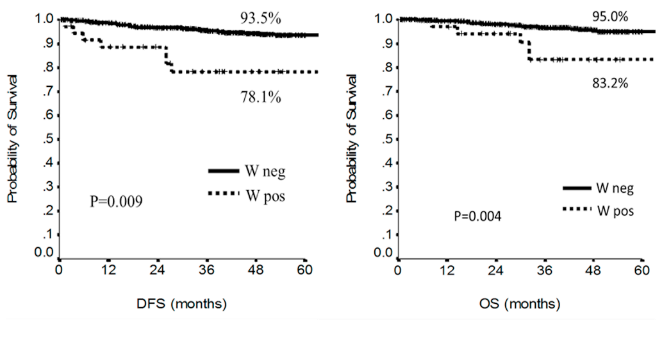
PPC: positive peritoneal cytology; NPC: negative peritoneal cytology; R: recurrence; PR: Pelvic recurrence; NR: nodal recurrence; DR: distant recurrence; NA: not available

Fig. 1. Five-year recurrence rate according to peritoneal cytology, FIGO stage < IB and L1-CAM in endometrial cancer.



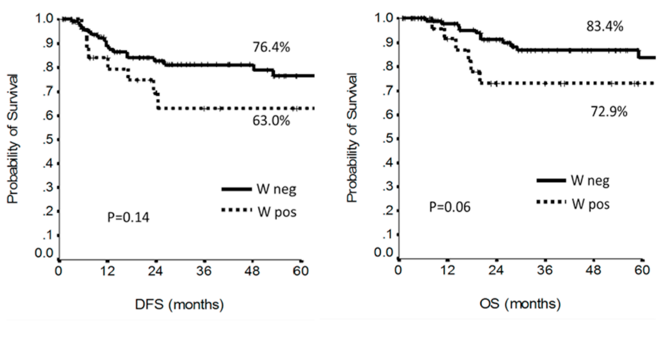
PPC: positive peritoneal cytology; NPC: negative peritoneal cytology; R: recurrence; PR: Pelvic recurrence; NR: nodal recurrence; DR: distant recurrence; NA: not available

Fig. 2. Five-year recurrence rate according to peritoneal cytology, FIGO stage > IB and L1-CAM in endometrial cancer.



DFS: Disease free survival; OS: overall survival

Fig. 3. DFS and OS according to peritoneal cytology in FIGO stage ≤ IB endometrial cancer.



DFS: Disease free survival; OS: overall survival

Fig. 4. DFS and OS according to peritoneal cytology in FIGO stage ≥ IB endometrial cancer.

3.2. Oncologic outcome

Median follow-up was 46 months (range 1–159). 5-yr DFS, 5-yr CSS and 5-yr OS were 89.4% and 92.1% and 82.2%, respectively. There were a total of 135 deaths, of which 85 (63%) were from endometrial cancer. The 5-year DFS and 5-year OS in the two group (NPC versus PPC) was evaluated according to the FIGO stage. In FIGO stage ≤ IB the OS was 95% for NPC vs. 83.2% for PPC (p = 0.004) while DFS was 93.5% vs. 78.1% (p = 0.009) (Fig. 3). In FIGO stage > IB, the OS was 83.4% for NPC vs. 72.9% for PPC (p = 0.06) while the DFS was 76.4% for NPC vs. 63% for PPC (p = 0.14) (Fig. 4).

In the univariate analysis, age, BMI, washing, histology, LVSI, grading and FIGO stage were significant for DFS. In the multivariate analysis, with the exception of LVSI and histology, all prognostic factors are confirmed. Moreover, PPC was found to be an independent risk factor of DFS in the whole cohort (HR 3.89; CI 95% 2.12–7.15; p < 0.0001) and in FIGO stage < IB (HR 3.43; CI 95% 1.47–8.03; p = 0.004) (Table 4). The same factors are prognostic factors of OS, in particular positive peritoneal cytology was an independent risk factor in the whole cohort (HR 4.65; CI 95% 2.25–9.62; p < 0.0001) and in FIGO stage < IB (HR 2.75; CI 95% 1.0–7.55; p = 0.05) (Table 5).

Table 5
Multivariate analysis for OS.

Variables	Multivariate OS		Multivariate OS stage IA-IB	
	HR (CI95%)	P value	HR (CI95%)	P value
Age	1.09(1.05–1.12)	< 0.0001	1.09 (1.03–1.16)	0.002
BMI	1.06(1.03–1.09)	< 0.0001	1.09(1.04–1.14)	< 0.0001
Grading (3 vs 1–2)	3.02(1.52–5.9)	0.001	5.66 (2.50–12.81)	< 0.0001
W (positive vs negative)	4.65(2.25–9.62)	< 0.0001	2.75 (1.0–7.55)	0.05
Stage (III-II vs I)	2.44 (1.24–4.81)	0.01	–	–

4. Discussion

Even though peritoneal cytology was removed from the FIGO staging, our results show the role of PPC as an indicator of aggressive tumor behavior rather than intra peritoneal disease spread, even in early stage endometrial cancer. Moreover, we found an interesting pattern of recurrence in the group of early stage endometrial cancer with NPC and positive L1CAM.

The incidence of PPC in endometrial cancer is very different, ranging from 4.9% to 68.0% [19–24]. Among patients with FIGO stage I, the incidence of PPC ranges between 2.9 and 29.8% [25]. The clinical and prognostic role of PPC in patients with the absence of extra-uterine disease is still under debate. In a systematic review, the prognosis of PPC was different according to the presence of other risk factors such as myometrial invasion, tumor grading, and lymphovascular space invasion. The presence of PPC in patients with low-risk endometrial cancer (grade 1/2, myometrial invasion < 50%, no cervical involvement, no lymphovascular space invasion) had a lower relapse rate (4.1% vs 32%) compared to patients with PPC and high-risk tumors [26]. Conversely, Garg et al. [27] demonstrated that PPC was an independent risk factor for mortality, regardless of histologic type, among women with early stage endometrial cancer in a large cohort of patients using data from the Surveillance, Epidemiology, and End Results (SEER) registry. Obermairet et al. [28] showed that such patients had a significantly worse disease free survival compared to similar patients with negative washings (67 vs. 96%, P = 0.001). Moreover, Zuna et al. [29] also demonstrated statistically significant survival differences when compared to patients with early endometrial cancer with positive and negative cytology.

Conversely, other studies have failed to show any worsening of overall survive in patients with early endometrial cancer with PPC [4–6]. The result of these controversial data implies that some physicians aggressively treat patients with early stage endometrial cancer based on PPC while others ignore the result.

The incidence of PPC in the whole cohort was 9.1% and, in particular, 6.1% in patients with early endometrial cancer (FIGO stage ≤ IB). We did not find an increased rate of PPC, despite the fact that 64% of our patients were treated with the minimally invasive approach (laparoscopy, robotic surgery, laparoscopic single site surgery), consequently supporting the data that mini invasive surgery does not increase the incidence of PPC among women with endometrial

Table 4
Multivariate analysis for DFS.

Variables	Multivariate DFS		Multivariate DFS stage IA-IB	
	HR (CI95%)	P value	HR (CI95%)	P value
Age	1.05 (1.03–1.08)	< 0.0001	1.06 (1.02–1.09)	0.004
BMI	1.06 (1.03–1.09)	< 0.0001	1.08 (1.03–1.13)	0.001
Grading (3 vs 1–2)	2.63 (1.51–4.60)	0.001	4.46 (2.28–8.72)	< 0.0001
W (positive vs negative)	3.89 (2.12–7.15)	< 0.0001	3.43 (1.47–8.03)	0.004
Stage (III-II vs I)	2.58 (1.48–4.49)	0.001	–	–

Table 6
Review of the studies over the last five years on the prognostic role of peritoneal cytology in endometrial cancer.

Author	Year	N° patients	N° patients		FIGO stage	Histotype	Adjuvant therapy		N° recurrence		Site of recurrence in PPC			Site of recurrence in NPC			OS	
		Total	PPC [%]	NPC [%]			PPC [%]	NPC [%]	PPC [%]	NPC [%]	PR [%]	NR [%]	DR [%]	PR [%]	NR [%]	DR [%]	PPC [%]	NPC [%]
Our study	2018	766	9.1	90.9	I-IV	Endometrioid Clear cell Squamous Serous	3.9 CT 29.2 RT 4.4 RTCT	17.1 CT 30 RT 28.6 RTCT	22.8	7.5	12.5	12.5	75	38.5	9.6	52	72.9	95
Matsuo K et al. [32]	2018	1668	7.5	92.5	I-II	Endometrioid	23.9 CT 4.7 RT	71.7 CT 89.2 RT	14.6	6.1	NA	NA	NA	NA	NA	NA	85.4	93.9
Seagle BL et al. [33]	2018	16851	5.6	94.3	I-II	Endomentrioid Serous Clear Cell Carcinosarcoma	35.0 CT 2.4 HT 39.8 RT	12.3 CT 0.3 HT 28.0 RT	NA		NA			NA			79.5	92.2
Turkmen O et al. [34]	2017	77	28.6	71.4	I-III	Endometrioid Serous Undifferentiated Mucinous Mixed	NA		24.6	NA	42.1	11.5	47.4	NA			69.1	68.3
Tanaka K et al. [35]	2017	168	16.7	79.2	I-II	Endometrioid	36.9	63.1	32.1	8.2	11.1	33.3	100	45.6	18.2	62.7	92.3	
Scott SA et al. [36]	2017	668	2.2	97.7	I	Endometrioid	46.7 CT 53.3 RT	1.1 CT 17.0 RT	20.0	7.96	0	100	0	65.3	25	9.62	86.7	NA
Shiozaky T et al. [37]	2014	265	10.1	89.8	I	Endometrioid Papillary Serous Clean Cell Undifferentiated	77.8 CT 3.7 RT	NA	22.7	NR	40.0	20.0	80.0	NA			75.0	93.0
Han KH et al. [38]	2014	490	6.5	93.5	I-IV	Endometrioid Papillary Serous Clean Cell Undifferentiated	38.0		6.0		NA			NA			NA	
Binesh F et al. [39]	2014	46	23.9	76.1	I-IV	Endometrioid	23.9		45.4	NA	NA			NA			54.6	NA
Kyrgiou M et al. [40]	2013	142	3.5	96.4	I-III	Endometrioid Papillary Serous Clean Cell Undifferentiated	40.0 RT 40.0 RTCT	1.5 CT 46.7 RT 1.5 RTCT	8.4	4.6	15.4	38.2		4.2	0.6		26 month	32 month
Milgrom SA et al. [41]	2013	196	23.0	77.0	IIIA	Endometrioid Papillary Serous Clean Cell Undifferentiated	RT: 60 CT: 80	RT: 74 CT: 68	49	26	14.0	30.0	37.0	11.0	9.0	19.2	34.0	72.0
Garg G et al. [27]	2013	14704	3.3	96.7	I-II	Endometrioid Clear Cell Carcinosarcoma	53.4	29.7	NA		NA			NA			80.8 50.4 32.3	95.1 78.0 64.7

PPC: positive peritoneal cytology; NPC: negative peritoneal cytology; CT: chemotherapy; RT: radiotherapy; RTCT: radiochemotherapy; HT: hormonal therapy.
PR: Pelvic recurrence, NR: nodal recurrence, DR: distant recurrence, NA: not available.

carcinoma [30,31]. The five-year recurrence rate was significantly higher ($p < 0.0001$) in the PPC group (46.9%) than in those with NPC (18.4%), and with a particular recurrence pattern. Patients with PPC were more likely to develop a distant relapse than those with NPC (86.7% vs. 53.4% $p = 0.03$). We found a similar five-year recurrence rate trend in the ≤ IB group (38.9% vs. 13.4% $p = 0.01$). Additionally, PPC had a significantly worse association with overall survival in patients with surgical FIGO stage I (95% for negative cytology *vs.* 83.2% for positive -$p = 0.004$) and when we performed the multivariate analysis, PPC was independently associated with a decrease in OS and DFS in the whole cohort and in the early stage endometrial cancer. Certainly, the retrospective nature of our study may have influenced our results, especially with regard to different adjuvant treatment ($p < 0.001$) and the oncologic outcomes.

From a review of the literature from the last 5 years (Table 6) [27,32–41], we noticed that among 34.373 patients analyzed, 4.9% displayed PPC and were more frequently subjected to undergoing adjuvant therapy than patients with NPC. However, the recurrence rate was higher in patients with PPC (range, 8.4%–40%) than in patients with NPC (range, 4.6%–26%). Moreover, the sites of relapse were more distant with consequent decrease of the OS in the PPC patients (range, 32.3%–86.7%) compared to the patients with NPC (range, 64.7%–95.1%) independent of the stage of disease and histotype. According to these studies, we suggest that PPC may be a potential prognostic factor in EC owing to its significant association with other prognostic factors and its significant influence on survival. Although only retrospective studies of the last five years were included in our review, our study is important because it systemically analyzes the clinical significance of PPC in EC.

When we analyzed the results of L1CAM according to the stage of disease and the peritoneal cytology, we observed that only in patients with early stage of disease (FIGO stage ≤IB) and NPC, generally a subgroup of patients with a good prognosis, the positivity of L1CAM had an increase in the rate of distant recurrence (60% vs 41.6%). Unfortunately, the small number of the sample examined for L1CAM in this study does not allow us to support further hypotheses on the prognostic role of this biomarker, which however was found in two randomized studies and one of our recent studies [12,42,43].

Even though our study is limited by its retrospective nature, our results support data indicating that PPC may be a potential prognostic factor in early EC, due to its significant association with other risk factors and its significant influence on survival. Our findings confirm the need for large studies demonstrating the role of PPC and new prognostic factors, including biomarkers as L1CAM. In fact, the development of more sensitive and accurate biomarkers, thanks to new technology, will be fundamental both for early detection of disease and for more effective surveillance in post-treatment. The goal of these new generation biomarkers will be to detect disease recurrence early, so that patients may be candidates for more effective and personalized treatments.

Competing interests

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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