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Prognostic factors and patterns of recurrence in lymphovascular space invasion positive women with stage IIIC endometriod endometrial cancer

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Abstract

Aim: The purpose of this study was to determine the prognostic factors and patterns of failure in lymphovascular space invasion (LVSI)-positive women with stage IIIC endometrioid endometrial cancer (EC).

Methods: A multicenter, retrospective, department database review was performed to identify LVSI-positive patients with stage IIIC endometrioid EC at five gynecological oncology centers in Turkey. Demographic, clinicopathological and survival data were collected.

Results: We identified 172 LVSI-positive women with stage IIIC endometrioid EC during the study period; 75 (43.6%) were classified as Stage $IIIC_1$ and 97 (56.4%) as Stage $IIIC_2$. The median age at diagnosis was 59 years, and the median duration of follow up was 34.5 months. The total number of recurrences was 46 (26.7%). We observed 14 (8.1%) locoregional recurrences, 12 (7.0%) retroperitoneal failures and 20 (11.6%) distant relapses. For the entire study cohort, 5-year progression-free survival (PFS) was 67.4%, while the 5-year overall survival (OS) rate was 75.1%. Grade 3 histology (hazard ratio [HR] 2.62, 95% confidence interval [CI] 1.34–5.12; $P = 0.005$), cervical stromal invasion (HR 2.33, 95% CI 1.09–4.99; $P = 0.028$) and myometrial invasion (MMI) ≥50% (HR 4.0, 95% CI 1.16–13.69; $P = 0.028$) were found to be independent prognostic factors for decreased OS.

Conclusion: Uterine factors such as grade 3 disease, cervical stromal invasion and deep MMI seem to be independently associated with decreased OS in LVSI-positive women with stage IIIC endometrioid EC. The high distant recurrence rate in this subgroup of patients warrants further studies in order to identify the most effective treatment strategy for those patients.

Key words: endometrioid-type endometrial cancer, lymphovascular space invasion, recurrence, stage IIIC disease.

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Introduction

Nodal involvement is a strong predictor of recurrence and survival in endometrial cancer (EC),[1] and its presence warrants upstaging to International Federation of Gynecology and Obstetrics (FIGO) stage IIIC disease.[2] Lymph node (LN) metastasis in EC is associated with the increased likelihood of recurrence (approximately 50%) and consequent poor survival.[3] However, considerable heterogeneity exists in node-positive patients based on various clinicopathological characteristics.[4,5]

Although clinical outcomes for advanced EC are generally reported in aggregate,[6–8] the literature is naive with regard to factors influencing outcomes.[9] The independent risk factors that affect survival in stage III EC have been reported to be age, external-beam radiotherapy, residual nodal disease and lymphovascular space invasion (LVSI).[9]

LVSI, the presence of tumors in the lymphatic and vascular channels of the uterus, has been reported to be the strongest predictor of compromised longevity in advanced EC.[9] Although LVSI is known to be an important adverse prognostic factor in EC, its role in relation to patterns of recurrence is not well defined,[10] particularly in women with nodal disease. Mahdi *et al*.[11] have reported that LVSI-positive endometrioid EC patients with positive nodal status have a high recurrence rate, especially as distant and para-aortic failures. However, prognostic factors and recurrence patterns in LVSI-positive patients with stage IIIC endometrioid EC have not been clearly delineated. The purpose of this multicenter retrospective study was to assess the prognostic factors and patterns of failure in LVSI-positive women with stage IIIC endometrioid EC.

Methods

Study design and eligibility

After Institutional Review Board approvals, patients with endometrioid EC who underwent primary surgical treatment between January 2001 and December 2016 at six gynecological oncology centers in Turkey were retrospectively reviewed. All patients provided informed consent for the surgical procedure and research use of their medical information at admission.

The study population included LVSI-positive women with stage IIIC pure endometrioid-type EC at the end of the final pathology report. Women with nonendometrioid-type EC, those with mixed histologies, patients with negative LVSI status, those with inadequate LN dissection and women with stage IV disease were excluded from the study. We also excluded patients with incomplete medical records as well as those with synchronous malignancies.

Clinical information

Patient data were extracted from five institutions with maintained EC databases. These five centers (all of them participated in our previous multicenter studies[12–14] on EC) were chosen because of their high volume of endometrioid EC presentations. Some of the patients in this study were within the context of one of our previous studies.[13] With the eligible cases, demographic characteristics were extracted from medical records. Tumor characteristics were extracted from original pathology reports, and the following data were recorded: FIGO grade, depth of myometrial invasion (MMI) (<50% or ≥50%), primary tumor diameter (PTD) in centimeters, the status of peritoneal cytology examination (negative or positive), cervical stromal invasion, serosal involvement, adnexal involvement and the stage of disease. The date of diagnosis, adjuvant treatment modality (radiotherapy, chemoradiotherapy or chemotherapy), recurrence (if applicable), time to recurrence (TTR) (as a continuous variable in months, if applicable), site of recurrence (locoregional, retroperitoneal, distant), length of follow up and survivals were noted. Data were collected from centers with an online standardized form.[12,13]

Surgical staging consisted of total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and peritoneal washings. All operations were performed by gynecological oncologists. Data on the extent of surgery included number of total LN harvested, number of pelvic LN removed, number of para-aortic LN removed, number of metastatic pelvic LN and number of metastatic para-aortic LN.[12,13]

All histological data were retrieved from the primary pathologist's report and were not reviewed centrally. All surgical specimens were examined and interpreted by gynecological pathologists. For pathological evaluation, the uterine specimen was initially inspected externally and was opened to expose the endometrium for macroscopic examination of an EC. The location, growth pattern, size and the extent of MMI and cervical involvement of the tumor were noted. The histological classification was performed

according to the World Health Organization classification.[1] Architectural grading was defined by standard FIGO criteria. Notable nuclear atypia inappropriate for the architectural grade raised grade 1 or grade 2 tumors by one grade. Tumor size was macroscopically measured on fresh tissue by gynecological pathologists, who noted size in the three largest dimensions. The largest of three dimensions of the tumor was defined as PTD.[15] LVSI was defined as the presence of adenocarcinoma of any extent in endothelium-lined channels of uterine specimens extracted at the time of surgery.[16] LVSI was assessed on hematoxylin and eosin-stained sections by the primary pathologist. All tumors were staged according to the 2009 FIGO staging system.[2] In patients treated before 2009, the stage was determined retrospectively on the basis of surgical and pathological assessment.

The treatment policies were decided by the attending physician or by the multidisciplinary tumor board at each participating institution. Adjuvant therapy was administered to all patients. Patients usually received platinum-based chemotherapy and/or external beam pelvic irradiation with or without para-aortic irradiation and with or without brachytherapy. Concurrent chemotherapy with irradiation consisted of cisplatin 40 mg/m^2 once a week. The standard primary chemotherapy regimen included paclitaxel 175 mg/m^2 plus carboplatin dosed at an area under curve of 5 or 6 every 21 days for six cycles. Adjuvant treatment was given based on the following guidelines: (i) extended-field irradiation (EFRT) for para-aortic LN involvement; (ii) whole pelvic irradiation (WPRT) for disease limited to the pelvis with negative para-aortic LNs; (iii) vaginal brachytherapy (VB) was offered for all patients undergoing external beam therapy; and (iv) chemotherapy for positive para-aortic LNs or refusal of radiation therapy. None of the patients in our cohort received adjuvant hormonal therapy. The median radiation dose prescribed was 45 Gy for whole pelvis and 54 Gy for extended field. As adjuvant therapy modalities have changed with time, the adjuvant treatment modalities were not standard within or among the institutions that participated in the study during the study period. Chemoradiotherapy was delivered in one of two ways: three cycles of chemotherapy upfront, followed by radiotherapy, followed by three additional cycles of chemotherapy ('sandwich' chemoradiotherapy) or radiotherapy with concurrent cisplatin 40 mg/m^2 weekly followed by carboplatin AUC 5 or 6 and paclitaxel 175 $mg/m^2 \times 4$ cycles.

Postoperative cancer surveillance included quarterly follow-up visits for the first 2 years and biannually thereafter. A chest radiograph and vaginal smears were obtained once a year. The visits included a gynecological medical history and a gynecological examination that was further supplemented with biopsies in case of suspicious findings and imaging studies in case of suspicion of distant metastases. If an isolated recurrence was diagnosed, treatment with curative intent was initiated unless precluded by the patient or disease factors. All women included in the study were followed until death or to the end of study period (31 December 2016). The survival status of the patients was determined as alive or dead at the time of the last follow up. For all study subjects with a recorded death, this was confirmed by performing a social security death index search.

Definitions

Lymphadenectomy was defined as the performance of pelvic and para-aortic LN dissection at the same time. We defined pelvic lymphadenectomy as the removal of lymphatic tissue from the external, internal and common iliac and obturator regions. Para-aortic lymphadenectomy was defined as the removal of lymphatic tissue over the inferior vena cava and aorta, beginning at the level of aortic bifurcation up to the left renal vessels. An adequate pelvic lymphadenectomy was defined as the removal of at least 10 pelvic LN, and an adequate para-aortic lymphadenectomy was defined as the removal of at least 5 para-aortic LN.[15–17]

Peritoneal, hematogenous and LN recurrences outside the retroperitoneal area (i.e. inguinal, axillary, mediastinal and supraclavicular) were considered distant failures.[18] Recurrences located in pelvic and/or para-aortic LN were considered retroperitoneal failures, whereas relapses at vaginal vault, vagina and/or central pelvis were considered locoregional relapses.

After initial diagnosis, recurrence was defined as the documentation of metastasis with physical examination and imaging techniques after a progression-free survival (PFS) ≥3 months. TTR was defined as the time frame from surgery to physical or radiological evidence of disease recurrence or the date of last contact for patients without recurrence. PFS was defined as the time from surgery to the first identification of recurrence or progression or death from any cause, whichever occurred first, or the date of last contact for patients remaining alive without recurrent disease.

Overall survival (OS) was calculated as the time period between initial surgery to the date of death or the last contact. Surviving patients were censored at their last known follow up.

Statistical analysis

Statistical analyses were performed using the statistical software package SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The data were expressed as median and range for continuous variables. Continuous variables such as age and tumor size have been divided into categories according to the median values. Binary variables were reported as counts and percentages.

Survival curves were generated using the Kaplan–Meier plots, and the differences between survival curves were calculated using the log-rank test. In order to evaluate the prognostic factors for PFS and OS, a univariate Cox regression model was used. Any *P*-value of less than 0.05 in the univariate analysis was subjected to multivariate analysis. A *P*-value <0.05 was considered to indicate statistical significance.

Results

During the study period, a total of 3571 endometrioid EC were treated at five participating centers. Of these women, 172 (4.8%) met the inclusion criteria; 75 (43.6%) were classified as Stage $IIIC_1$ and 97 (56.4%) as Stage $IIIC_2$. The median age at diagnosis was 59 years (range, 30–82 years), and the median duration of follow up was 34.5 months (range, 5–174 months). Histological grade was determined as grade 1 in 30 women (17.4%), whereas 82 patients had grade 2 (47.7%), and 60 (34.9%) had grade 3 disease. The median PTD was 4.5 cm (range, 1–12 cm). MMI was <50% in 39 women (22.7%), while 133 (77.3%) had MMI ≥ 50%. Among 133 patients with MMI ≥ 50%, there were 16 (12.0%) patients with serosal involvement. Table 1 demonstrates the clinical and pathological characteristics of LVSI-positive women with Stage IIIC endometrioid EC.

All women in the current study underwent pelvic and para-aortic lymphadenectomy. Adequate lymphadenectomy was achieved in all patients. The median number of total LN harvested was 45 (range, 20–166). The median number of pelvic and para-aortic LN removed was 30 (range, 10–105) and 14 (range, 5–87), respectively. There were 148 patients with pelvic LN involvement and 97 patients with para-aortic LN involvement. Isolated pelvic LN metastasis was detected in 75 women (43.6%). There were 24 patients with isolated para-aortic LN metastasis (14.0%);

Table 1 Baseline characteristics of lymphovascular space invasion-positive patients with stage IIIC pure endometrioid endometrial cancer

Characteristic	Values, *n* (%)
Age (year), median (range)	59 (30–82)
Menopausal status	
Postmenopausal	142 (82.6)
Premenopausal	30 (17.4)
Tumor size (median, range, cm)	4.5 (1–12)
Grade	
1	30 (17.4)
2	82 (47.7)
3	60 (34.9)
MMI	
<50%	39 (22.7)
≥50%	133 (77.3)
Number of LN removed (median, range)	45 (20–166)
Pelvic LN	30 (10–105)
Para-aortic LN	14 (5–87)
Number of metastatic LN (median, range)	
Pelvic	2 (0–37)
Para-aortic	1 (0–46)
Retroperitoneal LN metastases	
Pelvic	148
Para-aortic	97
Retroperitoneal LN metastases	
Pelvic only	75 (43.6)
Para-aortic only	24 (14.0)
Pelvic-para-aortic	73 (42.4)
Cervical involvement	
Yes	54 (31.4)
No	118 (68.6)
Adnexal involvement	
Yes	30 (17.4)
No	142 (82.6)
Serosal involvement	
Yes	16 (9.3)
No	156 (90.7)
Peritoneal cytology	
Positive	32 (18.6)
Negative	140 (81.4)
Stage	
IIIC1	75 (43.6)
IIIC2	97 (56.4)
Adjuvant treatment	
Radiotherapy	33 (19.2)
Chemotherapy	44 (25.6)
Chemoradiotherapy	95 (55.2)
Status	
Alive	138 (80.2)
Dead	34 (19.8)

LN, lymph node; MMI, myometrial invasion.

73 (42.4%) women had pelvic and para-aortic LN metastases at the same time. The median number of metastatic pelvic and para-aortic LN was 2 (range, 0–37) and 1 (range, 0–46), respectively.

Adjuvant treatment modalities included chemoradiotherapy in 95 (55.2%) women, whereas 33 (19.2%) patients received radiotherapy only in the postoperative period. The number of patients treated only with chemotherapy was 44 (25.6%).

The total number of the recurrences was 46 (26.7%). We observed 14 (8.1%) locoregional recurrences, 12 (7.0%) retroperitoneal failures and 20 (11.6%) distant relapses. The rates of vaginal, pelvic and extrapelvic recurrences were 15.2% (7/46), 15.2% (7/46) and 69.6% (32/46), respectively. Among extrapelvic recurrences, the rates of distant, peritoneal and para-aortic recurrences were 37.5% (12/32), 25.0% (8/32) and 37.5 (12/32), respectively. Median TTR was 15 months (range, 4–75 months). In our study, 30 of 46 recurrences (65.2%) occurred within 2 years after primary surgery, whereas 37 recurrences (80.4%) occurred within 3 years of initial diagnosis. Site of recurrences and type of salvage therapies are summarized in Table 2.

Treatment of the recurrences was applied according to the institutional practices at that time and consisted of radiation (n = 2, 4.3%), chemotherapy (n = 29, 63.0%), surgical resection plus radiation (n = 3, 6.5%), surgical resection plus chemotherapy (n = 6, 13.0%), chemoradiation (n = 1, 2.1%) and surgical resection plus chemoradiation (n = 2, 4.3%). Three patients did not receive any kind of treatment for their recurrences; two of them refused further treatment, and one died of disease before initiating treatment for relapse.

Overall, for the entire study cohort, the 5-year PFS was 67.4%, while the 5-year OS rate was 75.1%. Figure 1 shows the Kaplan–Meier plots for PFS and OS of LVSI-positive women with stage IIIC endometrioid EC. Univariate analysis revealed that PFS was significantly decreased in patients who were ≥ 60 years (P = 0.012), had grade 3 histology (P = 0.021) and had MMI ≥ 50% (P = 0.012) (Table 3). At the end of multivariate analysis, grade 3 disease (hazard ratio [HR] 2.92, 95% CI 1.09–7.75; P = 0.015) and MMI ≥ 50% (HR 3.47, 95% CI 1.23–9.80; P = 0.019) remained independent prognostic factors for decreased PFS (Table 3).

Univariate analysis revealed age ≥ 60 years (P = 0.034), grade 3 disease (P = 0.002), MMI ≥ 50% (P = 0.034), adnexal involvement (P = 0.029), cervical stromal invasion (P = 0.001) and serosal involvement (P = 0.003) as significant factors for decreased OS (Table 4). At the end of multivariate analysis, grade

Table 2 Recurrence characteristics of lymphovascular space invasion-positive patients with stage IIIC pure endometrioid endometrial cancer

Variables	Values, *n* (%)	Median time to recurrence, months (range)
Site of recurrence		
Locoregional	14 (30.4)	28 (5–65)
Retroperitoneal	12 (26.1)	20 (6–48)
Distant	20 (43.5)	10.5 (4–75)
Locoregional disease	14 (30.4)	
Vaginal cuff	7	
Central pelvic	7	
Extrapelvic disease	32 (69.6)	
Abdominal (peritoneal) disease	8	
Lung	3	
Bone	1	
Brain	1	
Liver	1	
Para-aortic LN	9	
Pelvic-Para-aortic	3	
Lung-bone	1	
Mediastinal LN-Pelvic LN-Bone	1	
Supraclavicular LN	2	
Lung-Abdominal (peritoneal) disease	1	
Liver-Lung-Adrenal	1	
Salvage Therapies		
RT alone	2 (4.3)	
Chemotherapy alone	29 (63)	
Surgical resection plus RT	3 (6.5)	
Surgical resection plus CT	6 (13)	
Surgical resection plus CRT	2 (4.3)	
CRT	1 (2)	
No further treatment	3 (6.5)	

CT, chemotherapy; CRT, chemoradiotherapy; LN, lymph node; RT, radiotherapy.

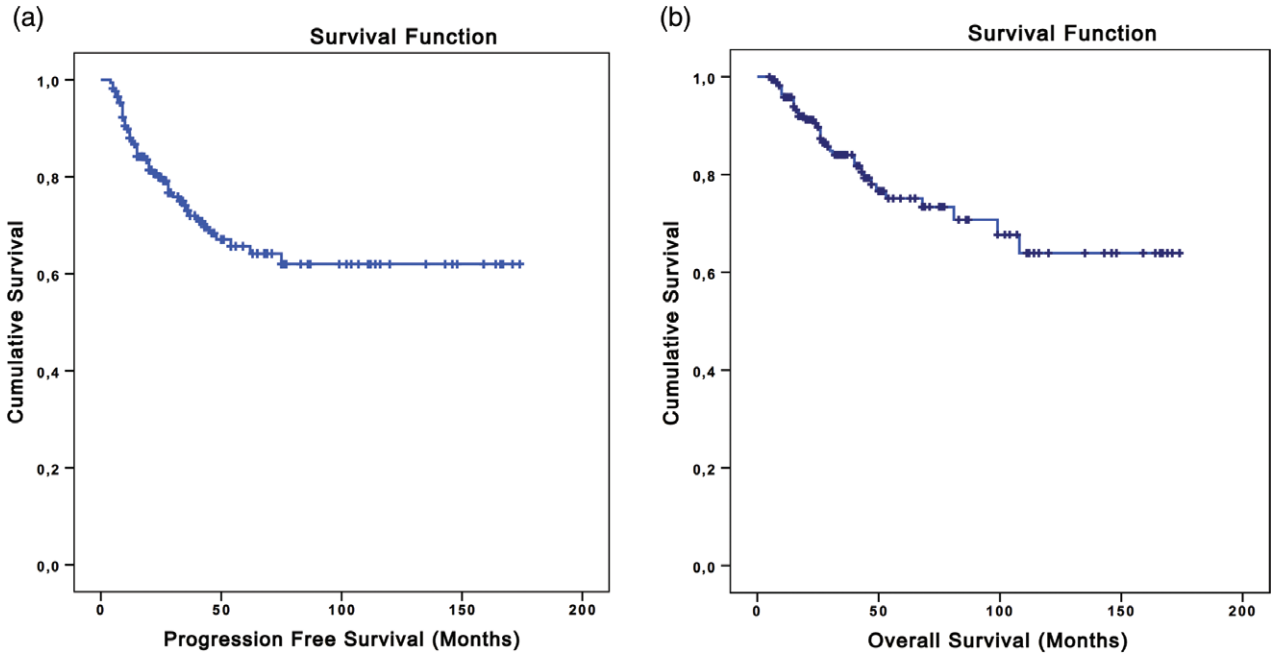

Figure 1 The Kaplan–Meier plots for progression-free survival (a) and overall survival (b) of lymphovascular space invasion-positive women with stage IIIC pure endometrioid endometrial cancer. (+), Censored.

3 histology (HR 2.62, 95% CI 1.34–5.12; $P = 0.005$), cervical stromal invasion (HR 2.33, 95% CI 1.09–4.99; $P = 0.028$) and MMI ≥ 50% (HR 4.0, 95% CI 1.16–13.69; $P = 0.028$) remained independent prognostic factors for decreased OS (Table 3). At the time of reporting, of 172 LVSI-positive women with stage IIIC endometrioid EC, 34 (19.8%) were dead, whereas 138 (80.2%) were alive.

Discussion

The key findings of the current study indicate that 26.7% of LVSI-positive women with stage IIIC endometrioid EC had recurrences in the follow-up period. Of those women with recurrences, 26.1% had retroperitoneal failures, whereas 43.5% experienced distant relapses. Grade 3 disease, cervical stromal invasion and MMI ≥ 50% were found to be independent prognostic factors for decreased OS in LVSI-positive women with stage IIIC endometrioid EC.

We should underline some limitations of the current study. First, the retrospective nature of the study cannot exclude any bias. Second, lack of central pathology review seems to be an important limitation. However, the prognostic significance of LVSI diagnosed by the primary pathologist has already been shown in a multicenter study including LVSI-positive patients with stage I endometrioid EC.[19] Third, our study of adjuvant therapy was limited by the lack of uniformity in the type of therapy used. Despite these limitations, our study provides additional information to the body of knowledge on this topic.

FIGO does not include LVSI as a prognostic factor for EC[2] even though it is clearly evident that the presence of LVSI strongly correlates with LN metastasis in EC.[20] Briet *et al*.[21] analyzed 609 patients and found that LVSI was an independent prognostic factor for relapse in all stages of the disease. It has been shown that LN-positive patients are at increased risk of recurrence when compared to patients with negative LN, with or without high-risk uterine characteristics, and that PFS is reduced.[22]

Pretreatment node positivity is significant for both nodal and distant failures in EC.[23] Once the tumor had been disrupted during hysterectomy and lymphadenectomy, inflammatory reactions and increased lymph flow would follow the path the tumor had already established, leading patients with LVSI and nodal metastases to a higher risk of subsequent nodal and distant failure.[23] It has been reported that positive LVSI had an HR of 8.8 ($P = 0.004$) for relapse in the presence of positive nodes.[23] On the contrary, LVSI has been reported to predict survival independent of

Table 3 Univariate and multivariate analyses of prognostic factors for progression-free survival

Variable	Univariate analysis		Multivariate analysis		
	PFS,† *n* (%)	*P*	HR	95% CI	*P*
Menopausal status					
Postmenopausal	38/142 (65.1)	0.19			
Premenopausal	5/30 (78)				
Tumor size, cm					
≤2	3/11 (69.3)	0.83			
>2	40/161 (67.4)				
Stage					
IIIC1	19/75 (70.4)	0.34			
IIIC2	22/97 (65.4)				
Number of involved LN					
1	14/58 (68.5)	0.92			
2–5	18/75 (68.4)				
>5	11/39 (64.5)				
Peritoneal cytology					
Positive	8/32 (69.3)	0.51			
Negative	35/140 (67.2)				
Adnexal involvement					
Yes	10/30 (51.4)	0.055			
No	33/142 (70.2)				
Serosal involvement					
Yes	7/16 (47.4)	0.057			
No	36/156 (69.6)				
Cervical involvement					
Yes	13/54 (57.4)	0.86			
No	26/118 (75.9)				
Adjuvant treatment					
RT	10/33 (64.9)	0.38			
CT	7/44 (80.8)				
CRT	26/95 (60.6)				
Age, year					
<60	16/88 (76.9)	0.012			
≥60	27/84 (58.3)				
MMI					
<50%	3/39 (87.7)	0.012	3.47	1.23–9.80	0.019
≥50%	40/133 (75.5)				
Grade					
1	5/30 (82)	0.021	2.92	1.09–7.75	0.015
2	18/82 (67.8)				
3	20/60 (57.1)				

†A 5-year progression-free survival rate. CI, confidence interval; CT, chemotherapy; CRT, chemoradiotherapy; HR, hazard ratio; MMI, myometrial invasion; PFS, progression-free survival; RT, radiotherapy.

nodal disease.[24,25] Jorge *et al*.[26] reported that when stratified based on the presence or absence of nodal metastases, LVSI remained associated with survival in node-negative patients (HR 2.06, 95% CI, 1.65–2.58) but was not associated with survival in women with LN metastases (HR 1.19, 95% CI, 0.70–2.00).

Narayan *et al*.[23] reported the relapse rate to be 35.7% (20/56) for LVSI-positive patients with positive nodal status. It should be noted that their series included nonendometrioid tumors as well as endometrioid histologies, and only patients with high to intermediate and high risk were included in their study. Mahdi *et al*.[11] reported the same rate to be 47% (18/38). With a larger cohort, we have found the recurrence rate to be 26.7% (46/172) for LVSI-positive women with stage IIIC pure endometrioid EC. Our lower recurrence rate may be explained by the effects of various adjuvant therapies on the natural history of disease as well as different study populations and median follow-up times.

The extrapelvic recurrence rate was 26.3% (10/38) in the Mahdi *et al*. study,[11] whereas the corresponding

Table 4 Univariate and multivariate analyses of prognostic factors for overall survival

Variable	Univariate analysis		Multivariate analysis		
	OS,† *n* (%)	*P*	HR	95% CI	*P*
Menopausal status					
Postmenopausal	27/142 (72.4)	0.32			
Premenopausal	3/30 (89.9)				
Tumor size, cm					
≤2	3/11 (70.7)	0.42			
>2	27/161 (75.5)				
Stage					
IIIC1	13/75 (78.1)	0.75			
IIIC2	17/97 (70.3)				
Number of involved LN					
1	10/58 (75.3)	0.34			
2–5	10/75 (80.6)				
>5	10/39 (64.3)				
Peritoneal cytology					
Positive	7/32 (67.8)	0.33			
Negative	23/140 (76.8)				
Adjuvant treatment					
RT	4/33 (82.8)	0.05			
CT	5/44 (85.2)				
CRT	21/95 (67.3)				
Age, year					
<60	10/88 (85.8)	0.034			
≥60	20/84 (64.8)				
Adnexal involvement					
Yes	7/30 (69.7)	0.029			
No	23/142 (76.5)				
Serosal involvement					
Yes	7/16 (39.6)	0.003			
No	23/156 (79)				
MMI					
<50%	2/39 (94)	0.034	4.00	1.16–13.69	0.028
≥50%	29/133 (69.6)				
Grade					
1	3/30 (86.9)	0.002	2.62	1.34–5.12	0.005
2	9/82 (80.2)				
3	18/60 (61.4)				
Cervical involvement					
Yes	14/54 (64)	0.001	2.33	1.09–4.99	0.028
No	16/118 (81)				

†A 5-year overall survival rate. CI, confidence interval; CT, chemotherapy; CRT, chemoradiotherapy; HR, hazard ratio; MMI, myometrial invasion; OS, overall survival; RT, radiotherapy.

figure was 69.6% (32/46) in the current study. The extrapelvic recurrence rate in the current study was even higher than the rate reported by Mahdi et al[11] who emphasized that LVSI-positive endometrioid EC patients with LN involvement had a high rate of para-aortic and distant relapses. The 5-year PFS and OS for node-positive LVSI-positive endometrioid EC patients have been reported to be 47.6 and 83.6%, respectively.[11] The corresponding figures were 67.4 and 75.1%, respectively, in the current study, comparable with the previous findings.[11]

In a retrospective review of 85 patients with FIGO stage IIIC EC, Hoekstra *et al*.[27] have reported age, nonendometrioid histology and MMI >50% as independent prognostic factors for OS. However, 51.8% of their cohort had nonendometrioid tumors, whereas 67.9% of their patients had positive LVSI status. Rajasooriyar *et al*.[28] reported the most important factors influencing survival and extrapelvic recurrence to be grade 3 endometrioid, clear cell and serous histologies and involvement of upper para-aortic LN in a cohort of 126 women with node-positive EC. However,

nonendometrioid histologies constituted 26% of their cohort, while 14% of their patients had no LVSI. In a retrospective cohort of 541 patients (stage III, $n = 464$; stage IV, $n = 77$) with pure endometrioid-type EC, Chen *et al*.[29] have recently reported that MMI >50% (HR 1.89, 95% CI 1.34–2.64; $P < 0.001$) and histological grade 3 (HR 2.42, 95% CI 1.75–3.35; $P < 0.001$) are independent prognostic factors for OS. It should be emphasized that 34.2% of their cohort had no LVSI. Most recently, histological grade has been reported to be the sole independent prognostic factor for OS in a cohort of 72 women with stage $IIIC_2$ EC.[30] However, 41.7% of women included in that study had nonendometrioid histologies.

Narayan *et al*. reported that histological type, grade and MMI were not significant prognosticators for relapse or OS in the presence of LVSI and positive LN.[23] However, grade 3 disease had an HR of 2.6, whereas cervical stromal invasion and deep MMI had HRs of 2.3 and 4.0, respectively, for decreased OS in the current study. To the best of our knowledge, our study is one of the few studies detailing prognostic factors and patterns of recurrence in LVSI-positive women with stage IIIC pure endometrioid EC.

The retrospective nature of our study, together with many modifications that have taken place over the years in the modes of adjuvant therapy, does not allow us to draw definitive conclusions regarding the impact of radiotherapy and/or chemotherapy on the recurrence patterns. Additionally, having no central pathology review might be seen as a shortcoming, which reduces the relevance of our findings. However, although most of the previous studies associated with the prognostic impact of LVSI in EC had central pathology review and a very detailed description of LVSI, this is not in line with daily clinical practice.[19] In the current study, we wanted to demonstrate the outcomes of LVSI-positive women with positive LN when LVSI is assessed in daily practice.

The strengths of the current study lie in its multicenter nature, with a large number of LVSI-positive patients with stage IIIC endometrioid EC, detailed analysis of various clinicopathological factors that might have an impact on prognosis and performance of uniform staging procedures with the same qualified gynecological oncologists. Our study is one of the largest retrospective cohorts associated with prognostic factors and recurrence patterns in LVSI-positive women with stage IIIC endometrioid EC.

We conclude that approximately one out of four LVSI-positive patients with stage IIIC pure endometrioid EC has a risk of recurrence. Most of the described recurrences are distant, which portend worse outcomes as they are more often nonsalvageable. Uterine factors such as grade 3 disease, cervical stromal invasion and deep MMI seem to be independently associated with decreased OS in LVSI-positive women with stage IIIC endometrioid EC. The high distant recurrence rate in this subgroup of patients warrants further studies in order to identify the most effective treatment strategy for those patients.

Disclosure

None declared.

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