Evaluation of peripheral nodal recurrence in patients with endometrial cancer

Fatih Kılıç[1], Günsu Kimyon Cömert[1], Serra Akar[1], Çiğdem Kılıç[1], Caner Çakır[1], Dilek Yüksel[1], Mehmet Ünsal[1], Nedim Tokgözoğlu[2], Salih Taşkın[3], Tolga Taşcı[2], Osman Türkmen[1], Fırat Ortaç[3], Taner Turan[1]

[1]Department of Gynecologic Oncology, University of Health Sciences Turkey, Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Turkey

[2]Clinic of Gynecologic Oncology, Okmeydanı Training and Research Hospital, İstanbul, Turkey

[3]Department of Gynecologic Oncology, Ankara University Faculty of Medicine, Ankara, Turkey

Abstract

Objective: To evaluate the clinico-pathological patient features, prognostic factors, treatment options and outcomes of peripheral nodal recurrence (PNR) of endometrial cancer (EC).

Material and Methods: The data of nine patients with PNR of EC from two institutions were reviewed. The electronic literature was reviewed from 1972 to May 2018 to identify articles about PNR in EC. Finally, 42 cases were evaluated.

Results: Nineteen (45.2%) patients were initially diagnosed with either stage I or II disease, whereas 20 (47.7%) patients had stage III or IV disease while the stages were not reported in three (7.1%). PNR developed as the first recurrence in 40 (95.2%) patients and as the second recurrence in 2 (4.8%) patients. Isolated PNR appeared in 35 (83.3%). Seven (16.7%) had PNR coexisting with multiple other sites of tumoral involvement. In the entire cohort, the 5-year and 10-year post-recurrence survival (PRS) were both 78%. Only the presence of distant hematogenous metastasis concurrent with PNR was significantly related to poor PRS ($p=0.005$). Among patients with isolated PNR, those who had surgery had 30% greater 5-year PRS than those treated without surgery, but this difference was not significant (80% vs 50%; $p>0.05$).

Conclusion: A concurrent distant hematogenous metastasis was the only factor related to poor survival. A wide range of therapies exists for PNR but none of the therapies appear to be more advantageous than another. However, surgery as a component of treatment can render a survival advantage for patients who have isolated PNR. (J Turk Ger Gynecol Assoc 2022; 23: 38-50)

Keywords: Endometrial cancer, lymphatic failure, peripheral nodal recurrence, survival, treatment

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Introduction

Endometrial cancer (EC) is the most common gynecological malignancy (1). Although EC has a high disease-free survival rate, its recurrence rate is 13-16% (2,3). EC usually recurs locally in the pelvis or vaginal cuff (4). The lymphatic failure in EC appears mostly in specific retroperitoneal lymph nodes, such as the pelvic and para-aortic nodes (3,5). Therefore, many studies have focused on the prognostic factors and treatment options of these frequently encountered recurrence sites (5-7). Various atypical recurrence sites have been reported (8). Peripheral nodal recurrence (PNR) is one of the rare failure patterns of EC. Due to its infrequency, it is important to detect patients who are at high risk for peripheral lymphatic failure. Treatment options range from local surgical excision to pelvic exenteration, chemotherapy, radiotherapy and palliative therapy (9-11). Furthermore, the limited information on PNR in EC is based solely on cases from the literature. Therefore, PNR treatment options in EC remain unclear.

Address for Correspondence: *Fatih Kılıç*
e.mail: drfatihkilic@hotmail.com ORCID: orcid.org/0000-0002-7333-4883

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In the current study, a case series of PNR from EC is presented. The aim of this study was to evaluate the clinico-pathological patient features, prognostic factors, treatment choices, and outcomes of PNR in EC.

Material and Methods

Data of 1,345 patients with epithelial EC who underwent at least a hysterectomy and bilateral salpingo-oophorectomy in our gynecological-oncology clinic between January 1993 and May 2013 were evaluated. These cases were assessed for the presence of PNR, which was defined as the presence of involved lymph nodes outside the abdominal cavity (except for the mediastinal lymph nodes) in cases with at least a one-month disease-free interval (DFI) following complete response to treatment before PNR. Patients who had a sarcomatous component identified in their histopathological examination or whose peripheral nodal involvement appeared without at least a one-month DFI were excluded. Recurrence developed in 162 of 1,345 cases with epithelial EC. The rate of PNR was 4.9% (8/162) among patients who developed all types of recurrences from epithelial EC. These eight patients from the first institution were added to the study group. One patient from the second participating institution who had PNR was also included (12). Thus, a study group was formed with a total of nine patients from two institutions. The University of Health Sciences Turkey, Etlik Zübeyde Hanım Women's Health Training and Research Hospital Institutional Committee has approved the study protocol (approval number: 47502, date: 25.06.2018). All patients signed an informed consent that allows the institution to use their clinical data.

Literature review

A systematic review of the medical literature was conducted to identify articles about PNR after initial treatment of EC. The electronic literature search was reviewed from 1972 to May 2018 using PubMed/MEDLINE for English language abstracts. The search included the following medical subject headings or keywords: "distant" or "peripheral" or "unusual" or "supraclavicular" or "inguinal" or "neck" or "axillar" or "jugular" lymph node recurrence of EC. After the completion of the search, 29 articles were found. Subsequently, 17 articles were excluded from the study for reasons that are presented in detail in the research chart (Figure 1). In four of the excluded articles, only the locations of the distant lymph nodes were detailed and the distribution of those were: cervical and

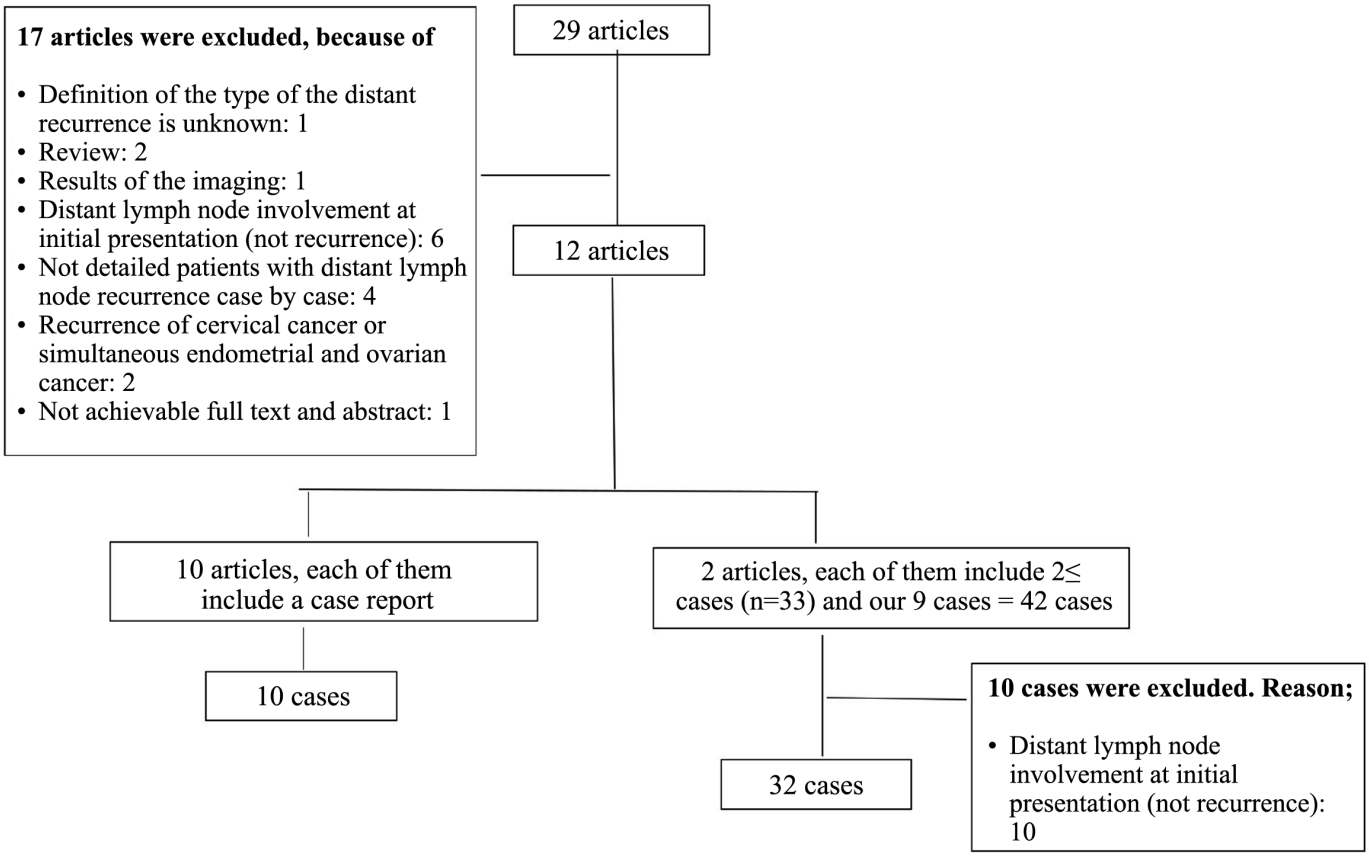

Figure 1. Chart showing details of the literature review

supraclavicular nodes, 5 cases (13); inguinal nodes, 5 cases (13-15); cervical nodes, 5 cases (14); supraclavicular nodes, 2 cases (16); subclavian nodes, 2 cases (14); and axillary lymph nodes, 1 case (16). Therefore, only the frequency of involved nodes for these cases from the four articles was included in the analysis. Cases (n=43) from the remaining 12 articles were evaluated comprehensively. Ten of the eleven cases with peripheral nodal involvement, reported in one article (17) were excluded because they had peripheral nodal involvement at initial presentation (not at recurrence). The follow-up time and end status of a case that had been previously published about PNR of EC was updated (12). Finally, we evaluated a total of 42 cases, including our case series of nine patients.

Data evaluation

Disease recurrence involving the peripheral lymph nodes alone was defined as isolated PNR. Recurrence, which developed in any other location in conjunction with peripheral lymph nodes was defined as PNR with multiple involved sites. Patients were staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) criteria (18). Therefore, stages of patients were updated for articles that were published before 2009, if the histopathological findings were available. Tumor size was defined as the largest tumor diameter for a recurrent tumor. Tumors with undifferentiated, clear cell and serous histology were accepted as grade 3 disease. DFI was described as the time period from initial treatment to PNR for patients with the first recurrence and from treatment before PNR to appearance of PNR for patients who had a secondary recurrence. The period from PNR to last patient visit or patient death was defined as post-recurrence survival (PRS). The follow-up time was defined as the interval between initial treatment to death or the last contact with the patient. Involved cervical lymph nodes included PNR that was described as neck, jugular, or cervical in articles from the medical literature. Subclavian lymph node involvement was classified as supraclavicular lymph node involvement.

Patients with suspected PNR were evaluated by clinical examination and radiological imaging methods. Subsequently, the diagnosis of PNR was made based on these findings. Radiological imaging was evaluated by a radiologist. Suspicious peripheral lymph nodes were biopsied. Management of PNR was directed by the institutional tumor board.

Patients who had a complete clinical response after treatment for recurrence were followed-up at three-month intervals for the first two years, at six-month intervals for the next three years, and annually thereafter. Pelvic examination, complete blood count, blood chemistry and abdominopelvic ultrasonography were performed as follow-up monitoring. Chest X-ray was performed yearly unless clinical suspicion indicated otherwise. Abdominal and/or thoracic computed tomography were used when required. Although not routinely used, CA-125 levels were utilized for follow-up.

Statistical analysis

SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were expressed as mean ± standard deviation or median (minimum-maximum) for continuous variables and number/percentage for categorical variables. The Kaplan-Meier method was used for the assessment of survival outcomes. Multivariate analysis was performed using a Cox proportional hazards model. All variables with a $p<0.25$ in univariate analysis were included in the multivariate analysis. Survival curves were compared using the log-rank test. A p-value less than 0.05 were considered to be statistically significant.

Results

The median (range) age of the study group was 60 (45-75) years. The histological types were endometrioid adenocarcinoma in 13 (31%), clear cell adenocarcinoma in 3 (7.1%), and mixed cell adenocarcinoma in 1 (2.4%) patient. Mixed cell adenocarcinoma was composed of grade 3 endometrioid adenocarcinoma with 25% mucinous differentiation and 15% clear cell adenocarcinoma. The type of adenocarcinoma was not specified in 22 patients. The differentiation of endometrioid adenocarcinoma was FIGO grade 1 in 7 patients, grade 2 in 3 patients, and grade 3 in 3 patients. In 22 patients, the grade was classified according to the 1988 Broder's classification (Table 1) (19). Distribution of the 2009 FIGO stages was as follows; stage 1, 17 (40.5%) patients; stage 3, 15 patients (35.8%); and stage 4, 5 patients (11.9%). The stages of the two patients (4.8%) with stage 2 disease could not be updated according to the 2009 FIGO criteria because of the absence of information on the type of cervical involvement. The stage was unknown in three patients. Three patients had a history of unopposed estrogen exposure (20) breast cancer (21), and rectal cancer (11), respectively. The clinico-pathological findings of the entire cohort are shown in Table 1, 2.

PNR developed as the first recurrence in 40 (95.2%) patients, while in 2 (4.8%) patients it appeared as the second recurrence. The median DFI was 15 months, ranging between 2 and 276 months. The sites of PNR reported in the four excluded articles were: inguinal lymph nodes in 26 (41.9%); supraclavicular lymph nodes in 22 (35.5%); cervical lymph nodes in 15 (24.2%); and axillary lymph nodes in 5 (8.1%). The median (range) diameter of the recurrent tumor was 3.75 (2-10) cm. Isolated PNR occurred in 35 (83.3%) patients. Seven (16.7%) had PNR with multiple involved sites. Other sites associated with PNR were the vagina including the peri-urethral area (n=1); pelvis

Table 1. Features related to the initial diagnosis of endometrium cancer in the entire cohort: systematic review of the literature

	Case no	A.	Tm type	Stage	Grade (G)	MI	Cx. Inv.	LVSI	Adx. Inv.	Initial treatment	Adjuvant therapy	Disease-free interval (m)	
Aalders et al. (17)	1	46	AC	IVB (inguinal node metastasis)	-	-	-	-	-	Primary RT (pelvic megavoltage) + progestagens (hydroxyl-progesterone caproate)	-	60	
Foote et al. (19)	1	63[b]	AC: 21p UK: 1p	I	Broder's[d]: G1: 2p G2: 9p G3: 7p G4: 3p UK: 1p	-	Absent	-	Absent	Hysterectomy	None	4	Median: 16 m (range, 3 m-10 years)
	2			II[c]		-	Present	-	Absent	Hysterectomy	RT (pelvic)	4	
	3			III		-	-	-	-	Hysterectomy	RT (abdominal)	13	
	4			III		-	-	-	-	Hysterectomy	RT (abdominal)	10	
	5			III		-	-	-	-	Hysterectomy	RT (abdominal)	36	
	6			III		-	-	-	-	Hysterectomy	RT (abdominal)	17	
	16p[a]			I: 9p II: 1p[c] III: 3p IV: 1p (omental met.) UK: 2p		-	-	-	-	Hysterectomy ± BSO: 15p Primary RT: 1p	None: 3p RT (pelvic): 8p RT (abdominal): 2p RT (intrauterine radium): 1p Hormonal therapy: 1p		
Carr et al. (20)	1	52	EAC	IA	G1	<1/2	Absent	UR	Absent	TH + BSO	None	12	
Wu et al. (31)	1	55	-	-	-	-	-	-	-	TH + BSO + pelvic LND	RT (VBT)	-	
Bilici et al. (32)	1	67	EAC	IIIC	G3	≥1/2	Absent	Present	Absent	TH + BSO + pelvic LND	RT (50.4 Gy pelvic + VBT)	15	
Alameda et al. (21)	1	72	EAC	IIIB	G1	Present	Absent	-	-	TH + BSO	None	8	
Ortaç and Taşkın (12)	1	45	EAC	IA	G2	<1/2	Absent	Absent	Absent	TH + BSO + Paraaortic-pelvic LND + partial omentectomy	None	7	
Kojima et al. (11)	1	74	-	IIIC	-	-	-	-		TH + BSO + pelvic LND	CT → after 12m →PA nodal rec.→ PA lymphadenectomy + CT	36	
Seagle et al. (33)	1	67	EAC	IB	G1	-	Absent	-	Absent	TH + BSO + pelvic LND	RT (VBT)	14	
Margolis et al. (9)	1	48	EAC	IIIC2	G3	≥1/2	Absent	Present	Absent	TH + BSO + paraaortic-pelvic LND	CT (carboplatin -paclitaxel) + RT (4500 cGy pelvic and 5040 cGy)	17	

Table 1. Continued

	Case no	A.	Tm type	Stage	Grade (G)	MI	Cx. Inv.	LVSI	Adx. Inv.	Initial treatment	Adjuvant therapy	Disease-free interval (m)
Akbar et al. (10)	1	65	EAC	IA	G3	<1/2	Absent	Present	Absent	TH + BSO	None	16
Yordanov et al. (34)	1	65	EAC	IA	G2	<1/2	Absent	Absent		TH + BSO	RT (54 Gy pelvic)	276
Present study 2018	1	66	Clear cell AC	IA	-	<1/2	Absent	-	Absent	TH + BSO + paraaortic-pelvic LND	CT (cisplatin)	45
	2	60	EAC	IIIC2	G1	≥1/2	Absent	-	Absent	TH + BSO + paraaortic-pelvic LND	RT (4500 cGy pelvic and 5040 paraaortic)	38
	3	60	Clear cell AC	IVB (L. Supraklavicular LN)	-	≥1/2	Present	-	Absent	TH + BSO + paraaortic-pelvic LND	CT (cisplatin + adriamisin)	5
	4	58	EAC	IVB (umblicus met.)	G1	≥1/2	Absent	Present	Absent	TH + BSO + paraaortic-pelvic LND	CT (carboplatin + paclitaxel)	84
	5	50	EAC	IA	G1	<1/2	Absent	Present	Absent	TH + BSO + paraaortic-pelvic LND	None	30
	6	61	Clear cell AC	IIIC2	-	Confined to end.	Present	-	Absent	TH + BSO + paraaortic-pelvic LND	CT (3 cycles carboplatin + paclitaxel; because of the side effects she refused the therapy)	3
	7	60	EAC	IIIC2	G2	≥1/2	Absent	Present	Absent	TH + BSO + paraaortic-pelvic LND	RT	10
	8	75	EAC	IIIC2	G1	≥1/2	Absent	Absent	Absent	TH + BSO + paraaortic-pelvic LND	CT (after 1 cycle carboplatin + paclitaxel, she refused the therapy)	32
	9	59	Mixt AC (endometrioid + Mucinous + clear cell)	IIIA	G3	≥1/2	Present	Present	Present	TH + USO (previous USO history)	CT (6 cycles carboplatin + paclitaxel) → after 8m → vaginal cuff + left internal iliac LN rec → CT (paclitaxel + carboplatin)	2

A: Age (years), cx.: Cervical, adx: Adnexal, inv.: Involvement, LN: Lymph node, Tm: Tumor, p.: Patient(s), UK: Unknown, AC: Adenocarcinoma, EAC: Endometrioid adenocarcinoma, MI: Myometrial invasion, end: Endometrium, LVSI: Lympho-vascular space invasion, RT: Radiotherapy, TH: Total hysterectomy, USO: Unilateral salpingo-oophorectomy, BSO: Bilateral salpingo-oophorectomy, LND: Lymphadenectomy, CT: Chemotherapy, VBT: Vaginal brachytherapy, FIGO: International Federation of Gynecology and Obstetrics, [a]: The remaining 16 patients, [b]: Median age of 22 patients, [c]: Stage II could not be updated according to 2009 because of the absence of the involvement type of cervix, [d]: Grade classification type (in 1988)

Table 2. Features of the entire cohort

Findings		n	%
Stage	I	17	40.5
	IA	6	14.3
	IB	1	2.4
	US stage I	10	23.8
	II[a]	2	4.8
	III	15	35.8
	IIIA	1	2.4
	IIIB	1	2.4
	IIIC	7	16.7
	IIIC2	5	11.9
	US	2	4.8
	US stage III	6	14.3
	IV	5	11.9
	IVB	3	7.1
	US stage IV	2	4.8
	UR	3	7.1
Histologic type	Endometrioid	13	31.0
	Grade 1	7	16.7
	Grade 2	3	7.1
	Grade 3	3	7.1
	Clear cell AC	3	7.1
	AC (not specified)	22	52.4
	Mixed cell AC (grade 3 endometrioid + mucinous + clear cell)	1	2.4
	UR	3	7.1
Myometrial invasion[b]	Confined to endometrium	1	1.6
	Presence of myometrial invasion	16	25.8
	Invasion <1/2	6	9.7
	Invasion ≥1/2	9	14.5
	US	1	1.6
	UR	45	72.6
Site of recurrent peripheral lymph node[b]	Axillar	4	6.4
	Right	1	1.6
	Left	1	1.6
	US	2	3.2
	Inguinal	26	41.9
	Right	9	14.5
	Left	10	16.1
	US	7	11.3
	Supraclavicular	16	25.9
	Right	8	12.9
	Left	4	6.5
	US	4	6.5
	Cervical	10	16.1
	Left	3	4.8
	US	7	11.3
	Cervical + supraclavicular	5	8.1
	Axillar + supraclavicular	1	1.6

Table 2. Continued

Findings		n	%
Involvement pattern	Isolated PNR	35	83.3
	PNR with multiple involved sites	7	16.7
Status of the distant recurrence sites other than PNR	Absent	40	95.2
	Present	2	4.8
Therapy options at recurrence[c]	Radiotherapy + hormone therapy	1	2.4
	Only chemotherapy	5	11.9
	Chemotherapy + radiotherapy	1	2.4
	Chemotherapy + hormone therapy	1	2.4
	Only surgery	2	4.8
	Surgery with adjuvant therapy	13	31
	Surgery + radiotherapy	6	14.3
	Surgery + chemotherapy	5	11.9
	Surgery + chemo-radiotherapy	1	2.4
	Surgery + chemotherapy + radiotherapy	1	2.4
	Surgery + hormone therapy	1	2.4
	UR	2	4.7
End status	AWOD	16	38.1
	DOD	18	42.9
	AWD	2	4.8
	LFU	3	7.1
	UR	3	7.1

PNR: Peripheral nodal recurrence; UR: Unreported; AWOD: Alive without disease; AWD: Alive with disease; LFU: Lost to follow-up; US: Unspecified, DOD: Dead of disease, [a]: Could not updated according to FIGO 2009 because of the absence of the involvement type of cervix, [b]: The distribution of the location analyzed among the 62 patients, [c]: 16 patients from report of the Foote et al. (19) were excluded because the therapy type was not given case by case

(n=1); retroperitoneal lymph nodes (n=2); and retroperitoneal lymph nodes together with involvement of the central pelvis (n=1). In addition, two patients had distant organ metastasis (liver parenchyma with or without the tail of the pancreas) concurrent with PNR. Details of the features of recurrent disease are given in Table 2, 3.

The rate of initial nodal involvement was higher in patients with inguinal PNR than patients with other sites of PNR [70% (7/10) vs 18.2% (2/11), p=0.03]. The frequency of the presence of cervical invasion was higher in patients with PNR localized in the supraclavicular nodes than in patients with PNR sites besides the supraclavicular nodes [100% (2/2) vs 12.5 (2/16); p=0.039].

In 16 (39.2%) patients, surgery was performed for the treatment of PNR. Seven (19.1%) had non-surgical treatment, including chemotherapy (n=5), chemotherapy with radiotherapy (n=1), hormonal therapy with radiotherapy (n=1) and hormonal

Table 3. Post-recurrence features of the entire group: systematic review of the literature

	Case no.	Which rec.	Type of involved peripheral LN[a]	Sizeof tm[a] (cm)	No. of the OIS[a]	Location of the OIS[a]	Presence of the other distant sites	Therapy	Postrec. situations	End status	FU time	
Aalders et al. (17)	1	First	Axillary	-	Isolated	-	No	RT + HT (progestagens)	-	AWOD	120	
Foote et al. (19)	1	First	R. inguinal	4	Isolated	-	No	S + CT (5-FU)	-	AWOD	205	Median: 34.5 m (7 m-17 years)
	2	First	R. supra-clavicular	2	Isolated	-	No	S + HT (progestagens)	-	AWOD	27	
	3	First	R. axillary	4.5	Isolated	-	No	S + RT (5000 Gy≤)	-	AWOD	45	
	4	First	R. inguinal	3	Isolated	-	No	S + RT (5000 Gy≤)	-	AWOD	31	
	5	First	R. inguinal	4	Isolated	-	No	S + RT (5000 Gy≤)	-	AWOD	59	
	6	First	L. supra-clavicular	3	Isolated	-	No	S + RT (5000 Gy≤)	-	AWOD	53	
	16pb)	All first	R. inguinal: 3p L. inguinal: 4p R. supra-clavicular: 7p L. supra-clavicular: 1p L. axillary + supra-clavicular: 1p	<4: 8p 4≤: 7p UK: 2p	Isolated	-	No	S + RT: 6 S + RT + HT: 2 RT: 1 S + CT: 2 (5-FU: 1; doxorubicin: 1) S + CT + HT: 1 S + HT: 5 (therapy distribution was given for 17 nodes of 16p)	16p had re-recurrence (postrec. DFI: 6 m (1-33 m)	DOD: 15p AWD: 1p	-	
Carr et al. (20)	1	First	L. inguinal	9*7	Multiple	LN (celiac and porta hepatis)	No	CT (cyclophosphamide +carboplatin +HT (megestrol acetate)	-	AWOD	12	
Wu et al. (31)	1	First	Inguinal	UR	Multiple	Bulky central rec. and pelvic-paraaortic nodes	No	S + whole pelvic chemo-RT (with concurrent cisplatin)	Mediastinal and neck nodal involvement appeared (during treatment) → carboplatin + paclitaxel → Neck node RT and epirubicin → 10 m later → central re-rec. → pelvic exenteration → for 5 years disease free	AWOD	At least 70	

Table 3. Continued

	Case no.	Which rec.	Type of involved peripheral LN[a]	Sizeof tm[a] (cm)	No. of the OIS[a]	Location of the OIS[a]	Presence of the other distant sites	Therapy	Postrec. situations	End status	FU time
Bilici et al. (32)	1	First	L. -anterior cervical	2*2	Isolated	-	No	CT (doxorubicin + cyclophosphamide + cisplatin)	-	AWOD	21
Alameda et al. (21)	1	First	L. axillary	UR	Isolated	-	No	UR	-	UR	UR
Ortaç and Taşkın (12)	1	First	R. inguinal	4*5	Isolated	-	No	S + RT	Re-recurrence occurred	DOD	43
Kojima et al. (11)	1	Second	L. supra-clavicular	UR	Isolated	-	No	S	-	AWOD	48
Seagle et al. (33)	1	First	L. inguinal	10*7.5	Isolated	-	No	CT (carboplatin + paclitaxel) + pelvic RT + inguinal LN boost RT (25 Gy)	-	UR	UR
Margolis et al. (9)	1	First	L. inguinal	1.8*2.6	Multiple	Vagina including peri-urethral area	No	S (anterior pelvic exenteration) + CT (carboplatin + gemcitabine)	-	AWOD	120
Akbar et al. (10)	1	First	L. inguinal	2.4*2.6	Multiple	LN (right external and left paraaortic)	No	S + pelvic-paraaortic-bilateral inguinal RT and inguinal LN boost RT (with concurrent cisplatin) + VBT + CT (carboplatin + docetaxel)	-	AWOD	29
Yordanov et al. (34)	1	First	L. inguinal	4*5	Isolated	-	No	S + RT (30 Gy)	-	AWOD	294
Presented study 2018	1	First	Inferior jugular	UA	Multiple	Liver parenchyma, tail of the pancreas	Yes	UA	-	LFU	45
	2	First	L. jugular	4.5*3.5	Isolated	-	No	CT (carboplatin + adriamycin)	2 Cycles CT → progression (in neck involvement and addition of axillar lymph node involvement) → instability due to the other vital systems → palliative therapy	DOD	45

Table 3. Continued

	Case no.	Which rec.	Type of involved peripheral LN[a]	Sizeof tm[a] (cm)	No. of the OIS[a]	Location of the OIS[a]	Presence of the other distant sites	Therapy	Postrec. situations	End status	FU time
Presented study 2018	3	First	L. supraclavicular	3*3	Multiple	Pelvic mass	No	CT (paclitaxel) → Stabile disease → progestagens (megestrol acetate)	-	AWD	19
	4	First	R. inguinal	3*2	Isolated	-	No	S (inguinal lymph node excision) CT (6 cycles, liposomal doxorubicin + cisplatin)	36 m later → Re-recurrence on psoas muscle → S + RT → 5 m later → R. inguinal rec. → RT	AWOD	132
	5	First	R. inguinal	9*8	Isolated	-	No	S + CT	47 m later → Abdominal re-recurrence:	AWD	88
	6	First	L. Inguinal	3*4	Multiple	Liver parenchyma	Yes	S	6 m later → Pelvic and abdominal rec.	DOD	15
	7	First	Cervical	3*3	Isolated	-	No	CT (paclitaxel + cisplatin, 4 cycles)	-	LFU	13
	8	First	L. Jugular	3.5*3	Isolated	-	No	CT (paclitaxel + carboplatin; 5 cycles)	After the 4. cycles, the diameter of tumor reduced to 1 cm according to imaging	LFU	36
	9	Second	L. inguinal	UA	Isolated	-	No	Surgery + CT (cisplatin + adriamisin)	-	AWOD	38

Rec.: Recurrence, LN: Lymph nodes, Tm: Tumor, p.: Patient(s), UK: Unknown, UA: Unavailable, UR: Unreported, DFI: Disease-free interval, FU: Follow-up, AWOD: Alive without disease, AWD: Alive with disease, DOD: Dead of disease, LFU: Lost to follow-up, S: Surgery, RT: Radiotherapy, CT: Chemotherapy, HT: Hormonal therapy, 5-FU: 5-fluorouracil, VBT: Vaginal brachytherapy, No: Number, OIS: Other involved sites, R.: Right, L.: Left, [a]: At recurrence, [b]: The follow-up time and end status updated

therapy with chemotherapy (n=1). The treatment modality was unknown in two patients. The remaining 16 patients could not be grouped based on treatment modality because the type of therapy was not reported for each case so these patients were not included in the survival analysis (19).

The median (range) PRS was 22 (3-201) months. The 5-year and 10-year PRS were both 78%. The median follow-up time was 45 (12-294) months. During follow-up, 18 patients dead of disease. In addition, two patients were alive with disease, 16 patients were alive without disease, three patients were lost to follow-up and the final status of three patients was not reported.

In univariate analysis, the presence of distant hematogenous metastasis, as seen with PNR, was significantly associated with poor PRS (p=0.005). The five-year PRS was 83% for patients who did not have distant hematogenous metastasis during PNR, whereas the patient who had distant hematogenous metastasis with PNR did not survive beyond 5 years (Figure 2). While the five-year PRS of the patients who had PNR with >4 cm diameter was 50%, all of those with ≤4 cm PNR survived passed 5 years (p=0.09). Age, stage, histological type, DFI, the presence of recurrence before PNR, location or side of the recurrence, the diameter of the recurrent tumor, the presence of any other recurrences concurrent with PNR, and treatment types were not significantly associated with PRS. The relationship between clinico-pathological factors and PRS is shown in Table 4. Based on the analysis of the treatment options for isolated PNR (n=18), patients undergoing surgery had a 30% higher 5-year PRS than those who did not undergo surgery. However, this difference was not significant (80% vs 50%; p>0.05).

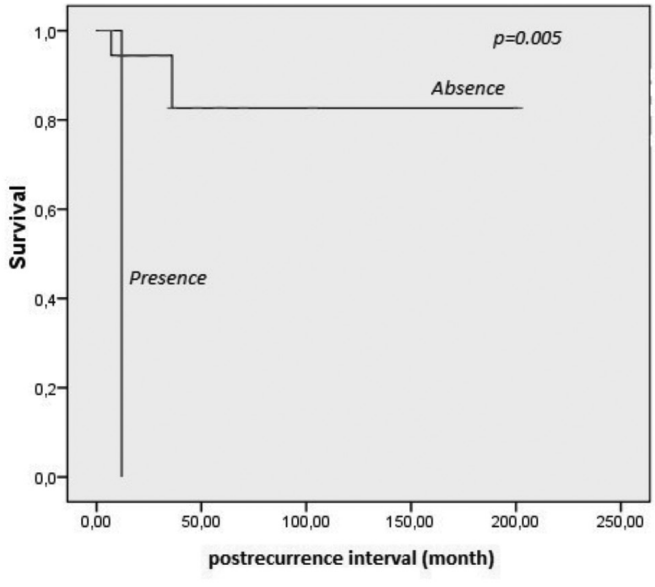

Figure 2. The presence of distant hematogenous metastasis, as seen with peripheral nodal recurrence, was significantly related to poor post-recurrence survival

Variables which were associated with a p<0.25 in univariate analysis were tested in the multivariate analysis. The multivariate analysis model included tumor diameter (>4 cm vs ≤4 cm) and the presence of distant hematogenous metastasis coexisting with PNR (absent vs present). Multivariate analysis revealed that none of the variables was an independent prognostic factor for PRS (Table 5).

Discussion

The present study showed that the most common site of PNR were the inguinal lymph nodes. The major finding of our study was that concomitant hematogenous metastasis with PNR was related to poor PRS. Our study showed that no treatment options for PNR were superior to others.

Peripheral lymphatic failure is extremely rare in EC. The frequency of PNR was 1.92% in all EC cases and 9.3% among recurrent cases with EC (13). In our center, the frequency of PNR was 0.59% and 4.9% within the entire cohort and the group of patients with recurrent EC, respectively.

The most common lymphatic failure sites were the external iliac nodes (22). Kurra et al. (8) reported that the left supraclavicular lymph nodes are the most common distant lymphatic failure sites in EC. In our study, the most common site of PNR was the inguinal lymph nodes. The mechanisms underlying PNR remain unclear. One of the major mechanisms is thought to be the flow of tumoral cells via the thoracic duct (8). Although this explains tumor spread to the supraclavicular area, it cannot account for the inguinal nodal involvement in EC. Carr et al. (20) suggested that unopposed estrogen can cause proliferation of tumor cells in the lymphatic channels of the round ligament. However, only one of the cases with inguinal recurrence had a history of unopposed estrogen based on our literature review. The other hypothesis for isolated PNR is that there is a possibility of missing a metastasis due to the poor value of preoperative imaging in the detection of inguinal micrometastasis, especially for advanced disease (10). There is also a lower rate of detection of micrometastasis on initial evaluation of the retroperitoneal lymph nodes for early stages.

Foote et al. (19) reported that the five-year PRS was 12% for patients with isolated PNR. In our analysis, the five-year PRS was 78%. One of the most likely reasons for the higher survival rate could be the advances in imaging that help in the early detection of recurrence and the high detection rate of metastases in other sites. The factors related to the prognoses of distant recurrences in EC vary (22-26). Only the presence of concomitant distant recurrence with PNR was associated with poor prognosis in PNR, although none of the factors affect the prognosis independently, according to our analysis.

A wide range of options exists for PNR treatment, including local excision, pelvic exenteration, chemotherapy, and

Table 4. The relation between clinico-pathologic factors and post-recurrence survival

		n	5-year PRS (%)	p
Age[a,b] (years)	<60	10	89	0.186
	≥60	6	75	
Stage	1&2	6	67	0.890
	3&4	15	83	
Histologic type[a]	Endometrioid	10	86	0.577
	Non-endometrioid	3	67	
DFI (months)[b]	<15	9	44	0.339
	≥15	12	90	
Presence of the rec. before PNR	Absent (first rec.)	20	77	0.622
	Present (second rec.)	2	100	
Site of recurrence	Inguinal	12	76	0.952
	Others	10	86	
Recurrence site	Right	8	75	0.453
	Left	11	78	
Diameter of the tumor at recurrence[b]	<4 cm	10	100	0.090
	≥4 cm	8	50	
Presence of multiple involved sites during PNR	Isolated PNR	17	77	0.784
	PNR with multiple involved sites	5	80	
Presence of the concomitant distant hematogenous metastasis during PNR	Absent	21	83	**0.005***
	Present	1	None	
Therapy options at recurrence	Surgery vs no surgery			
	Surgery	16	80	0.299
	No surgery	6	67	
	CT absent vs CT present			
	CT absent	10	60	0.525
	CT present	12	88	
	RT absent vs RT present			
	RT absent	13	80	0.584
	RT present	9	75	

PRS: Post-recurrence survival, DFI: Disease-free interval, PNR: Peripheral nodal recurrence, CT: Chemotherapy, RT: Radiotherapy, rec.: Recurrence, *p<0.05 is statistically significant, [a]: Two-year survival, [b]: Median value

Table 5. Multivariate analysis of factors predicting post-recurrence survival after peripheral nodal recurrence

	Hazard ratio (95% CI)	p
Model		
Diameter of the tumor at recurrence (<4 cm vs ≥4 cm)	285164.3 (0.001- …)	0.973
Presence of concomitant distant hematogenous metastasis during PNR (absent vs present)	6.4 (0.405-103.8)	0.187
*P<0.05 is statistically significant, CI: Confidence interval, PNR: Peripheral nodal recurrence		

radiotherapy. Treatment may also include a combination of these therapies and palliative therapy. Unfortunately, there are still no accepted criteria to aid in choosing the type of therapy for PNR. Surgical resection has an important value in isolated distant recurrence of EC, and the probability of achieving complete resection is an important consideration in choosing surgery (24,26-28). However, based on recent knowledge, the necessity of multimodal therapies, especially systemic therapy, cannot be applicable, even for patients with negative margins following complete resection (29). In our study, no specific

treatment had prognostic or survival superiority over any other. Therefore, the management approach in PNR is still at the discretion of the physician and also dependent upon patient preference. However, although not statistically significant, our results indicate that surgery could provide some survival advantage. Therefore, surgical treatment should be kept in the forefront as one component of treatment for isolated PNR. Similar to the interval of onset of other EC recurrences (29-33), 80% of PNR appeared in the first three years. However, PNR can develop as late as 23 years after initial diagnosis (34). Furthermore, a considerable number of patients had stage I disease (40.5%) at initial diagnosis and developed PNR as their first recurrence. Therefore, long-term, close follow-up is critical for early diagnosis.

Study limitation

One of the limitations of the study is its retrospective design. Due to the differences in treatment approaches such as various doses of therapy, chemotherapeutic agents, radiotherapy equipment used, and surgical techniques, distinct conclusions cannot be drawn about outcomes of therapy. Although the other limitation appears to be a small sample size, our study included a relatively large sample of patients with PNR, which results from an extremely rare failure of EC. As far as we know, this is the first and largest study to evaluate factors associated with survival following peripheral nodal failures in EC patients.

Conclusion

Peripheral lymphatic failure was frequently localized in the inguinal lymph nodes. A concurrent distant hematogenous metastasis was the only factor related to poor survival. A wide range of therapies exists but none of the therapies appear more advantageous than any other. However, surgery can provide a survival benefit in patients who have isolated PNR. Further large-scale studies are needed to make definitive conclusions regarding treatment options.

Ethics Committee Approval: *The study was approved by the Ethical Committee of the University of Health Sciences Turkey, Etlik Zübeyde Hanım Women's Health Training and Research Hospital (approval number: 47502, date: 25.06.2018).*

Informed Consent: *All patients signed an informed consent that allows the institution to use their clinical data.*

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