Original Investigations

Evaluation of peripheral nodal recurrence in patients with endometrial cancer
Kılıç et al. Analysis of peripheral nodal recurrence

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

[1]Clinic 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

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

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Abstract

Objective: We aimed 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 9 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: 19 (45.2%) patients were initially diagnosed with either stage I or II disease, whereas 20 (47.7%) patients had stage III or IV disease. The stages were not reported in 3 patients. 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%) patients. Seven (16.7%) patients 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% higher 5-year PRS than those treated without surgery, however, this difference was not found as statistically 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 exist for PNR but none of the therapies appear to be more advantageous over others. However, surgery as a component of treatment can render a survival advantage for patients who have isolated PNR.
Keywords: Endometrial cancer, lymphatic failure, peripheral nodal recurrence, survival, treatment.

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 paraaortic nodes (3,5). Therefore, many studies have focused on the prognostic factors and treatment options of these frequently encountered recurrence sites (5-7). On the other hand, various atypical recurrence sites have been reported (8). The 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.
In the current study, we presented a case series of PNR from EC. The aim of this study is to evaluate the clinico-pathological patient features, prognostic factors, treatment choices, and outcomes of PNR in EC.

Material and Methods

Data of 1345 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 following complete response to treatment before PNR. Patients who had a sarcomatous component identified in their histopathological exam or whose peripheral nodal involvement appeared without at least a one-month disease-free interval were excluded. Recurrence developed in 162 of 1345 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 8 patients from this first institution were added to the study group. One patient from the second participating institution who had PNR was also included in the study (12) A study group was formed with a total of 9 patients from two institutions. The institutional committee on human research has approved the study protocol (IRB Approval Number 47502/ Date 25.06.2018).

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 rewieved from 1972 to May 2018 using PubMed/ MEDLINE for English language abstracts. The search included the following medical subject headings (MeSH) 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 the four excluded articles, only the locations of the distant lymph nodes were revealed and the distribution of those were as follows; cervical and 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 were 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 (n = 9).

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 in undifferentiated, clear cell and serous histology were accepted as grade III disease. Disease-free interval (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 which was termed 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 determined by institutional tumor board.

Patients who had a complete clinical response after treatment for recurrence were followed-up with 3 month intervals in first two years, with 6 month intervals in next three years afterwards, and annually later on. 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 computerized tomography were used when required. Although not routinely used, CA-125 levels were utilized for follow-up.

Statistical analysis

SPSS 20.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. Descriptive statistics were expressed as mean±standard deviation (SD) or median (min-max) 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 value of <0.25 in univariate analysis were included in the multivariate analysis. Survival curves were compared using the log-rank test. P-values less than 0.05 were considered to be statistically significant.

Results

The median age of the study group was 60 years (range: 45-75 years). The histological types were endometrioid adenocarcinoma in 13 (31%) patients, clear cell adenocarcinoma in 3 (7.1%) patients, 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 I, 17 (40.5%) patients; stage III, 15 patients (35.8%); and stage IV, 5 patients (11.9%). The stages of the two patients (4.8%) with stage II 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. 3 patients had a history of unopposed estrogen exposure (20) breast cancer (21), and rectal cancer (11). The clinico-pathological findings of the entire cohort are shown in Tables 1 and 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 to 276 months. The sites of PNR reported in the four excluded articles were as follows; inguinal lymph nodes in 26 (41.9%) patients; supraclavicular lymph nodes in 22 (35.5%) patients; cervical lymph nodes in 15 (24.2%) patients; and the axillary lymph nodes in 5 (8.1%) patients. The median diameter of the recurrent tumor was 3.75 cm (range: 2-10 cm). Isolated PNR appeared in 35 (83.3%) patients. Seven (16.7%) patients had PNR with multiple involved sites. Other sites associated with PNR were the vagina including the peri-urethral area (n: 1); pelvis (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 Tables 2 and 3.

The rate of initial nodal involvement was higher in patients with inguinal PNR than patients with other sites of PNR [70% (n: 7/10) vs. 18.2% (n: 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% (n: 2/2) vs. 12.5 (n: 2/16); p=0.039].

In 16 (39.2%) patients, surgery was performed for the treatment of PNR. Seven patients (19.1%) had non-surgical treatment, including chemotherapy in 5 patients, chemotherapy with radiotherapy in 1 patient, hormonal therapy with radiotherapy in 1 patient and hormonal therapy with chemotherapy in 1 patient. The treatment modality was unknown in 2 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 post-recurrence survival was 22 months, ranging between 3 to 201 months. The 5-year and 10-year PRS were both 78%. The median follow-up time was 45 months (12-294 months). During follow-up, 18 patients died of disease. Two patients alive with disease, 16 patients were alive without disease, 3 patients were lost to follow-up and the end status of 3 patients was not reported. In the univariate analysis, the presence of distant hematogenous metastasis, as seen with PNR, was associated with poor PRS as significantly ($p=0.005$). 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, disease-free interval (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 did not found as statistical significantly (80% vs. 50%; $p>0.05$).
Variables which were found as $p<0.25$ in the 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 endometrial cancer. 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. reported that the left supraclavicular lymph nodes are the most common distant lymphatic failure sites in EC (8). In our study, the most common site of PNR were 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. suggested that unopposed estrogen can cause proliferation of tumor cells in the lymphatic channels of the round ligament (20). 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.

Foot et al. reported that the five-year PRS was 12% for patients with isolated PNR (19). In our analysis, the five-year PRS was 78%. One of the most likely reasons for the higher survival rate could be the advancements 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 study.

A wide range of options exist for PNR treatment including local excision, pelvic exenteration, chemotherapy, and radiotherapy; treatment may also include a combination of these therapies and palliative therapy. Unfortunately, there are still no distinct 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 dependant upon patient preference. However, although not statistically significant, our results indicate that surgery could provide some survival advantage. Therefore, it can 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.

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, 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 is 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 exist and none of the therapies appear more advantageous over others. 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: This study was approved by the Etlik Zübeyde Hanım Women's Health Training and Research Hospital Institutional Ethical Committee on 25/06/2018, with the approval number of 47502.

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

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

	Case no.	**A.**	**Tm type**	**Stage**	**Grade (G)**	**MI**	**Cx. Inv.**	**LVSI**	**Adx. Inv.**	**İnitial treatment**	**Adjuvant therapy**	**Disease Free Interval (m)**	
Aalders et al. 1984 (17)	1	46	AC	IVB (inguinal node metastasis)	-	-	-	-	-	Primary RT (pelvic megavoltage) + progestagens (hydroxyl-progesterone caproate)	-	60	
	1	63[b]	AC: 21p	I	Broder'sd:	-	Absent	-	Absent	Hysterectomy	None	4	

Foote et al. 1988 (19)	2		UK: 1p	II [c]	G1: 2p G2: 9p G3: 7p G4: 3p UK:1p	-	Present	-	Absent	Hysterectomy	RT (pelvic)	4	Median: 16 m (range; 3 m-10 years)
	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. 1996 (20)	1	52	EAC	IA	G1	<1/2	Absent	UR	Absent	TH + BSO	None	12	
Wu et al. 2004 (31)	1	55	-	-	-	-	-	-	-	TH + BSO + pelvic LND	RT (VBT)	-	
Bilici et al. 2008 (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. 2010 (21)	1	72	EAC	IIIB	G1	Present	Absent	-	-	TH + BSO	None	8	
Ortac and Taskin 2012 (12)	1	45	EAC	IA	G2	<1/2	Absent	Absent	Absent	TH + BSO + Paraaortic-pelvic LND +partial omentectomy	None	7	
Kojima et al.	1	74	-	IIIC	-	-	-	-		TH + BSO + pelvic LND	CT→after 12m→PA nodal	36	

2012 (11)											rec.→ PA lymphadenectomy + CT	
Seagle et al. 2015 (33)	1	67	EAC	IB	G1	-	Absent	-	Absent	TH + BSO + pelvic LND	RT (VBT)	14
Margolis et al. 2017 (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
Akbar et al. 2017 (10)	1	65	EAC	IA	G3	<1/2	Absent	Present	Absent	TH + BSO	None	16
Yordanov et al. 2018 (34)	1	65	EAC	IA	G2	<1/2	Absent	Absent		TH + BSO	RT (54 Gy pelvic)	276
Presented 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 [d])	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 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	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
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	3	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.

[a] Could not updated according to FIGO2009 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 Foot et al. were excluded because the therapy type was not given case by case

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

	Case no.	Which rec.	Type of involved peripheral LN [a)]	Size of 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.* 1984 (17)	1	First	Axillary	-	Isolated	-	No	RT + HT (progestagens)	-	AWOD	120	
Foote *et al.* 1988 (19)	1	First	R. inguinal	4	Isolated	-	No	S+CT (5-FU)	-	AWOD	205	Median : 34.5 m (7m-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	
	16p[b)]	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 (1-33m)	DOD: 15p AWD: 1p		
Carr *et al.* 1996 (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.* 2004 (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→ 10m later →central re-rec. →pelvic	AWOD	At least 70	

									exenteration →for 5 years disease free		
Bilici *et al.* 2008 (32)	1	First	L.-anterior cervical	2*2	isolated	-	No	CT (doxorubicin + cyclophosphamide + cisplatin)	-	AWOD	21
Alameda *et al.* 2010 (21)	1	First	L. axillary	UR	isolated	-	No	UR	-	UR	UR
Ortac *et al.* 2012 (12)	1	First	R. inguinal	4*5	isolated	-	No	S+RT	Re-recurrence occurred	DOD	43
Kojima *et al.* 2012 (11)	1	Second	L. supra-clavicular	UR	isolated	-	No	S	-	AWOD	48
Seagle *et al.* 2015 (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.* 2017 (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.* 2017 (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.* 2018 (34)	1	First	L. inguinal	4*5	isolated	-	No	S+RT (30 Gy)	-	AWOD	294
Presented	1	First	Inferior jugular	UA	multiple	Liver parenchyma	Yes	UA	-	LFU	45

study 2018						, tail of the pancreas					
	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
	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)	36m 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	47m later→ Abdominal re-recurrence:	AWD	88
	6	First	L. Inguinal	3*4	multiple	Liver parenchyma	Yes	S	6m 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

Table 4. The relation between clinico-pathologic factors and post-recurrence survival (PRS)				
		n	**5-year PRS (%)**	**P value**
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
	Nonendometrioid	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	İnguinal	12	76	0.952
	Others	10	86	
Recurrence side	Right	8	75	0.453
	Left	11	78	
Diameter of the tumor at recurrence [b]	<4cm	10	100	0.090
	4cm≤	8	50	
Presence of multiple involved sites during PNR	İsolated 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	

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. Multi-variant analysis of factors predicting post-recurrence survival after peripheral nodal recurrence

	Hazard Ratio (95% CI)	***p* value**
Model		
Diameter of the tumor at recurrence (<4cm vs. 4cm≤)	285164.3 (0.000—…)	0.973
Presence of the concomitant distant hematogenous metastasis during PNR (absent vs. present)	6.4 (0.405—103.8)	0.187

*p <0.05 is statistically significant

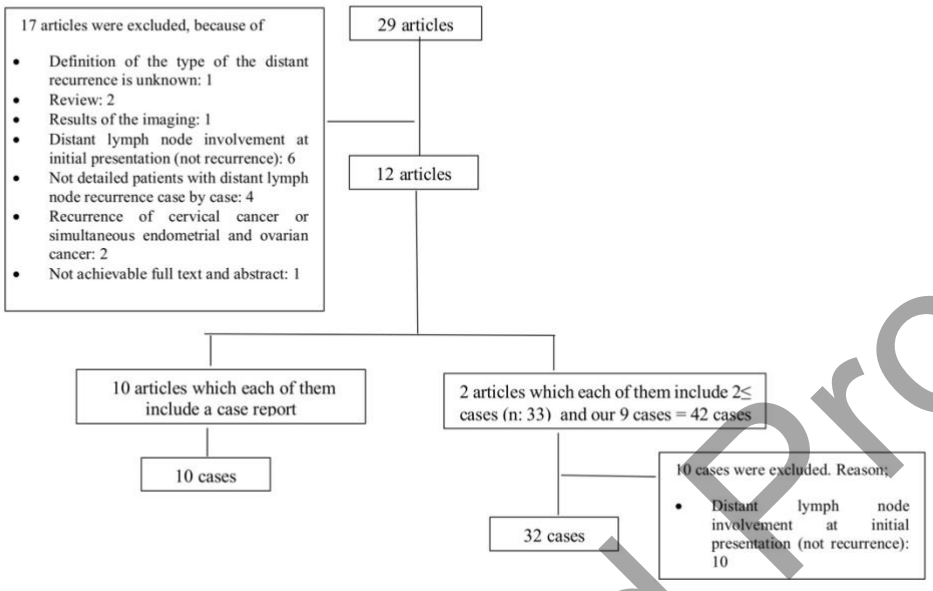

Figure 1. Chart for the literature review

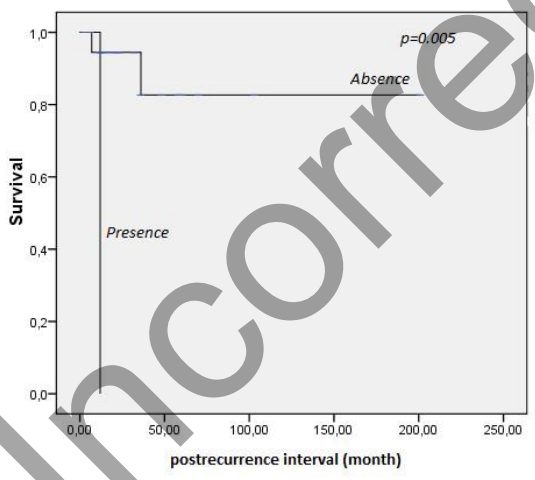

Figure 2. The presence of the distant hematogenous metastasis, as seen with peripheral nodal recurrence, was significantly related to poor post-recurrence survival