Evaluation of peripheral nodal recurrence in patients with endometrial cancer

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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.
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...

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**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 (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 | Initial treatment | Adjuvant therapy | Disease-free interval (m) |
|---------|----|---------|-------|-----------|----|----------|------|------------------|-----------------|------------------------|
| Aalders et al. (17) | 1 | 66 | AC | IVB (inguinal node metastasis) | - | - | - | Primary RT (pelvic megavoltage) + progestagens (hydroxyl-progesterone caproate) | - | 60 |
| Foote et al. (19) | 1 | 63 | AC: 21p UK: 1p | I | - | Absent | - | Absent | Hysterectomy | None | 4 |
| | 2 | - | UK: 1p | II | - | Present | - | Absent | Hysterectomy | RT (pelvic) | 4 |
| | 3 | - | II: 1p | III | - | - | - | Hysterectomy | RT (abdominal) | 13 |
| | 4 | - | III | III | - | - | - | Hysterectomy | RT (abdominal) | 10 |
| | 5 | - | III | III | - | - | - | Hysterectomy | RT (abdominal) | 17 |
| | 6 | 16p | I: 9p II: 1p^c III: 3p IV: 1p (omenta met.) UK: 1p | G1: 2p G2: 9p G3: 7p G4: 3p UK: 1p | - | - | - | Hysterectomy ± BSO: 15p Primary RT: 1p | None: 3p RT (pelvic): 8p RT (abdominal): 2p RT (intratumoral radium): 1p Hormonal therapy: 1p | Median: 16 m (range, 3 m-10 years) |
| 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 + Paraortic-pelvic LND + paraaortic 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 |
| Case no | Age (years) | Tumor type | Stage | Grade (G) | Myometrial invasion | Lympho-vascular space invasion | Adnexal involvement | 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 |
| | 2 | 66 | Clear cell AC | IA | - | <1/2 | Absent | - | Absent | TH + BSO + paraaortic-pelvic LND | CT (cisplatin) | 45 |
| | 3 | 60 | Clear cell AC | IIIIC2 | G1 | ≥1/2 | Absent | - | Absent | TH + BSO + paraaortic-pelvic LND | RT (4500 cGy pelvic and 5040 paraaortic) | 38 |
| | 4 | 58 | EAC | IVB | - | ≥1/2 | Present | - | Absent | TH + BSO + paraaortic-pelvic LND | CT (cisplatin + adriamisin) | 5 |
| | 5 | 50 | EAC | IVB (umbilicus met.) | G1 | ≥1/2 | Absent | Present | Absent | TH + BSO + paraaortic-pelvic LND | CT (carboplatin + paclitaxel) | 84 |
| Present study 2018 | 6 | 61 | Clear cell AC | IIIIC2 | - | 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 | IIIIC2 | G2 | ≥1/2 | Absent | Present | Absent | TH + BSO + paraaortic-pelvic LND | RT | 10 |
| | 8 | 75 | EAC | IIIIC2 | 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)
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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 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*      | 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 a |   |   |
| 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,

*Could not updated according to FIGO 2009 because of the absence of the involvement type of cervix,

bThe distribution of the location analyzed among the 62 patients,

c16 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* | Size of tm (cm) | No. of the OIS | Location of the OIS | Presence of the other distant sites | Therapy | Postrec. situations | End status | FU time |
|----------|------------|---------------------------------|-----------------|----------------|---------------------|-----------------------------------|---------|---------------------|------------|---------|
| Foote et al. (19) | 1 | First | L. supra-clavicular | 3 | Isolated | - | No | S + RT (5000 Gy≤) | - | AWOD | 53 |
| | 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 |
| Aalders et al. (17) | 1 | First | Axillary | - | Isolated | - | No | RT + HT (progestagens) | - | AWOD | 120 |
| | 2 | First | R. inguinal | 4 | Isolated | - | No | S + CT (5-FU) | - | AWOD | 205 |
| | 3 | First | R. supra-clavicular | 2 | Isolated | - | No | S + HT (progestagens) | - | AWOD | 27 |
| | 4 | First | R. axillary | 3 | Isolated | - | No | S + RT (5000 Gy≤) | - | AWOD | 45 |
| | 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 |
| Carr et al. (20) | 1 | First | L. inguinal | 9*7 | Multiple LN (celiac and porta hepatitis) | No | S + 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 |
| Case no. | Which rec. | Type of involved peripheral LN* | Size of tm* (cm) | No. of the OIS* | Location of the OIS* | Presence of the other distant sites | Therapy | Postrec. situations | End status | FU time |
|-------|-----------|----------------------------------|------------------|----------------|----------------------|-----------------------------------|---------|---------------------|------------|---------|
| 1     | First     | L. -anterior cervical            | 2*2              | Isolated       | -                    | No                                | CT (doxorubicin + cyclophosphamide + cisplatin) | -        | AWOD                | 21         |
| 1     | First     | L. axillary                      | UR               | Isolated       | -                    | No                                | UR                  | -                    | UR         | UR      |
| 1     | First     | R. inguinal                      | 4*5              | Isolated       | -                    | No                                | S + RT              | Re-recurrence occurred | DOD        | 43      |
| 1     | Second    | L. supra-clavicular              | UR               | Isolated       | -                    | No                                | S                   | -                    | AWOD       | 48      |
| 1     | First     | L. inguinal                      | 10*7.5           | Isolated       | -                    | No                                | CT (carboplatin + paclitaxel) + pelvic RT + inguinal LN boost RT (25 Gy) | -        | UR                  | UR         |
| 1     | First     | L. inguinal                      | 1.8*2.6          | Multiple        | Vagina including peri-urethral area | No                                | S (anterior pelvic exenteration) + CT (carboplatin + gemcitabine) | -        | AWOD                | 120        |
| 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         |
| 1     | First     | L. inguinal                      | 4*5              | Isolated       | -                    | No                                | S + RT (30 Gy)      | -                    | AWOD       | 294     |
| 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 axillary lymph node involvement) → instability due to the other vital systems → palliative therapy | DOD      | 45      |

Table 3. Continued

*LN: Lymph node, OIS: Other involved site, CT: Chemotherapy, RT: Radiotherapy, UA: Urothelial adenocarcinoma, LFU: Lost to follow-up, VBT: Vapothermy, AD: Adjuvant, AWOD: Alive with disease, DOD: Dead of disease.
| Case no. | Which rec. | Type of involved peripheral LN | Size of tumor (cm) | No. of the OIS | Location of the OIS | Presence of the other distant sites | Therapy | Postrec. situations | End status | FU time |
|----------|------------|-------------------------------|-------------------|----------------|---------------------|------------------------------------|---------|---------------------|------------|---------|
| 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, °: At recurrence, °°: 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, 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.

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
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

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

| Agea,b (years) | <60 | 10 | 89 | 0.186 |
|----------------|-----|----|----|-------|
| ≥60 | 6 | 75 |
| Stage | 1&2 | 6 | 67 | 0.890 |
| 3&4 | 15 | 83 |
| Histologic typea | 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 recurrenceb | <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 |

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
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. 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 Hanum 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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