Arch Gynecol Obstet (2012) 285:1119–1124
DOI 10.1007/s00404-011-2030-7

GYNECOLOGIC ONCOLOGY

What is the impact of cervical invasion on lymph node metastasis in patients with stage IIIC endometrial cancer?

Taner Turan · Deniz Hızlı · Saynur Sarici Yılmaz · Burcu Gundogdu · Nurettin Boran · Gokhan Tulunay · Ahmet Ozfuttu · M. Faruk Kose

Received: 4 January 2011 / Accepted: 17 July 2011 / Published online: 7 September 2011

Abstract
Purpose The aim of this study was to evaluate whether the presence of cervical invasion has altered the site of lymph node (LN) metastasis in stage IIIC endometrial cancer (EC) patients.
Methods Fourty-six patients who had systematic pelvic and para-aortic lymphadenectomy surgery for EC and staged as IIIC were included in the study. Patients with cervical invasion were defined as Group A and patients without cervical invasion were defined as Group B. The groups were compared according to surgical-pathologic characteristics. Chi-square and Annova table test were used to examine the effect of cervical invasion on LN metastasis.
Results The mean age of patients was 59 years (range 38–81) and tumor size was 47 mm (range 10–80). Twenty-three patients had cervical involvement (Group A) and 23 had no cervical metastasis (Group B). Groups were not different with regard to cell type, grade, depth of myometrial invasion, tumor size, adnexal involvement, peritoneal metastasis and lymphovascular space invasion. Among 46 patients obturator LN was the most involved site of LN metastasis, however, when there is cervical metastasis external iliac LN was found to be the most involved LN site. Patients without cervical invasion had 21.7% of external iliac LN metastasis while patients with cervical invasion had 60.9% of external iliac LN metastasis. Also, cervical invasion has increased the risk of pelvic LN and obturator LN involvement from 82.6 to 95.7% and 39.1 to 52.2%, respectively.
Conclusion Cervical invasion may have an effect on lymphatic spread and change the site of metastatic LNs. Large prospective studies are needed to clarify the alteration of LN metastasis in cervix invaded EC patients.

Keywords Endometrial cancer · Cervical invasion · Stage IIIC · Lymph node involvement

T. Turan · D. Hızlı (✉) · S. S. Yılmaz · B. Gundogdu · N. Boran · G. Tulunay · M. Faruk Kose
Gynecologic Oncology Division, Zubeyde Hanim Women's Health Research and Teaching Hospital, Etlik Street, Kecioren, 06010 Ankara, Turkey
e-mail: denizhizli@yahoo.com

T. Turan
e-mail: turantaner@yahoo.com

A. Ozfuttu
Pathology Division, Zubeyde Hanim Women's Health Research and Teaching Hospital, Ankara, Turkey

Introduction

Endometrial cancer (EC) is the most common gynecological cancer and International federation of gynecology and obstetrics (FIGO) recommended surgical staging in 1988 due to limitation of clinical staging and updated the staging system in 2009 [1, 2]. In most clinics, pelvic lymph node (PLN) and para-aortic lymph node (PALN) dissection addition to total hysterectomy and bilateral salphingo-oophorectomy is a routine operative procedure in patients with poor prognostic factors such as cervical involvement, non-endometrioid histologic subtypes, or >1/2 myometrial invasion [3, 4]. By significant improvement in training and instrumentation and innovative adaptation of instruments and techniques, minimally invasive approaches for the treatment of women with all gynecologic malignancies had become popular [5].

Lymphatic spread is one of the ways of tumor dissemination and the presence of metastatic PLN and PALN is one of the most important factor related to stage and prognosis [6, 7]. Recent studies about sentinel LN in EC improved our knowledge about lymphatic spread in EC and

obturator, internal iliac and the common iliac LNs were found to be the most common sites of metastasis [20–24]. However, little is known about the way of endometrial tumor's lymphatic spread. Does the lymphatic spread follows the same route in all patients or does it change due to presence of different prognostoc factors? The answers are not clear yet and this issue still remains controversial [8–12].

The aim of this study was to evaluate whether the presence of cervical invasion has altered the site of LN metastasis in stage IIIC EC patients.

Materials and methods

Between 1993 and 2009, patients who had open systematic pelvic and para-aortic lymphadenectomy surgery extending to renal vessels for EC at gynecologic oncology department were studied retrospectively. All stage IIIC patients who had at least 15 LNs removed from their pelvic region and 10 LNs from para-aortic region were included in the study. Further, patients were divided into two groups according to cervical involvement. Patients with cervical invasion was defined as Group A and patients without cervical invasion was defined as Group B. Patients who had other malignancies diagnosed within 2 years before or after their diagnosis were excluded. All surgical procedures were performed by the same gynecologic oncology team and frozen sections (FS) by the same pathologists. FS was studied routinely for all cases and provided information on the grade of neoplasia, histology, depth of myometrial invasion, tumor diameter, sites of extrauterine spread and lymphovascular invasion.

Bilateral PLN and PALN dissections were performed when one of the following criteria was determined by frozen section examination:

1. Grade 2–3
2. ≥1/2 myometrial invasion
3. Tumor size >2 cm
4. Adnexial metastasis
5. Cervical involvement
6. High risk histopathology (clear cell, adenosquamous or serous papillary).

The staging was defined in accordance with the 1988 FIGO surgical staging system. Bilateral pelvic lymphadenectomy was performed to complete skeletonization, with all lymphatic tissue of the common, external and internal iliac vessels and the obturator fossa removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was the aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. The presacral lymphatic tissue was harvested separately. The upper limit of para-aortic lymphadenectomy was renal vessels. All lymphatic tissue was then harvested from all patients from the lateral, anterior, and medial aspects of the vena cava and aorta to the renal veins. The lymph-node-bearing tissue from the PLNs (bilateral common iliac arteries, external iliac arteries, internal iliac arteries, obturator fossa and presacral) and the PALNs was submitted for analysis. All surgeries and pathologic findings were performed and interpreted at a single institution. All relevant patients' data, including history, surgical data and histological reports, were abstracted from the patients' records.

Statistical analysis was performed using SPSS version 17.0. Chi-square and Annova table test were used to examine the effect of cervical invasion on LN metastasis. The cut-off value for statistical significance was set at $p < 0.05$.

Results

Between study period, 1,500 patients were operated for endometrial cancer at our hospital and 56.9% of them had lymphadenectomy. Total of 204 consecutive patients who had open systematic pelvic and para-aortic lymphadenectomy surgery extending to renal vessels and whose total number of harvested LN was adequate were evaluated. Among 204 patients, 46 fulfilled inclusion criteria and were included in the study. The mean age and tumor size of patients were 59 years (range 38–81) and 47 mm (range 10–80), respectively. Twenty-three patients had cervical involvement (Group A) and 23 had no cervical metastasis (Group B). Of these 23 patients with cervical involvement 4 had glandular, 19 had glandular and stromal invasion. Clinicopathologic features of all patients are shown in Table 1.

Tumor was disseminated to PALN in 26 patients and to PLN in 41 patients. Obturator LN was the most and presacral LN was the least common site of PLN involvement (Table 1).

The mean number of removed LNs was 21.4 (range 9–41) for PALN, 41.6 (range 23–78) for PLN region and number of metastatic LNs was 4.7 (range 1–30) for PALN, 4.5 (range 1–35) for PLN. Detailed distribution of removed and metastatic LNs is shown in Table 2.

Furthermore, groups were compared with regard to cell type, grade, depth of myometrial invasion, tumor size, adnexal involvement, peritoneal metastasis and lymphovascular space invasion. The difference was not statistically significant, however, patients in Group A were younger than patients in Group B (55.8 vs. 62, $p = 0.017$) (Table 3). The statistical analysis was evaluated to determine whether the age had an effect on lymph node spread. When the mean age was set as cut-off value, statistical analysis showed that

Table 1 Surgical and pathologic characteristics of patients

Parameter	*n*	%
Cell type		
Endometrioid	33	71.7
Clear cell	3	6.5
Serous	9	19.6
Mixed type	1	2.2
Grade		
1	15	32.6
2	13	28.3
3	18	39.1
Depth of myometrial invasion		
Only endometrium	1	2.2
<1/2	8	17.4
≥1/2	32	64.6
Serosal infiltration	5	10.9
Peritoneal cytology		
Negative	36	78.3
Positive	10	21.7
Metastasis to ovary		
Negative	35	76.1
Positive	11	23.9
Metastasis to tuba uterine		
Negative	36	78.3
Positive	10	21.7
Cervical invasion		
Negative	23	50
Glandular	4	8.7
Stromal	19	41.3
Lymphovascular space invasion		
Negative	9	19.6
Positive	23	50
Unreported	14	30.4
Para-aortik lymph node		
Negative	20	43.5
Positive	26	56.5
Pelvic lymph node		
Negative	5	10.9
Positive	41	89.1
Common iliac lymph node		
Negative	29	63
Positive	17	37
External iliac lymph node		
Negative	27	58.7
Positive	19	41.3
Internal iliac lymph node		
Negative	29	63
Positive	17	37
Obturator lymph node		
Negative	25	54.3
Positive	21	45.7
Presacral lymph node		
Negative	44	95.7
Positive	2	45.7

Table 2 Number of removed and metastatic lymph nodes

Region	Number of removed lymph node		
	Mean	Median	Range
Removed lymph node from all regions	62.9	58	35–119
Para-aortic lymph node			
Removed	21.4	21	10–41
Metastatic	4.7	2	1–30
Pelvic lymph node			
Removed	41.6	39	23–78
Metastatic	4.5	3	1–38
Common iliac lymph node			
Removed	9.4	8	3–21
Metastatic	2.6	2	1–8
External iliac lymph node			
Removed	10.9	10	3–24
Metastatic	2.1	2	1–8
Internal iliac lymph node			
Removed	5.9	6	1–20
Metastatic	1.5	1	1–11
Obturator lymph node			
Removed	14.2	14	3–27
Metastatic	2.5	2	1–9
Presacral lymph node			
Removed	1.4	1	0–9
Metastatic	5.5[a]	5	4 and 7

[a] Only in two patients metastatic presacral LN was detected. One of them had four the other had seven metastatic LNs

age had no effect on lymph node spread pattern (for para-aortic region $p = 0.678$, pelvic region $p = 0.262$, common iliac LN $p = 0.809$, external iliac LN $p = 0.446$, internal iliac LN $p = 0.708$ and obturator LN $p = 0.264$).

Mean number of removed LNs was similar between groups. The relation between cervical invasion and site of LN metastasis was evaluated. Cervical invasion was found to have increased the rate of external iliac LN metastasis from 21.7 to 60.9% ($p = 0.07$). Cervical invasion has increased the risk of PLN and obturator LN involvement from 82.6 to 95.7% and 39.1 to 52.2%, respectively ($p = 0.155$ and $p = 0.375$). Moreover, internal iliac and PALN metastasis were found to have decreased in patients with cervical invasion, but the difference was not significant (Table 4).

We analysed whether presence of glandular or stromal involvement had changed lymph node spread pattern. Our results showed that glandular or stromal involvement did not change the pattern of lymphatic spread. *P* values for each region was: para-aortic region $p = 0.231$, pelvic region $p = 0.639$, common iliac LN $p = 0.651$, external iliac LN $p = 0.106$, internal iliac LN $p = 0.957$, obturator LN $p = 0.315$ and presacral LN $p = 0.497$.

Table 3 Distribution of surgical and pathologic factors (%)

Parameter	No cervical invasion	Positive cervical invasion	*P*
Age, mean ± SD (range, median)	62.2 ± 8.5 (48–81, 61)	55.8 ± 9 (38–73, 54)	0.017
Tumor size (mm), mean ± SD (range, median)	44.2 ± 20, (10–80, 50)	50.3 ± 16.5 (18–70, 50)	0.272
Cell type			
Endometrioid	69.6	73.9	0.688
Clear cell	8.7	4.3	
Serous	21.7	17.4	
Mix type	–	4.3	
Grade			
1	34.8	30.4	0.612
2	21.7	34.8	
3	43.5	34.8	
Depth of myometrial invasion			
Only endometrium	–	4.3	0.610
<1/2	21.7	13	
≥1/2	65.2	73.9	
Serosal invasion	13	8.7	
Ovarian metastasis			
Negative	82.6	69.6	0.300
Positive	17.4	26.1	
Metastasis to tuba uterina			
Negative	82.6	73.9	0.475
Positive	17.4	26.1	
Lymphovascular space invasion			
Negative	33.3	21.4	0.457
Positive	66.7	78.6	
Peritoneal cytology			
Negative	87.7	69.6	0.153
Positive	13	30.4	

Table 4 Distribution of removed and metastatic LN number according to groups

Parameter	No cervical invasion	Positive cervical invasion	*P*
Number of removed lymph node, mean (range, median)			
All region LN	59.4 (39–93,58)	66.4 (39–119, 42)	0.244
Para-aortic LN	20.8 (9–41, 21)	22 (10–41, 20)	0.644
Total pelvic LN	38.7 (23–65, 35)	44.5 (25–78, 42)	0.189
Common iliac LN	8 (9–41, 7)	10.8 (3–20, 10)	0.051
External iliac LN	10.4 (3–24, 9)	11.4 (4–21, 12)	0.487
Internal iliac LN	5.4 (1–13, 5)	6.4 (1–20, 7)	0.477
Obturator LN	14 (3–25, 15)	14.4 (5–27, 13)	0.817
Presacral LN	0.9 (0–5, 1)	1.9 (1–9, 1)	0.136
Metastatic LN (%)			
Para-aortic LN	65.2	47.8	0.234
Total pelvic LN	82.6	95.7	0.155
Common iliac LN	39.1	34.8	0.760
External iliac LN	21.7	60.9	0.007
Internal iliac LN	47.8	26.1	0.177
Obturator LN	39.1	52.2	0.375
Presacral LN	–	8.7	0.148

LN Lymph node

Discussion

EC is the most common gynecologic cancer and in approximately 75% of the cases, the tumor is confined to the uterus at the initial diagnosis [13]. Patients with cervical invasion may present with stage II, III, or IV disease (FIGO 2009) [2]. Of note, histologically documented cervical involvement is relatively uncommon and accounts for only 11% of all endometrial cancers [14]. Five-year survival of patients with EC involving the cervix is approximately 64% [15].

Lymphatic spread is the main way of dissemination of gynecologic cancers but the route of spread may differ between malignancies. For primary cervical cancer, lateral pathway flowing to obturator, internal iliac, external iliac and common iliac LNs is known to be the most important way. Also anterior pathway flowing to external iliac LNs and posterior pathway flowing to common iliac, sacral and PALNs are the other ways for lymphatic spread in primary cancer of cervix [16, 17]. Is the route of spread is similar in patients with cervix invaded EC? Studies about sentinel LN in EC were performed to find the answer [18–20]. First, it was thought that EC with cervical involvement may have similar lymphatic tumor dissemination to primary cervical cancer, however, further studies revealed that the pattern of tumor dissemination was quite different. Obturator, internal iliac and common iliac LNs were found to be the most common involved sites in EC [21, 22]. In the present study, similarly obturator LN was the most common site of metastasis, however, external iliac LN was found to be the most common site when cervix was invaded.

In 2001, Mariani et al. [23] compared patients with EC limited to the uterine corpus and invading the cervix; and found that EC with cervical metastasis spread more readily to the common iliac LNs. Furthermore, they concluded that para-aortic LN metastases spread via a route shared by the common iliac LNs when tumor involves the cervix but spread predominantly via a route common to the obturator LNs (and/or external iliac LNs) when the primary tumor site is only the corpus.

In addition, in 2008 Mariani et al. [24] reported that ovarian vessels are one of the way of tumor spread to para-aortic region and further concluded that tumor localized to fundus and corpus uteri may spread more frequently to

PALN compared to tumors localized to isthmus uteri. Similarly, we found 17% less PALN metastasis in patients with stage IIIC cervix invaded EC.

Cervical invasion is considered to increase the risk of nodal metastasis and parametrial invasion [25]. However, in a current study it was reported that parametrial spread cannot be predicted by cervical involvement alone but may be predicted by various lymphovascular space invasion-related histopathologic factors and parametrial spread may not be an independent prognostic factor in individuals with uterine endometrial cancer [25].

Preoperative cervical evaluation for predicting cervical involvement in EC was studied and found to predict cervical metastasis in most cases [26]. Furthermore, authors have suggested pap smear, colposcopy, cervical palpation and rectal parametrial examination prior to surgery; however, this procedure is not routinely performed in clinical practice at present [26]. Of note, extension of cervical invasion was measured and impact on recurrence and survival was studied but no relation was found [27].

Retrospectivity and small number of patient are the limitations of our study, but considering the number of removed LNs as inclusion criteria and performing PALN dissection up to the renal vessels in all patients is the favorable sides of our study. Since it would not be reliable to comment about LN metastasis in a patient who had only one LN removed, patients who had <15 removed LNs from the pelvic region and <10 LNs from the para-aortic region were not included in the study. Mean 62.9 LNs removed from each patient was considered to be enough to comment about LN status. Also surgical and pathologic features including total number of removed LNs were similar between groups. This was also a desirable object for exact statistical analysis.

Of note, in our clinic, accordance of LVSI determined by FS and final pathology was evaluated and results showed that LVSI may be determined by FS with a 50% of sensitivity, 100% of specificity, 94.4% of NPV and 100% of PPV.

As we know, LN dissection increases the morbidity compared with TAH+BSO alone and therefore patient selection who will undergo LN dissection is important. From this point of view, much effort has been expended to define the factors affecting the route of lymphatic spread in EC up to now because once the predictive factors and the route are clarified the question of "In which patients and to what extent should we perform LN dissection" can be resolved. The "ASTEC trial", a randomised prospective large trial, was set out to determine whether pelvic lymphadenectomy could improve the survival of women with EC. The lymphadenectomy study concluded that there was "no evidence of benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with early endometrial cancer," and that "pelvic lymphadenectomy cannot be recommended as routine procedure for therapeutic purposes outside of a clinical trial" [28]. However, some authors claimed that this conclusion cannot be made because a systematic lymphadenectomy was not performed in most patients in the lymphadenectomy [29]. Also, other authors criticised that the risk factors were not equalized in the two arms of the study [30]. As can be seen, there is still no consensus about indication and extent of lympadenectomy in EC. This dilemma should be more clarified until the risk factors for LN metastasis and the route of lymphatic spread were determined.

In summary, our study revealed a slight change in LN involvement whether cervix was invaded. External iliac LNs were more common and PALNs were less common sites of LN metastasis in patients with cervix invaded stage IIIC EC. However, obturatuar LNs were the most common involved LNs in patients without cervical invasion. Large prospective studies are needed to clarify the alteration of LN metastasis in cervix invaded EC patients.

Conflict of interest None.

References

1. Announcements: FIGO (the International Federation of Obstetricians and Gynecologists) stages: 1988 revision. Gynecol Oncol 1989; 35: 125–126
2. Creasman W (2009) Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 105:109
3. Watanabe Y, Aoki D, Kitagawa R et al (2007) Status of surgical treatment procedures for endometrial cancer in Japan: results of a Japanese Gynecologic Oncology Group survey. Gynecol Oncol 105:325–328
4. Barnes MN, Kilgore LC (2000) Complete surgical staging of early endometrial adenocarcinoma: optimizing patient outcomes. Semin Radiat Oncol 10:3–7
5. Frumovitz M, Escobar P, Ramirez PT (2011) Minimally invasive surgical approaches for patients with endometrial cancer. Clin Obstet Gynecol 54:226–234
6. Mariani A, Webb MJ, Galli L et al (2000) Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer. Gynecol Oncol 76:348–356
7. Creasman WT, Morrow CP, Bundy BN et al (1987) Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. Cancer 60:2035–2041
8. Karube Y, Fujimoto T et al (2010) Histopathological prognostic factors predicting para-aortic lymph node metastasis in patients with endometrioid uterine cancer. Gynecol Oncol 118:151–154
9. Nomura H, Aoki D et al (2006) Analysis of clinicopathologic factors predicting para-aortic lymph node metastasis in endometrial cancer. Int J Gynecol Cancer 16:799–804
10. Yaegashi N, Ito K, Niikura H (2007) Lymphadenectomy for endometrial cancer: is paraaortic lymphadenectomy necessary? Int J Clin Oncol 12:176–180
11. Mariani A, Keeney GL et al (2004) Endometrial carcinoma: paraaortic dissemination. Gynecol Oncol 92:833–838
12. Morrow CP, Bundy BN, Kurman RJ et al (1991) Relationship between surgical–pathological risk factors and outcome in clinical

stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 40:55–65
13. Greenlee RT, Hill-Harmon MB, Murray T, Thun M (2001) Cancer statistics, 2001. CA Cancer J Clin 51:15–36
14. Petersen F (ed) (1991) Annual report of the results of treatment in gynecologic cancer, vol 20. Elsevier, Stockholm
15. Boente MP, Orandi YA, Yordan EL et al (1995) Recurrence patterns and complications in endometrial adenocarcinoma with cervical involvement. Ann Surg Oncol 2:138–144
16. Sakuragi N, Satoh C, Takeda N et al (1999) Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with Stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy. Cancer 85:1547–1554
17. Buchsbaum HJ (1979) Extrapelvic lymph node metastases in cervical carcinoma. Am J Obstet Gynecol 133:814–824
18. Pelosi E, Arena V, Baudino B et al (2003) Pre-operative lymphatic mapping and intra-operative sentinel lymph node detection in early stage endometrial cancer. Nucl Med Commun 24:971–975
19. Niikura H, Okamura C, Utsunomiya H et al (2004) Sentinel lymph node detection in patients with endometrial cancer. Gynecol Oncol 92:669–674
20. Lelievre L, Camatte S, Le Frere-Belda M et al (2004) Sentinel lymph node biopsy in cervix and corpus uteri cancers. Int J Gynecol Cancer 14:271–278
21. Altgassen C, Pagenstecher J, Hornung D et al (2007) A new approach to label sentinel nodes in endometrial cancer. Gynecol Oncol 105:457–461
22. Frumovitz M, Bodurka DC, Broaddus RR et al (2007) Lymphatic mapping and sentinel node biopsy inwomenwith high-risk endometrial cancer. Gynecol Oncol 104:100–103
23. Mariani A, Webb MJ, Keeney GL et al (2001) Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical ınvolvement. Gynecol Oncol 83:72–80
24. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, Podratz KC (2008) Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 109:11–18
25. Watanabe Y, Satou T, Nakai H et al (2010) Evaluation of parametrial spread in endometrial carcinoma. Obstet Gynecol 116:1027–1034
26. Pristauz G, Winter R, Fischerauer E et al (2009) Can routine gynecologic examination contribute to the diagnosis of cervical involvement by primary endometrial cancer? Eur J Gynaecol Oncol 30:497–499
27. JS Ferriss, W Brix, M Henretta et al. 2009 Extent of cervical involvement in endometrial cancer as a predictor of outcome. J Clin Oncol, ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 15S (20 May Supplement), 2009
28. ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmer MK (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomized study. Lancet 373:125–136
29. Barton DP, Naik R, Herod J (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC Trial): a randomized study. Int J Gynecol Cancer 19:1465
30. Creasman WT, Mutch DE, Herzog TJ (2010) ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? Gynecol Oncol 116:293–294