Gynecologic Oncology 125 (2012) 400–403

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# The novel criteria for predicting pelvic lymph node metastasis in endometrioid adenocarcinoma of endometrium

Ozgur Akbayir [a], Aytul Corbacioglu [a], B. Pinar Cilesiz Goksedef [b,*], Ceyhun Numanoglu [a], Aysu Akca [a], Hakan Guraslan [c], Lale Vuslat Bakir [a], Ahmet Cetin [b]

[a] Kanuni Sultan Suleyman Teaching and Research Hospital, Department of Gynecologic Oncology, Istanbul, Turkey
[b] Haseki Teaching and Research Hospital, Department of Gynecologic Oncology, Istanbul, Turkey
[c] Bakirkoy Sadi Konuk Teaching and Research Hospital, Obstetrics and Gynecology, Istanbul, Turkey

ARTICLE INFO

*Article history:*
Received 7 December 2011
Available online 3 February 2012

*Keywords:*
Endometrial carcinoma
Pelvic lymph node metastasis
LVSI
Cervical involvement

ABSTRACT

*Objective.* To identify clinicopathological risk factors for pelvic lymph node metastasis, and to evaluate the clinical validity of these factors in selecting patients who need pelvic lymph node dissection.

*Methods.* The data of 466 patients who had lymphadenectomy for endometrioid adenocarcinoma of the endometrium between January 2002 and December 2010 were reviewed retrospectively.

*Results.* All patients underwent pelvic lymphadenectomy and 192 (41.2%) patients also underwent paraaortic lymphadenectomy. The median number of pelvic lymph node was 16 (range: 2–46) and of paraaortic lymph node was 5 (range: 2–16). 10.1% (47/466) of all patients had pelvic lymph node involvement and 7.8% (15/192) of the patients had paraaortic lymph node involvement (LNI). Pelvic LNI was significantly more common in the presence of higher grades of tumor, LVSI, deep myometrial invasion, positive peritoneal cytology and cervical involvement. The logistic regression analysis revealed that LVSI, cervical glandular invasion and cervical stromal invasion remained to be the independent risk factors for LNI. When the LVSI and/or cervical involvement were considered as high risk for pelvic lymph node metastasis, NPV and specificity were found to be 96.3% and 68.4%, respectively. LNI was correctly estimated in 323 women (69%), overestimated in 132 women (28%) and underestimated in 11 women (2%).

*Conclusion.* LVSI, cervical glandular and stromal involvement were independent risk factors for pelvic LNI. These variables can be assessed pre- or intraoperatively with a high rate of accuracy, the model which uses these variables may be successfully used in the prediction of pelvic lymph node metastasis.



## Introduction

Endometrial carcinoma is one of the most common gynecologic tumor in the world and lymph node involvement is the most important prognostic factor for the clinically early stage disease [1]. The incidence of pelvic lymph node metastases is approximately 10% when cancer is clinically confined to the uterus [2]. Although the International Federation of Obstetricians and Gynecologists (FIGO) staging system is based on the surgical findings including the pelvic and paraaortic lymph node dissemination [3], there is no standard protocol for the assessment of lymph node involvement. Even though the additional surgical morbidity related to pelvic lymphadenectomy appears to be minimal, women who receive lymphadenectomy are more likely to experience surgically related systemic morbidity or lymphoedema/lymphocyst formation [2]. Furthermore, in a review of randomized controlled trials, it is reported that there is no evidence that lymphadenectomy decreases the risk of death or disease recurrence compared with no lymphadenectomy in clinical stage I disease [2]. As a consequence, different algorithms for the surgical treatment of early stage endometrial cancer have been used, reflecting the individual surgeon's preferences. While some authors performed lymphadenectomy as a routine procedure [4–6], others considered that surgical staging was not necessary for any patients with clinically early disease [7,8]. Alternatively, some authors suggested to perform lymphadenectomy only for patients at high risk of extrauterine disease with the aim of preventing over- and undertreatment [9,10].

Cervical invasion and deep myometrial invasion carry an increased risk of lymph node involvement, recurrence and death from disease [11–13]. Even though tumor grade, histologic type, positive peritoneal cytology, lymphovascular space involvement (LVSI) and tumor volume are not included in the staging system, they are also demonstrated to be prognostically important factors [14]. However, whether the absence of these risk factors is reliable enough to omit lymphadenectomy remains to be a controversial issue.

The purpose of this study was to identify clinicopathological risk factors for pelvic lymph node metastasis, and to evaluate the clinical

* Corresponding author at: Haseki Egitim ve Arastirma Hastanesi, Kadin Dogum Servisi, Aksaray, Istanbul, Turkey.
*E-mail address:* bpgoksedef@yahoo.com (B.P.C. Goksedef).

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doi:10.1016/j.ygyno.2012.01.051

validity of these factors in selecting patients who need pelvic lymph node dissection.

## Material and methods

The data of all patients who had retroperitoneal lymph node dissection for endometrioid adenocarcinoma of the endometrium in two teaching hospitals between January 2002 and December 2010 were reviewed retrospectively. Primary treatment consisted of extrafacial abdominal hysterectomy or radical hysterectomy, bilateral salpingo-oopherectomy, peritoneal cytology, bilateral pelvic and paraaortic lympadenectomy. Radical hysterectomy was performed when cervical involvement was suspected. In both clinics, pelvic lymphadenectomy was performed to all patients except for those with no myometrial invasion regardless of the tumor grade and some of the morbidly obese patients due to technical difficulty. Pelvic lymphadenectomy was defined as the removal of all lymphatic nodes including the common, external and internal iliac, and obturator lymph nodes. Paraaortic lymph node dissection was performed to high risk patients, namely those with grade 3 tumor, >50% myometrial invasion and cervical involvement. Paraaortic lympadenectomy involved the nodes located from the bifurcation of the aorta to the level of renal vein, including the region above the inferior mesenteric artery (IMA). All surgical procedures were performed by the gynecologic oncologists.

The data regarding history, surgery and histopathologic evaluation were abstracted from patients' records. The role of prognostic clinicopathologic factors (age, body mass index (BMI), menopause status, grade, LVSI, depth of myometrial invasion, cervical involvement, peritoneal cytology and tumor size) in the prediction of pelvic lymph node metastases was evaluated. Stage was determined according to FIGO guidelines revised in 2009 [3]. Carcinomas were classified using a three-grade system in which a solid pattern was shown less than 5% in grade 1, 5–50% in grade 2 and more than 50% in grade 3. We included only the patients that at least eight pelvic lymph nodes were dissected. The patients who underwent a prior chemotherapy or pelvic radiation were excluded, as well as those whose data were not recorded sufficiently.

Pearson chi-square test was used for compared categorical data. A univariate and multivariate analysis was used to assess the effect of the various factors on lymph node involvement. A $p$ value of $<0.05$ was considered significant. All statistical analyses were performed using SPSS for Windows version 15.0.

## Results

511 patients were operated for endometrial cancer between 2002 and 2010. 25 were excluded due to incomplete data, and 10 were excluded as the number of removed pelvic lymph node did not fulfill the criteria. 10 patients could not undergo lymphadenectomy because of morbid obesity. Therefore, a total of 466 patients were analyzed for this study. The mean age of patients was 56.7 ± 9.7 and most of the patients were postmenopausal (n = 349, 74.7%) at the time of surgery. The majority of cases were diagnosed at FIGO stage I disease (n = 374, 80.3%). The clinical characteristics of the patients with endometrial carcinoma are summarized in Table 1.

All patients underwent pelvic lymphadenectomy and 192 (41.2%) patients also underwent paraaortic lymphadenectomy. The median number of pelvic lymph node was 16 (range: 2–46) and of paraaortic lymph node was 5 (range: 2–16). 10.1% (47/466) of all patients had pelvic lymph node involvement and 7.8% (15/192) of the patients who underwent paraaortic lymphadenectomy had paraaortic lymph node involvement. Table 2 summarizes lymph node involvement status of the patients.

Table 3 shows the clinicopathologic features of the patients with and without lymph node involvement. Pelvic lymph node involvement was significantly more common in the presence of higher grades of tumor, LVSI, deep myometrial invasion, positive peritoneal cytology and cervical involvement (p = 0.002, p = 0.0001, p = 0.0001, p = 0.0001 and p = 0.0001, respectively). Multivariate logistic regression analysis was performed introducing these significant variables into the model. The logistic regression analysis revealed that LVSI (OR 0.22; 95% CI 0.10–0.45, p = 0.0001), cervical glandular invasion (OR 0.25; 95% CI 0.09–0.64; p = 0.004) and cervical stromal invasion (OR 0.44; 95% CI 0.20–0.96; p = 0.03) remained to be the independent risk factors for lymph node involvement (Table 4).

Table 5 shows the diagnostic performance of two different criteria in the prediction of lymph node involvement. When we considered the patients with grade 3 tumor and/or deep myometrial invasion at high risk for pelvic lymph node involvement as recommended in the Gynecologic Oncology Group (GOG) studies [11,14], negative predictive value (NPV) was 94.6% and specificity was 63.4%. This model accurately predicted lymph node involvement in 298 patients (64%), overestimated in 153 patients (33%) and underestimated in 15 patients (3%). When the patients with LVSI and/or cervical involvement were considered at high risk for pelvic lymph node metastasis, NPV and specificity were found to be higher at a rate of 96.3% and 68.4%, respectively. Lymph node involvement was correctly estimated in 323 women (69%), overestimated in 132 women (28%) and underestimated in 11 women (2%).

**Table 1**
Demographic characteristics of the patients.

| Characteristics | n = 466 | % |
|---|---|---|
| Age (mean ± sd) | 56.7 ± 9.7 | – |
| Gravida (median–range) | 4 (0–14) | – |
| Parity (median–range) | 3(0–12) | – |
| Menopause | 349 | 74.7 |
| BMI > 30 | 238 | 51.1 |
| Diabetes mellitus | 100 | 21.5 |
| Hypertension | 210 | 45.1 |
| Currently smoker | 58 | 12.4 |
| Stage | | |
| I | 374 | 80.3 |
| II | 26 | 5.6 |
| III | 54 | 11.6 |
| IV | 12 | 2.5 |

BMI, body mass index.

## Discussion

In an attempt to prevent unnecessary morbidity of surgical staging in the early stage of endometrioid adenocarcinoma, the factors that affect the pelvic lymph node metastasis have been investigated in this study. We have found that LVSI, higher grades of tumor, deep myometrial invasion, positive peritoneal cytology, and both glandular and stromal cervical involvement were significantly more common in patients with positive pelvic lymph nodes when these factors were evaluated individually. However, only LVSI, cervical glandular and cervical stromal involvement remained to be independent risk factors in multivariate analysis. Patients with <8 lymph nodes removed from the pelvic region were not included in this study. The rationale of this

**Table 2**
Lymph node involvement status of the patients.

| | n | % |
|---|---|---|
| Pelvic LND | 466/466 | 100 |
| Paraaortic LND | 192/466 | 41.2 |
| N. of pelvic LNM | 47/466 | 10.1 |
| N. of paraaortic LNM | 15/192 | 7.8 |
| N. of pelvic + paraaortic LNM | 12/192 | 6.3 |
| N. of paraaortic only LNM | 3/192 | 1.5 |

n, number; LND, lymph node dissection; LNM; lymph node metastases.

**Table 3**
Clinicopathologic features of patients with and without pelvic nodal involvement.

| | With PLNM n (%) | Without PLNM n (%) | p |
|---|---|---|---|
| Age (year) | | | 0.19 |
| <60 | 27 (57.4) | 280 (66.8) | |
| >60 | 20 (42.6) | 139 (33.2) | |
| BMI (kg/m$^2$) | | | 0.12 |
| <30 | 28 (59.6) | 200 (47.7) | |
| >30 | 19 (40.4) | 219 (52.3) | |
| Menopause | | | 0.17 |
| Yes | 39 (83.0) | 310 (74.0) | |
| No | 8 (17.0) | 109 (26.0) | |
| Grade | | | **0.002** |
| 1 | 9 (19.1) | 163 (38.9) | |
| 2 | 21 (44.7) | 184 (43.9) | |
| 3 | 17 (36.2) | 72 (17.3) | |
| LVSI | | | **0.0001** |
| Yes | 31 (66.0) | 90 (21.5) | |
| No | 16 (34.0) | 329 (78.5) | |
| Myometrial invasion | | | **0.0001** |
| <50% | 18 (38.3) | 299 (71.4) | |
| ≥50% | 29 (61.7) | 120 (28.6) | |
| Cervical involvement | | | **0.0001** |
| None | 33 (70.3) | 363 (86.6) | |
| Glandular involvement | 4 (8.5) | 34 (8.1) | |
| Stromal involvement | 10 (21.3) | 22 (5.3) | |
| Tumor diameter | | | 0.054 |
| <20 mm | 10(21.3) | 148 (35.3) | |
| ≥20 mm | 37(78.7) | 271 (64.7) | |
| Positive peritoneal cytology | | | **0.0001** |
| Yes | 15 (31.9) | 45 (10.7) | |
| No | 32 (68.1) | 374 (89.3) | |

BMI, body mass index; LVSI, lymphovascular space invasion.

cut off was that it represented one node from common, external and internal iliac and obturator lymph nodes bilaterally, as discussed previously in the literature [5]. Therefore, we assume that even though the patients were operated in two different clinics, this limit enabled to standardize the number and extent of the removed pelvic lymph nodes providing adequate sample to discuss the status and involvement of pelvic lymph nodes.

The relationship between obesity and endometrioid uterine cancer has been widely investigated [15]. It has been reported that an increment of 1 kg/m$^2$ causes an 18% increase in endometrioid adenocarcinoma[16]. However, Jeong et al. did not find a significant association between pelvic lymph node metastasis and obesity [16], and this result was in agreement with our findings. We also did not find a significant association between age and menopause status, and pelvic nodal involvement.

**Table 4**
Univariate and multivariate analysis of variables on the presence of pelvic lymph node metastases in patients with endometrial cancer.

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p | OR | 95%CI | p |
| Age >60 years | 0.67 | 0.36–1.23 | 0.20 | – | | |
| BMI >30 kg/m$^2$ | 1.61 | 0.87–2.98 | 0.12 | – | | |
| Grade | | | | | | |
| 1 | ref. | | | ref. | | |
| 2 | 0.23 | 0.10–0.54 | **0.001** | 0.48 | 0.18–1.28 | 0.14 |
| 3 | 0.48 | 0.24–0.96 | **0.04** | 0.69 | 0.31–1.52 | 0.36 |
| Positive cytology | 0.32 | 0.14–0.73 | **0.007** | 0.55 | 0.25–1.22 | 0.14 |
| ≥50% of MI | 0.24 | 0.13–0.46 | **0.0001** | 0.60 | 0.29–1.25 | 0.60 |
| LVSI | 0.14 | 0.07–0.27 | **0.0001** | 0.22 | 0.10–0.45 | **0.0001** |
| Cervical involvement | | | | | | |
| None | ref. | | | ref. | | |
| Glandular | 0.20 | 0.08–0.45 | **0.0001** | 0.25 | 0.09–0.64 | **0.004** |
| Stromal | 0.25 | 0.07–0.92 | **0.001** | 0.44 | 0.20–0.96 | **0.03** |
| Tumor diameter ≥20 mm | 0.49 | 0.23–1.02 | 0.06 | – | | |

BMI, body mass index; MI:,myometrial invasion; LVSI, lymphovascular space invasion.

**Table 5**
Diagnostic indices of two different models in the prediction of lymph node involvement.

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| Grade 3 and/or deep MI (GOG criteria) | 68.0% | 63.4% | 17.2% | 94.6% |
| LVSI and/or cervical involvement | 76.5% | 68.4% | 21.4% | 96.3% |

GOG, gynecologic oncology group; LVSI,lymphovascular space invasion; MI, myometrial invasion.

GOG studies showed that pelvic nodal metastasis could be predicted based on the tumor grade and the depth of myometrial invasion in early stage endometrial cancer [11,14]. Chi et al. also reported a correlation between the increasing tumor grade and depth of myometrial invasion, and the incidence of pelvic node involvement in their study of 349 patients with clinical stage I cancer [5]. Similarly, both of these factors appeared to be significantly correlated with pelvic node metastasis in univariate analysis in our study. However, when the other variables were incorporated, they lost their significance in the prediction of pelvic nodal involvement. From our point of view, the association between these factors and lymphatic involvement in the previous studies, was a result of the lack of evaluation by multivariate analysis. There are also several studies that are in agreement with our findings. Zuurendonk et al. reported that tumor grade and the depth of myometrial invasion had low sensitivity (45% and 55%, respectively) in the prediction of pelvic node involvement [10]. Furthermore, Geisler et al. in their study of 349 women, reported that positive lymph nodes were common in all grades [5].

The new FIGO staging system revised in 2009 merged the stage IIA with stage I disease [3]. However, in this large cohort of endometrial cancer, we found that cervical glandular involvement was as significant as stromal involvement for the prediction of lymphatic metastasis. We believe that the new staging system disregards the importance of cervical glandular involvement, and agree with the statement of Mariani et al.: 'Hiding an occult cervical involvement can potentially lead to overlooking the need for a more aggressive local treatment' [17].

In the present study, we did not find a significant association between pelvic lymph node involvement and the size of tumor when 20 mm is determined as a cut-off. This is consistent with the findings of Geisler et al. who detected positive lymph nodes in tumors as small as 10 mm in size [18]. By contrast, Turan et al. reported that tumor size was an independent prognostic factor for pelvic lymph node metastasis when the cut-off was determined as 40 mm [19].

LVSI is more likely to have pelvic nodal involvement compared with those without LVSI. The findings of previous studies regarding LVSI were consistent with the results of our study [20]. This data can be utilized in clinical decision in two ways. Firstly, the association between LVSI and pelvic lymph node involvement leads surgeons to perform lymphadenectomy when the frozen section reveals LVSI. Secondly, adjuvant pelvic radiotherapy should be considered in the stage I 'low' risk patients with LVSI to prevent pelvic relapse as recommended by Briët et al. [20].

As pre- or intraoperative assessment of tumor grade and depth of myometrial invasion are used to predict lymph node involvement traditionally, we applied these criteria in our cohort. The NPV and the specificity of this model were 94.6% and 63.4%, respectively. 153 patients would undergo lymph node dissection unnecessarily, while 15 patients would be undertreated. Therefore, we aimed to establish a new model which identifies the patients that do not need lymphadenectomy more accurately. As cervical invasion and LVSI were independent risk factors for pelvic nodal involvement, we investigated the performance of these criteria in the prediction of pelvic lymph node involvement. The NPV (96.3%) and the specificity (68.4%) of this model were higher than that of the GOG criteria. The number of

overtreated patients decreased to 132, while we missed only 11 patients with pelvic nodal invasion.

The diagnostic accuracy of the pre- and intraoperative assessment of these criteria plays an important role in their practical application. The preoperative assessment of cervical invasion by transvaginal ultrasound can be performed with a diagnostic accuracy of 98% [21]. Cervical invasion can also be predicted by intraoperative frozen section with a diagnostic accuracy of 87% [22]. Furthermore, frozen section is reported to be in agreement with permanent section at a rate of 68% for LVSI [22]. This is comparable with grade and depth of myometrial invasion for which the corresponding rates are 65% and 72%, respectively [22]. The only drawback of this model is that frozen section is necessary for the detection of LVSI and is not available in every center. Nevertheless, frozen section is becoming more and more prevalent in the management of endometrium cancer.

In conclusion, we have shown that tumor grade, myometrial invasion, positive peritoneal cytology, LVSI and cervical invasion were significant in the prediction of pelvic lymph node metastasis, when univariate analysis was performed. However, among these variables, only LVSI, cervical glandular and stromal involvement were independent risk factors for pelvic nodal involvement. When these parameters were used as the high risk criteria for the prediction of pelvic lymph node metastasis, NPV and specificity were found to be as high as 96.3% and 68.4%, respectively. Since these variables can be assessed pre- or intraoperatively with an acceptable rate of accuracy, we suggest that this new model may be successfully used in the prediction of pelvic lymph node metastasis.

**Conflict of interest statement**
The authors declare that there are no conflicts of interest.

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