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Prognostic factors for lymph node metastasis in high-grade endometrial cancer

L. Baquedano[1], M. A. Ruiz-Conde[1], S. Castan[1], Y. José[1], M. A. Martinez-Maestre[2], D. Judez[3], P. J. Coronado[4]

[1]Department of Obstetrics and Gynecology, Hospital Miguel Servet, Zaragoza
[2]Department of Obstetrics and Gynecology, Hospital Virgen del Rocio, Sevilla; [3]Department of Anesthesiology, Hospital Alcañiz, Teruel
[4]Department of Obstetrics and Gynecology, Hospital Clínico San Carlos, Complutense University of Madrid (Spain)

Summary

Objective: To study what are the prognostic factors of lymph nodes (LN) metastasis in all types of high-grade endometrial carcinoma (EC): poorly differentiated endometrioid carcinoma (ECG3), clear-cell carcinoma (CCC), uterine serous carcinoma (USC), and carcinosarcoma (CS). *Materials and Methods:* A multicentric, retrospective cohort study including 252 patients with lymphadenectomy (LND) (pelvic and /or para-aortic). The authors assessed the predictive value for LN metastasis of myometrial invasion, lymphovascular space involvement (LVSI), isthmus affectation, tumor size, presurgical CA 12.5 value, Ki67 expression, and p53 immunohistochemistry in samples from hysterectomy. *Results:* Of the 252 patients with high-grade EC that were included in the study, 94 had ECG3, 69 USC, 43 CCC, and 46 CS. Pelvic LND was performed in 248 (98.4%) patients and para-aortic in 111 (44%). No significant differences were observed in the number of LN resected according to their histological subtype ($p = 0.161$; para-aortic, $p = 0.051$). The authors found positive LN in 79 (31.3%) of the 252 patients. Deep myometrial invasion (OR 6.006 IC 95%: 2.715-13.287, $p \leq 0.001$), LVSI (OR 11.805 IC 95%: 5.829-23.907, $p \leq 0.001$), isthmus affectation (OR 5.481 IC: 95% 2.743-10.952, $p \leq 0.001$). and abnormal presurgical CA 12.5 value ($p = 0.006$) were significantly associated with the presence of metastasis confirmed by histological examination. The remaining factors included in the study were not observed to have any predictive value for LN metastasis. *Conclusions:* Myometrial invasion, LVSI, uterine isthmus affectation, and preoperative value of CA 12.5 were found to be predictor factors of LN metastasis in high-grade EC. Tumor size, Ki67 expression, and p53 were not observed to have any predictive value for LN metastasis.

Key words: High-grade endometrial cancer; Lymph node metastasis; Lymphadenectomy.

Introduction

The lymph nodes (LN) are the most common site of extrauterine tumor spread in endometrial carcinoma (EC). The identification of locoregional node involvement as an important prognostic factor [1] caused a major change of paradigm in EC staging. Thus, EC staging passed from being based on clinical evaluation to be based on surgical-pathological findings [2].

The therapeutic benefit of lymphadenectomy (LND) in EC in terms of survival is controversial. There is strong evidence that routine LND does not confer any clinical benefits in EC [3, 4], and it is widely accepted that it should not be performed in patients with low-risk EC [5]. Research has consistently shown that LND should not be performed in patients with intermediate-risk EC either [6]. However, a study in patients with high-risk EC to assess the therapeutic benefit of LND in patients with Stage IIIC EC (with LN involvement) revealed that LND improves disease-free survival [7]. There is a doubt about whether LND provides therapeutic benefit in patients without LN metastasis. Therefore, identifying the patients who are most likely to have LN metastasis is crucial to spare patients from maybe ineffective surgery.

LND for EC is be used to guide decisions on adjuvant therapy. In low or intermediate-grade EC (G1-2), chemotherapy is only recommended from Stage III. In contrast, chemotherapy and radiotherapy are indicated even for early stages of high-grade EC (G3) according to traditional histological factors [8].

The most effective method for detecting LN metastasis is through LND. It is a complex surgical procedure associated with a significant risk of vascular and nerve injury, which can lead to severe complications. The ideal approach would be to identify the disease that has spread outside the uterus and reached the LNs using non-invasive techniques, and determine the appropriate surgical intervention accordingly. In the light of these facts, several predictive models for LN metastasis have been developed, most based on traditional histopathological parameters [9, 10]. However, their applicability to daily practice is limited and no specific models are available for high-risk EC.

LN metastasis at diagnosis is very frequent in high-grade EC [10, 11]. This subgroup includes poorly differentiated endometrioid carcinoma (ECG3), clear-cell carcinoma

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Table 1. — *Lymphadenectomy and nodes removed in 252 cases of high grade EC.*

	EG3 (n=94)	USC (n=69)	CCC (n=43)	CS (n=46)	*p* value
Isolated nodes					
• Pelvic (n=248)	15.1(7.1)	13.1(7.7)	13.6(7.3)	13.9(7.2)	0.16
• Para-aortic (n=111)	6.1(5.1)	8.7(5.6)	8.8(12.6)	5.4(4.9)	0.051
Node involvement	21(22.3)	24(34.7)	18(41.8)	16(34.7)	1.130
Localization of positive nodes					
• Pelvic (n=248)	19/93 (20.4)	21/68 (30.8)	16/41 (39)	14/46 (30.4)	0.216
• Para-aortic (n=111)	5/36 (14.7)	10/38 (26.3)	6/21 (28.5)	5/18 (27.7)	0.461

EG3: poorly differentiated endometrioid carcinoma; USC: uterine serous carcinoma; CCC: clear-cell carcinoma; CS:carcinosarcoma.

(CCC), uterine serous carcinoma (USC), and carcinosarcoma (CS).

The purpose of this study was to identify predictors factors of LN metastasis in high-grade EC: ECG3, USC, CCC and CS.

Materials and Methods

The authors performed a multicentric, retrospective cohort study from 2001 to 2014 involving three third-level hospitals in Spain (Hospital Universitario Miguel Servet Hospital in Zaragoza, Hospital Clínico San Carlos Hospital in Madrid, and Hospital Virgen del Rocío in Seville). EC was managed according to the same protocols and clinical guidelines [12]. A total of 1,509 EC were diagnosed during the study period, of which 373 were high-grade EC. The 252 (67.6%) LND performed for high-grade EC composed this study sample. LND was not performed in 121 (32.4%) patients due to surgical field problems or the presence of comorbidities for which prolonged surgery was not recommended. Patients with uterine sarcoma, EC G1-2, not treated with surgery or not LND (pelvic or para-aortic) were excluded from the study.

Histopathological examination was performed by two experts in gynecologic oncology pathology following WHO guidelines [13]. Tumor staging was done according to FIGO criteria [14]. In case of controversy, the sample was analyzed by another pathologist. Mixed mesodermal tumors (two different histological types which constituted at least 5% of tumour volume) were re-categorized according to the subtype with the worst prognosis.

The authors assessed the predictive value for LN metastasis of the following factors: myometrial invasion, lymphovascular space involvement (LVSI), isthmus affectation, tumor size, presurgical CA 12.5 value, Ki67 expression, and p53 immunohistochemistry in samples from hysterectomy. Informed consent was obtained from all patients. The study was approved by all local Ethics Committees.

Data on the study variables were collected from medical records and entered into a specific datasheet. For statistical analysis, the data obtained were transcribed into a computerized database using the Statistics Process Social Sciences 22.0 package.

Continuous variables were expressed as means and standard deviations (SD) and interquartile ranges (IQR). Comparisons were performed using ANOVA tests for normal distribution and Kruskal Wallis for abnormal distribution. Quantitative variables were compared by the X^2 test or Fisher's exact test when expected frequencies were small. Magnitude of association was assessed using odds ratio (OR) with a 95% confidence interval (CI). Statistical significance was defined as a p value less than 0.05.

Results

Of the 252 patients with high-grade EC that were included in the study, 94 had ECG3, 69 USC, 43 CCC, and 46 CS. The mean number of isolated LN was 14.04 for the pelvic region (SD 7.34; IQR 9) and 7.34 for the para-aortic region (SD 7.31; IQR 8). No significant differences were observed in the number of LN resected according to their histological subtype (p = 0.161; para-aortic p = 0.051) (Table 1). Pelvic LND was performed in 248 patients (98.4%) and para-aortic in 111 (44%). LND was limited to the pelvic region in 141 (55.9%) patients, and to the para-aortic region in four (1.6%). LN were resected from the two regions in 107 (42.4%) patients .

The authors found positive LN in 79 of the 252 patients (31.3%). Metastasis was confined to pelvic LN in 70 patients (28.2%), to the para-aortic region in nine patients (8.1%), and involved the two regions in 15 patients (14%). No differences were observed among the four histological high-grade subtypes (p = 1.130) (Table 1).

Deep myometrial invasion (OR 6.006 IC 95%: 2.715-13.287 p = <0.001), LVSI (OR 11.805 IC 95%: 5.829-23.907, $p \leq 0.001$), isthmus affectation (OR 5.481 IC: 95% 2.743-10.952, $p \leq 0.001$), and abnormal presurgical CA 12.5 value (p = 0.006) were significantly associated with the presence of metastasis confirmed by histological examination. The remaining factors included in the study were not observed to have any predictive value for LN metastasis (Table 2).

The risk for LN metastasis was calculated using the uterine predictors identified, according to whether the tumor was or not endometrioid. Deep myometrial invasion and LVSI were mostly risk factors for LN metastasis in endometrioid EC, whereas isthmus affectation involved a higher risk for LN metastasis in non-endometrioid EC (Table 3).

Discussion

Deep myometrial invasion, LVSI, isthmus affectation, and presurgical CA 12.5 levels were found to predict LN metastasis in high-grade EC. Given the association between high-grade EC and LN metastasis, it is not surprising that the rate of LN metastases for the study sample was high

Table 2. — *Predictor factors of metastatic lymph nodes.*

	Positive Nodes (n = 79)	*Negative Nodes (n = 173)*	*p value**
Myometrial invasion < 50%	9/85 (10.6)	76/85 (89.4)	<0.001
Myometrial invasion > 50%	70/167 (41.9)	97/167 (58.1)	
LVSI−	15/142 (10,5)	127/142 (89,5)	<0.001
LVSI+	65/110 (59.1)	45/110 (40.9)	
Isthmus−	37/176 (21.1)	139/176 (78.9)	<0.001
Isthmus+	45/76 (59,3)	31/76 (40,7)	
Tumor size, cm	2.2 (37)	2.4	p=0.492
CA 12.5, U/L	47.3 (684.2)	98.1	0.006
Ki67 expression, % §	69.8 (38)	65.5	0.491
p53 < 50% δ	12/46(26.1)	34/46(73.9)	0.374
p53 > 50%	14/73 (19.2)	59/73 (80.8)	

*Data are shown as median (interquartile range) or cases (%). *The t-test in variables with normal distribution, Mann-Whitney U test for the other continuous variables, and W2 test or Fisher exact test indiscrete variables. δ was measured in 123 patients. In 60 patients the value of immunohistochemical overexpression was > 50%. § was measured in 100 patients.*

Table 3. — *Predictor factors of metastatic lymph nodes depending on the histology*

LN involvement	OR (95%CI)	*p* value*
Myometrial invasion > 50%		
Endometrioid EC	8.936 (1.124-71.045)	0.038
No endometrioid EC ¥	6.445 (2.663-15.601)	< 0.001
LVSI		
Endometroid EC	16.765 (3.445-81.585)	< 0.001
No endometrioid EC ¥	11.628 (5.121-26.405)	< 0.001
Isthmus affectation		
Endometrioid EC	4.950 (1.201-20.397)	0.027
No endometrioid EC ¥	5.694 (2.524-12.824)	< 0.001

** The significance was calculated compared to poorly differentiated endometrioid carcinoma group. ¥ No endometrioid EC includes: uterine serous carcinoma, clear-cell carcinoma, and carcinosarcoma.*

(31.3%), which is consistent with the results of previous studies [2]. No differences were observed in the prevalence of LN metastasis among the four subtypes of high-grade EC, which is suggestive that LN metastasis is common to all subtypes. As LN metastasis has an important prognostic value in EC, research efforts are currently focused on identifying prognostic factors for nodal metastasis.

The Gynecologic Oncology Group's surgical pathology study of EC found that uterine risk factors were strong predictors of LN metastasis. The risk of LN metastases was 25% in women with deep myometrial invasion compared to 5% in women with superficially invasive tumor, whereas the presence of LVSI increased the risk of LN disease nearly four-fold. Most of the patients included in this study had endometrioid EC –primarily G1,2– and the percentage of patients with subtype II EC was very low (< 5%) [2].

In the present study, deep myometrial invasion was found to be significantly associated with higher risk of LN metastasis in all subtypes. A recent study concludes that in high grade EC with myometrial invasion > 50%, the risk of LN metastasis development is three- to five-fold times larger, which matches the present results [15]. However deep myometrial invasion was a factor with greater association to LN metastasis in subtype ECG3. It is consistent with previous reports of a higher probability of LN metastasis in non-endometrioid subtypes even without myometrial invasion [16].

LVSI is considered to be the first step of EC spread to the LN. LVSI has been associated with LN metastasis and could be highly valuable in predicting the risk for LN metastasis. It has been reported the LVSI space to be an independent prognostic factor with a negative predictive value for pelvic and para-aortic pelvic LN metastasis [17]. Deep myometrial invasion and LVSI are two crucial factors for the redefinition of risk groups of EC recurrence to guide adjuvant therapy. At present, low, intermediate, and high-intermediate risks have been introduced in the new risk groups classification [8].

Lower uterine segment or isthmus involvement can be easily verified during surgery. A correlation between isthmus involvement and LN metastasis in patients with EC has been documented [18]. In a classic study, Creasman *et al.* concluded that unlike tumors in the upper uterine corpus, isthmus involvement increases the risk for LN involvement by two-fold [2]. A multicentric study was conducted to assess the potential association between isthmus involvement, tumor size, and LN disease in high-grade EC. Tumor size ≥ 2 cm was associated with pelvic LN disease and lower uterine segment tumors were associated with pelvic and para-aortic LN disease [19]. Some experts recommend the intraoperative determination of tumor size and verification of myometrial invasion to guide decisions on whether to perform or not a LND [20]. In the present study, tumor size was not found to predict LN metastasis. A possible explanation is that it could be dependent on vasculolymphatic or myometrial invasion.

Several studies have investigated CA 12.5 preoperative value as a marker for EC and they have evaluated it as a predictive factor for LN metastasis [21, 22]. In the present study, presurgical level of CA 12.5 in blood was observed to be related to a higher probability of nodal involvement. Other authors such as Coronado *et al.* [6] and Baek *et al.* [23] also report a relationship between high CA 12.5 levels

and a higher probability of LN involvement in high-grade EC. Thus, CA 12.5 may serve as prognostic factor estimating the likelihood of extrauterine disease and consequently, assist the preoperative counseling of women with high-grade EC. However there is still some disagreement in the literature over what value of preoperative serum CA 12.5 is the "best" cut-off for predicting the likelihood of finding occult metastatic disease [24]. Therefore it would be necessary more studies in this area.

The Ki67 antibody recognizes proliferating cell nuclear antigens. This antibody has not been considered in research on EC as in other types of tumors such as breast or prostatic tumors. In the present study, Ki67 expression was found to be elevated in all histological subtypes, (mean value of 65.95%) being a marker of tumor aggressiveness, but it was not associated with a higher risk for LN metastasis. To the best of the present authors' knowledge, the predictive value of Ki67 for LN involvement in EC has not been assessed yet.

Immunohistochemical overexpression of p53 is associated with biologically aggressive and poorly differentiated EC. The interpretation of the results is not well standardized for CE. A value of strong immunohistochemical overexpression above 50% of p53 in the tumor is usually considered pathological [25]. When high- and low-grade histological subtypes were compared, it was proven to be a predictor of metastatic disease [26], although no research has been conducted on p53 ovexpression between high-grade EC. The present study showed that p53 expression above 50% was not associated with a higher risk for LN involvement.

The main limitation of this study was the limited number of patients with pelvic and para-aortic LND. It was performed in 67.6% of high-grade EC, depending on the intra-operative pathologic examination finding and the surgeon's criterion. Moreover it did not systematically include para-aortic LND that was performed only in 44% of patients. The strengths of the study are the inclusion of CS as a high-grade type and its multicentric design.

Conclusions

Nodal involvement at diagnosis is frequent in high-grade EC, without any significant differences among subtypes ECG3, USC, CCC, and CS. Myometrial invasion, LVSI, uterine isthmus affectation, and preoperative value of CA 12.5 were found to be predictors of lymph node metastasis in this type of tumors.

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Corresponding Author:
L. BAQUEDANO, M.D.
Eras 8
Mediana De Aragon
Zaragoza 50135 (Spain)
e-mail: lbaquedanome@hotmail.com