

# Factors Predictive of Retroperitoneal Lymph Node Metastasis in Endometrial Cancer



## Factores Preditivos de Metastização Ganglionar Retroperitoneal no Cancro do Endométrio

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### ABSTRACT

**Introduction:** It has been suggested that a complete staging may be safely omitted in endometrial carcinoma patients at low risk for lymph node metastasis. The purposes of our study were to explore the prognostic significance of pathologic factors for pelvic and paraaortic nodal spread and to validate the Mayo algorithm in order to identify patients in whom lymphadenectomy may be avoided.

**Material and Methods:** We conducted a retrospective review including 208 patients, regarding the evaluation of pathologic variables and nodal metastases. Statistical analysis was performed using the chi-square test, the Fisher exact test and the Student's *t*-test.

**Results:** Myometrial invasion > 50% ( $p < 0.001$ ), cervical invasion ( $p = 0.001$ ), lymphovascular space invasion ( $p = 0.003$ ) and positive peritoneal cytology ( $p = 0.03$ ) were significant predictors of retroperitoneal lymph node dissemination. Pelvic lymph node metastases were predictive of positive paraaortic lymph nodes ( $p < 0.001$ ).

**Discussion:** The Mayo algorithm identified patients without pelvic or paraaortic nodal metastases with a 98.4% negative predictive value (61/62). Myometrial invasion  $\leq 50\%$  and absence of cervical and lymphovascular invasion presented a negative predictive value of 98.8% (79/80).

**Conclusion:** Although the Mayo criteria predict a very low likelihood of retroperitoneal nodal metastases, the combination of myometrial invasion  $\leq 50\%$  and absence of cervical or lymphovascular invasion would have safely avoided lymphadenectomy in a larger number of women.

**Keywords:** Endometrial Neoplasms; Lymphatic Metastasis; Lymph Node Excision; Neoplasm Staging; Predictive Value of Tests; Retroperitoneal Space; Portugal.

### RESUMO

**Introdução:** Tem sido sugerido que o estadiamento completo possa ser omitido com segurança em doentes com carcinoma do endométrio e baixo risco de metástases ganglionares. Os objectivos do nosso trabalho foram a exploração do significado prognóstico de factores patológicos para disseminação ganglionar pélvica e para-aórtica e a validação do algoritmo da Clínica Mayo, de forma a identificar as doentes em que a linfadenectomia possa ser dispensada.

**Material e Métodos:** Efectuámos um estudo retrospectivo incluindo 208 doentes, para a avaliação de variáveis tumorais patológicas e metástases ganglionares. A análise estatística foi realizada através dos testes qui-quadrado, exacto de Fisher e *t* de Student.

**Resultados:** A invasão miometrial > 50% ( $p < 0,001$ ), a invasão do colo ( $p = 0,001$ ), a invasão dos espaços linfovasculares ( $p = 0,003$ ) e a citologia peritoneal positiva ( $p = 0,03$ ) constituíram preditores significativos de disseminação ganglionar retroperitoneal. A metastização ganglionar pélvica foi preditiva de metastização ganglionar para-aórtica ( $p < 0,001$ ).

**Discussão:** O algoritmo da Clínica Mayo identificou as doentes sem metástases nos gânglios pélvicos ou para-aórticos com um valor preditivo negativo de 98,4% (61/62). A combinação de invasão miometrial  $\leq 50\%$  e ausência de invasão cervical ou linfovascular apresentou um valor preditivo negativo de 98,8% (79/80).

**Conclusão:** Apesar de os critérios da Clínica Mayo predizerem uma probabilidade muito reduzida de metástases ganglionares retroperitoneais, a combinação de invasão miometrial  $\leq 50\%$  e ausência de invasão cervical ou linfovascular teria evitado a linfadenectomia num número superior de mulheres.

**Palavras-chave:** Espaço Retroperitoneal; Estadiamento de Neoplasia; Neoplasias do Endométrio; Metástases Ganglionares; Factores Preditivos; Linfadenectomia; Portugal.

### INTRODUCTION

Endometrial carcinoma stands as the most common gynaecological neoplasm in developed countries presenting in Portugal an annual incidence and mortality rates of 10.3 and 1.9 per 100,000 women, respectively. Based on clinical, histological and molecular profiling, two types of endometrial carcinoma have been described. Type I is responsible for 80% of the cases and is related to hyper-estrogenism (anovulation, nulliparity, late menopause, tamoxifen treatment and liver cirrhosis) affecting younger and obese women. It is of the endometrioid type, a well differentiated

tumour and with a better prognosis. Type II relates to an atrophic endometrium, rarely expresses hormone receptors, stands for the non-endometrioid histological type (clear cell, serous, carcinosarcoma) and is associated with deep myometrial invasion and frequent lymph node involvement. Overall, endometrial carcinoma affects mainly women who are in their sixth or seven decade of life, with an ever increasing incidence associated to increasing longevity and obesity. Early clinical manifestations, allowing for an early-stage diagnosis in more than 75% of the patients, a gener-

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ally favourable prognosis, with 5-year survival rates of 80 to 85%.<sup>1</sup> The FIGO (International Federation of Gynaecology and Obstetrics) surgical staging system, adopted in 1988, allowed for a better classification of patients in prognostic groups, helping to compare results between institutions and mainly contributing for a better adjustment of adjuvant treatment to prevent the risk of tumour recurrence (Table 1).<sup>2</sup>

We should refer to Protocol 33, developed by the Gynecologic Oncology Group, which has described the presence of extra-uterine disease in 22% of patients with endometrial carcinoma clinically-limited to the uterus, including pelvic lymph node territory involvement in 9% and para-aortic involvement in 5%.<sup>3</sup> In line with this study, systematic lymphadenectomy became a routine procedure following peritoneal lavage and biopsy of any suspicious lesion together with total extrafascial hysterectomy and bilateral salpingo-oophorectomy should be performed. The extension of anatomical dissection and number of lymph nodes for a correct evaluation were left to surgeon's consideration, according to the estimated risk of neoplastic invasion, without definition of low and high risk categories. Two decades later, surgical strategies are still non-standardized and the decision on therapy approach still depends on individual opinions, on patient's biotype, on surgeon's expertise or on time management in the operating room, creating controversy in the field.

Although regional lymphadenectomy is considered essential for complete endometrial carcinoma staging, the opponents to its systematic indication have suggested a subgroup definition of low-risk patients, based on tumour characteristics, in which the procedure may be omitted. We aim to identify predictive pathological factors of pelvic

and/or para-aortic lymph node involvement, allowing for the development of an algorithm aimed at considering the need for lymphadenectomy in accordance with patient's individual requirements, to be compared to the criteria used by the Mayo Clinic (Table 2).<sup>4</sup>

**MATERIAL AND MÉTHODS**

Our group of patients was selected through a retrospective analysis of medical records of 284 patients submitted to primary surgery due to endometrial carcinoma between 2002 and 2011. Lymphadenectomy was left to the surgeon's decision, according to pre and intraoperative pathological signs and the estimated risk related to individual comorbidities. We only included 208 patients submitted to total hysterectomy, bilateral salpingo-oophorectomy and pelvic and/or para-aortic lymphadenectomy, excluding 76 patients which were not submitted to lymph node dissection. Tested variables related with an eventual association with lymph node involvement included the patient's age, histological type, degree of differentiation and tumour diameter, depth of myometrial invasion and the presence or absence of neoplastic cells in peritoneal lavage. Cervical stromal or epithelial infiltration, lymphovascular invasion and dissemination through adnexae were also taken into account. All tumour-related factors were assessed by a pathologist. Patients' age was analysed as a continuous variable. Histological classification was established according to the WHO classification and the degree of glandular differentiation met FIGO recommendations. Tumours with histological degree 1 or 2 (G1/G2) were classified as low-grade. Deep myometrial invasion was defined as extending over its internal half or > 50%. Lymphadenectomy was

Table 1 - Surgical staging system for endometrial carcinoma (FIGO, 2009)

Stage	
I	Tumour confined to the uterine body
IA	None or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumour invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumour
IIIA	Tumor invades the serosa of the uterine body and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes, with or without positive pelvic lymph nodes
IV	Tumour invades bladder and/or bowel mucosa and/or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Table 2 - Mayo Clinic risk criteria of retroperitoneal lymph node involvement in endometrial carcinoma

Pathological factors	Low-risk	High-risk
Histological type	endometrioid	non-endometrioid
Histological degree	G1 / G2	G3
Myometrial invasion	≤ 50%	> 50%
Tumour diameter	≤ 2 cm	> 2 cm

considered as the removal of at least one lymph node. Pelvic and/or para-aortic dissemination was defined as lymph node structural involvement at the time of surgery. Tumour stage was determined according to the 2009 FIGO system. Patients were divided in three groups: positive pelvic lymph nodes group, regardless of para-aortic lymph node involvement status (GPP), positive retroperitoneal (pelvic or para-aortic) lymph nodes group (GRP) and positive para-aortic lymph nodes group, regardless of pelvic lymph node involvement status (GPAP). Statistical analysis was carried out using SPSS Statistics 17.0 software. Correlation between categorical variable pairs was tested by applying Fisher exact and chi-square tests, with the results expressed as an absolute number and as a percentage. We used Student's *t*-test for age distribution comparison. Correlations with a value under the 0.05 limit were considered as statistically significant and expressed rounded to the nearest thousandth.

## RESULTS

Our study included 208 patients, 87.0% in stage I, 3.8% in stage II and 9.2% in stage III. Mean ( $\pm$  SD) age was 64.7  $\pm$  8.6 (min. 46, max. 81): 68.8  $\pm$  8.4 patients in the GRP and 63.6  $\pm$  8.5 in the remaining groups. Table 3 presents the frequencies of pathological signs and lymph node involvement in our total group of patients.

Two-hundred and six patients (99.0%) were submitted to pelvic lymphadenectomy and 118 patients (56.7%) were submitted to para-aortic lymph node dissection. On average, 19.0 lymph nodes (min 4, max 47) and 4.5 para-aortic lymph nodes (min 1, max 10) were removed per patient;

we found that in 97.1% of pelvic lymphadenectomies, 10 or more lymph nodes were removed and in 46.6% of para-aortic lymphadenectomies at least five lymph nodes were removed. Tumour cell dissemination to pelvic lymph nodes was identified in 17 patients (8.3% of pelvic lymphadenectomies) and to para-aortic lymph nodes in six (5.1% of para-aortic lymphadenectomies), corresponding to 18 patients (five patients presented simultaneously positive pelvic and para-aortic lymph nodes). In the GRP group, the presence of deep myometrial invasion ( $p < 0.001$ ), cervical infiltration ( $p = 0.003$ ) and lymphovascular invasion ( $p = 0.002$ ) was related to lymph node dissemination. In the GRP group, the following factors showed a significant association to lymph node tumour invasion: deep myometrial invasion ( $p < 0.001$ ), cervical infiltration ( $p = 0.001$ ), lymphovascular invasion ( $p = 0.003$ ), patient's age ( $p = 0.02$ ) and positive retroperitoneal cytology ( $p = 0.03$ ) (Table 4).

In the GPAP group, pelvic lymph node invasion was a predictive factor for para-aortic lymph node invasion ( $p < 0.001$ ). In stage I endometrioid G1/G2 tumours, the presence of  $>50\%$  myometrial invasion was related with a 15% incidence of pelvic and/or para-aortic lymph node invasion. The presence of endometrioid-type G1/G2 tumour, with a diameter  $\leq 2$ cm and myometrial invasion  $\leq 50\%$  had a negative predictive value of 98.4% (61/62) for retroperitoneal lymph node dissemination. A simultaneous value of  $\leq 50\%$  myometrial invasion, the absence of cervical epithelial, stromal infiltration or lymphovascular invasion showed a negative predictive value of 98.8% (79/80), with an incidence of lymph node involvement in 15.3% of the patients that did not meet these criteria (Table 5).

**Table 3** - Distribution of 208 patients per stage, histological type and histological degree, according to definitive pathological examination

Pathological factors	N	%
<b>FIGO staging</b>		
IA	112	53.8
IB	69	33.2
II	8	3.8
IIIA	1	0.5
IIIC1	12	5.8
IIIC2	6	2.9
<b>Histological type</b>		
Endometrioid	184	88.5
Papillary serous	13	6.2
Mucinous	2	1.0
Clear cells	4	1.9
Squamous cells	2	1.0
Carcinosarcoma	3	1.4
<b>Histological degree</b>		
G1	130	62.5
G2	57	27.4
G3	21	10.1

## DISCUSSION

The diagnostic value of lymphadenectomy is well established, unlike other methods of retroperitoneal lymph node chain pre and intraoperative assessment.<sup>5</sup> In addition, lymph node status is an important predictor in clinical stage I, with a recurrence odds ratio six times higher when invasion is confirmed (48 *versus* 8%).<sup>6</sup> Procedure morbidity has been the main argument against its systematic use, taking into account the advanced age of most patients and the frequency of comorbidities.<sup>7</sup> The complexity of lymphatic drainage of the uterus hinders sentinel node detection, which is a promising minimally-invasive alternative. Several techniques for lymphatic mapping and injection location have been attempted, although validation is limited by detection and sensitivity rate heterogeneity, lack of reproducibility and the need to show a clear cost-benefit advantage.

However, establishing if lymphadenectomy really involves a diagnostic (leading to an improvement in the adjuvant therapy approach) or therapeutic benefit (directly influencing overall disease-free survival rate) is the real issue on which individual risks are based. Among prospective trials and although limited by the lack of criteria uniformity for lymphatic dissection and adjuvant radiotherapy and by the reduced number of lymph nodes removed, the ASTEC study included 1,408 patients from 85 healthcare

**Table 4** - Frequency of tumour variables in 208 patients and percentage of pelvic and/or para-aortic lymph node involvement

Pathological factors	Patients n / %	Positive nodes n / %	p
> 50% Myometrial invasion	89 / 42.8	25 / 28.1	< 0.001
Cervical infiltration	28 / 13.5	12 / 42.9	0.001
Lymphovascular invasion	75 / 36.1	25 / 33.3	0.003
Positive peritoneal cytology	38 / 18.3	12 / 31.6	0.030
Tumour diameter > 2 cm	126 / 60.6	30 / 23.8	0.120
Adnexae dissemination	2 / 1.0	1 / 50.0	0.280
Non-endometrioid type	24 / 11.5	7 / 29.2	0.370
G3	21 / 10.1	4 / 19.0	0.650

Exact Fisher and Chi-square tests

**Table 5** - Negative predictive value of the decision algorithms for omitting lymphadenectomy in staging surgery for endometrial carcinoma

Endometrioid type G1 / G2 ≤ 50% Myometrial invasion Tumour diameter ≤ 2 cm	≤ 50% Myometrial invasion Absence of cervical invasion Absence of lymphovascular invasion
98.4% NPV	98.8% NPV

institutions and did not show any statistical difference on 5-year survival rate between surgical arms with and without pelvic lymphadenectomy.<sup>8</sup> In addition, PORTEC-2 study rejected any benefit. In a group of 514 patients with clinical stage I endometrial carcinoma, Panici *et al.* limited lymphadenectomy utility to more correct staging, without any effect on 5-year survival rate and with significant morbidity increase. Time interval between recurrence diagnosis was also similar between both arms (14 *versus* 13 months).<sup>9</sup> A randomized meta-analysis including 1,945 stage I patients showed no evidence that lymphadenectomy may reduce the risk of death or recurrence.<sup>10</sup>

In this ongoing debate, in order to avoid under or overtreatment, a consideration of predictive factors of regional lymph nodes involvement is advisable. Therefore, a new trend has emerged assuming both the presence of a group of patients without the need for complete surgical staging, based on an estimated low-risk of lymph-node involvement and one other high-risk group that may benefit with this staging for diagnostic purposes. The analysis of these clinical and pathological factors was discussed in several publications.<sup>11,12</sup> In line with our results, the group led by Tang has identified deep myometrial invasion, cervical infiltration and lymphatic permeation as pathological factors of retroperitoneal lymphatic involvement risk in 310 patients, with a negative odds ratio of 5.97; 2.72 and 12.01, respectively.<sup>13</sup> The importance of lymphovascular invasion has also been confirmed, with a negative predictive value of 95.6% on a group of 628 patients.<sup>14</sup> Regarding cervical invasion, its presence had been associated with pelvic

involvement risk of 15%, about three times lower than we have estimated when considering for stromal and/or epithelial involvement.<sup>15</sup> Interestingly, the identification of tumour cells in peritoneal lavage did not represent a relevant predictive factor in the GRP group, although correlation became statistically significant in the GRP group. With a 10 to 17% incidence in patients with endometrial carcinoma, positive peritoneal cytology is more frequent in the presence of extra-uterine disease.<sup>16</sup> Data indicate that it may be a negative prognostic marker, reinforcing other detrimental indicators, without a consensus being reached for the single presence of extra-uterine disease as independent factor.<sup>17</sup>

Pelvic lymph node involvement is a predictive factor for para-aortic lymphatic dissemination, found in 29.4% of patients with positive pelvic lymph nodes. Incidences described in previous publications vary widely between 32 and 80%, which seems to represent the influence of invaded pelvic nodes and of pathological pattern of lymphatic involvement.<sup>18</sup> On the contrary, the presence of para-aortic lymph node involvement without neoplastic invasion of pelvic lymph nodes is relatively rare, between 0 and 6%.<sup>19</sup> Single para-aortic dissemination, with an incidence of 0.05% in our study, may be explained by the presence of a direct dissemination pathway from the uterine body through infundibulopelvic ligament or, as an alternative, by the presence of a hidden disease in the pelvic lymph nodes, not identified in routine histology.

Lee *et al.* found 0.47% of lymphatic involvement in 834 patients with endometrioid type G1/G2 carcinoma, reinforcing the significance of histological classification and



myometrial invasion depth, while Cusidó *et al.* found the presence of pelvic and/or para-aortic invasion in 37% of the patients with > 50% myometrial infiltration and in 45.5% of G3 tumours.<sup>20,21</sup> In our study, > 50% myometrial invasion was the strongest risk-factor of lymphatic involvement. Even with endometrioid-type low-grade tumours, the presence of deep myometrial invasion determined a 15% risk of pelvic and/or para-aortic lymph node involvement, higher than the 9% risk obtained by Kwon *et al.* in the same context.<sup>22</sup> In a previous multivariable analysis, when evaluated along with the distance of the tumour to the serosa and taking into account the percentage of invaded myometrium, myometrial invasion depth showed to be a single independent risk factor.<sup>23</sup> Although of no statistical relevance, we found a trend towards a correlation between retroperitoneal invasion incidence and a tumour diameter > 2 cm. The predictive value of this variable was referred by Schink *et al.*, when studying a group of 142 women with clinical stage I endometrial carcinoma, detecting the presence of lymphatic involvement in 4% of the patients with tumours ≤ 2 cm and in 15% of patients with tumours > 2 cm.<sup>24</sup> The group of Mariani showed the absence of dissemination in lymphadenectomy specimens in patients with endometrioid G1/G2 carcinoma with ≤ 50% myometrial invasion and measuring ≤ 2cm, as opposed to the record of lymphatic invasion in 22% of the remaining patients.<sup>4,25</sup> The algorithm adopted by Mayo Clinic was recently applied by other authors using the Kaplan-Meier method, with a lymph node involvement incidence of just 1.8% among the 110 patients meeting criteria.<sup>26</sup> In Portugal, the combination of these factors identified those patients with stage I endometrial carcinoma in whom lymphadenectomy could be omitted, with a negative predictive value of 98.4%. When the factors that were associated in our study with a low-risk of lymph node involvement (≤ 50% myometrial invasion, absence of cervical and lymphovascular invasion), were included as selection parameters, we obtained a slightly higher

negative predictive value (98.8%). We should emphasize that, using these criteria, retroperitoneal lymphadenectomy would have been safely omitted in 79 patients (38.0%), allowing for a favorable comparison with the application of Mayo Clinic's algorithm and in this way overtreatment would have avoided in 61 patients in our group (29.3%). We are aware of the limitations concerning the heterogeneity of our sample and number of patients with positive nodes that were included in the study, which prevented the application of regression analysis. Moreover, the difficulty in assessment of lymphovascular invasion in peroperative histological examination is emphasized. Finally, the small average number of removed para-aortic nodes requires a confirmation of the reproducibility of the results. This study represents a local validation of an algorithm adopted through a national consensus. Although originally developed in USA Midwest population in which there is a small percentage of Portuguese descendants, it seems to be quite relevant.

## CONCLUSION

We confirm that pelvic and para-aortic lymphadenectomy can be omitted in stage I endometrioid type G1/G2 endometrial carcinoma, with a tumour diameter ≤ 2 cm and ≤ 50% myometrial invasion, with the advantage of avoiding a surgical complete staging in a higher number of patients. However, negative predictive value of ≤ 50% myometrial invasion with the absence of cervical invasion for retroperitoneal lymphatic involvement was slightly higher in our group of patients.

## CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

## FINANCIAL SOURCES

There were no external financial sources in the writing of this manuscript.

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