

Surgical treatment of endometrial cancer in developing countries: reasons to consider systematic two-step surgical treatment

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OBJECTIVE : The aim of this study was to determine the lymph node status in a large cohort of women with endometrial cancer from the public health system who were referred to an oncology reference center in Brazil to identify candidates for the omission of lymphadenectomy based on clinicopathological parameters.

METHODS : We retrospectively analyzed a cohort of 310 women with endometrial cancer (255 endometrioid, 40 serous, and 15 clear cell tumors) treated between 2009 and 2014. We evaluated the histological type, grade (low vs. high), tumor size (cm), depth of myometrial invasion ($\leq 50\%$, $> 50\%$) and lymphovascular space invasion to determine which factors were correlated with the presence of lymph node metastasis.

RESULTS : The factors related to lymph node involvement were tumor size ($p=0.03$), myometrial invasion ($p<0.01$), tumor grade ($p<0.01$), and lymphovascular space invasion ($p<0.01$). The histological type was not associated with the nodal status ($p=0.52$). Only twelve of 176 patients (6.8%) had low-grade endometrioid carcinoma, tumor size ≤ 2 cm and $< 50\%$ myometrial infiltration.

CONCLUSIONS : The omission of lymphadenectomy based on the histological type, grade, tumor size and depth of myometrial invasion is not likely to have a large impact on the surgical treatment of endometrial cancer in our population because most patients present with large and advanced tumors. New strategies are proposed that prioritize hysterectomy performed in a general hospital as soon as possible after diagnosis, followed by an evaluation of the need for lymph node dissection at a reference center.

KEYWORDS: Endometrial cancer; Lymph node dissection; Myometrial invasion; Lymphovascular space invasion; Surgery.

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INTRODUCTION

Endometrial cancer is among the most frequently diagnosed malignancies of the female genital tract in industrialized nations (1). Although this disease is 10 times more common in developed countries than in the developing world, the incidence of and the mortality related to endometrial cancer have increased dramatically in underprivileged regions in past decades, and this neoplasm will certainly constitute a major health care problem in the near future (2).

Since 1988, the international scientific agenda regarding endometrial cancer has been dominated by a debate about nodal dissection. Although there have been technical discussions about the most appropriate surgical approach for treating endometrial cancer, regional disparities in access to proper oncologic therapies have rarely been discussed in the literature (3,4). Intuitively, one may assume that insufficient human resources and medical technology are available in the developing world. The lack of professionals with advanced surgical expertise and the ability to perform retroperitoneal lymphadenectomy is evident. In addition, many cancer institutions in the developing world cannot offer adequate operative treatments to meet patient demand. This situation poses major difficulties in implementing standard oncologic therapies and results in unacceptable treatment delays that may lead to tumor progression and can negatively impact survival (5). Thus, the scientific discussion of lymphadenectomy in the developed world may be considered distant from

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the realities of the great number of women in developing countries who are affected by the disease (5).

Several algorithms have been designed to guide the selective omission of nodal dissection in patients with endometrial cancer (6–11). The Mayo Clinic criteria (12), which are based on histological type, differentiation grade, tumor size, and myometrial invasion, are the most commonly applied. The presence of lymphovascular space invasion (LVSI) has also been used to predict lymph node (LN) metastasis (13). Although this algorithm was independently validated (10), it has never been tested in a large cohort of women in Brazil.

Following the 2009 release of guidelines for the surgical staging of endometrial cancer by the International Federation of Gynecology and Obstetrics (FIGO) (14) and because of the current lack of consensus regarding the importance of retroperitoneal lymphadenectomy (9,15,16), our institution initiated a protocol in 2009 in which all patients with clinical disease are considered candidates for complete surgical staging with pelvic and para-aortic nodal dissection, independent of prognostic risk factors.

The primary study objective was to use the Mayo Clinic algorithm to determine the percentage of patients in our institution for whom LN dissection could be avoided. The secondary objective was to determine whether these criteria are as useful in Brazil as they were found to be in the previous validation study (10).

PATIENTS AND METHODS

After receiving ethics review board approval (ICESP no. 394/13), we conducted a retrospective study of patients with endometrial cancer who underwent primary surgical treatment at the Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, Brazil, between January 2009 and February 2014. We included all patients with histologically confirmed endometrial carcinoma (FIGO stages Ia–IIIc2) and no evidence of extrapelvic disease on initial imaging staging (computed tomography or magnetic resonance imaging) who underwent primary operative therapy that included total hysterectomy with bilateral salpingo-oophorectomy. We excluded patients who had received neoadjuvant therapies and those who did not undergo a total hysterectomy with bilateral salpingo-oophorectomy.

The medical records of all patients were reviewed, and the following epidemiologic and operative information was collected: age at diagnosis, surgical route (laparoscopic, laparotomic, or vaginal), and the magnitude of the procedure (complete staging with pelvic and para-aortic LN dissection, incomplete staging with only pelvic or para-aortic LN dissection, or lack of nodal dissection). Pathological analyses were performed at the institution's central laboratory. Tumors were classified according to the World Health Organization criteria as endometrioid (endometrioid or mucinous) or non-endometrioid (serous or clear cells). Endometrioid tumors were classified according to FIGO criteria (14) as low grade (1 or 2) or high grade (3). Non-endometrioid histology was considered high grade. Data on tumor size (\leq or $>$ 2 cm), the depth of myometrial invasion (\leq 50% or $>$ 50%), and LVSI were obtained from the pathological descriptions.

The final tumor staging was established according to the FIGO 2009 classification (14). The patients included in the study were divided into two major groups according to their

surgical staging. Group 1 comprised women for whom lymphadenectomy was omitted or who underwent incomplete nodal dissection for diverse reasons, including poor clinical condition, massive LN involvement, or intraoperative complications. Group 2 comprised women who underwent pelvic and para-aortic lymphadenectomy and who were categorized as LN positive (LN+) or LN negative (LN-).

Statistical analysis

The associations between LN metastasis and histological parameters, tumor size, myometrial invasion, tumor grade, and LVSI were assessed using chi-squared tests. The statistical analyses were performed using MedCalc for Windows (version 11.5.0.0; MedCalc Software, Mariakerke, Belgium), and *p*-values $<$ 0.05 were considered significant.

RESULTS

The cohort comprised 310 patients (134 [43%] in group 1 and 176 [57%] in group 2). The mean patient age was 64 ± 10.2 (range, 32–86) years. In group 1, no LN dissection was performed in 119 (38%) patients, and only pelvic or para-aortic LN dissection was performed in 15 (5%) patients. Most ($n=192$ [62%]) of the surgeries were laparoscopic, and laparotomy was performed in 138 (38%) patients.

According to the histological analysis, 255 (82.3%) tumors were endometrioid, 40 (12.9%) were serous, and 15 (4.8%) were clear cell tumors. Table 1 summarizes the pathological characteristics of the patients in groups 1 and 2. No differences in age, histology, grade, tumor size, myometrial infiltration, or LVSI were observed between the groups (Table 1).

Among the patients in group 2, the median numbers of pelvic and para-aortic LNs dissected were 14 (range, 1–47) and 9 (range, 1–41), respectively. Table 2 shows the pathological features of the surgical specimens according to the participant's LN status. The risk of LN involvement was related to the tumor size ($p=0.03$; OR 0.13 [0.01-0.90]), depth of myometrial invasion ($p<0.01$; OR 0.18 [0.07-0.44]), LVSI ($p<0.01$; OR 0.14 [0.06-0.33]), and grade ($p=0.01$; OR 0.39 [0.18-0.85]) but not to histological type ($p=0.52$; OR 0.77 [0.32-1.99]). Twelve of the 176 (6.8%) patients in group 2 fulfilled the Mayo Clinic criteria for the omission of LN dissection (endometrioid carcinoma with tumor size \leq 2 cm, \leq 50% depth of myometrial infiltration, and low grade).

DISCUSSION

Surgeons have not reached a consensus regarding the advantages of LN dissection for all patients with endometrial cancer. Almost three decades after FIGO recommended including lymphadenectomy in the surgical treatment of endometrial cancer, much doubt remains about the extension and benefits of this procedure (15,17,21). Even in reference centers, complete LN dissection increases morbidity, operative time, and treatment costs (22,23). Many algorithms have been proposed to predict LN involvement and to stratify patients according to their need for a lymphadenectomy (12,24). The most commonly used parameters are histological type, grade, tumor size, myometrial invasion (9), tumor markers (25), LVSI (13), and imaging characteristics (26).

Mariani et al. (12) proposed the use of the Mayo Clinic algorithm to predict LN involvement in endometrial cancer. Patients with low-grade endometrioid carcinoma, tumor size



Table 1 - Age and pathological characteristics of 310 patients with endometrial carcinoma.

Characteristic	All patients	Complete surgical staging (group 2)	Incomplete surgical staging (group 1)	p-value
Age (years), mean (range)	63 (32–86)	64 (32–86)	63 (36–85)	
Histology				0.14
Endometrioid	255 (82.3%)	116 (86.6%)	140 (79.5%)	
Non-endometrioid	55 (17.7%)	18 (13.4%)	36 (20.5%)	
Tumor size				0.22
≤2 cm	42 (13.5%)	22 (16.4%)	20 (11.4%)	
>2 cm	178 (57.4%)	70 (52.2%)	108 (61.3%)	
Unknown	90 (29.0%)	42 (31.3%)	48 (27.3%)	
Myometrial invasion				0.13
≤50%	158 (53.0%)	77 (57.5%)	81 (46.0%)	
>50%	140 (46.9%)	53 (39.5%)	87 (49.4%)	
Unknown		4 (3.0%)	8 (4.6%)	
Tumor grade				0.25
Low (1–2)	222 (71.6%)	101 (75.4%)	121 (68.7%)	
High (3 and non-endometrioid)	88 (28.4%)	33 (24.6%)	55 (31.3%)	
LVSI				0.40
No	197 (63.6%)	89 (66.4%)	108 (61.3%)	
Yes	104 (33.5%)	40 (29.8%)	64 (36.4%)	
Unknown	9 (2.9%)	5 (3.7%)	4 (2.3%)	

Data are presented as n (%) unless otherwise noted. LVSI, lymphovascular space invasion.

<2 cm, and ≤50% myometrial invasion are considered to be at low risk of LN involvement and are thus candidates for lymphadenectomy omission. These criteria indicated that lymphadenectomy was not required for 27% of patients (all low risk) and 33% of endometrioid cases (12). Despite the omission of lymphadenectomy, the 5-year cause-specific survival rate was 99.0%. This intraoperative algorithm has been validated in two independent studies (12,24)

Comparing our population to that examined by Mariani et al. (12), we found that 20% vs. 18% of cases were classified as the non-endometrioid histological subtype, 72% vs. 68% of tumors were low grade, and 77% vs. 46% of tumors had ≤50% myometrial invasion. In addition, only 11% of our patients presented a tumor size ≤2 cm. Mariani et al. (12) determined that 27% of all patients and 33% of patients with endometrioid tumors fulfilled the criteria for lymphadenectomy omission; in contrast, only 6.8% of the patients in our population fulfilled these criteria. Most of our patients

presented with deep myometrial invasion and large tumors; thus, the use of the Mayo Clinic criteria is unlikely to have a large impact on surgical treatment in a population such as ours.

LVSI is another strong predictor of LN metastasis (13). In the presence of LVSI, an overall recurrence rate of 17% has been reported (27), along with a hazard ratio of 4.9 ($p=0.000$) that increased to 8.8 ($p=0.004$) when the LNs were positive (28). The estimated 5-year survival rates of patients with stage IIIc endometrial cancer with and without LVSI are 50.9% and 93.3%, respectively ($p=0.0024$) (29). Thus, LVSI is associated with a high risk of recurrence and poor overall survival, even in the early stages of endometrial cancer (30).

The main characteristics of endometrial cancer in our Brazilian population were large tumors, deep myometrial invasion, and a high rate of LVSI. This presentation of more advanced disease may be associated with difficulties in providing timely oncologic treatment for all cases within the

Table 2 - Tumor parameters according to lymph node status in 176 patients with surgically staged endometrial carcinoma.

Parameter	All patients	Lymph node positive	Lymph node negative	p-value	OR (95% CI)
Histology				0.52	0.77 (0.32–1.99)
Endometrioid	140 (79.5%)	32 (76.2%)	108 (80.6%)		
Non-endometrioid	36 (20.5%)	10 (23.8%)	26 (19.4%)		
Tumor size				0.03	0.13 (0.01–0.90)
≤2 cm	20 (11.4%)	1 (2.4%)	19 (14.2%)		
>2 cm	108 (61.3%)	31 (73.8%)	77 (57.5%)		
Unknown	48 (27.3%)	10 (23.8%)	38 (28.3%)		
Myometrial invasion				< 0.01	0.18 (0.07–0.44)
≤50%	81 (46.0%)	8 (19.0%)	73 (54.5%)		
>50%	87 (49.4%)	33 (78.6%)	54 (40.3%)		
Unknown	8 (4.6%)	1 (2.4%)	7 (5.2%)		
Tumor grade				0.01	0.39 (0.18–0.85)
Low (1–2)	121 (68.7%)	22 (52.4%)	99 (73.9%)		
High (3 and non-endometrioid)	55 (31.3%)	20 (47.6%)	35 (26.1%)		
LVSI				< 0.01	0.14 (0.06–0.33)
No	108 (61.3%)	12 (27.3%)	96 (72.7%)		
Yes	64 (36.4%)	30 (68.2%)	34 (25.8%)		
Unknown	4 (2.3%)	2 (4.5%)	2 (1.5%)		

Data are presented as n (%). OR, odds ratio; CI, confidence interval; LVSI, lymphovascular space invasion.



public health system. New strategies are thus needed to address the challenge of providing adequate treatment. We believe that it is most important to consider offering early hysterectomy with bilateral salpingo-oophorectomy to all patients as soon as possible after diagnosis. LN dissection should be postponed until patients have been evaluated at a reference center.

Developing countries lack sufficient numbers of reference centers that perform oncologic surgery. In Brazil, and likely in many other countries, patients with endometrial cancer have two options: (1) undergoing a simple hysterectomy and salpingo-oophorectomy at a general hospital, in discordance with the protocol proposed by FIGO, or (2) waiting for several months until treatment can be provided at one of the few reference centers. General obstetricians and gynecologists are discouraged from surgically treating endometrial cancer, even in cases of clinical suspicion, because they are not sufficiently trained in LN dissection. When patients finally arrive at reference centers, the disease is often advanced, and tumors are large; in such scenarios, discussions about whether to perform LN dissection are not relevant. In our opinion, the main issue is determining how to reduce the interval between diagnosis and surgical treatment at existing general hospitals.

The delayed diagnosis of endometrial cancer has been demonstrated to impact survival rates. In a retrospective study of 190 postmenopausal patients with symptomatic endometrial cancer and 123 asymptomatic patients with suspicious endometria detected with transvaginal ultrasound, the 5-year disease-free survival rates were 74% and 62% in patients with ≤ 8 weeks and > 16 weeks of bleeding, respectively (31). Delayed surgical treatment can reasonably be considered to have the greatest impact on patients with cancer diagnoses compared with other patient groups. We believe that efforts should be made to perform a hysterectomy while the disease is still in an early stage with a low probability of LN metastasis. For patients with early-stage disease, LN dissection has no benefit; in fact, it increases morbidity and mortality. Previous studies have shown that LN dissection with customized adjuvant treatment has a potential advantage only in patients with LN positivity (32,33); even among these patients, the benefits of systematic LN dissection are questionable (15).

To overcome current obstacles to the surgical treatment of endometrial cancer in Brazil, we recently proposed a two-step approach to the systematic management of the condition (34). In this approach, women with type I endometrial cancer undergo total extrafascial hysterectomy with bilateral salpingo-oophorectomy but without nodal dissection upon diagnosis. Following this primary intervention, all women are referred to cancer centers, where specialists evaluate the clinical and pathological risk factors based on the analysis of surgical specimens. Decisions about the need for an eventual reoperation to perform retroperitoneal lymphadenectomy are based on the risk of nodal metastasis. We consider that an early simple hysterectomy performed by a general gynecologist in a general hospital would be more advantageous for these women than delayed, albeit supposedly ideal, surgery. If necessary, lymphadenectomy is performed in a tertiary hospital. A large, collaborative, prospective study should be performed to evaluate the impacts of this innovative strategy on morbidity, mortality, and treatment cost in patients with endometrial cancer, particularly in developing countries.

In conclusion, the prediction of LN involvement based on histology, grade, tumor size ≤ 2 cm and $\leq 50\%$ myometrial invasion appears unlikely to have a large impact on surgical treatment of endometrial cancer in the Brazilian population. Our patients presented with larger and more advanced tumors, generally associated with delayed treatment. To address this situation in Brazil, we consider recommending performing a hysterectomy at a general hospital as soon as possible after diagnosis and later evaluating the need for LN dissection at a reference center. However, prospective studies to evaluate the morbidity, feasibility and cost of this systematic two-step surgical treatment need to be conducted before a national recommendation is made.

AUTHOR CONTRIBUTIONS

Anton C collected the data, analyzed the samples and wrote the paper. Favero G and Köhler C analyzed and interpreted the samples. Carvalho FM revised the pathological reports. Baracat EC participated in the study design. Carvalho JP conceived the study and analyzed the samples.

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