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Original Research

Low-risk endometrial carcinoma: is it time to subclassify it?

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Summary

Objective: Endometrial cancer in Argentina represents the second most frequent gynecological cancer, accounting for 6% of all cases of cancer in women. The prognostic significance of lymphovascular space invasion (LVSI) and the patterns of tumor penetration in patients with FIGO Stage IA endometrial adenocarcinoma have not been established. The authors sought to determine if the pattern of tumor penetration and the LVSI status in patients with early-stage, low-risk endometrial cancer are correlated with recurrence and survival. *Materials and Methods:* The records of all women who underwent hysterectomies for the primary treatment of endometrial cancer from June 2010 to June 2015 at the Hospital Italiano de Buenos Aires were reviewed. Patients with Grade 1 or 2 endometrioid histology and FIGO Stage IA endometrial adenocarcinoma were analyzed. Fisher's exact test and the Wilcoxon rank-sum test were used to compare patients with different types of tumor penetration [expansive or infiltrative/microcystic elongated and fragmented (MELF)] and different LVSI status. Recurrence-free survival (RFS) and overall survival (OS) were calculated using the Kaplan-Meier method. *Results:* Eighty-two (n = 82) patients met the inclusion criteria. Those patients without myometrial infiltration (M0) were excluded (n=72). Fourteen (17%) had LVSI. Fifty-one (62.19%) had an expansive type of penetration, 20 (24.39%) had an infiltrative type of penetration, and only 11 (13.41%) had a MELF type of penetration. The authors recorded six (7.31%) cases of recurrence after a mean follow-up period of 1,368 days (3.8 years). Five of those six cases had recurrences at the vaginal cuff, and one had recurrence in the peritoneum. It was possible to confirm a statistically significant relation between LVSI and the recurrence index. The incidence of recurrence in patients with LVSI was 35%, and in patients without LVSI, it was 0.7% ($p < 0.000$). No correlation between the type of tumor penetration and the incidence of recurrence was demonstrated in this study. *Conclusion:* Patients with low-risk endometrial cancer and LVSI have worse RFS and OS. No correlation between the type of tumor penetration and the incidence of recurrence was demonstrated in this study.

Key words: Endometrioid endometrial cancer; Lymphovascular space invasion; Pattern of tumor penetration; Recurrence; Survival

Introduction

Endometrial cancer is the second most frequent gynecologic malignancy in Argentina, accounting for 6% of all cases of cancer in women [1]. Approximately 75% of patients have Stage I or II cancer according to FIGO (International Gynecology and Obstetrics Federation) staging system at the time of diagnosis. The overall survival rates are 91% and 74% in Stages I and II, respectively, and the rates decrease to 57% and 20% in Stages III and IV, respectively [2].

In the 1980s, Bokhman described two distinct type of tumors: type 1 tumors are estrogen dependent and are associated with endometrial hyperplasia and a good prognosis, and type 2 tumors are estrogen independent and are associated with endometrial atrophy and a worse prognosis [3].

When we refer to low-risk endometrial cancer, we include tumors with the following characteristics: endometrioid carcinoma, the most frequent type in the Bokhman's type I classification and clinical stages limited to the uterus (FIGO Stage I). This subgroup has a five-year recurrence rate of approximately 7% to 13%, according to different publications [4]. Recurrence has been related to age, histological grade, tumor size, and myometrial invasion.

For several years, different groups have evaluated the presence of lymphovascular space invasion (LVSI) and the pattern of tumor penetration [expansive or infiltrative/microcystic elongated and fragmented (MELF)] as predictors of relapse, but there is no clear relationship between these factors and the patient's risk of recurrence and survival [5]. The relationship between LVSI and a worse prognosis is mentioned in several studies. One of the most important studies is that by O'Brien *et al.*, who demonstrated the negative impact of LVSI on survival rates in women with low-risk endometrial tumors [6].

When referring to myometrial patterns of invasion, the tumor may compromise the myometrium in an expansive way, in an irregular form. or in an infiltrative way.

The objective of this study is to determine if the type of tumor penetration and LVSI status in patients with early-stage, low-risk endometrial cancer are correlated with recurrence and survival.

Materials and Methods

This study was approved and controlled by the Ethical Investigation Protocol Committee (CEPI) at the Hospital Italiano in

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Buenos Aires. The files of patients who had been diagnosed with endometrial cancer between June 2010 to June 2015 at the Gynecologic Oncology Department of this institution were retrospectively reviewed. All patients diagnosed with Grade I or II endometrioid adenocarcinomas with less than 50% myometrial invasion confined to the uterus (FIGO IA) in the hysterectomy specimens were included in this analysis. All identified cases had histologic material available for review by at least one gynecologic pathologist at this institution.

These patients were excluded: component of high-grade carcinoma, cases with a synchronous primary tumor, and patients with a follow-up time shorter than 43 months. All patients included in the study had a histological diagnosis of endometrioid endometrial adenocarcinoma obtained by hysteroscopic biopsy or curettage at our institution prior to surgery.

All patients underwent a pre-treatment evaluation, including a physical examination and MRI study. Primary surgery included a total hysterectomy, with or without bilateral salpingo-oophorectomy. Pelvic, para-aortic, or both pelvic and para-aortic lymphadenectomy was performed according to the results of the intraoperative frozen-section analysis.

The variables evaluated in this study included the following: age, BMI, history of previous cancer, imaging, follow-up period, surgical approach (minimally invasive or open surgery), histological type, depth of myometrial invasion, pattern of tumor invasion, presence of LVSI, tumor size (measured in millimeters), stage prior to and after surgery, and time to relapse.

The literature describes two additional arrays of tumor invasion: 1) MELF is composed of slit-like, microcystic glands lined by a cubic-to-flattened epithelium with an eosinophilic cytoplasm and is usually associated with a fibro-myxoid stromal reaction with inflammatory cells and 2) single cell invasion (SCI) is associated with infiltration of the myometrium by groups or isolated eosinophilic cells without the formation of a defined structure and is frequently surrounded by an edematous or myxoid stroma without direct continuity with the tumor, which makes it difficult to assess the depth of invasion and the presence of LVSI. It has been shown that the presence of this type of infiltration is associated with an increased risk of metastasis compared with tumors that only had expansive myometrial infiltration [7].

The follow-up after treatment was performed by physicians from this institution and included visits every three months during the two first years and then every six months until the three- to five-year mark. Once per year, a Pap smear was performed at the vaginal cuff.

The statistical significance of p was set at 0.05. Kaplan-Meier estimates were used to calculate the survival, recurrence, and death rates of the disease. STATA 13 was used for this study.

Results

Of the 226 patients with FIGO Stage IA endometrioid carcinomas treated at this institution within the time period studied, only 82 patients met the inclusion criteria. Those patients without myometrial infiltration (M0) were excluded (n=72). The median age was 65 (SD 65.26) years, and the median BMI at the time of the study was 30 (SD 7.23).

Regarding the preoperative staging of these patients, 64 (78.05%) had an abdominal and pelvic MRI with intravenous contrast, which allowed the evaluation of myometrial infiltration and the identification of suspicious nodes prior to surgery.

Table 1. — *Demographic characteristics.*

	n=82
Age in years, median ±(DS)	65.26 (9.79)
BMI ± (DS)	30.15 (7.23)
Previous surgeries, n (%)	56 (68.29)
MRI n (%)	64 (78.05)
Median follow-up	3.8 years = 1368 days

Table 2. — *Anatomo-pathological features.*

Myometrial penetration n (%)	M0	72 (46.75)
	M1	82 (53.25)
Cervical compromised n (%)		13 (8.50)
Histological grade n (%)	G1	68 (82.93)
	G2	14 (17.07)
LVSI n (%)		14 (17.07)
Size of tumor (DS)		27.35 (13.21)

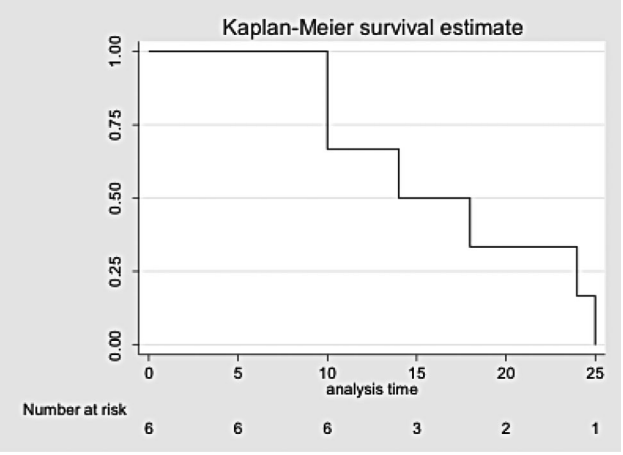

Figure 1. — Global estimation of recurrence. The mean time until recurrence was 14 months (IC 95%, 7.45-22.26).

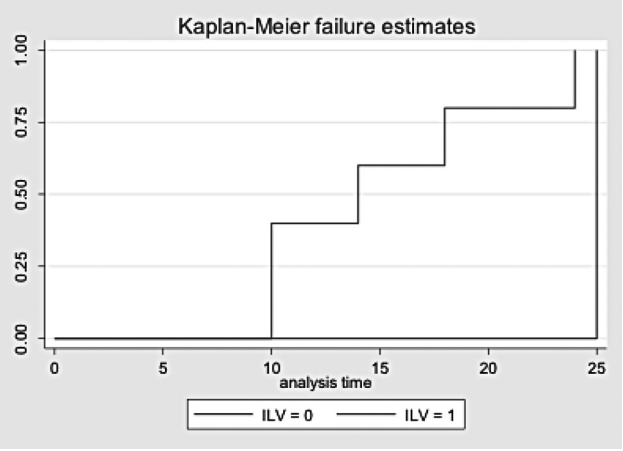

Figure 2. — Estimation of relapse in the presence of ILV. The estimation of recurrence in patients with and without LVSI, showing the prognostic significance of LVSI in this study is illustrated.

Table 3. — *Analysis of recurrence and the correlation with LVSI.*

	LVSI (n=14)	No LVSI (n=68)
Recurrence		
Yes	5 (35,71%)	1 (1.47%)
No	9 (64,28%)	67 (98,5%)
Recurrence location		
Vaginal	4 (28,57%)	1 (1,47%)
Distant	1 (7,14%)	-

Table 4. — *Analysis of recurrence and the correlation with infiltration pattern.*

	Pattern 1 Expansive (n=51)	Pattern 2 Infiltrative (n=20)	Pattern 3 MELF (n=11)
Relapse			
Yes	4 (7,9%)	2 (10%)	-
No	47 (92,1%)	18 (90%)	11 (100%)
Relapse location			
Vaginal	4 (8,33%)	1 (5%)	-
Distant	-	1 (5%)	-

A minimally invasive approach was the choice of surgery in the majority of cases, and 79 (96.34%) patients underwent laparoscopy. The mean surgical time was 131 minutes, with a standard deviation of 54 minutes. This difference could be explained by the fact that some patients (23 cases, 28.04%) underwent pelvic lymphadenectomy, whereas 20 (24.91%) patients underwent pelvic and para-aortic lymphadenectomies. In three cases, due to the presence of a BMI > 35 and comorbidities, staging superior to the primitive iliac arteries was omitted. The median follow-up time was 1,368 days (3.8 years) (Table 1).

Seventy-two (46%) patients did not have myometrial infiltration at the time of treatment. Only 14 (17%) patients had histological grade 2 tumors. The median size of the tumors was 27 mm (SD 13.21) (Table 2). Six (7.31%) patients experienced recurrent disease. Five of these were located at the vaginal cuff, and only one was located in the peritoneum. The mean time until recurrence was 14 months (IC 95%, 7.45-22.26) (Figure 1).

According to the analysis of the pathologic variables of greatest interest in this study, of the 14 patients with LVSI, five (35.71%) had tumor recurrence during the follow-up period, and only one patient without LVSI had a recurrence at the vaginal cuff (Table 3). Thus, in patients with LVSI, the relative risk of recurrence was 24.2 (95% CI 3.06-192.1) ($p < 0.000$) (Figure 2).

The analysis of the tumor penetration patterns did not provide the expected results in terms of the recurrence rates. The infiltrative pattern was associated with only two cases of recurrence during the follow-up period, and the expansive pattern was associated with four cases, indicating that there was not a significant relationship between these patterns of invasion and recurrence ($p < 0.08$) (Table 4).

Another relevant factor that has already been described in the literature in this field is the tumor size. In the present cohort, patients who suffered recurrence had a median tumor size that was larger than that in the control group (29 *vs.* 21 mm), but this factor was not statistically significant ($p = 0.11$).

Discussion

Endometrial cancer management has evolved over the last 30 years based on the initial pathological signs reported in the Gynecologic Oncology Group (GOG) 33 study [8]. Currently, endometrial cancer is defined as a heterogenous group of lesions whose management must be tailored based on prognostic factors. A large number of patients with this pathology have a low risk of an extrauterine occurrence of their disease, and in these patients, the cure is achieved with a simple total hysterectomy because they will not benefit from more extensive surgical interventions or adjuvant treatments, which undoubtedly cause complications that affect their quality of life.

The most relevant prognostic factors in endometrioid adenocarcinoma are histological grade, myometrial penetration, and peritoneal extension of disease. The GOG stratified these patients as low-, moderate-, and high-risk based on the abovementioned factors. In low-risk patients (G1 M0, without peritoneal compromise) with 0% lymphatic involvement, lymphadenectomy was not performed; however, this group represented only 7% of the cases evaluated. By contrast, high-risk patients (G3-M2 and/or intraperitoneal disease) had 15-60% lymphatic involvement and represented 24% of the patients studied. The group with the most difficult definition was the intermediate risk, which represented 70% of all cases and had 3-6% lymph node involvement. The tumor size was not considered a risk factor in the first early investigations. This factor was introduced by Schink *et al.* in 1991 and is an important independent risk factor for lymphatic dissemination. Although the specific tumor sizes that indicate the risk levels are not well defined, three arbitrary categories have been considered, albeit without good evidence: < 2 cm, > 2 cm, and compromise of the entire uterine cavity [9].

In the present series, patients who suffered from recurrence had a mean tumor size at the time of primary treatment that was larger than that in the control group (29 *vs.* 21 mm), although this relationship was not statistically significant ($p = 0.11$).

In 2000, Mariani *et al.* confirmed the prognostic role of tumor size in a retrospective study of 328 patients and found that the lymph node involvement was almost zero in cases with G1-2 M1 tumors smaller than 2 cm. These findings generated a change in daily practice: lymphadenectomy is no longer performed in low-risk patients with G1-2

M1 tumors less than 2 cm in size [10]. While waiting for the final results, the omission of lymph node dissection in these low-risk patients does not seem to impact the excellent survival rate (> 95%) at five years, but it does reduce both the rate of complications and the costs of healthcare.

Other authors, such as Cox Bauer *et al.* [11], have shown that one in four endometrial cancers are low risk and that the management criteria of Mariani *et al.* [10], which recommend omitting lymphadenectomy in these patients, can be followed . However, these authors suggest that the population of truly low-risk endometrioid endometrial cancers is likely larger. After including several combinations of risk factors, the factors with the highest predictive value for low-risk cancers include tumor size, with a cut-off of 5 cm, and myometrial invasion, with a cut-off of 33%. Although these models require validation, they may be useful, given the difficulty that still exists in the categorization of risk levels and the definition of prognostic variables, such as tumor size.

LVSI is defined as the presence of tumor cells within the endothelium of blood vessels. Initial studies evaluating nonclassical prognostic factors, including LVSI, did not establish the impact of LVSI on recurrence and survival of patients with early-stage, low-risk tumors [6, 12]. Therefore, the prognostic significance of LVSI in this group of patients is not well established. FIGO scoring does not include LVSI as a prognostic factor, although it has been described as a predictor of nodal involvement and disease recurrence in several series [3, 13]. This risk increases in patients with LVSI and deep myometrial penetration, cervical involvement and high histological grades [14].

In the present study, in a total of 14 patients with LVSI, six (35.2%) patients had recurrence during the follow-up period. Only one patient who did not have LVSI had vaginal cuff recurrence. That is, there was a significant relationship between the presence of intratumoral lymphatic vessel (ILV) and recurrence ($p = 0.000$). These data are similar to those published recently by dos Reis *et al.* [5], who studied 240 patients with Stage IA low-risk endometrial cancer. In this cohort, 40 (16.7%) patients had LVSI, and this finding was more frequent in patients with deep myometrial invasion and histological Grade 2 tumors. The reported recurrence rate was 3.8% in patients without LVSI and 14.2% in those with LVSI, which confirmed a statistically significant relationship.

The publication by Sefre *et al.* was interesting because it not only related the percentage of LVSI to the stage of disease, but also emphasized the anatomopathological techniques that were used, such as immunohistochemistry, which allows better identification than H&E, particularly in Stage I tumors [15, 16].

Patterns of myometrial invasion were postulated as another nonclassical prognostic factor for endometrioid carcinoma. Different publications have demonstrated the relationship between an infiltrative pattern of myometrial invasion and a worse prognosis [17, 18]. The study of invasion patterns has aroused interest not only because they are associated with adverse outcomes, but also because they represent a morphological spectrum that may hinder the histological determination of myometrial invasion.

The MELF pattern was initially described by Murray *et al.* [19], and other patterns have since been added, including infiltrative, broad front, adenoma malignum-like invasion, adenomyotic-like invasion [20], and the most recently described, invasion with single cells.

In his first description, Murray *et al.* suggested that the glandular changes observed in the MELF invasion pattern were degenerative in nature, but that when they were accompanied by a stromal fibromyxoid response, associated with LVSI, and had a worse long-term prognosis.

Stewart *et al.* [21] confirmed the association of the MELF pattern with LVSI. They noted that this pattern was observed in FIGO Grade 1 or 2 endometrioid adenocarcinomas and that these tumor cells are found along the deepest point of the invasion. Stewart and Little later observed that along the invasive front in tumors with a MELF-like morphology, tumor cells had reduced expression of hormone receptors and E-cadherin [22], which has been observed in the epithelial-mesenchymal transition in other tumors. The epithelial-mesenchymal transition phenomena favor infiltration in the surrounding stroma and potentiate tumor progression.

Based on studies that link the pattern of myometrial invasion to prognosis, the present authors included this variable in the present study. The overall incidence of MELF in our study was 11 (13.41%) cases, similar to the reported frequency of MELF, which ranged from 7-48% [22, 23]. The present authors did not find a pattern of infiltration of single cells in the analyzed cases.

Although the present results did not show a relationship between the patterns of myoinvasion and the general prognosis, the authors believe that it is important to continue reporting this finding as a tool to provide more information about the prognosis of these patients.

This study has several strengths, such as the following: inclusion only of patients with low-risk endometrial cancer from a single institution who underwent surgery performed by gynecologic oncologists from the same department, reassessment of all cases by pathologists who were experts in gynecology from the same institution, and prolonged post-treatment follow-up period

The greatest weaknesses of the study are its retrospective nature and the low number of recurrence events, which may have hindered the statistical validation of the prognostic factors analyzed.

Conclusion

Gynecologic oncology has evolved towards less-invasive surgeries and fewer adjuvant treatments in most gynecol-

ogical cancers. Explaining recurrence in patients with low-risk endometrial cancer involves validating models that include new non-standardized prognostic factors. However, the present authors believe that it is important to add the biological behavior of the lesions to the morphological evaluation of tumors. In this sense, a new biomolecular classification of four types of endometrial cancer can, without doubt, lead to better knowledge of the behavior of this disease and more appropriate therapeutic management.

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