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Reviewing prognostic factors associated with recurrence in clinically early-stage low-risk endometrial cancer

Revisando os fatores prognósticos associados à recorrência no câncer de endométrio de baixo risco clinicamente em estágio inicial

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ABSTRACT

Objective: We sought to re-explore the association between well-known prognostic factors and recurrence in presumed early-stage low-risk endometrial cancer (EC). **Methods:** A retrospective cohort study was carried out on patients who underwent surgical treatment by the same surgeon for presumed early-stage low-risk EC between September 2003 to August 2017. The prognostic value of well-known clinicopathological factors for disease-free survival (DFS) was reviewed by univariate log-rank test. **Results:** One hundred and five patients fit the criteria for this analysis. These patients underwent total hysterectomy plus bilateral salpingo-oophorectomy with no lymph nodes dissection (10.5%) or with a sampling dissection alone (89.5%). Adjuvant therapies were applied in 52 (40.1%) of them as pelvic radiotherapy (29.5%) or chemoradiation (11.4%). Our cumulative 3y-DFS and OS were 88.1% and 97.7%, respectively. The univariate survival analysis confirmed histological grade 3 (3y-DFS of 89.9% vs. 33.3%, p=0.004), MMI ≥50% (3y-DFS of 95.2% vs. 71.3%, p=0.003), lymph node metastasis (3y-DFS of 88.3% vs. 60%; p=0.028) and more advanced pathological stages (3y-DFS of 91.2% vs. 56.3; p<0.001) as significantly associated to recurrences. **Conclusion:** We confirmed the association of classical prognostic factors such as high histological grade, deeper MMI, lymph node metastasis and more advanced pathological stages with disease recurrence in this cohort of patients from Northeast Brazil. Further efforts are needed to avoid overtreatment in patients with low risk of relapses.

Keywords: Endometrial neoplasm; Prognosis; Survival analysis; Disease-free survival; Locoregional neoplasm recurrences.

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RESUMO

Objetivo: Reexplorar a associação entre fatores prognósticos bem conhecidos e recorrência em pacientes com câncer de endométrico (EC) de baixo risco em em estágio presumivelmente inicial. **Métodos:** Foi realizado um estudo de coorte retrospectivo em pacientes submetidos a tratamento cirúrgico pelo mesmo cirurgião para EC de baixo risco em estágio inicial entre setembro de 2003 a agosto de 2017. O valor prognóstico de fatores clínico-patológicos conhecidos para sobrevida livre de doença (DFS) foi revisado pelo teste log-rank univariado. **Resultados:** Cento e cinco pacientes preencheram os critérios para esta análise. Essas pacientes foram submetidas à histerectomia total mais salpingo-ooforectomia bilateral sem dissecção de linfonodos (10,5%) ou apenas com dissecção por amostragem (89,5%). Terapias adjuvantes foram aplicadas em 52 (40,1%) deles como radioterapia pélvica (29,5%) ou quimiorradiação (11,4%). As taxas de 3y-DFS e OS foram de 88,1% e 97,7%, respectivamente. A análise de sobrevida univariada confirmou grau histológico 3 (3y-DFS de 89,9% vs. 33,3%, *p*=0,004), MMI ≥50% (3y-DFS de 95,2% vs. 71,3%, *p*=0,003), metástase linfonodal (3a-DFS de 88,3% vs. 60%; *p*=0,028) e estádios patológicos mais avançados (3a-DFS de 91,2% vs. 56,3; *p*<0,001) como significativamente associados às recidivas. **Conclusão:** Confirmamos a associação de fatores prognósticos clássicos como alto grau histológico, MMI profunda, metástase linfonodal e estágios patológicos mais avançados com recorrência da doença nesta coorte de pacientes do Nordeste do Brasil. Mais esforços são necessários para evitar o tratamento excessivo em pacientes com baixo risco de recaídas.

Descritores: Neoplasia endometrial; Prognóstico; Análise de sobrevivência; Sobrevida livre de doença; Recorrências de neoplasias locorregionais.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological tumor worldwide and patients suffering of this malignancy are usually faced with high cancer-specific survival rates due to an early-staged diagnosis after the surgical treatment.[1,2] However, the extension of disease as a prognostic factor must be supplemented by several other clinicopathological factors in order to define a clear prognosis for the patients at risk of recurrence that need a complementary treatment.[3-5]

Historically classified as type I (i.e., low-grade, hormone-dependant, young patients, good prognosis) or type II (i.e., high-grade, hormone-independent, older patients, poor prognosis), the EC was posteriorly stratified in four molecular subtypes based on The Cancer Genome Atlas (TCGA).[6] Despite subsequent studies have demonstrated the utility of this molecular classification in predicting prognosis,[7,8] it remains unclear whether it may be integrated to current clinicopathological prognostic models, since classical histopathological factors shows a crucial prognostic value independently of the TCGA molecular subgroups.[9] Moreover, the predictive value of molecular subtypes was mainly confirmed and validated in retrospective cohorts,[7,8] which it may aggregate some bias related to high rates of adjuvant therapy based on classical prognostic models.[3-5]

In these settings, we sought to re-explore the association of well-known prognostic factors with recurrence in presumed early-stage low-risk EC patients using our 15-year single-surgeon experience from Northeast Brazil. Furthermore, we add special attention to explore rate of adjuvant therapy in this cohort of patients from our private surgical practice.

METHODS

A retrospective cohort study was carried out on patients who underwent surgical treatment for EC at the level of our private clinic, from September 2003 to August 2017. Using a prospectively maintained database by Bezerra ALR, we selected patients underwent simple hysterectomy plus bilateral salpingo-oophorectomy due to EC, histologically confirmed by a preoperative endometrial sampling. We limited our study to adults (≥18 years) with presumed early-stage low-risk disease (i.e., FIGO I, endometrioid histology, grade 1 or 2, and limited myometrial invasion), and excluded those cases in whom the main medical records were not available, those with non-endometrioid histology at the final pathology and also cases with follow-up losses. The study protocol was reviewed by our ethics research committee (CAAE: 88368818.3.0000.5569, acceptance protocol No.: 040861/2018; April 25, 2018).

We re-explore well-known clinicopathological prognostic factors such as age, lymph node dissection, histological grade, myometrial invasion (MMI; <50% vs. ≥50%), cervical stroma involvement, lymph node metastasis, peritoneal cytology, lymphovascular invasion (LVI) and pathological stage. Lymph nodes dissection was performed at the surgeon's discretion in patients with clinically suspicious nodal involvement or just as a sampling dissection. The post-operative pathological exams were also reviewed in order to fit the pathological stage to the current version (AJCC/TNM, 2018). During the period of this study, the adjuvant therapies were conducted as most of guidelines available recommended. Follow-up scheduling included physical exam every 3 to 6 months for 2 years, every 6 to 12 months for the next 3 years, and then, annually. Imaging exams such as pelvic/abdominal ultrasound or CT-scans and tumor markers such as serum CA 125 were performed every 6-12 months or when clinically required.

Continuous variables were summarized as medians (interquartile range) and categorical variables as frequencies (percent). We explored overall (OS) and disease-free survivals (DFS) rates by Kaplan-Meier estimates from the date of surgery to the corresponding event, and the prognostic value of clinicopathological factors for DFS was assessed by univariate analyses. The association of clinicopathological factors with recurrence was assessed using the log-rank test as an univariate analysis. Statistical analyses were performed using the STATISTICA Data Analysis Software System, Version 8.0 (Statsoft, Inc., Tulsa, OK, U.S.), considering a significant two-tailed *p*-value of 0.05.

RESULTS

Over a 15-year of our private surgical practice, 141 patients who underwent surgical treatment for clinically early-stage endometrioid carcinomas were selected to study and 105 of them fit the criteria for this analysis. Patients excluded from this review involved those with a diagnosis other than endometrioid adenocarcinoma in the hysterectomy specimens (n=6), lost from follow-up (n=19) and missing or unclear data at the medical records (n=11). Patients in this sample underwent total hysterectomy plus bilateral salpingo-oophorectomy without any lymph nodes dissection (n=11, 10.5%) or with a pelvic sampling dissection (n=94, 89.5%), and the preoperative staging was based on magnetic resonance imaging in 68.6% (n=72/105) of patients. Their baseline characteristics are summarized in Table 1. At the time of this analysis, the median DFS and OS were not reached after a median follow-up of 37.8 months (Q25=24.5 - Q75=61.5), and our cumulative 3y-DFS and OS were 88.1% and 97.7%, respectively (Figure 1). Relapses occurred in 13 (12.4%) patients as loco-regional (n=8, 7.6%) or systemic (n=5, 4.7%) recurrences; three of them occurring after 3-year of follow-up. Ninety-seven patients (92.4%) remained alive without any relapses and eight (7.6%) had died as a somewhat consequence of disease recurrences (n=5/105, 4.8%) or due to other non-oncological reasons (n=3/105, 2.8%).

Table 1. Baseline characteristics according to prognostic factors.

Prognostic factors	n (%) or median (*Q25 – Q75*)
Age (years)	59 (53 – 68)
<60	55 (52.4)
≥60	50 (47.6)
Final histological grade	
G1	67 (63.8)
G2	34 (32.4)
G3	4 (3.8)
Myometrial invasion	
<50%	74 (70.5)
≥50%	31 (29.5)
Lymphovascular invasion	
Present	6 (5.7)
Absent	22 (21)
Not Reported	77 (73.3)
Cervical involvement	
Present	8 (7.6)
Absent	97 (92.4)
Lymphnode metastasis	
Present	5 (4.8)
Absent	89 (84.8)
Not Assessed	11 (10.4)
Pelvic washing	
Positive	2 (1.9)
Negative	95 (90.5)
Not Assessed	8 (7.6)
Pathological stage	
I	92 (87.6)
II	6 (5.7)
III	7 (6.7)

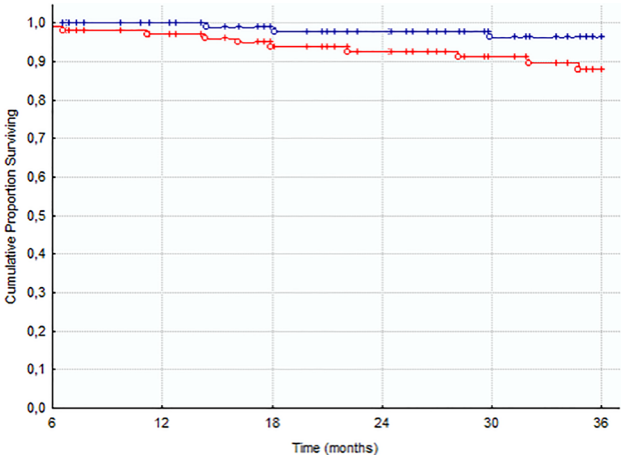

Figure 1. Kaplan-Meier survival estimates for disease-free (red line) and overall (blue line) survivals. The 3-year survivals were 88.1% and 97.7%, respectively.

Adjuvant therapies ware applied in 43 (40.1%) of patients as pelvic radiotherapy (n=31, 29.5%) or chemoradiation (n=12, 11.4%).

Our univariate analysis confirmed histological grade 3 (3y-DFS of 89.9% vs. 33.3%, *p*=0.004), MMI ≥50% (3y-DFS of 95.2% vs. 71.3%, *p*=0.003), lymph node metastasis (3y-DFS of 88.3% vs. 60%; *p*=0.028) and more advanced pathological stages (3y-DFS of 91.2% vs. 56.3; *p*<0.001) as significantly associated to recurrences. An overview of this univariate analysis is shown in Table 2. Multivariate analysis were not possible because of the low rates of events (i.e., recurrences) in this cohort of patient with clinically low-rick early-stage EC.

Table 2. Disease-free survival (DFS) according to prognostic factors.

Variable (categorized as in parenthesis)	3y-DFS	*p*-value
Age (<60 vs. ≥60)	91% vs. 84.5%	0.313
Grade (G1/2 vs. G3)	89.9% vs. 33.3%	0.004
Myometrial invasion (<50% vs. ≥50%)	95.2% vs. 71.3%	0.003
Cervical involvement (Absent vs. Present)	90.1% vs. 56.4%	0.128
Lymphovascular invasion (Absent vs. Present)[3]	80% vs, 66.7%	0.547
Pelvic washing (Negative vs. Positive)[3]	87.8% vs. 0%	0.760
Lymph node metastasis (Absent vs. Present)[3]	88.3% vs. 68%	0.028
Pathological staging (I vs. II or III)	91.2% vs. 56.3%	0.005

DISCUSSION

The present study confirmed the association of classical prognostic factors such as high histological grade, deeper MMI, lymph node metastasis and more advanced pathological stages with disease recurrence in this cohort of patients with clinically early-stage low-risk EC. As previously reported in a cohort of our patients from the public health system,[2] we also noticed a lack of clear description of some prognostic factor in the pathological exams and a high rate use of adjuvant therapies. In these settings, we highlight the need for standardization of practices to avoid overtreatment in these patients with low risk of relapses.

The prognosis for patients with EC is markedly affected by the extension of the disease at the time of diagnosis and clinicopathological prognostic factors that may impact on survival.[3-5] These factors classically involved gross and microscopic pathologic findings and some clinical factors;[10-12] however, molecular parameters have also been recently integrated to these histopathological prognostic factors in order to improve the identification of potentially under-treated patients with poor molecular prognosis[7,8,13-17] despite being at low/intermediate clinical risk of relapse by classical prognostic models.[3-5]

The prognostic tools named *"Proactive molecular risk classifier for endometrial cancer"* (ProMisE) is the most promising molecular classification system based on The Cancer Genome Atlas (TCGA),[6] a landmark cancer genomics program molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types. Their authors developed and validated a pragmatic molecular classification that provides consistent categorization of tumors and identifies four distinct prognostic molecular subtypes (i.e., MMR-D: mismatch repair-deficient; p53 abn: null/missense p53 mutation; p53 wt: wild-type p53; and POLE EDM: polymerase-ε exonuclease domain mutation).[7,8] This prognostic tool proved to be feasibly using clinically applicable methods and provides independent prognostic information beyond established clinicopathologic risk factors that may guide future clinical managements. It could also be applied to diagnostic samples (i.e., biopsy/curettings) and thus could be used early to guide surgical procedures and the need of adjuvant therapies.[7,8]

Despite promising, the interpretation of data in the cohorts exploring both the feasibility and prognostic ability of ProMisE may have suffered of some bias related to multimodal approaches based on classical prognostic models[3-5] and high rates of adjuvant therapy.[7,8] For example, in the confirmation cohort,[7] multivariable survival analysis using parameters that were available at diagnosis and molecular subgroup as assigned by ProMisE demonstrated that only ProMisE subgroup was associated with overall (*p*=.021), disease-specific (*p*=.016) and progression-free survivals (*p*=.001). Nevertheless, accounting for postoperative parameters that were available in the surgical specimens (i.e., stage, lymph node status, MMI and LVI) in addition to that were parameters available at the time of diagnosis, the authors were insufficiently powered to demonstrate an independent association of ProMisE with these survival outcomes (i.e., *p*-values were not significant for all survival outcomes). Adjusting for the effect of treatment on these outcomes in the validation cohort,[8] ProMisE remained a significant prognostic marker for progression and disease-specific survival but not for OS in a multivariable survival analysis using parameters available at the time of diagnosis. For this last cohort of patients, the authors did not provided a multivariable survival analysis including postoperative parameters from the surgical specimens.[8] In other words, these findings highlight the critical role of adjuvant therapies for compensating the negative impact of prognostic factors.

High rates of adjuvant therapy have been reported in retrospective series of EC patients[2,8,12] in contrast with prospective data from clinical trials of surgically treated patients.[18,19] In this current study, the use of complementary treatment was applied in 40.1% of patients, which contrasts with a rate of 67.5% in our previous report involving patients from the public health system.[2] Accordingly, this increased use of adjuvant treatments was probably related to the inaccuracies of our preoperative staging[20] and the lack of standardized reports on the pathological exams (i.e., clear description of LVI) into the context of patients undergoing sampling lymph node dissection instead of systematic lymphadenectomy or sentinel lymph node mapping.[2]

The corresponding rates of complementary treatment and stage FIGO/TNM I tumors in the ProMisE studies were 47.4% and 70.2% for the confirmation cohort,[7] and 62.2% and 80.8% for the validation cohort.[8] Of note, 50.9% of patients in the validation cohort were reported as low-risk according to criteria of the ESMO/ESGO/ESTRO 2016 guideline,[4] which demonstrate the high risk of overtreatment for patients managed outside of clinical trials and the limitations of using real world data as a validation set of new molecular classifications such as ProMisE. Accordingly, it was demonstrated that consideration of this molecular classification in adjuvant therapeutic decisions should be evaluated in prospective trials,[8] which proved to be feasible with a satisfactory patient acceptance rate.[21]

Our study was intrinsically limited by its retrospective design and the long period analyzed. Unfortunately, we were also not able to provide a stratification of risk based on the ESMO/ESGO/ESTRO 2016 guideline[4] for this cohort due to the lack of clear description of LVI on the pathological exams in lot of our patients. This could make our data more comparable with those from previous surgical reports.[7,8,18,19] Finally, the low rates of events (i.e., recurrences) in a cohort of patient with clinically early-stage EC may also have served to mitigate some of our subset analysis. On the other hand, we highlight our scientific merit of exploring a single-surgeon real-world data from Northeast Brazil and to present it into the context of our previous report involving patients from the public health system.

CONCLUSION

We confirmed the association of classical prognostic factors such as high histological grade, deeper MMI, lymph node metastasis and more advanced pathological stages with disease recurrence in this cohort of patients from Northeast Brazil. Further efforts are needed to avoid overtreatment in patients with low risk of relapses.

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