Pathology & Oncology Research (2020) 26:783–790
https://doi.org/10.1007/s12253-019-00624-1

ORIGINAL ARTICLE

# The Haphazard Pattern in Grade-3 Endometrioid Carcinoma Is Associated with Poor Prognosis and Tumor Lymphocyte Infiltration

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Received: 3 January 2019 / Accepted: 19 February 2019 / Published online: 27 February 2019


## Abstract

The aim of this study was to examine the associations among the haphazard invasive patterns, defined as directionless infiltration into the myometrium; expression of key proteins; tumor infiltrative lymphocytes (TILs); and the prognosis of gade-3 endometrioid carcinoma (G3EC). Between 1990 and 2013, patients with G3EC who underwent surgery at our hospital were identified. Invasive patterns were classified into either haphazard, infiltrative, or expansile patterns. The estrogen, progesterone, androgen receptor, cytokeratin 5/6, epidermal growth factor receptor, E-cadherin, snail-2, vimentin, ZEB1, chromogranin A, synaptophysin, MLH1, MSH2, MSH6, and PMS2 levels were evaluated by immunochemical analysis. The degree of strong or weak lymphocyte infiltration (LI) were evaluated using zone formation of LI at the invasive front. Haphazard, infiltrative, and expansile patterns were discovered in 8 (18%), 6 (13%), and 31 (69%) cases, respectively. Cases with the haphazard patterns were diagnosed at a more advanced stage ($p < 0.01$) and recurred more frequently ($p < 0.01$). There were statistical differences in progression-free survival (PFS) and overall survival (OS) between the three groups (PFS; $p < 0.01$: OS; $p < 0.01$). In multivariate analysis, only the haphazard pattern was found to be an independent, worse prognostic factor of PFS (Hazard ratio (HR) =10.8, $p < 0.01$) and OS (HR = 23.3, $p < 0.01$). Furthermore, the haphazard invasive pattern was related with weak LI ($p < 0.01$) but not with the expression of all proteins analyzed. The haphazard pattern was found to be a worse prognostic factor and was associated with weak LI in G3EC. The aggressive feature of G3EC might be associated with LI but not tumor biology.

**Keywords** Endometrial carcinoma · Endometrial endometrioid carcinoma · Invasive pattern · Tumor infiltrating lymphocyte

## Introduction

Endometrial carcinoma (EC) is the most common of the gynecological malignancies [1]. Until now, histological subtypes have played an important role in determining the treatment strategy in clinical settings, although genomic analysis for EC clarified the tumor biology and the classification according to genomic features established [2, 3]. Among them, endometrioid carcinomas were the most prevalent histological subtype, and were classified into 3 grades according to their architecture and nuclear atypia [4, 5]. Grade-3 endometrioid carcinoma (G3EC) is the subtype with the worst prognosis [6]. According to the survival analysis for G3EC, prognostic or recurrent factors were reported as follows; morphological findings such as myometrial invasion [7], adnexal involvement [7], and lympho-vascular invasion [8], immunologic findings such as tumor infiltrating lymphocytes [9], and genetic changes including PIK3CA missense mutations [10] and POLE exonuclease domain mutations [11].

However, several reports have examined the association between invasive tumor patterns and prognosis in EC [12, 13]. A report demonstrated patterns of myometrial invasion could be classified into three patterns; expansile, defined as tumor cells which expanded with distinct borders from the

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**Table 1** Primary Antibodies

| Molecule | Antibody | | | | | |
|---|---|---|---|---|---|---|
| | Type | Clone/ code | Manufacturer | Dilution | Localization | Control tissue |
| Estrogen receptor | Monoclonal (Mouse) | 1D5 | Dako | ×100 | Nucleus | Mammary gland |
| Progesterone receptor | Monoclonal (Mouse) | PgR636 | Dako | ×100 | Nucleus | Mammary gland |
| Androgen receptor | Monoclonal (Mouse) | AR441 | Dako | ×50 | Nucleus | Mammary gland |
| CK5/6 | Monoclonal (Mouse) | D5/16 B4 | Dako | ×100 | Cytoplasm | Mammary gland |
| EGFR | Polyclonal (Rabbit) | PharmDx | Dako | Ready to use | Membrane | Epidermis |
| E-cadherin | Monoclonal (Mouse) | NCH-38 | Dako | ×100 | Membrane | Epidermis |
| Snail-2 | Polyclonal (Rabbit) | PAB1923 | Abnova | ×200 | Nucleus | MCF7, MDA-MB-231 |
| Vimentin | Monoclonal (Mouse) | V9 | Dako | ×100 | Cytoplasm | Fibroblast |
| ZEB1 | Polyclonal (Rabbit) | ab87280 | Abcam | ×100 | Nucleus | MCF7, MDA-MB-231 |
| Chromogranin A | Polyclonal (Rabbit) | A430 | Dako | ×500 | Cytoplasm | Pancreas |
| Synaptophysin | Monoclonal (Mouse) | 27G12 | Nichirei | None | Cytoplasm | Pancreas |
| MLH1 | Monoclonal (Mouse) | ES05 | Dako | ×100 | Nucleus | Appendix |
| MSH2 | Monoclonal (Mouse) | FE11 | Dako | ×400 | Nucleus | Appendix |
| MSH6 | Monoclonal (Rabbit) | EPR3945 | Gene Tex | ×200 | Nucleus | Colon |
| PMS2 | Monoclonal (Rabbit) | EP51 | Dako | ×10 | Nucleus | Appendix |

surrounding tissue, infiltrative, defined as tumor cells which infiltrated growth with an indistinct border from the surrounding tissue, and mixed, defined as the mixture of expansile and infiltrative patterns [12]. The infiltrative pattern was associated with the worst prognosis in all grades of EC [12]. Thus, the invasive pattern was important with regard to findings related to clinical outcome. However, because previous reports included all grades of EC, the clinical significance of the invasive pattern in G3EC is unclear.

Herein, we classified the invasive pattern into three patterns; haphazard, newly defined as directionless infiltration into the myometrium, infiltrative, and expansile patterns. The aim of this study was to examine the association between each invasive pattern and the clinicopathological features in G3EC. Furthermore, the association between the worst invasive pattern and tumor biology and TILs was investigated.

## Material and Methods

Between 1990 and 2013, patients with EC who underwent surgery at the National Defense Medical College Hospital were identified. We conducted central pathological reviews for all patients and selected 51 patients with G3EC. Tissue microarray (TMA) slides of solids parts of G3EC were made. Cores of 1.5 mm were gouged from these blocks and inserted into a new block. All specimens were cut in 4 μm thick slices and immunohistochemically stained. Satisfactory

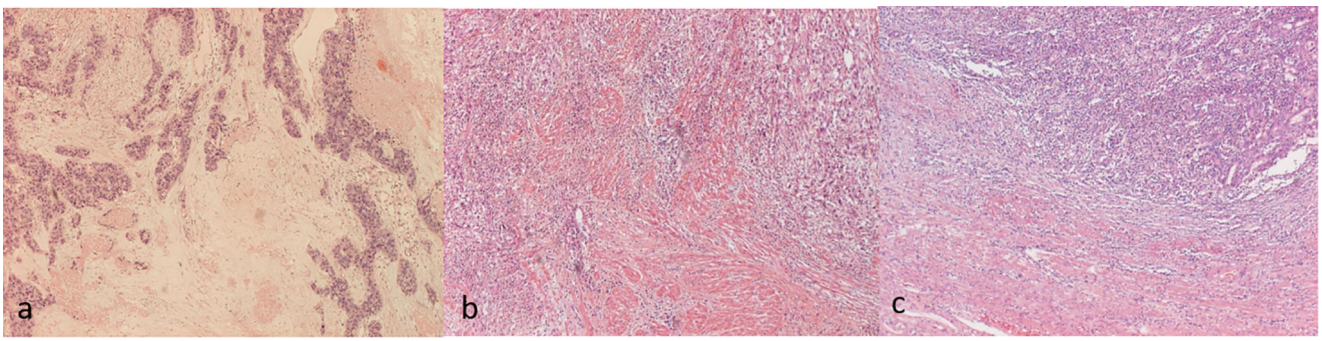


**Fig. 1** The representative images of the classification of invasive patterns. **a** showed the haphazard pattern defined as even, small foci of directionless infiltration into the myometrium with an indistinct border from the surrounding myometrium. **b** showed the infiltrative pattern defined as even, small foci of the tumor with infiltrating growth and an indistinct border from the surrounding myometrium without a haphazard pattern. **c** showed the expansile pattern defined as a tumor with expanding growth and a distinct border from the surrounding myometrium, without small foci with haphazard or infiltrative patterns

**Table 2** The characteristics of all patients with grade-3 endometrioid carcinoma according to haphazard pattern status

| Variables | | Haphazard pattern | | Infiltrative pattern | | Expansile pattern | | |
|---|---|---|---|---|---|---|---|---|
| | | $n = 8$ | | $n = 6$ | | $n = 31$ | | $p$ value |
| Age Median (years) | 60≦ | 6 | (75%) | 2 | (33%) | 17 | (55%) | 0.31 |
| | 60> | 2 | (25%) | 4 | (67%) | 14 | (45%) | |
| FIGO stage | I | 2 | (25%) | 2 | (33%) | 24 | (77%) | <0.01 |
| | II | 0 | | 0 | | 3 | (10%) | |
| | III | 2 | (25%) | 3 | (50%) | 3 | (10%) | |
| | IV | 4 | (50%) | 1 | (17%) | 1 | (3%) | |
| Adjuvant therapy | Done | 7 | (88%) | 5 | (83%) | 22 | (71%) | 0.76 |
| | Not done | 1 | (12%) | 1 | (17%) | 9 | (29%) | |
| Recurrence | Yes | 8 | (100%) | 3 | (50%) | 3 | (10%) | <0.01 |
| | No | 0 | | 3 | (50%) | 28 | (90%) | |

immunohistochemical (IHC) staining of solid parts was obtained in 45 cases. Thus, 45 patients were included in our study. Patients complicated with other cancers, such as ovarian cancer, or other pathologies were excluded.

Antibodies used for IHC staining are listed in Table 1. TMA slides were hydrated with alcohol and deparaffinized in xylene, boiled in citrate buffer (pH 6.0) in an autoclave at 121 °C for 15 min, and cooled at room temperature. Endogenous peroxidase activity was blocked by 0.3% $H_2O_2$/methanol. The slides were incubated at 4 °C overnight with a primary antibody at several concentrations and then reacted with the DAKO EnVision+ system-HRP labeled polymer as a secondary antibody for 30 min at room temperature. Specific antigen-antibody reactions were visualized with 0.2% diaminobenzidine tetrahydrochloride and hydrogen peroxide, and counterstained with Mayer hematoxylin. For each antibody, negative control studies were performed without the primary antibody. No significant staining was observed in the negative control sections.

To analyze IHC staining, positive cells (score 0–5) and staining intensity (score 0–3) were scored for the estrogen, progesterone, and androgen receptor. When the sum of these scores was more than 4, the case was considered as positive. For the analysis of CK5/6, EGFR, E-cadherin, Snail-2, Vimentin, ZEB1, Chromogranin A, and Synaptophysin antigens, if a positive IHC reaction was observed in more than 10% of the tissue, the case was considered to be positive. Also, for the analysis of MSH1, MSH2, MSH6, and PMS2 antigens, if a positive IHC reaction was observed in more than 1% of the tissue, the case was considered to be positive. Furthermore, cases with loss of at least one protein among MSH1, MSH2, MSH6, and PMS2 proteins was defined as loss of mismatch repair protein. Two observers independently evaluated and interpreted the results of the IHC staining without knowledge of the clinical data of each patient. During the course IHC staining analysis, any discrepancies between the 2 observers were discussed and resolved.

Invasive patterns invading the myometrium were classified into three categories; haphazard, infiltrative, and expansile. The haphazard pattern was defined as even, small foci of directionless infiltration into the myometrium with an indistinct border from the surrounding myometrium (Fig. 1a.). The infiltrative pattern was defined as even, small

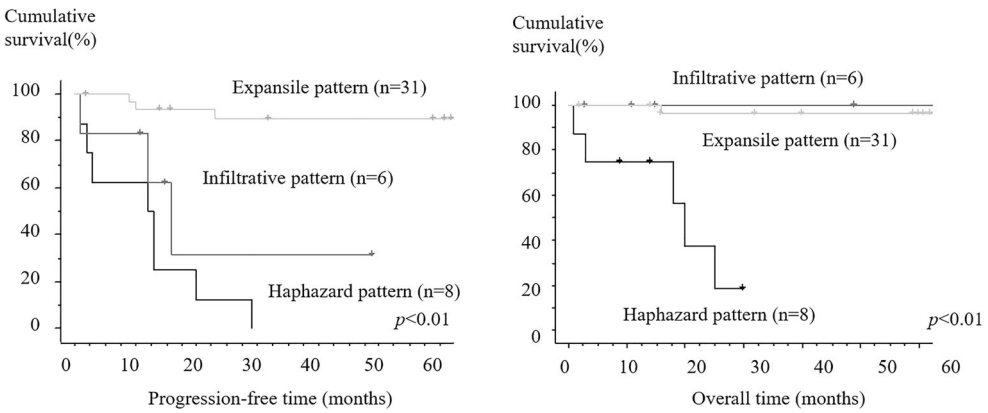


**Fig. 2** Progression-free survivals (PFS) and overall survivals (OS) of all patients according to invasive patterns. PFS and OS of patients positive for the haphazard pattern were worse than those negative for the haphazard pattern (PFS; $p < 0.01$: OS; $p < 0.01$)

**Table 3** Multivariate analysis for progression-free or overall survivals in patients with grade-3 endometrioid carcinoma

| Variables | | Progression-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|---|
| | | Hazard ratio | 95% CI | *p* value | Hazard ratio | 95% CI | *p* value |
| Age | ≥60 vs. 60> | 1.24 | (0.35–5.35) | 0.75 | 1.65 | (0.30–12.9) | 0.57 |
| FIGO | II/III/IV vs. I | 3.52 | (0.97–17.0) | 0.06 | 4.91 | (0.67–107) | 0.13 |
| Adjuvant therapy | Done vs. Not done | 1.47 | (0.24–28.3) | 0.71 | 0.30 | (0.02–6.83) | 0.38 |
| Invasive pattern | Infiltrative Pattern vs. Expansile Pattern | 8.03 | (1.30–51.3) | 0.03 | 5.57 | (0.19–173) | 0.28 |
| | Haphazard Pattern vs. Expansile Pattern | 10.8 | (2.55–61.9) | <0.01 | 23.3 | (2.59–658) | <0.01 |

foci of the tumor with infiltrating growth and an indistinct border from the surrounding myometrium without a haphazard pattern (Fig. 1b.). The expansile pattern was defined as a tumor with expanding growth and a distinct border from the surrounding myometrium, without small foci with haphazard or infiltrative patterns (Fig. 1c.). The definition of the infiltrative and expansile patterns in our study have been cited in a previous report [12].

Zone formation of lymphocyte infiltration (LI) was defined in a previous report [9]. In brief, the distribution of lymphocyte infiltration along the tumor-myometrium junction at the invasive front was evaluated. Thick zones of LI, continuously without tear-shaped LI into myometrium, and thick or thin zones of LI formed, and scattered tear-shaped LI into myometrium were defined as strong LI. Zones of LI were not formed at the invasive front, but small foci of LI and LI

**Table 4** The association between patients with the haphazard pattern and immunochemical analysis or zone formation of lymphocyte infiltration

| Variables | | Haphazard pattern | | Infiltrative pattern | | Expansile pattern | | |
|---|---|---|---|---|---|---|---|---|
| | | *n* = 8 | | *n* = 6 | | *n* = 31 | | *p* value |
| Estrogen receptor | Positive | 5 | (62%) | 3 | (50%) | 26 | (84%) | 0.12 |
| | Negative | 3 | (38%) | 3 | (50%) | 5 | (16%) | |
| Progesterone receptor | Positive | 4 | (50%) | 3 | (50%) | 16 | (52%) | 0.99 |
| | Negative | 4 | (50%) | 3 | (50%) | 15 | (48%) | |
| Androgen receptor | Positive | 0 | (0%) | 1 | (17%) | 3 | (10%) | 0.28 |
| | Negative | 8 | (100%) | 5 | (83%) | 28 | (90%) | |
| CK5/6 | Positive | 2 | (25%) | 1 | (17%) | 1 | (3%) | 0.08 |
| | Negative | 6 | (75%) | 5 | (83%) | 30 | (97%) | |
| EGFR | Positive | 4 | (50%) | 4 | (67%) | 15 | (48%) | 0.82 |
| | Negative | 4 | (50%) | 2 | (33%) | 16 | (52%) | |
| E-cadherin | Positive | 7 | (87%) | 4 | (67%) | 28 | (90%) | 0.23 |
| | Negative | 1 | (13%) | 2 | (33%) | 3 | (10%) | |
| Snail-2 | Positive | 8 | (100%) | 4 | (67%) | 31 | (100%) | 0.16 |
| | Negative | 0 | (0%) | 2 | (33%) | 0 | (0%) | |
| Vimentin | Positive | 7 | (87%) | 5 | (83%) | 25 | (81%) | 0.99 |
| | Negative | 1 | (13%) | 1 | (17%) | 6 | (19%) | |
| ZEB1 | Positive | 0 | (0%) | 1 | (17%) | 5 | (16%) | 0.64 |
| | Negative | 8 | (100%) | 5 | (83%) | 26 | (84%) | |
| Chromogranin A | Positive | 1 | (13%) | 0 | (0%) | 3 | (10%) | 0.99 |
| | Negative | 7 | (87%) | 6 | (100%) | 28 | (90%) | |
| Synaptophysin | Positive | 1 | (13%) | 0 | (0%) | 3 | (10%) | 0.99 |
| | Negative | 7 | (87%) | 6 | (100%) | 28 | (90%) | |
| Loss of mismatch repair protein. | Positive | 1 | (13%) | 2 | (33%) | 12 | (39%) | 0.38 |
| | Negative | 7 | (87%) | 4 | (67%) | 19 | (61%) | |
| Zone formation of lymphocyte infiltration | Strong | 1 | (13%) | 5 | (83%) | 23 | (65%) | <0.01 |
| | Weak | 7 | (87%) | 1 | (17%) | 8 | (35%) | |

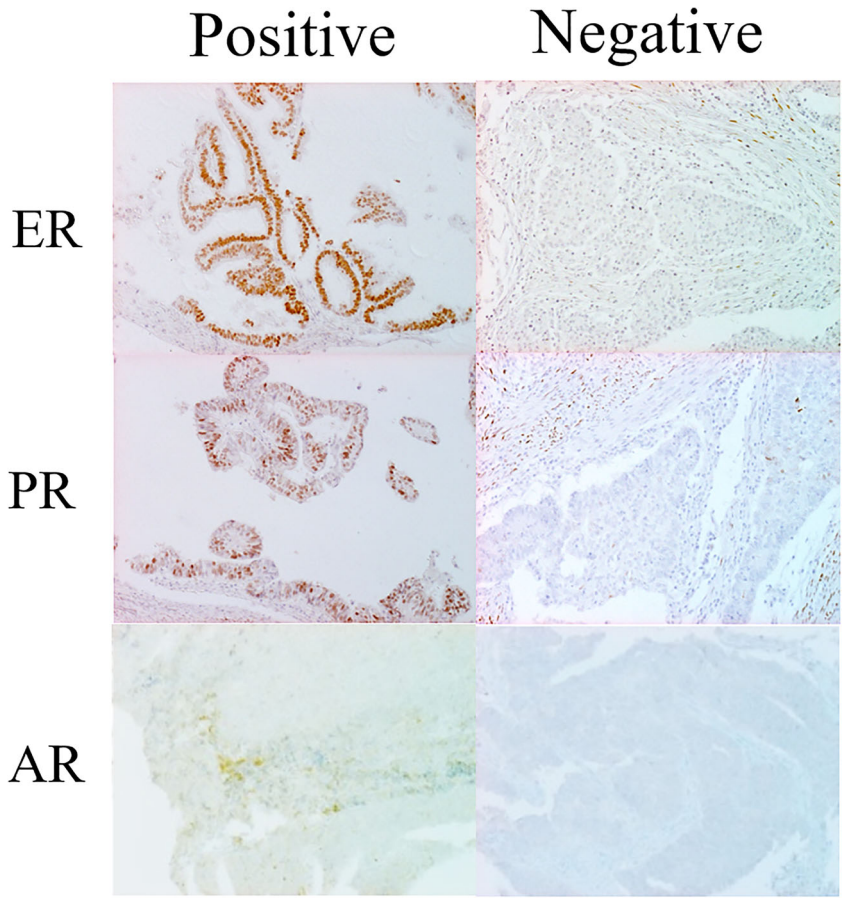


**Fig. 3** The representative images of immunochemical stains by the estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR)

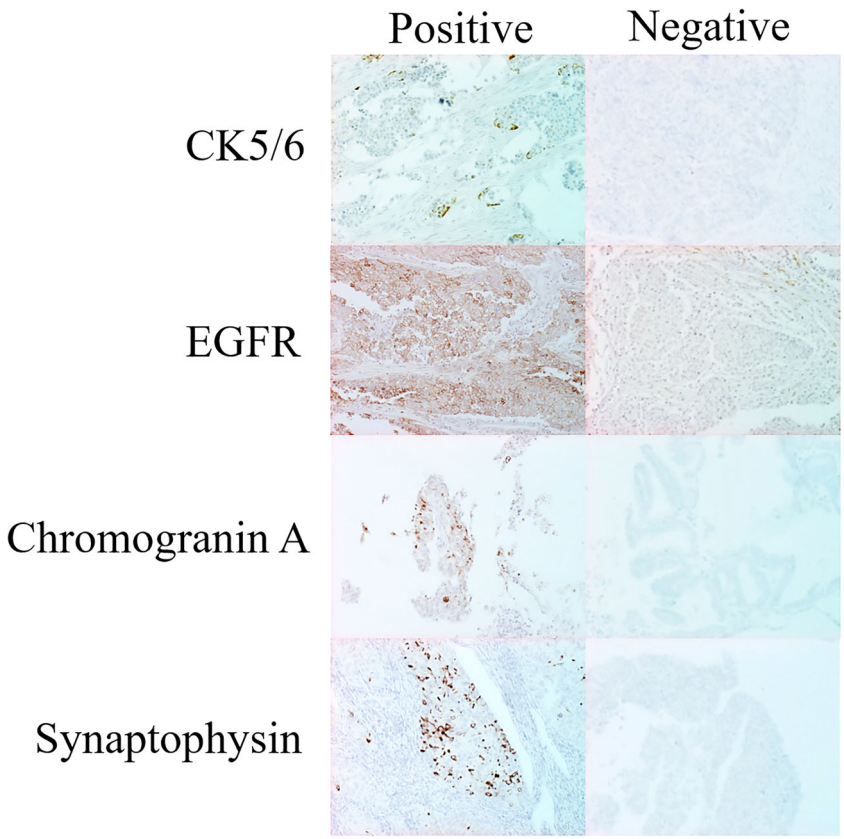


**Fig. 4** The representative images of immunochemical stains by the CK5/6, EGFR, chromogranin A, and Synaptophysin

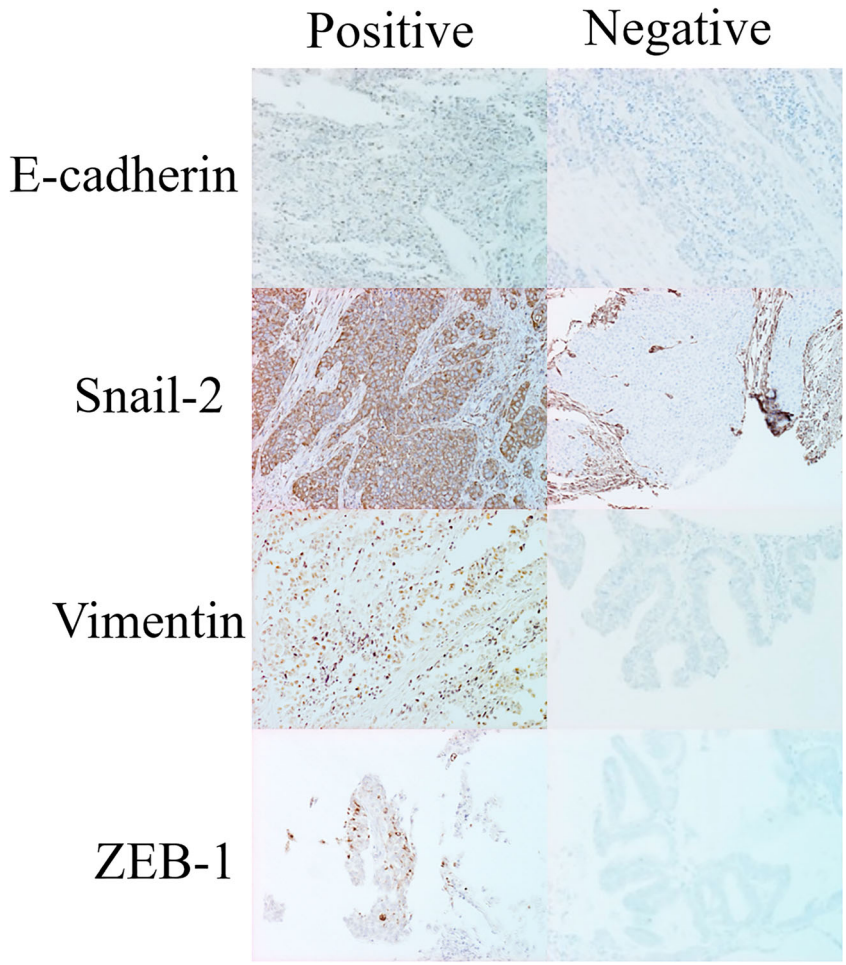


**Fig. 5** The representative images of immunochemical stains by the E-cadherin, Snail-2, Vimentin, and ZEB1

rarely observed at the invasive front of the tumor margin were defined as weak LI.

The Stat View ver. 5.0 (SAS Institution Inc., Cary, NC, USA) was used for all statistical analysis. The chi-square test and Fisher exact test were used for statistical analysis. Progression-free survival (PFS) was defined as the duration from primary surgery to recurrence or death. Overall survival (OS) was defined as the duration from primary surgery to death. Staging was determined by the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. A $p$ value of <0.05 was considered statistically significant.

## Results

Among all patients, the haphazard pattern was observed in 8 (18%) cases. The characteristics of all patients are listed in Table 2. Patients positive for the haphazard pattern had a more advanced disease with higher rates of reoccurrence than patients negative for the haphazard pattern. PFS and OS of patients positive for the haphazard pattern were worse than those negative for the haphazard pattern (PFS; $p < 0.01$: OS; $p < 0.01$) (Fig. 2.). In multivariate analysis, being positive for the haphazard patterns was the worst prognostic factor of PFS (Hazard ratio (HR) =10.8, $p < 0.01$) and OS (HR = 23.3, $p < 0.01$) (Table 3).

The results of IHC analysis is shown in Table 4 and Figs. 3, 4, 5, and 6. Several invasive patterns were not related with the expression of all proteins analyzed. However, the haphazard pattern was associated with weak LI ($p < 0.01$).

## Discussion

To our knowledge, this study was the first report to define the haphazard pattern. This study demonstrated that the haphazard pattern has important pathological findings that are associated with the prognosis of EC. Furthermore, the expression of several proteins related with endocrine, epithelium, epithelial mesenchymal transition, and neuroendocrine were not associated with the haphazard pattern. Surprisingly, the haphazard pattern was related with weak LI.

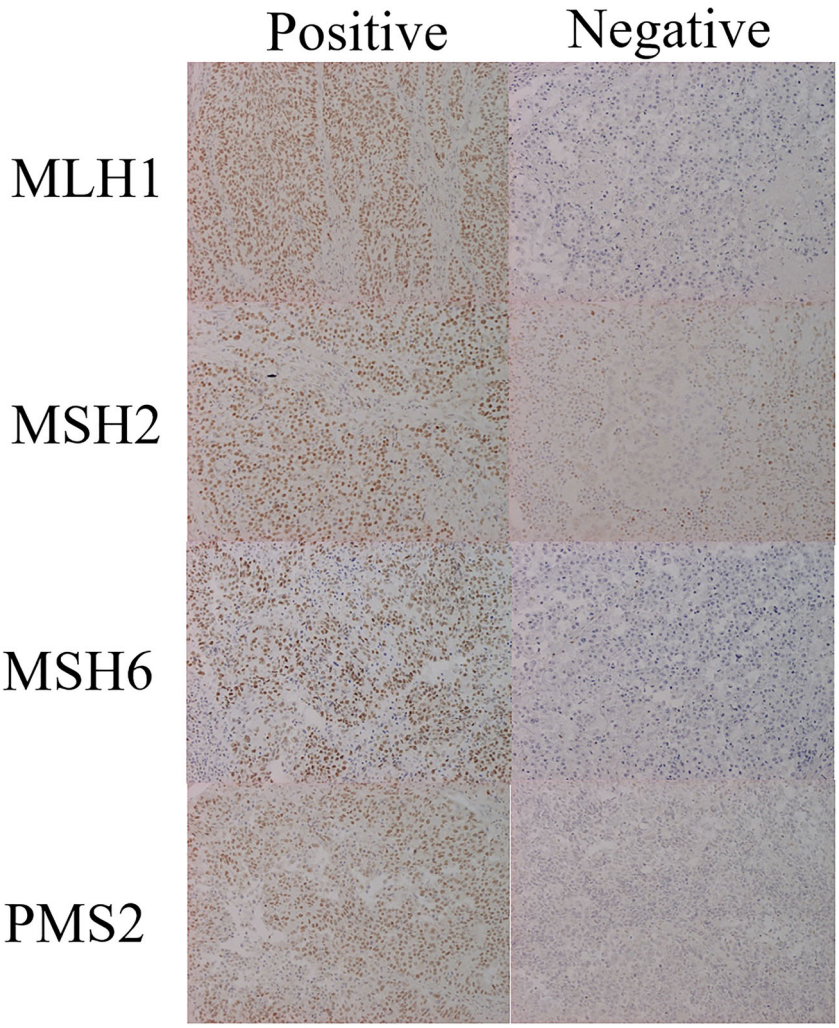


**Fig. 6** The representative images of immunochemical stains by the MLH1, MSH2, MSH6, and PMS2

The haphazard pattern defined in our study might include the infiltrative pattern according to the definition given in previous reports [12, 13]. Previous reports demonstrated that the infiltrative pattern in EC invading into the myometrium was associated with poor prognosis [12, 13]. Meanwhile, in our study, the infiltrative pattern was the subtype with the worst prognosis for PFS but not OS and the haphazard pattern was the worst prognostic factor for both PFS and OS. Our invasive classification was able to more exactly identify the aggressive subtypes in G3EC. Thus, we considered it might be meaningful to classify the haphazard pattern.

The epithelial–mesenchymal transition (EMT) is associated with cancer metastasis. EMT cells invade into the stroma, enter the circulation, and are transported to distant organs [14]. In EC, EMT was the key function associated with tumor invasion [15]. Also, neuroendocrine carcinomas in several cancers including EC have been reported to be the aggressive histological subtype [16, 17]. Furthermore, overexpression of EGFR or loss of CK5/6 was reported to be associated with aggressive subtypes in EC [18, 19]. Thus, although we examined the association between the haphazard pattern and an array of proteins, several proteins were not associated. Also, several hormone receptors were not related. Furthermore, of the proteins analyzed, several were not associated with any invasive patterns defined in this study. However, the haphazard pattern was only related to weak LI. Therefore, the original malignant degree of G3EC might be associated with lymphatic reaction but not tumor biology.

Recently, the association between TILs and POLE exonuclease domain mutations and microsatellite instability in EC was reported [20]. POLE exonuclease domain mutations were identified in 8 of 53 (15%) G3ECs [11]. Loss of MSH-1 and MSH-2 were discovered in 3/25 (12%) and 1/24 (4%) [21]. Thus, we considered, because POLE exonuclease domain mutations and loss of mismatch repair proteins were often observed, it is possible that they might be associated with the haphazard pattern. However, our study did not demonstrate the association between loss of mismatch repair proteins and haphazard pattern. Further study should examine the relation between POLE exonuclease domain mutations and haphazard pattern.

The limitations of this study were a small sample size and the single-institutional nature of this study. However, the haphazard pattern was a poorer prognostic factor than the infiltrative or expansile patterns and was associated with weak LI, but not with expression of several proteins.

In conclusion, G3EC with a haphazard pattern results in a more aggressive tumor. This classification was useful to identify more aggressive subtypes in G3EC.

**Acknowledgements** We would like to thank Editage (www.editage.jp) for English language editing.

**Data Availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Research Involving Human Participants and/or Animals** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This study was approved by the Ethics Committee of the National Defense Medical College, Tokorozawa, Japan.

**Informed Consent** Because our study was retrospective study, informed consent was not obtained.

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