# Pathological Features of Endometrial Carcinoma

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**Abstract**

Endometrial carcinoma most frequently arises in the corpus proper, but it may also originate in the lower uterine segment. In early stages, it is common to find no evidence of residual disease after diagnostic endometrial curettage. Localized disease manifests as round, polypoid expansile masses that are friable and often hemorrhagic while diffuse involvement of the endometrium may show an indurated-appearing surface without a visible exophytic component, necrosis and hemorrhage may be seen. There are no distinctive gross appearances to differentiate individual subtypes. Foci of myometrial invasion generally appear grossly as well-demarcated gray-white areas that are lighter in color than the surrounding uninvolved myometrium. Extension from the surface lesion is commonly demonstrated.

**Keywords:** Endometrial Carcinoma

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## Introduction

Historically, the first subtype classification of endometrial carcinoma, as proposed by Bokhman in 1983 [2], distinguished between Type I and Type II endometrial cancers based on clinical and hormonal features:

- **Type I:** The most common type. They are usually endometrioid adenocarcinoma and mucinous carcinoma.
- **Type II:** They include serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, and carcinosarcoma [3].

Today, the histologic classification of EC according to the World Health Organization (WHO) 2020 classification system [4] is predicated on tumor morphology and tumor grade, based on glandular architecture and nuclear grade with the aid of immunohistochemistry [5]. The genetic profiling of different histologic subtypes has led to the understanding that they can be distinguished by defining early driver mutations [5].

Histological subtypes of EC according to WHO 2020 include:

1. **Endometrioid carcinoma:** Endometrioid carcinoma is by far the most commonly encountered malignant epithelial uterine tumor, accounting for 70 to 80% of all endometrial cancers [6]. This type is defined as a carcinoma with varying architecture that may be glandular, papillary, or solid, composed of tumor cells showing endometrioid differentiation with mild to moderate nuclear atypia, typically arising in a background of atypical hyperplasia with some areas of squamous and mucinous changes. Glandular differentiation and the degree of cellular components are used to differentiate low-grade and high-grade endometrioid tumors [7].

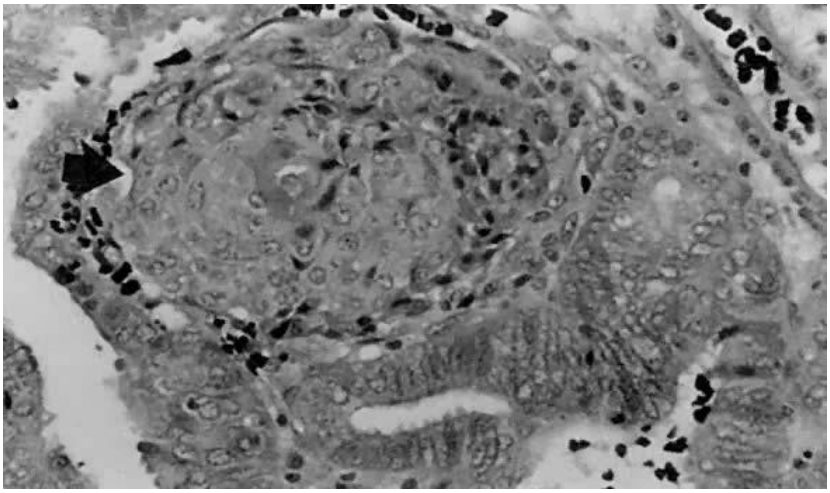

**Fig. 1. Squamous differentiation in endometrial adenocarcinoma is frequent. This is an example of a squamous morule ( arrow ), which is a collection of polygonal cells with abundant eosinophilic cytoplasm forming a nodular structure between neoplastic endometrial glands.**

2. **Serous carcinoma:** Serous carcinoma is the second most common endometrial carcinoma, accounting for approximately 10% of all cases [8]. It is characterized by typically papillary and/or glandular growth patterns, although solid architecture may be encountered, with diffuse and striking nuclear pleomorphism. This carcinoma is not graded as it is high-grade by definition [8].

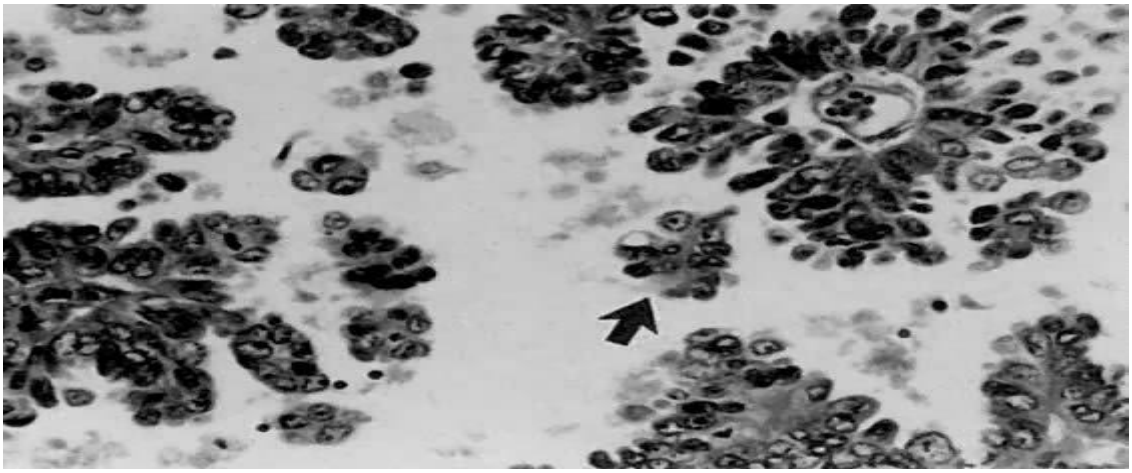

**Fig. 2. Serous carcinoma. The papillae have fibrovascular cores and are lined by vesicular nuclei with prominent eosinophilic nucleoli. Small clusters of cells that have separated from the papillae are referred to as cellular budding ( arrow ).**

3. **Clear cell carcinoma:** Its exact frequency is not known; it represents <10% and likely around 2% of all EC [9]. The tumor is defined as a carcinoma composed of variably pleomorphic cells that may be polygonal, cuboidal, flat, or hobnail, and show eosinophilic or clear glycogen-filled cytoplasm, thus having the appearance of being surrounded by a "clear" halo. The cells may be arranged in papillary, tubulocystic, and/or solid architectural patterns [9].

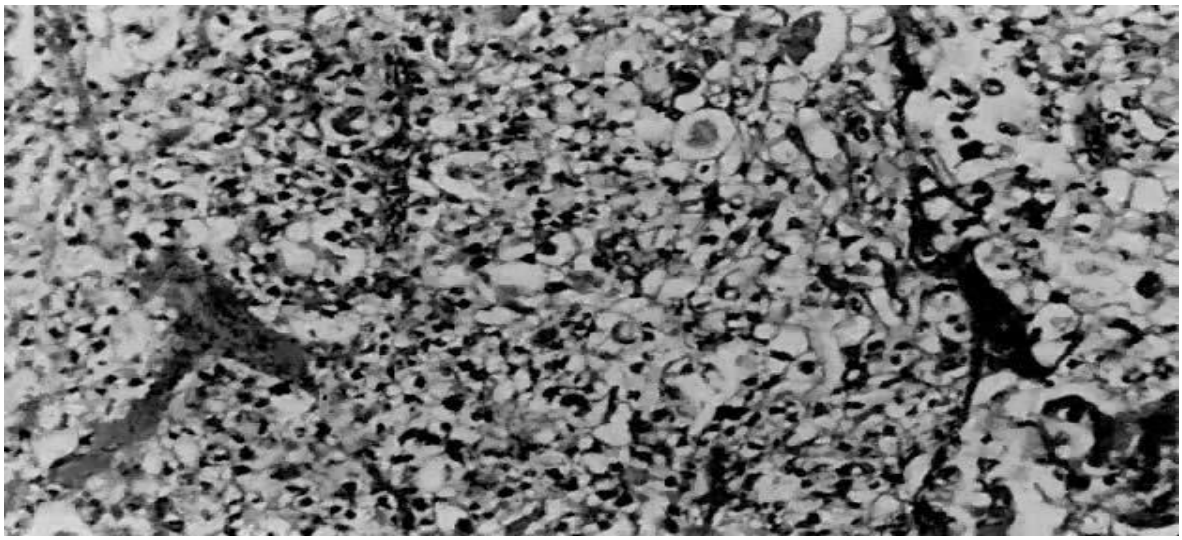

**Fig. 3. Clear cell carcinoma may exhibit a solid pattern consisting of sheets of clear cells separated focally by thin fibrous bands.**

4. **Undifferentiated and Dedifferentiated carcinoma:** Undifferentiated carcinoma comprises 9% of endometrial carcinoma, while dedifferentiated endometrial carcinoma represents 40% of undifferentiated carcinoma. Both are clinically aggressive EC types [10]. These tumors are defined as epithelial tumors showing no specific lineage differentiation. They are characterized by a relatively monotonous population of small to intermediate-sized tumor cells arranged in solid sheets. There is no gland, trabecular, or nest formation. Foci of abrupt keratinization, necrosis, and hemorrhage can be present [10].

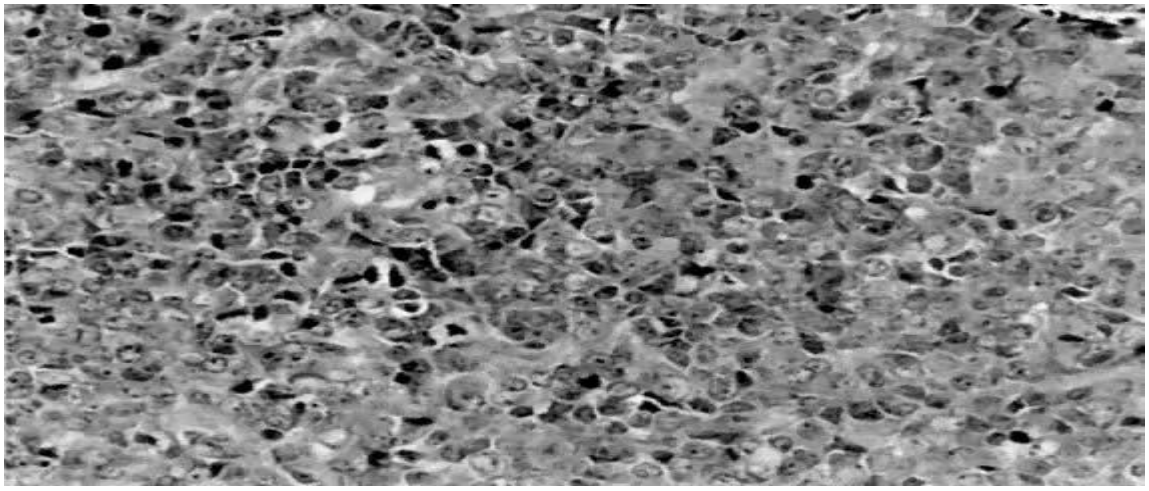

**Fig. 4. Small cell carcinoma is characterized by sheets of round to oval cells with granular chromatin and often dot-like nucleoli. The mitotic rate is quite high in these clinically aggressive lesions.**

5. **Mixed carcinoma of the uterine corpus:** It is a rare tumor, representing <10% of all endometrial cancers [11]. It is composed of two or more discrete histological types of endometrial carcinoma that must be identified by histology and immunohistochemistry, where at least one component is either serous or clear cell [11].

6. **Mesonephric and mesonephric-like adenocarcinoma (MLA):** Mesonephric and Mesonephric-like adenocarcinomas are rare neoplasms with a reported incidence of 1% of all endometrial carcinomas [12]. It is still a matter of controversy whether these tumors are of mesonephric origin or represent Müllerian neoplasms closely mimicking mesonephric adenocarcinomas. They show morphological, immunohistochemical, and molecular similarities to mesonephric adenocarcinomas (MA) that originate from true mesonephric remnants [13]. They are characterized by a variety of histologic patterns that may be present within the same tumor; the most frequently seen are small tubules with ductal or glandular growth. Also, papillary, solid growth, trabecular, retiform, sex cord-like, sieve-like, glomeruloid, and spindle cell areas could be seen. A characteristic luminal eosinophilic secretion is also found. The tumor cells can be flattened, cuboidal, or columnar with mild to moderate cytological atypia [14].

7. **Squamous cell carcinoma, NOS:** Primary endometrial squamous cell carcinoma is an exceedingly rare tumor, accounting for less than 5% of all endometrial malignancies [15]. Morphologically, these are identical to squamous cell carcinoma seen elsewhere in the body, but may exhibit less cytological atypia, and have broad invasive fronts [15].

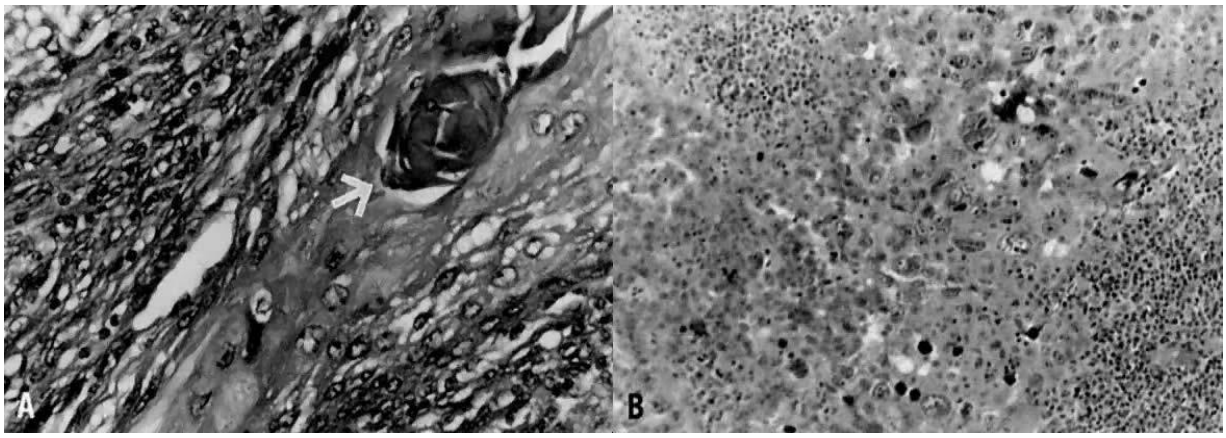


**Fig. 5. ( A) As with squamous cell carcinoma in other locations, the presence of keratin pearls ( arrow) or intercellular bridges is diagnostic. (B) The neoplastic cells have voluminous eosinophilic cytoplasm and marked nuclear atypia.**

8. **Mucinous carcinoma, gastrointestinal type:** Primary gastrointestinal type carcinoma of the endometrium is a rare and biologically aggressive EC showing gastric and intestinal differentiation [16]. This is described as a mucinous adenocarcinoma with glandular and solid patterns of growth with necrosis both intra and extra glandular. Neoplastic cells showed large, pale eosinophilic or clear cytoplasm with distinct cell borders with variable amounts of intracytoplasmic eosinophilic mucin and mild to moderate nuclear atypia with a high mitotic rate [17].

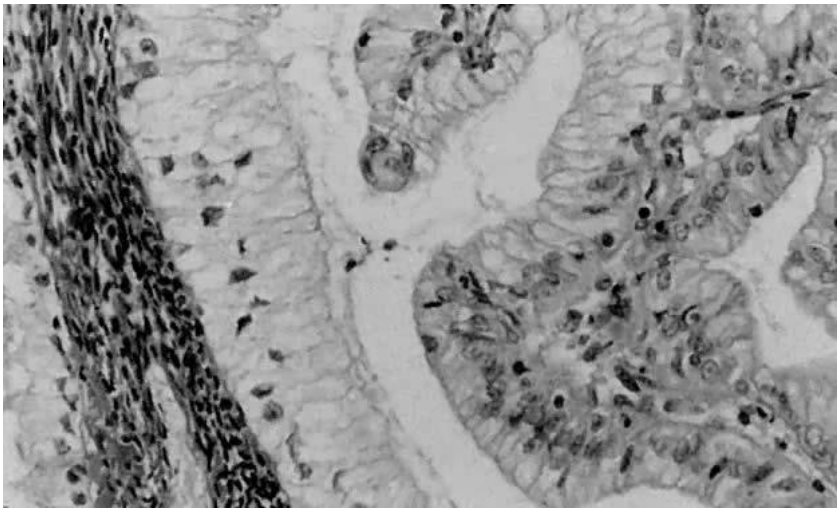

**Fig. 6. Mucinous carcinoma is generally well differentiated and is characterized by columnar cells with basally located nuclei and mucin-rich cytoplasm.**

9. **Carcinosarcoma:** Endometrial carcinosarcoma is a rare and aggressive high-grade endometrial carcinoma with secondary sarcomatous trans-differentiation [9, 18]. It is a biphasic malignant tumor consisting of endometrial adenocarcinomas admixed with a mesenchymal component [19]. The epithelial part is the most dominant element and is typically a high-grade (serous, endometrioid, clear cell, mixed, or undifferentiated) histotype, whereas the sarcomatous element can be either homologous (leiomyosarcoma, fibrosarcoma, endometrial stromal sarcoma) or heterologous (rhabdomyosarcoma, chondrosarcoma, osteosarcoma), according to whether the mesenchymal component resembles or not the uterine tissues [9, 18, 20].

Prognostic factors of Endometrial Carcinoma:

1. **Tumor grading:**

| | |
|---|---|
| Stage I | Confined to the uterine corpus and ovaryc |
| IA | Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease |
| | IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium |
| | IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI |
| | IA3 Low-grade endometrioid carcinomas limited to the uterus and ovaryc |
| IB | Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSId |
| IC | Aggressive histological typese limited to a polyp or confined to the endometrium |
| Stage II | Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion |
| IIA | Invasion of the cervical stroma of non-aggressive histological types |
| IIB | Substantial LVSId of non-aggressive histological types |
| IIC | Aggressive histological typese with any myometrial involvement |
| Stage III | Local and/or regional spread of the tumor of any histological subtype |

2. In Endometrioid endometrial carcinoma (EEC); according to The International Federation of Gynecology and Obstetrics (FIGO), the percentage of solid non-glandular growth areas determines the grade, while all serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are high-grade by definition [21].

3. FIGO and the World Health Organization recommend the following grading parameters for ECC:

• Grade 1: Solid non-glandular growth ≤5% (low grade) • Grade 2: Solid non-glandular growth 6% to 50% (low grade) • Grade 3: Solid non-glandular growth >50% (High grade)

Non-aggressive histological types are composed of low-grade (grade 1 and 2) EECs. Aggressive histological types are composed of high-grade EECs (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.

Nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumor by one.

It should be noted that high-grade EECs (grade 3) are a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making [21].

***3) Lymph and blood-vessel invasion:***

The presence of tumor cells inside endothelial-lined channels, known as lymphovascular space invasion (LVSI), has been postulated as one of the first steps in the metastatic spread of endometrial cancer [22].

The presence of LVSI has been significantly correlated with lymph node involvement, as well as lower progression-free and overall survival rates [23].

In 2015, LVSI positive status was introduced in European Society of Gynecological Oncology (ESGO) guidelines as a recommendation for lymphadenectomy, even in the absence of other well-known histological risk factors. Patients with LVSI and low risk factors were upgraded and considered intermediate-high risk [24].

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