Classification of endometrial carcinoma: more than two types

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Endometrial cancer is the most common gynaecological malignancy in Europe and North America. Traditional classification of endometrial carcinoma is based either on clinical and endocrine features (eg, types I and II) or on histopathological characteristics (eg, endometrioid, serous, or clear-cell adenocarcinoma). Subtypes defined by the different classification systems correlate to some extent, but there is substantial heterogeneity in biological, pathological, and molecular features within tumour types from both classification systems. In this Review we provide an overview of traditional and newer genomic classifications of endometrial cancer. We discuss how a classification system that incorporates genomic and histopathological features to define biologically and clinically relevant subsets of the disease would be useful. Such integrated classification might facilitate development of treatments tailored to specific disease subgroups and could potentially enable delivery of precision medicine to patients with endometrial cancer.

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Introduction

Endometrial cancer is the most common gynaecological malignant disease, and the fourth most common cancer in European and North American women, accounting for about 6% of new cancer cases and 3% of cancer deaths per year.[1,2] Incidence is steadily increasing;[3] age-adjusted annual incidence was 24·3 per 100 000 women in the USA in 2006–10, and 19·4 per 100 000 in the UK in 2008.[1,3] Around 75% of patients with endometrial cancer are diagnosed in the early stages (International Federation of Gynecology and Obstetrics [FIGO] stages I or II), and 5-year overall survival is 74–91%.[1,4] For women with advanced stage III or IV disease, 5-year overall survival of 57–66% and 20–26%, respectively, has been reported.[4]

Traditionally, endometrial carcinomas have been classified as type I or type II, as defined by Bokhman,[5] on the basis of clinical, endocrine, and epidemiological observations. Type I tumours were oestrogen dependent, and associated with endometrial hyperplasia, whereas type II tumours were oestrogen independent and associated with endometrial atrophy.[5] Endometrial carcinoma is also classified according to histopathological characteristics,[6] with the most common subtypes being endometrioid carcinoma, serous carcinoma, carcinosarcoma, and clear-cell carcinoma. Correlations have been noted between the subtypes in these two classification systems—type I cancers generally have endometrioid histology and most type II cancers are serous carcinomas—but these correlations are imperfect.

In the past decade it has become increasingly clear that endometrial cancer comprises a biologically, clinically, morphologically, and genetically heterogeneous group of tumours. Traditional classifications do not entirely take into account this heterogeneity and, being prognostic in nature, are limited in predicting response to therapy. A genomic classification of endometrial carcinoma has been proposed[7] in an attempt to identify potential targets for treatment in different subgroups of the disease.

In this Review, we provide an overview of traditional and genomic classifications of endometrial carcinoma, and discuss their potential and their limitations. In view of the substantial morphological and molecular heterogeneity in endometrial cancer, we suggest that classification systems based on limited sets of parameters are insufficient for the development of effective individualised treatments. We propose a rationale for establishing an integrated classification system that incorporates molecular and histopathological features to define biologically and clinically relevant subsets of endometrial cancer.

Traditional classification

Dualistic and histological classification

Bokhman[5] proposed that endometrial cancers can be categorised into two pathogenetic types that are primarily based on clinical, metabolic, and endocrine characteristics (table 1).[7–17] Type I tumours were associated with oestrogen excess, obesity, hormone-receptor positivity, and endometrial hyperplasia, were moderately or highly differentiated, and had favourable outcomes; type II tumours were more common in non-obese women, arose in the absence of endocrine and metabolic disturbances, were associated with an atrophic endometrium, were poorly differentiated, and had less favourable outcomes.[5] Subsequent studies aimed to elucidate the clinicopathological, histological, and molecular correlates of type I and type II cancers. However, although these studies advanced understanding of endometrial cancers, some misconceptions emerged, as discussed in this Review.

Tumours of the uterine corpus comprise several distinct histological types that WHO classifies as epithelial carcinomas (endometrioid, serous, clear cell, mucinous, squamous cell, transitional cell, small cell, and undifferentiated), mixed epithelial and mesenchymal tumours (eg, carcinosarcomas), or mesenchymal tumours (eg, endometrial stromal and smooth-muscle tumours), gestational trophoblastic diseases, and other malignant tumours.[6] In this Review we focus on epithelial tumours—of which endometrioid, serous, and

	Type I	Type II
Clinical, endocrinological, and morphological components (Bokhman classification[5])		
Distribution	60–70%	30–40%
Reproductive function	Decreased	No disturbances
Onset of menopause	After age 50 years	Younger than age 50 years
Background endometrium	Hyperplasia	Atrophy
Oestrogen associated	Yes	No
Associated obesity, hyperlipidaemia, and diabetes mellitus	Yes	No
Tumour grade	Low (grades 1–2)	High (grade 3)
Myometrial invasion	Superficial	Deep
Potential for lymphogenic metastatic spread	Low	High
Prognosis	Favourable	Unfavourable
Sensitivity to progestagens	High	Low
Outcome (5-year survival)	86%	59%
Clinicopathological and molecular correlates[7–10]		
Prototypical histological type	Endometrioid	Serous
Oestrogen-receptor or progesterone-receptor expression	High	Low
Stage at diagnosis	Early (FIGO stage I–II)	Advanced (FIGO stage III–IV)
Common genetic alterations[10–17]		
PTEN mutation	52–78%	1–11%
PIK3CA mutation	36–52%	24–42%
PIK3R1 mutation	21–43%	0–12%
KRAS mutation	15–43%	2–8%
ARID1A mutation	25–48%	6–11%
CTNNB1 mutation	23–24%	0–3%
TP53 mutation	9–12%	60–91%
PPP2R1A mutation	5–7%	15–43%
HER2 amplification	0	27–44%
Microsatellite instability	28–40%	0–2%

FIGO=International Federation of Gynaecology and Obstetrics.

Table 1: **Dualistic classification of epithelial endometrial cancer, including clinical, pathological, and common molecular genetic correlates**

clear-cell carcinomas account for 75%, 5–10%, and 1–5%, respectively[6]—as they are the most extensively studied (figure 1).[18–21] Endometrioid adenocarcinomas represent a range of neoplasms, from well to poorly differentiated tumours (ie, low to high grade), whereas serous and clear-cell carcinomas are high grade by definition. Low-grade endometrioid carcinomas are often seen in premenopausal women, are associated with endometrial hyperplasia, and generally exhibit indolent clinical behaviour. By contrast, serous carcinomas frequently develop in postmenopausal women in association with atrophic endometrium, and generally show an aggressive clinical course (figure 1).[4,6,9,22]

Bokhman's model[5] formed the basis of the tenet that type I tumours comprise low-grade endometrioid carcinomas associated with unopposed oestrogen exposure and excellent prognosis, and that type II tumours are largely non-endometrioid tumours (ie, serous and clear-cell carcinomas) with poor outcomes (tables 1 and 2).[7,8] Molecular data to support this dichotomous classification were also available. For example, endometrioid (type I) carcinomas are preferentially associated with mutations in *PTEN*, *KRAS*, *CTNNB1*, and *PIK3CA*, and microsatellite instability, whereas serous (non-endometrioid, type II) carcinomas show *HER2* amplification and recurrent *TP53* mutations (table 1).[7,9,10] Endometrioid and serous carcinomas are also generally distinct at the transcriptional level and in gene copy numbers.[23,24] These findings were perceived as being consistent with the type I and type II division of endometrial cancers; subsequently, histological type and molecular features became integral components of the dualistic Bokhman classification.

Limitations of traditional classification schemes

The Bokhman and histological classification systems are undoubtedly conceptually useful. Their implementation has advanced understanding of endometrial cancers, and provided a framework for studies, particularly those of molecular features. Yet, the correlations between the subtypes defined by the traditional taxonomies are imperfect (table 2).[5,6,11] Furthermore, there has been widespread misconception that the Bokhman types define diseases that are homogeneous with respect to their biological, genetic, and pathological features. Several lines of evidence, however, have shown that there is not only overlap between type I and type II tumours, but that there is also heterogeneity within each of these types.

Bokhman's dualistic model was based on clinical and epidemiological characteristics of women with endometrial cancer in the former Soviet Union more than 30 years ago.[5] Characteristics in current patients might, therefore, differ—eg, because of increased use of hormone-replacement therapy and increased numbers of overweight or obese patients.[25–27] Bokhman's model also does not account for endometrioid cancers occurring in patients with Lynch syndrome, who generally are thin and whose tumours are not often associated with hyperplasia.[28] Furthermore, epidemiological data suggest that obesity is also associated with type II cancers, although to a lesser extent than with type I cancers.[25,29] Type I and II tumours also share multiple risk factors with a history of diabetes being associated with increasing parity, age at menarche, use of oral contraceptives, and pack-years of smoking being associated with reduced risk.[25,29]

While low-grade endometrioid and serous carcinomas integrate well into Bokhman's model (being, respectively, prototypical type I and II tumours), many in the range of endometrioid cancers fall outside a simple dichotomous classification. Between 10% and 19% of endometrioid carcinomas are high grade[4,29] and have clinical, histopathological, and molecular features that are either intermediate between those of types I and II or are more akin to those of type II cancers, including lack of association with endometrial hyperplasia and poor outcomes.[29,30] By contrast, not all serous carcinomas behave as prototypical type II cancers. For example, 2%