

# Current Issues in the Diagnosis and Treatment of Endometrial Carcinoma

## Aktuelle Aspekte zur Diagnostik und Therapie des Endometriumkarzinoms

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### Abstract

Endometrial carcinoma is the most common carcinoma of the female genital tract. Its most important clinical sign is postmenopausal bleeding. An endometrial biopsy is essential for diagnosis. Treatment decisions are governed by tumour risk assessment and patient comorbidity, which is often present. Pelvic and paraaortic lymph node dissection is unnecessary in low risk cases (definition: pT1 a, G1/2) and adjuvant radiotherapy and systemic treatments are usually avoidable. Treatment of high-risk patients (G3 and/or pT1b) and palliative cases is difficult and not well standardised. New molecular-based subtype classification may help treatment decision making in future.

### Zusammenfassung

Das Endometriumkarzinom ist das häufigste Karzinom des weiblichen Genitales. Führendes klinisches Zeichen ist die postmenopausale Blutung. Für die Diagnosestellung ist immer eine Endometriumbiopsie notwendig. Die Therapieentscheidung hängt von der Risikoeinschätzung des Karzinoms und der häufig vorliegenden Komorbidität ab. In Fällen mit niedrigem Risiko (Definition: pT1 a, G1/2) ist eine pelvine und paraaortale Lymphknotendissektion unnötig. Eine adjuvante Bestrahlung und eine Systemtherapie sind zumeist vermeidbar. Die Behandlung von Hochrisikopatientinnen (G3 und/oder pT1b) und von Patientinnen in palliativer Situation ist schwierig und weniger gut standardisiert. Neue, molekular definierte Subtypen könnten hier zukünftig Therapieentscheidungen erleichtern.

### Introduction

According to the Robert Koch institute, the lifetime risk of endometrial carcinoma amongst German women is 2.2% (annual incidence approx. 28 new cases per 100 000 women). It ranks fourth in gender specific carcinoma frequency and amongst gynaecological malignancies is second only to breast carcinoma [1]. With the main presenting symptom being postmenopausal bleeding (PMB), diagnosis is usually made early and prognosis thus comparatively favourable. 70% of cases are diagnosed at T1 stage and relative 5-year survival is around 81%. Despite its relatively high incidence endometrial carcinoma is only in 11th place in cancer mortality statistics. With an average mean age at diagnosis of 69 years a significant proportion of patients die of comorbid, non-cancer related causes within 5 years of diagnosis (absolute 5-year survival rate 72%).

Current topics of discussion include the diagnostic process and the development of stage-appropriate treatment protocols that avoid over treatment while ensuring optimal management of patients with high recurrence risk.

### Synopsis

#### Is biopsy essential for postmenopausal bleeding (PMB) when the endometrium is thin?

PMB is usually the main clinical sign of endometrial carcinoma. It is mostly an early symptom of the disease and should prompt the clinician to perform an endometrial biopsy. In Germany and most western European countries this is performed via hysteroscopy and fractionated curettage. The validity of fractionation is however questionable since differentiation between cervix and corpus is imprecise and therapeutic conse-

**Table 1** Risk factors for the development of endometrial carcinoma.

Risk factor	Estimated relative risk
<b>Obesity</b>	<b>2–5</b>
Increased age	2–3
PCO Syndrome (anovulation)	>5
Early menarche	1.5–2
Late menopause	2–3
Nulliparity/infertility	3
Tamoxifen	2–3 (7)
Long-term oestrogen substitution without progesterone	6–9
Oral contraceptives	0.5
Diabetes mellitus type 2	2–3

quences rarely follow. Vacuum aspiration biopsy is an alternative method of tissue sampling that is seldom practiced in Germany and elsewhere [2]. It requires no anaesthesia and can be performed on an outpatient basis. The optional use of local anaesthesia e.g. 20% benzocaine spray simplifies sampling by allowing fixation of the uterus by grasping the anterior lip of the cervix with a tenaculum. Dilatation of the cervix is usually not necessary prior to insertion of the 3.1 mm thick polypropylene biopsy catheter. Given that it is now possible to assess the endometrium with high-resolution transvaginal ultrasound, the question arises whether endometrial biopsy can be avoided in certain patients with PMB. In one metaanalysis endometrial carcinoma was present in 8.9% of approximately 2900 patients with PMB [3]. With a threshold of 3 mm for endometrial thickness 97.9% of carcinomas would have been diagnosed with a false positive rate of 64.6% (i.e. almost 2/3 of patients without carcinoma also had endometrial thickness > 3 mm). When endometrial thickness was ≤ 3 mm the likelihood of carcinoma dropped from 10 to 0.6% despite the presence of PMB. The authors concluded that endometrial biopsy could be avoided when endometrial thickness was ≤ 3 mm. Undiagnosed cases of type 2 serous endometrial carcinoma remain a problem with this approach. The working group for gynaecological oncology (AGO) of the German Society of Obstetrics and Gynaecology therefore recommends histological assessment of all cases of PMB using hysteroscopy and fractionated curettage [4]. Defining indications for the investigation of perimenopausal bleeding remains difficult. There should be a low threshold for curettage for menorrhagia and metrorrhagia, especially after an extended bleeding-free interval or when typical risk factors such as the metabolic syndrome are present.

### Is biopsy indicated for endometrial thickening in postmenopausal women without bleeding?

A British case-control study that included over 48 000 postmenopausal women without PMB correlated the incidence of endometrial carcinoma or atypical hyperplasia within a year of study inclusion with endometrial thickness [5]. Endometrial thickness was ≥ 5 mm in 77.1% of women with carcinoma, however, had this measure been used as the indication for histological investigation, carcinoma would have been present in only 1.4% of cases investigated. By far the majority would have had no carcinoma. Put another way, in the absence of PMB 58 women would need to be investigated histologically to diagnose one case of carcinoma [6]. And despite this rather low threshold for investigation 19% of carcinomas would still be missed. Histology should thus not be performed solely on the basis of ultrasound criteria. It is

also doubtful whether early carcinoma detection improves prognosis; there are no prospective data on the subject. A retrospective analysis showed no prognostic advantage with early ultrasonographic carcinoma detection [7]. There was no difference in disease-free survival or overall survival between patients whose carcinomas were diagnosed solely on ultrasound criteria (endometrium ≥ 10 mm and/or endometrial irregularity) and those diagnosed because of PMB, provided that bleeding was investigated within 8 weeks of its occurrence [7]. Other retrospective analyses have also shown no difference in disease-free or overall survival between asymptomatic patients and those with PMB [8, 9]. Ultimately a significant number of endometrial carcinomas may never become clinically apparent, as was shown in an autopsy study that found a 4–6 times higher incidence [6, 10]. In summary, current data do not support ultrasound screening for endometrial carcinoma and further investigation of incidental endometrial thickening in the absence of PMB provides no benefit. This also applies to patients at increased risk, such as those with the metabolic syndrome and current tamoxifen therapy [11]. The only exception is proven Lynch syndrome, where the life-time risk of endometrial carcinoma is 40–60% [12]. Approximately 1.8% of endometrial carcinomas are presumed due to Lynch syndrome (incidence approx. 1 : 500), these tumours occurring more frequently before the menopause. Thus tissue samples from patients under 50 years of age should be specifically tested for the presence of this syndrome [13], which is an autosomal dominantly inherited disorder of mismatch repair genes that can be diagnosed on history using the Amsterdam criteria [12]. Where the disease is present vaginal ultrasound and endometrial vacuum aspiration biopsy are advised annually from the age of 35 years. In addition prophylactic hysterectomy should be considered once family planning is complete.

### Treatment of precursor lesions

In contrast to the 1994 WHO classification, which subdivided endometrial hyperplasia into four categories, the current simplified classification from 2014 only discriminates between forms of hyperplasia with and without atypia [14]. Atypical hyperplasia (syn. endometrial intraepithelial neoplasia [EIN]) shows many of the molecular genetic changes of invasive carcinoma, yet only the presence of atypia is associated with a definite increase in carcinoma risk (Table 3) [15]. The expected rate of carcinoma development within 10 years is about 30% [16]. When considering the risk of progression to invasive carcinoma it should be taken into account that invasive carcinomas are found in up to 48% of hysterectomy samples in this setting [17, 18]. In addition, one study found that atypical hyperplasia was reclassified as invasive carcinoma on second pathological assessment in 29% of cases [17]. In contrast, the development of invasive carcinoma was very seldom in cases of hyperplasia without atypia (<5%) [16]. The following treatment recommendations can be deduced: Hyperplasia without atypia can be treated conservatively. Progesterone therapy is recommended in premenopausal patients (e.g. 10–20 mg MPA on cycle days 12–25). Alternatively local treatment in the form of a progesterone containing intrauterine pessary (e.g. Mirena®) is recommended or a monophasic progesterone dominant contraceptive in PCO syndrome with an irregular cycle. Hormonal IUDs produce better endometrial regression rates than oral treatments (95–100% vs. 64–84% respectively) [19, 20]. Ultrasound should be repeated after 3 to 6 months and if abnormal a repeat curettage performed [21]. Continuous progesterone therapy (2.5 mg MPA daily) should be considered in

**Table 2** Lesions and their likelihood of progression [15]. The current WHO hyperplasia classification only considers the presence or absence of atypia.

Type	Progression to invasive carcinoma (on average after 13.4 years)
Simple hyperplasia	1%
Complex hyperplasia	3%
Simple hyperplasia with atypia	8%
Complex hyperplasia with atypia	29%

postmenopausal patients, a possible alternative being regular follow-up without medical treatment. Hysterectomy is recommended if atypia is found. An individualised approach is necessary for patients who still wish to fall pregnant. Women must be informed that despite progesterone therapy atypia will persist in 14% of cases and 3–7% will progress [22,23]. Ultimately a quarter of cases will recur, the most important risk factor being obesity (body mass index  $\geq 35$  kg/m<sup>2</sup>) in which case treatment with metformin is recommended [24]. Here again the levonorgestrel containing free intrauterine pessary (Mirena®) produces better results than oral progesterone [25,26]. Close ultrasound monitoring of the endometrium and repeat biopsy after 3 and 6 months are essential, as is hysterectomy as soon as family planning is complete. MRI provides an additional option for estimating infiltration depth (● Fig. 1).

### New molecular classification

Tumour stage (● Table 2) and grade of differentiation remain important prognostic factors for endometrial carcinoma. In addition, the histological subtype carries prognostic significance. As per the classical view, endometrioid type 1 carcinoma and serous/clear cell type 2 carcinoma [27] are differentiated. The first of these (type 1 carcinoma) develops on a background of chronic oestrogen stimulation (classical risk factor!) (● Table 1) with progression through the precursor stages of hyperplasia; prognosis is generally favourable. The second (type 2 carcinoma) occurs in 30% of cases. These tumours develop independently of oestrogen on background atrophic endometrium. They are characterised by poor differentiation, are highly aggressive and at diagnosis tumour stage is often advanced (FIGO III–IV). Both subtypes are associated with characteristic mutation patterns (type 1:



**Fig. 1** High resolution pelvic MRI with gel-filled vagina. 25-year-old patient (BMI 59.5 kg/m<sup>2</sup>) with histologically confirmed endometrioid adenocarcinoma of the uterine corpus; previous fractionated curettage for hypermenorrhoea. Intrauterine tumour with surrounding myometrium prior to surgery. Postoperative classification: pT1b (infiltration depth max. 17/20 mm) pN1 (1/36) cM0 L1 Pn0 V0 R0 G2. Microsatellite instability not present (consistently positive expression of MLH1, MSH2, MSH6 and PMS2).

PTEN mutation in up to 80%, type 2: p53 mutation in over 90%). More recent molecular genetic analyses have shown that endometrioid type 1 carcinomas in particular should be further divided into subclasses. Some endometrioid carcinomas should even be grouped together with serous type 2 carcinoma. Currently 4 subclasses with differing prognoses are differentiated; these may be essential for future risk-adapted treatment decision making (● Table 3) [27,28]. Of particular importance in this regard is the fact that hypermutated carcinomas express numerous neoantigens, thus presenting potential targets for the mediation of an inherent immune response. This antitumour cytotoxicity is however prevented by the self tolerance mediated interaction of lymphocytic PD (programmed death) receptors and their ligands (PD-L1) on tumour cells [29]. The antibody mediated blockade of this “rescue” mechanism by so-called immune checkpoint inhibitors may be meaningful for future treatment, and is currently the focus of clinical studies [30].

**Table 3** Molecular classification of endometrial carcinoma [27,28]. Four subtypes are defined. The POLE (polymerase  $\epsilon$ ) mutated forms (5–6% of all endometrial carcinomas, mostly in younger women) have a good prognosis despite high mutation rates. MSI type is associated with Lynch syndrome. A subgroup of endometrioid carcinoma is molecular biologically grouped together with serous carcinomas.

Type	POLE (ultramutated)	MSI (hypermuted)	Copy number low (endometrioid)	Copy number high (serous-like)
Copy number aberrations	low	low	low	high
MSI/MLH1 methylation*	mixed high and low MSI, stable	high MSI	MSI stable	MSI stable
Mutation rate	very high	high	low	low
Selection of commonly mutated genes (frequency in %)	POLE (100%) PTEN (94%)	PTEN (88%)	PTEN (77%)	TP53 (92%)
Histological subtype	endometrioid	endometrioid	endometrioid	serous, endometrioid and mixed
Grade	G1–3	G1–3	G1–2	G3
Prognosis	good	moderate	moderate	poor

\* MSI – microsatellite instability, MLH1 – mismatch repair gene inactivated by DNA methylation; if there is a germline mutation Lynch syndrome is present.

### When is lymph node dissection indicated?

Lymph node metastases occur in less than two percent of low risk endometrial carcinomas (pT1 a G1/2) [31]. In this context lymph node dissection carries no therapeutic benefit and it significantly increases morbidity, thus increasing treatment costs [32–35]. The disease-specific 5-year survival rate at this stage is over 95% even without lymph node dissection, which should thus not be performed [36]. The risk of lymphatic spread increases dramatically with myometrial infiltration of over 50% and in poorly differentiated carcinoma (G3)/the serous/clear cell subtype. Here lymph node dissection should be aimed for. In view of lymphatic drainage via the parametrium (caudal part) as well as via the adnexa (cranial part) both pelvic and paraaortic lymph nodes should be systematically removed. Ideally a pathologist should be available for intraoperative frozen section analysis.

### What type of hysterectomy?

According to results of the GOG Lap2 trial the laparoscopic and conventional (laparotomy) hysterectomy approaches are equivalent from the oncological perspective [37]. After 5 years there was no significant difference in recurrence rate (11.4 vs. 10.2%, HR 1.14) or overall survival. Approximately 70% of patients included in the trial had FIGO stage IA carcinomas. On average patients who underwent a laparoscopic hysterectomy were mobilised more quickly and had fewer complications. Obese patients in particular benefitted from the laparoscopic approach despite increased technical difficulty in this context.

Comorbid illnesses, particularly more severe adiposity, are often limiting factors in the operative treatment of endometrial carcinoma. In these cases vaginal hysterectomy (with removal of the adnexa where possible) is an alternative with few complications and a 5-year survival rate of over 90% for FIGO stage I tumours [38].

Previously, assuming parametrial tumour spread, radical hysterectomy was recommended for carcinoma involvement of the cervix. However pathological studies have shown that infiltration of the parametrium occurs in less than ten percent of carcinomas even amongst those that are locally advanced. In an analysis of 334 radical hysterectomy specimens none of the 16 FIGO stage II tumours showed parametrial infiltration and less than 20% of all cases of parametrial infiltration had cervical involvement [39]. Parametrial spread was most often found (21.3%) in FIGO stage III tumours (old classification). The prognosis at this stage is however determined by the high rate of distant metastases. The AGO no longer recommends parametrial resection for FIGO stage II carcinoma.

### The role of adjuvant radiotherapy for FIGO stage I carcinoma

The indication for adjuvant radiotherapy at FIGO stage I is risk-based. According to a Cochrane metaanalysis (7 trials, 3628 patients) percutaneous radiotherapy (teletherapy) reduces locoregional recurrence (HR 0.36; 95% CI 0.25–0.52) without improving overall or carcinoma specific survival – this also applies to high-risk FIGO stage I cases [40]. This may partly be due to the fact that radiation does not influence the occurrence of distant metastases (RR 1.04, 95% CI 0.80–1.35). In low-risk cases (G1/2, pT1 a) teletherapy even appears to be disadvantageous; carcinoma specific survival was worse for this important subgroup (RR 2.64; 95% CI 1.05–6.66). A 20-year follow-up of a Norwegian trial (n = 568 patients) showed that teletherapy provided no survival advantage for stage I carcinoma. In fact mortality among patients under the

age of 60 was significantly higher in the group receiving percutaneous radiation (HR 1.36; 95% CI 1.06–1.76); this was probably due to a higher rate of secondary carcinomas (HR 2.02; 95% CI 1.30–3.15) [41]. In addition there was increased teletherapy-associated morbidity in the form of chronic radiation damage to bladder and bowel. On direct comparison [42] brachytherapy was no less effective than teletherapy for FIGO stage I tumours in terms of locoregional recurrence rate. The risk-reducing effects of brachytherapy for low-risk cases is so slight [43] that radiation should be avoided in this situation (G1/2, pT1 a, endometrioid type). Brachytherapy is currently recommended for intermediate risk cases (FIGO stage IA and G3 or FIGO stage IB and G1/2); the PORTEC-4 trial is currently assessing whether radiation can be avoided in this setting. High-risk cases ( $\geq$  FIGO stage IB, G3) should receive adjuvant radiotherapy – the decision to use percutaneous forms should be made on an individual basis (e.g. when lymph node staging is not performed).

### When should systemic adjuvant therapy be recommended?

The prognosis of endometrioid carcinomas above FIGO stage IB, G3 and all serous-papillary/clear cell subtypes is unfavourable with 5-year survival rates under 60% [44]. The poor prognosis is due to a high rate of distant metastases and is only improved by effective systemic adjuvant therapy. All randomised, controlled trials with high-risk cases were included in a Cochrane metaanalysis [45]. Almost all trials were platinum-based (cisplatin). The efficacy of adjuvant chemotherapy was compared to a) no further systemic treatment after standard surgery and radiotherapy or b) compared directly to adjuvant radiotherapy. It was shown that adjuvant chemotherapy significantly improved overall 5-year survival (HR 0.88; 95% CI 0.79–0.99). There was a 3% absolute reduction in risk of death. 30 patients had to be treated to prevent one death (number needed to treat, NNT). The effect was even greater (NNT 25) when only the more recent platinum-based trials were considered. The positive effect was most obvious on direct comparison of chemotherapy vs. radiotherapy (HR 0.87; 95% CI 0.76–0.99); only a positive trend was shown for adjuvant chemotherapy on a background of previous adjuvant radiation (HR 0.94; 95% CI 0.72–1.22). The AGO advises sequential adjuvant carboplatin-paclitaxel chemotherapy and radiotherapy from FIGO stage IB, G3 up to FIGO stage III and for all serous and clear cell carcinomas. Adjuvant endocrine therapy has shown no efficacy and the AGO specifically advises against it.

The high rate of often severe comorbidity in these patients needs to be taken into account in practice. It is often the decisive life-limiting factor, relativising the purported therapeutic benefits of adjuvant systemic therapy. At the very least, comorbidity severely limits chemotherapy options.

### Treatment options for tumour recurrence

There is little data to support treatment recommendations for tumour recurrence. Operative removal of locoregional and intra-abdominal recurrences should be attempted wherever possible with complete tumour excision being the primary aim. Radiotherapy is indicated for inoperable tumours and postoperative residual tumour. Intraoperative clip marking can help to better define radiation volume. Palliative systemic therapy should be reserved for cases in which the above mentioned options are not possible. Analogous to adjuvant therapy recommended first line treatment is platinum-based chemotherapy, if necessary in combination with a taxane. Anthracyclines are an alternative

**Table 4** Response rates for endocrine therapy in palliative cases of endocrine sensitive (hormone receptor positive) low-grade carcinomas [47]. Response to commonly used monochemotherapeutic agents is comparable (10–20%).

Endocrine substance	Response rate
Progesterones (e.g. MPA 200 mg/d)	11–56%
Tamoxifen	10–35%
GnRH analogues	11%
Aromatase inhibitors	9%
Fulvestrant	proven efficacy
Onapristone (progesterone receptor antagonist)	?

although pegylated liposomal doxorubicin is preferable in view of better tolerance [46]. Other drugs such as ifosfamide, topotecan and ixabepilone used as monotherapy have response rates of 10–20%. Endocrine therapy can be considered in low-grade tumours that are oestrogen and/or progesterone receptor positive. Response rates for the individual substances are comparable (Table 4) [47].

### Uterine carcinosarcoma: a special case

With the most unfavourable prognosis of all, uterine carcinosarcoma (syn. malignant mixed Mullerian tumour) should be managed surgically as for high-risk endometrial carcinoma: hysterectomy and removal of the adnexa plus pelvic and paraaortic lymph node dissection [48]. Here too radiotherapy reduces the risk of local recurrence but does not improve survival [49]. Adjuvant chemotherapy may improve survival when the tumour is locally advanced and after surgical management of tumour recurrence. A combination of ifosfamide and paclitaxel (GOG 161 study) is recommended or alternatively paclitaxel combined with carboplatin (less toxicity, response rates of 54–62%).

### Conclusion

In most cases endometrial carcinoma is diagnosed early due to postmenopausal bleeding. Ultrasound measurement of endometrial thickness can be helpful in the risk assessment of tumour occurrence, however since its use has not been shown to improve prognosis, and since type 2 carcinomas that occur on a background atrophic endometrium may be missed, ultrasound alone should not be relied on for early tumour detection in asymptomatic women, nor should it be the sole instrument of diagnostic decision making in the assessment of postmenopausal bleeding. Both lymph node dissection and radiotherapy can be avoided in the management of early stage disease with low recurrence risk. In contrast high-risk carcinoma requires multimodal treatment consisting of extensive surgery plus radiotherapy and chemotherapy. Comorbidity in this patient population, however, makes management strictly according to guidelines impossible in many cases. New molecular biologically based risk classification is likely to be relevant to treatment decision making in future.

### Conflict of interest

The authors declare no conflict of interest.

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