REVIEW ARTICLE

The Diagnosis and Treatment of Endometrial Cancer

Progress and Controversies

Dominik Denschlag, Uwe Ulrich, and Günter Emons

SUMMARY

Background: Endometrial carcinoma is the fourth most common type of cancer among women in Germany, with more than 11 000 newly diagnosed cases each year. The present lack of clarity about the optimal clinical management of these patients is due in part to inconsistencies in the scientific evidence and in part to recent modifications of the FIGO classification. In this article, the issues requiring clarification are presented and discussed.

Methods: This article is based on a selective review of the pertinent literature, including evidence-based guidelines and recommendations.

Results and conclusion: Current scientific evidence does not support the screening of asymptomatic women. On the other hand, women with postmenopausal and acyclic bleeding should undergo histopathological evaluation, particularly if they have risk factors for endometrial cancer. The current FIGO classification divides endometrial cancer into stages depending on the findings at surgery. On the basis of risk stratification (e.g., by tumor stage and histological differentiation grade), women who are judged to be at high risk (FIGO Stage IB and above, Grade 3) should undergo not just hysterectomy and adnexectomy, but also systematic pelvic and para-aortic lymphadenectomy. Risk stratification also determines whether adjuvant radiotherapy should be given. The additional or alternative administration of chemotherapy is a particular consideration for women at high risk, although the pertinent clinical trials to date have yielded conflicting evidence on this point.

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Endometrial carcinoma (EC) is the fourth most common type of cancer among women in Germany, accounting for 5.6% of all malignant neoplasms with more than 11 000 newly diagnosed cases each year (1). Its five-year survival rate (all stages) has been estimated at 75% to 83% (1). Among German women, EC is commonest between the ages of 65 and 85 years but can also arise premenopausally (in as many as 20% of cases) or even before age 45 (in up to 5%) (2). Its prevalence rose by 10% to 20% from 1990 to 2004 and may well continue to rise, particularly in women over 70, because of the aging of the population (2).

In this review article, we present the current scientific evidence concerning the treatment of women with endometrial carcinoma.

Methods

The information presented in this article was obtained by a selective search of the Medline database (via PubMed) for pertinent literature, in addition to the existing guidelines of the German Working Group on Gynecological Oncology *(Arbeitsgemeinschaft Gynäkologische Onkologie)*.

Etiology and pathogenesis

Endometrial carcinoma is a malignant neoplasm of the epithelial portion of the endometrium. It has two recognized subtypes (3):

- estrogen-associated type I carcinoma and
- estrogen-independent type II carcinoma.

Type I carcinoma

Type I carcinoma is the more common type, accounting for 75% to 80% of cases. It is classified as an endometrioid adenocarcinoma, sometimes with a squamous-cell component.

Type I carcinoma is thought to be due to an excess of endogenous or exogenous estrogens, whose effect is inadequately antagonized by gestagens (or not at all). Endometrial hyperplasia is its histological precursor (4). The causes of estrogen excess include obesity, anovulatory cycles in polycystic ovarian (PCO) syndrome, use of the partial estrogen agonist tamoxifen, and estrogen replacement therapy *(Table 1)*.

TABLE 1

Risk factors for type I carcinoma, adapted from Smith RA: American Cancer Society Guidelines for Early Endometrial Cancer Detection (Update 2001)

	Relative Risk
Long-term unopposed estrogen therapy (depending on duration), e.g., post-menopausal hormone therapy	2–10
Metabolic syndrome	NA
Obesity	2–4
Diabetes mellitus	2
Polycystic ovary syndrome	3
Long phase of life with menstrual bleeding	2
Nulliparity	2
Infertility	NA
History of breast cancer	NA
Tamoxifen therapy	2
High estrogen concentrations (incl. estrogen- or androgen-secreting tumors)	NA

NA, not available

The current WHO classification subdivides endometrial hyperplasia into simple hyperplasia (cancer risk less than 1%), complex hyperplasia without atypia (cancer risk ca. 2%), simple hyperplasia with atypia (cancer risk ca. 8%), and complex hyperplasia with atypia (cancer risk ca. 30%) (5).

Type II carcinoma

Ten to 15% of endometrial carcinomas are of type II, which is histologically characterized as either serous or clear-cell carcinoma and is classified as poorly differentiated, by definition.

Women with type II endometrial carcinoma tend to be older than those with type I carcinoma; they are often thin and lack the typical risk factors for estrogen dominance. These cancers characteristically arise from atrophic endometrial tissue by way of a preliminary stage (endometrial intraepithelial carcinoma), and they express neither estrogen nor progesterone receptors. The only known risk factors are age and prior irradiation of the uterus (e.g., for the treatment of cervical cancer) (e1).

Diagnostic evaluation

Uterine bleeding in a postmenopausal woman is the main presenting sign of endometrial carcinoma. Pre- or perimenopausal women with acyclical bleeding should also undergo thorough diagnostic evaluation, particularly if they have risk factors for endometrial carcinoma.

Targeted screening examinations for early detection, with endovaginal sonography followed by endometrial biopsy, may be reasonable for women at high risk (e.g., those with Lynch syndrome); yet, even for these women, there is no evidence to date confirming the benefit of screening.

Women with abnormal bleeding of the types described should undergo the following studies:

- Gynecological examination to localize the source of bleeding and determine its physical extent; transvaginal ultrasonography for evaluation of the endometrium and adnexa. In postmenopausal patients with uterine bleeding, an endometrial thickness exceeding 5 mm is considered suspect (6). In contrast, no reliable cut off has been reported in pre- or perimenopausal women, as well as in postmenopausal women taking hormone replacement therapy or tamoxifen.
- Hysteroscopy and fractionated uterine curettage.

Staging

The surgical staging of endometrial carcinoma according to the classification of the *Fédération Internationale de Gynécologie et d'Obstétrique* (FIGO) has been obligatory since 1988. A modified classification was issued by the FIGO on 1/1/2010 *(Table 2)*. As a rule, all patients should undergo surgical staging, except those who are inoperable because of other accompanying diseases. Complete surgical staging can also be omitted for premenopausal women with early

type I carcinoma who still wish to bear children (i.e., the uterus and adnexa are left in place). In such cases, contrast-enhanced magnetic resonance imaging (MRI) of the uterus and adnexa combined with diagnostic laparoscopy may be a reasonable fertility-preserving approach, although it affords less diagnostic certainty than complete surgical staging.

For patients who undergo surgical staging—consisting of open abdominal exploration, hysterectomy, bilateral adnexal removal, and pelvic and para-aortic lymphadenectomy (in the modified FIGO classification, peritoneal lavage cytology is no longer considered in tumor staging)—the following presurgical studies are recommended:

- a thorough physical examination (including the supraclavicular lymph nodes),
- a chest X-ray (posteroanterior and lateral views),
- abdominal ultrasonography to rule out urinary obstruction and metastasis to the upper abdominal organs, and
- (optionally) cystoscopy and rectoscopy to rule out FIGO Stage IVa disease.

Treatment

Hyperplasia without atypia

Cyclic gestagen treatment is recommended for premenopausal women who have hyperplasia without atypia. Alternatively, gestagen can be applied locally with an intrauterine device. For women with chronically oligo- or anovulatory cycles (e.g., in polycystic ovarian syndrome), it is reasonable to prescribe an oral contraceptive mainly containing gestagen (evidence level I).

In addition, an estrogen-producing tumor should be sought as a potential cause of hyperplasia. A follow-up ultrasonographic examination should be performed after three to six months of conservative treatment; any suspect findings should be investigated further with hysteroscopy and uterine curettage.

For postmenopausal women who have hyperplasia without atypia, surgical extirpation with hysterectomy and bilateral adnexal removal can be considered, in the light of the patient's estimated individual risk. Regular follow-up is a reasonable alternative; if postmenopausal bleeding occurs again, hysteroscopy and curettage should be repeated.

Hyperplasia with atypia

For women who have hyperplasia with atypia and are postmenopausal, or are premenopausal but do not plan to bear any more children, hysterectomy with adnexal removal is urgently recommended, in view of these patients' estimated 30% risk of developing an invasive carcinoma. Moreover, studies have shown that about 30% of women who had no worse histological finding than hyperplasia with atypia in their curettage specimen already have invasive carcinoma in their hysterectomy specimen (7) (evidence level II).

A conservative approach is feasible for women who still wish to bear children and for women who are at elevated operative risk.

TABLE 2

A comparison of the old and new FIGO classifications (www.bgcs.org.uk)

New	FIGO	Old
Tumor confined to corpus uteri	I	Tumor confined to corpus uteri
Tumor limited to endometrium or invades less than one-half of myometrium	IA	Tumor limited to the endometrium
Tumor invades one-half or more of the myometrium	IB	Tumor invades less than half of the myometrium
—	IC	Tumor invades one-half or more of the myometrium
Tumor invades stromal connective tissue of the cervix but does not extend beyond the uterus[*1]	II	Tumor extends into the uterine cervix but does not extend beyond the uterus
—	IIA	Tumor confined to the endocervical glands
—	IIB	Tumor invades the cervical stroma
Local and/or regional spread	III	Local and/or regional spread
Tumor involves serosa and/or adnexa[*2]	IIIA	Tumor involves serosa and/or adnexa and/or tumor cells in ascites or peritoneal lavage
Involvement of the vagina and/or parametrium	IIIB	Involvement of the vagina
Pelvic and/or para-aortic lymph node involvement	IIIC	Pelvic and/or para-aortic lymph node involvement
Positive pelvic lymph nodes	IIIC1	—
Positive para-aortic lymph nodes, with or without positive pelvic lymph nodes	IIIC2	—
Infiltration of the vesical and/or rectal mucosa	IVA	Infiltration of the vesical and/or rectal mucosa
Distant metastases	IVB	Distant metastases

[*1] Only endocervical glandular involvement counts as FIGO I
[*2] Positive cytology should be noted separately but does not change the FIGO stage

TABLE 3

Adjuvant therapy of endometrial carcinoma (3), old classification

After hysterectomy with bilateral adnexal removal and systematic lymphadenectomy (15 pelvic and 10 para-aortic lymph nodes)	
pT1a G1/2, pT1b G1, pN0	No adjuvant therapy
pT1a G3, pT1b G2/3, pT1c, pT2, pN0	Vaginal brachytherapy
pT3, pT4, pN0, and all pN1	Teletherapy ± brachytherapy and/or chemotherapy
Serous and clear-cell carcinoma	Teletherapy ± brachytherapy and/or chemotherapy
After hysterectomy with bilateral adnexal removal but no systematic lymphadenectomy	
pT1a G1/2 and T1b G1 Nx/cN0	No adjuvant therapy
pT1b G2 Nx/cN0	Vaginal brachytherapy
If secondary complete surgical staging is not possible	
pT1a G3, pT1b G3 Nx/cN0	Vaginal brachytherapy; additional teletherapy can be considered as well
pT1c, pT2 Nx/cN0	Teletherapy ± brachytherapy
pT3/pT4a Nx/cN0, and all cN1	Teletherapy ± brachytherapy and/or chemotherapy
Serous and clear-cell carcinoma	Teletherapy ± brachytherapy and/or chemotherapy

Women who have hyperplasia with atypia should receive relatively high-dosed gestagen therapy (e.g., medroxyprogesterone acetate 100 mg/day, megestrol acetate 60 mg/day). A gestagen-containing intrauterine device can be used in this situation as well.

The prerequisites for conservative treatment are comprehension and compliance on the patient's part and meticulous follow-up by the treating gynecologist. Even after initial remission under gestagen therapy, recurrences ranging from atypia to invasive carcinoma will develop in about one-third of cases (8). Thus, the response to conservative treatment must be checked by hysteroscopy and curettage after three to six months of conservative treatment.

Invasive carcinoma

Even some women with invasive carcinoma can be offered the option of a trial of conservative treatment, if they are premenopausal and still wish to bear children, and if the histological finding is of a well-differentiated carcinoma (grade I) without suspicion of myometrial invasion. Candidates for such fertility-preserving treatment must be informed of the 25% primary failure rate and the roughly 30% chance of recurrence associated with it, because of which they will need frequent clinical follow-up (8). A prerequisite for such treatment is the exclusion of myometrial infiltration or ovarian involvement by transvaginal ultrasonography and/or magnetic resonance imaging. Complete emptying of the cavum uteri by hysteroscopy and curettage is advisable for both diagnostic and therapeutic purposes. Laparoscopy should be considered for further exclusion of extrauterine disease, particularly because endometrioid ovarian carcinoma is a common simultaneous finding (in up to 25% of cases) and is often hard to identify in imaging studies (e2).

The pharmacotherapy of choice is continuous oral gestagen intake (megesterol acetate 160 mg/day, medroxyprogesterone acetate 200 to 250 mg/day), for a period of at least three months; a follow-up investigation is then performed with transvaginal ultrasonography, hysteroscopy, and curettage. Women found to be in complete remission can try to conceive; the optimal time window for this remains unknown. Because of the high probability of recurrence after conservative treatment, these women are advised to undergo hysterectomy once they have born as many children as they wish to have (8) (evidence level IV).

Surgical treatment

In general, the FIGO recommends systematic surgical staging for most patients, consisting of hysterectomy with bilateral adnexal removal and systematic pelvic and para-aortic lymphadenectomy (up to the inferior aspect of the left renal vein). The findings obtained through this basic initial treatment serve as the definitive guide to the potential use of further adjuvant measures, depending on the stage of disease.

Patients with tumor stage IA and grade 1 or 2 are unlikely to have lymph node involvement, and their prognosis is usually very good. Thus, systematic lymphadenectomy is not indicated for such patients, as it offers them no more than a marginal survival advantage, if any (3) (evidence level I).

On the other hand, patients with incurable advanced disease can benefit from surgical intervention (e.g., debulking of large tumor masses, or hysterectomy just to stop bleeding) in addition to various palliative measures. The potential benefits include, for example, better control of pain.

In experienced hands, laparoscopic hysterectomy with adnexal removal and lymphadenectomy seems to be just as safe and effective as an open abdominal procedure (9) (evidence level I). Current data imply that laparoscopic surgery is superior to open abdominal surgery with respect to postoperative morbidity and recovery (e3).

If curettage reveals a serous or clear-cell carcinoma, omentectomy and multiple peritoneal biopsies (including the domes of the diaphragm) should be performed in addition, analogously to the surgical staging of ovarian carcinoma (3) (evidence level IV). In stage pT2 (involvement of the cervical stroma in the curettage specimen), additional resection of the parametrial tissues is recommended, i.e., radical hysterectomy as described by Wertheim and Meigs and by Okabayashi (3) (evidence level II).

Stage-dependent surgery for endometrial carcinoma is summarized in the *eBox*.

Lymphadenectomy

In the surgical treatment of endometrial carcinoma, controversy surrounds the question whether the additional performance of pelvic and para-aortic lymphadenectomy in fact yields any general benefit, be it diagnostic (because decisions on adjuvant therapy may be based on the presence or absence of lymph node involvement) or therapeutic (because the removal of involved lymph nodes might prolong survival).

A large-scale, retrospective, multivariate analysis of data in the SEER database (Surveillance, Epidemiology and End Results; National Cancer Institute, USA) led to the conclusion that lymphadenectomy prolongs survival to a statistically significant extent, both in advanced-stage endometrial carcinoma (5-year survival: stage III, 74% vs. 63%; stage IV, 53% vs. 27%) and in poorly differentiated stage I carcinoma (grade 3) (5-year survival: 90% vs. 85%) (10) (evidence level II).

An analysis of the same data by a different group of researchers revealed, in addition, that the resection of at least 11 lymph nodes was associated with significant improvement of disease-specific and overall survival (11). This group of researchers, however, also pointed out the difficulty of interpreting the findings of a retrospective analysis.

These findings are apparently contradicted by those of two very recently published randomized controlled trials (12, 13): Women in an ostensibly early stage of the disease (clinical FIGO stage I) had no statistically significant survival benefit from lymphadenectomy (evidence level I).

The value of both of these studies is diminished, however, by the fact that, in general, only pelvic (and not para-aortic) lymphadenectomy was performed. Furthermore, in the British study (12), only a sample of lymph nodes (fewer than 10 nodes) was excised in about one-third of cases. Both studies included many women whose risk of lymph node involvement was low (pT1a, grade 1 or 2), and who thus *a priori* did not stand to benefit much from lymphadenectomy.

With regard to the value of systematic para-aortic lymphadenectomy in addition to pelvic lymphadenectomy, a recent study confirms earlier knowledge of the complex lymphatic outflow of endometrial carcinoma, as a result of which, in many women with lymph-node metastases (16% to 29%), only the para-aortic lymph nodes are involved, while the pelvic lymph nodes are spared (14).

Moreover, a recently published, large-scale retrospective cohort study (the SEPAL study) revealed that, in patients at high risk for lymph-node involvement (pT1b, grade 3), the risk of death was significantly reduced (by more than 50%) by the performance of systematic, combined pelvic and para-aortic lymphadenectomy, compared to pelvic lymphadenectomy alone (multivariate hazard ratio, 0.44; 95% confidence interval, 0.30–0.64; $p<0.0001$; absolute benefit for 5-year overall survival, 10.6%) (15) (evidence level II).

Adjuvant therapy

Radiotherapy

The value of stage- and risk-adapted postoperative adjuvant radiotherapy (vaginal brachytherapy and/or external teletherapy) was studied in the past in a number of randomized controlled trials and meta-analyses (16–19). It was shown that radiotherapy significantly lowers the rate of local recurrence without improving overall survival (evidence level I).

In view of the toxicity of external teletherapy, vaginal brachytherapy seems to be a reasonable compromise. In a randomized controlled trial of adjuvant external teletherapy versus vaginal brachytherapy (the PORTEC-2 trial), no significant difference was found between the two groups with respect to vaginal recurrence rates, the occurrence of distant metastases, disease-free survival, or overall survival (20). As expected, women who had received only vaginal brachytherapy had significantly fewer adverse effects and therefore had a better quality of life (21) (evidence level I).

Systemic chemotherapy

The putative benefit of adjuvant hormone therapy with high-dose gestagens has not yet been conclusively demonstrated (22) (evidence level I).

Moreover, controversy also surrounds the question whether systemic chemotherapy (sometimes in patients who also receive radiotherapy) improves overall survival for the particular subgroup of patients who are at high risk of recurrence (advanced stage, grade 3 histology).

A study of patients who had undergone optimal surgical treatment (residual tumor <2 cm) for stage III and IV endometrial carcinoma without any hematogenous metastases revealed a survival advantage from adjuvant chemotherapy (adriamycin/cisplatin) compared to total abdominal radiotherapy with a pelvic and para-aortic boost (5-year recurrence-free survival, 50% vs. 38%; overall survival, 55% vs. 42%) (23) (evidence level I). Other studies comparing chemotherapy to conventional external teletherapy have revealed that adjuvant chemotherapy with cyclophosphamide, epirubicin, and cisplatin may be just as effective as (24), or, in a retrospective subgroup analysis, perhaps even superior to teletherapy with respect to recurrence-free and overall survival (25). These studies, however, do not permit any firm conclusions, either because the case numbers were too small (24) or because the results were generated by retrospective analysis (25).

On the basis of the available data, the S2k guideline of the Association of Scientific Medical Societies in Germany (AWMF) recommends the stage- and risk-adapted adjuvant therapies summarized in *Table 3*.

Future prospects

Recent randomized and controlled trials have cast doubt on two mainstays of the primary treatment of

KEY MESSAGES

- The modified staging classification for endometrial carcinoma that was issued by the FIGO on 1/1/2010 should be used in routine clinical practice from now on, as it reflects patients' stage-dependent prognosis better than the old classification.
- The FIGO classification assigns tumor stages according to the surgical findings. Thus, as a rule, every patient with endometrial carcinoma should undergo surgery.
- There is no evidence to support the screening of asymptomatic women. Postmenopausal or acyclical bleeding (metrorrhagia) may be presenting signs of endometrial carcinoma; thus, any woman with these problems should undergo tissue biopsy for histopathological examination, particularly if she has risk factors for endometrial carcinoma.
- Depending on the stratified risk (tumor stage, degree of differentiation, etc.), systematic pelvic and para-aortic lymphadenectomy should be performed in addition to hysterectomy and bilateral adnexal removal. Systematic lymphadenectomy is obligatory for high-risk patients, i.e., those in FIGO Stage IB or above or with grade 3 tumors.
- Adjuvant radiotherapy is given depending on the stratified risk. For high-risk patients, the alternative or additional administration of chemotherapy should be considered.

endometrial cancer: surgical lymphadenectomy and adjuvant external radiotherapy. The benefit of adjuvant chemotherapy or combined radio- and chemotherapy in stages I and II has yet to be demonstrated in clinical trials. Especially for cancers with a high risk of recurrence (e.g., grade 3, serous or clear-cell histology), the current forms of treatment still yield highly unsatisfactory survival rates. Better treatments can be developed only with the aid of new prospective, randomized and controlled clinical trials that are well designed, adequately funded, and properly conducted, and that include as many patients as possible, so that they can conclusively address the questions and controversies discussed in this article (e4).

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eBOX

Stage-dependent surgical treatment of endometrial carcinoma (old classification) (3)

- **Stages pT1a, pT1b, G1, G2**
  - total hysterectomy with bilateral adnexal removal
  - cytology
  - optional: pelvic and para-aortic lymphadenectomy

- **Stages pT1a, pT1b, G3, and stages T1c G1 to G3**
  - total hysterectomy with bilateral adnexal removal
  - cytology
  - pelvic and para-aortic lymphadenectomy

- **Stage pT2a**
  - total hysterectomy with bilateral adnexal removal
  - cytology
  - pelvic and para-aortic lymphadenectomy

- **Stage pT2b**
  - extended radical hysterectomy with bilateral adnexal removal
  - cytology
  - pelvic and para-aortic lymphadenectomy

- **Stage pT3a**
  - total hysterectomy with bilateral adnexal removal
  - pelvic and para-aortic lymphadenectomy
  - omentectomy
  - debulking (maximal cytoreduction)

- **Stage pT3b (vaginal involvement)**

If the patient's general condition allows and the tumor is locally operable:
  - extended radical hysterectomy with bilateral adnexal removal
  - partial/total colpectomy
  - pelvic and para-aortic lymphadenectomy

For patients in poor condition or with locally inoperable tumors:
  - hysterectomy with bilateral adnexal removal
  - tumor debulking in the vagina
  - lymphadenectomy as indicated

- **Stage pN1 (FIGO IIIC)**
  - total hysterectomy with bilateral adnexal removal
  - pelvic and para-aortic lymphadenectomy

- **Stage pT4 (FIGO IVA)**
  - in isolated involvement of the bladder and/or rectum, consider anterior and/or posterior exenteration and bilateral adnexal removal with pelvic and para-aortic lymphadenectomy

- **Stage M1 (FIGO IVB)**
  - If the tumor is locally operable, hysterectomy (to control bleeding) and intra-abdominal debulking to improve the effectiveness of palliative chemo- and radiotherapy

- **Special considerations for serous and clear-cell carcinoma**

Stage-appropriate surgery as above (including pelvic and para-aortic lymphadenectomy, as these tumors are high-grade by definition), as well as:
  - omentectomy
  - multiple peritoneal biopsies
  - in case of extrauterine disease: maximal tumor debulking

- **Procedure if no lymphadenectomy or an inadequate lymphadenectomy has been performed, or if the adnexa have not been removed**

Stages pT1a, pT1b; G3; pT1c, pT2, pNx
  - completion of surgical staging if possible, then stage-appropriated adjuvant therapy
  - if surgical staging cannot be completed: adjuvant therapy