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Franco Muggia
Alessandro D. Santin
Esther Oliva *Editors*

Uterine Cancer

Screening, Diagnosis, and Treatment

Second Edition

Springer

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Maurie Markman, MD
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Franco Muggia • Alessandro D. Santin
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Editors

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Editors
Franco Muggia
NYU Langone Medical Center
New York, NY, USA

Alessandro D. Santin
Division of Gynecologic Oncology
Yale University, Yale School of Medicine
New Haven, CT, USA

Esther Oliva
Department of Pathology
Massachusetts General Hospital
Boston, MA, USA

Professor of Pathology
Harvard Medical School
Boston, MA, USA

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Preface to the Second Edition

For this second edition, *Uterine Cancer: Screening, Diagnosis, and Treatment* is represented by an additional editor, Alessandro Santin, joining Esther Oliva and me as editors. The first edition was inspired by the recognition that a book focusing on uterine cancer was timely: emergent sophistication in diagnosis and staging began having an increasing impact on clinical decision-making, particularly in the systematic application of new treatment modalities beginning with full integration of chemotherapy in the oncologists' armamentarium. Amalgamating epidemiology, diagnosis, and staging with the evolving applications of treatments beyond surgery promised to become a valuable reference among oncologists. Six years later, the rationale for a book on *Uterine Cancer* has become even stronger as oncologists grapple daily with the application of molecular diagnostic tools to refine applying diagnostic tools and treatments upon presentation. Important lifestyle and genetic factors in the causation of uterine malignancies have come to light. We also foresee that beyond the enhanced awareness on this somewhat neglected area of therapeutics, clinicians will welcome the dawn of interest on preventive measures. Hopefully, this will enhance awareness that these areas have rarely been a focus for drug development and the need for "borrowing" results from other gynecologic cancer in guiding the treatment of individual patients. Although the chapters appear with nearly the same titles of the first edition, this last message resonates throughout this second edition and seeks to accelerate the integration of "targeted therapies" and related concepts in the management of women at risk of or who have already manifested uterine cancer.

The current volume, therefore, have widely revised chapters with the theme of better tailoring the treatment to our emerging knowledge of cancer biology. As a result, premalignant lesions are dealt with by medical methods, and properly staged low-grade cancers can be treated by surgery alone. Both chemotherapy and radiation are being tailored for the treatment of stage I, properly staged patients when adverse prognostic areas are identified. Preliminary data justify these approaches but are not a substitute for clinical trials.

With my co-editors, we hope that this second edition will speed up the development of trials to provide future answers in the prevention and treatment of uterine cancers.

New York, NY, USA — Franco Muggia
New Haven, CT, USA — Alessandro D. Santin
Boston, MA, USA — Esther Oliva

Preface to the First Edition

For the editors, the task of writing a preface is most satisfying. It represents the completion of the book and a moment of reflection on whether the whole is more than the sum of all the parts. And also, one must reflect on how this book is likely to be utilized in this era of rapid communications.

The editors first met in May 2003 at a stimulating Italian symposium on endometrial cancer (organizers Drs. Luigi Frigerio, Roberto Grassi, and Andrea Lissoni, with participation of the deans of Italian Gynecologic Oncology, Ugo Bianchi and Constantino Mangioni) that took place at Bergamo and Caravaggio. The impressive gains in biology and clinical trials were further discussed by the two editors and others that are coauthors in this venture on this side of the Atlantic at a 2004 Educational Session at the American Society of Clinical Oncology (ASCO). The pace of progress in various aspects of the management of uterine cancer was noteworthy, not only was tumor biology fueling novel hypotheses such as questioning the mesenchymal origin of carcinosarcomas, but knowledge of molecular pathways was beginning to be applied as prognostic and as predictive factors portending benefit from systemic therapies. Surgical staging and sensitive imaging provided the underpinning for refining our treatment algorithms. Finally, a role for chemotherapy had finally become established, principally through phase III studies comparing chemotherapy to radiation in mostly locally advanced stages III and IV that had undergone resection.

Inevitably, this task brought back thoughts of prior efforts going into books covering endometrial cancer. In 1987, an international symposium resulted in the publication of a multiauthored book. To this day, it remains a valuable reference to the advent of pharmacology and hormone receptor work in the evaluation of hormonal therapy relevant to endometrial cancer. However, in the intervening 20 years biomedical science has moved far beyond focusing systemic therapy on the first of "targeted therapies." We are indebted to all the contributors, mostly selected on firsthand knowledge of their expertise and often based on interactions within our institutions or in cooperative groups and scientific societies. We know we added some additional work to their already busy daily lives, but hope they will be pleased with the results.

Covering the subject in a comprehensive manner is a challenge for the editors. On the one hand, one needs to discourage encyclopedic reviews in order to focus on what is new – the prime motivation for highlighting various aspects of uterine cancer. On the other hand, if one of the functions will be to become a handy reference on which to build the near future of therapeutics, all aspects of the foundations as well as of advancing science need to be included. In finally surveying the components that make up this new venture, we are hopeful that we have come close to our goals to emphasize new aspects while providing useful reference material.

January 2, 2009

Franco Muggia
Esther Oliva

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Contributors

Patricia M. Baker Department of Pathology, Health Science Center, Winnipeg, MB, Canada

Onyinye Balogun Department of Radiation Oncology, Laura and Isaac Perlmutter Cancer Center, NYU School of Medicine, NYU Langone Medical Center, New York, NY, USA

Jonathan D. Black Division of Gynecologic Oncology, Yale University, Yale School of Medicine, New Haven, CT, USA

Leslie R. Boyd Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, NYU School of Medicine, New York, NY, USA

Karine Chung Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Paola Dal Cin Department of Pathology, CAMD, Brigham and Women's Hospital, Boston, MA, USA

Marcela G. del Carmen Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Laura M. Divine Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO, USA

Linda R. Duska Department of Gynecology Oncology, University of Virginia Medical Centre, Charlottesville, VA, USA

Leslie I. Gold Gynecology & Reproductive Sciences, New York University School of Medicine, New York, NY, USA

Annekathryn Goodman Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA, USA

Neil S. Horowitz Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Jessica J. Kraeft Department of Radiology, Tufts Medical Center, Boston, MA, USA

Susanna I. Lee Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Stella Lymberis Department of Radiation Oncology, Laura and Isaac Perlmutter Cancer Center, NYU School of Medicine, NYU Langone Medical Center, New York, NY, USA

George Monemvasitis Gynecology Service, Department of Surgery, Memorial Sloan Ketering Cancer Center, New York, NY, USA

Fernanda Musa Division of Gynecologic Oncology, New York University Langone Medical Center, New York, NY, USA

Esther Oliva Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Professor of Pathology, Harvard Medical School, Boston, MA, USA

Sara Olson Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Jose Palacios Servicio de Anatomía Patológica, Hospital Universitario Ramón y Cajal, Madrid, Spain

Celeste L. Pearce Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA

Malcolm C. Pike Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Matthew A. Powell Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO, USA

Dana M. Roque Department of Obstetrics, University of Maryland School of Medicine, Baltimore, MD, USA

Alessandro D. Santin Division of Gynecologic Oncology, Yale University, Yale School of Medicine, New Haven, CT, USA

Peter B. Schiff Department of Radiation Oncology, Laura and Isaac Perlmutter Cancer Center, NYU School of Medicine, NYU Langone Medical Center, New York, NY, USA

Yukio Sonoda Gynecology Service, Department of Surgery, Memorial Sloan Ketering Cancer Center, New York, NY, USA

Robert A. Soslow Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Anna H. Wu Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

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The Essential Epidemiology of Cancer of the Endometrium: An Update

Malcolm C. Pike, Karine Chung, Sara Olson, Celeste L. Pearce, and Anna H. Wu

Abstract

The central epidemiologic features of cancer of the endometrium are the following: a much increased risk associated with obesity, evident both in premenopausal and postmenopausal women; a decreased risk with increasing parity; a decreased risk with increasing duration of use of combination-type oral contraceptives (COCs); an increased risk with menopausal estrogen therapy (ET) use; and a marked reduction in this risk when a progestin is added to ET (estrogen–progestin therapy, EPT) and continuous-combined EPT may be associated with a decreased risk, especially in heavier women. These observations are readily explained by a simple "unopposed estrogen hypothesis"; that is, estrogen "unopposed" by a progestin increases risk. The basis for this hypothesis is that estrogen unopposed by a progestin increases cell division in the endometrium. Analysis shows that reducing the standard dose of ET by as much as a half will have no effect on the ET-associated risk of endometrial cancer. This hypothesis also provides an explanation of why 1 year of COC use has a smaller preventive effect than a birth. It also suggests that the recently introduced COCs with an increase in the number of days of active pill intake from 21 to 24 days per 28-day COC cycle will significantly increase the protective effect of COC use. Use of the progestin-containing intrauterine system (IUS) with its continuous release of progestin reduces the risk of endometrial cancer to a marked extent; a year of such use may provide as much protection as a birth. Some of this progestin-containing

M.C. Pike (✉) and S. Olson
Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

K. Chung
Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

C.L. Pearce
Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA

A.H. Wu
Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

IUS effect may, however, not be due to the progestin as non-hormonal IU devices (IUDs) have also been shown to decrease endometrial cancer risk although to a lesser extent. It is now clear that the protective effect of parity is markedly affected by the age at which the last birth occurs: for the same number of total births, there is a 45 % greater effect of a last birth after age 40 than a last birth before age 25. It remains to be seen if this age effect is also seen with the protection afforded by hormonal IUSs or with COCs where the active pills are given for 12 weeks out of every 13.

Keywords
Endometrial cancer • Births • Body mass index • Weight • Estrogen • Estrogen therapy

Introduction

The risk of endometrial cancer increases markedly with increasing body mass index (BMI; kg/m^2) and use of menopausal estrogen therapy (ET), while increasing parity and use of combination-type oral contraceptives (COCs) decrease risk significantly. The effects of these factors can be explained by a simple "unopposed estrogen hypothesis" for endometrial cancer [1, 2]; that is, endometrial cancer risk is increased by exposure of the endometrium to estrogen "unopposed" by progesterone or a synthetic progestin, and the increased risk is essentially caused by the increased mitotic activity of the endometrium induced by such exposure. Increased mitotic activity as a general risk factor is supported by a considerable amount of evidence; essentially, for a given tissue, the mitotic rate plays a central role in determining the rates at which the underlying carcinogenic processes, such as mutation, proliferation, and cell death, will occur in some stem cell compartment [3, 4].

The Age Incidence of Endometrial Cancer

The incidence of the common non-hormone-dependent adult cancers (e.g., stomach, colon) rises continuously and increasingly rapidly with age. On a log–log scale the age-incidence curve of such cancers is linear. The incidence of endometrial cancer also increases with age, but there is a distinct slowing of the rate of increase after menopause. This is clearly seen in Fig. 1, which shows the age-specific incidence rates for endometrial cancer in the Birmingham Region of the UK from 1968 to 1972 [5]. Note: This

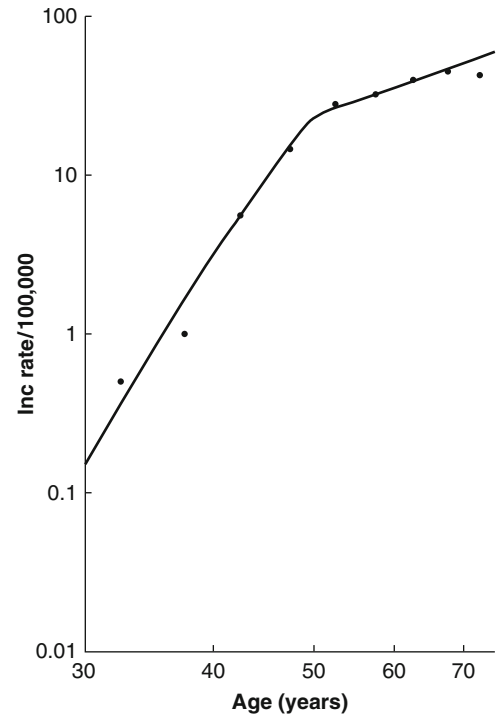

Fig. 1 Age-specific incidence rates for endometrial cancer in the Birmingham region of the UK, 1968–1972

"historical" data is used in order to avoid distortion due to high hysterectomy rates, high obesity rates, and widespread use of COCs and menopausal hormone therapy in the USA, all of which profoundly affect the incidence of endometrial cancer. It should be noted that the incidence of endometrial cancer does not decrease at menopause; it is just that its rate of increase is sharply curtailed.

Figure 1 indicates that the hormonal pattern of premenopausal women [cyclic production of relatively large amounts of estradiol (E_2) and progesterone (P_4)] causes a much greater rate of increase in risk of endometrial cancer than the hormonal pattern of postmenopausal women (constant low E_2 and effectively no P_4). The premenopausal level of E_2 "unopposed" by progesterone although present for only 50–60 % of the cycle has a greater effect than the constant low postmenopausal E_2: we would expect that some of the greater increase in the premenopausal period is caused by the repopulation of the functionalis of the endometrium at the start of each cycle [6, 7].

The increase in the incidence of endometrial cancer is very rapid at premenopausal ages: from age 35 to 40, the incidence increases ~250 % while age increases only 14 %, and years since menarche only increases from ~22 to ~27 years, a 23 % increase. This large increase in incidence is because incidence increases as the 6th power of years since menarche (this is shown approximately in Fig. 1). It is this power relationship that explains the large preventive effects of relatively short periods of COC use and the large increases in risk associated with relatively short periods of menopausal ET use.

Estrogen Dose and Endometrial Cell Mitotic Rate

E_2 is the predominant intracellular estrogen in the endometrium and estrogens stimulate mitosis in endometrial cells [8]. Progestins dramatically reduce mitotic activity by reducing the concentration of estrogen receptors, by increasing the metabolism of E_2 to the less active estrone [9], and by stimulating differentiation of endometrial cells to a secretory state.

Figure 2 shows the plasma concentrations of E_2 and P_4 and the mitotic rate of the glandular endometrial cells during the menstrual cycle [10–12]. The mitotic rate reaches a near maximal level early on in the cycle around day 5. The rate stays roughly constant for ~14 days, until around day 19, after which it drops to a very low level when P_4 increases.

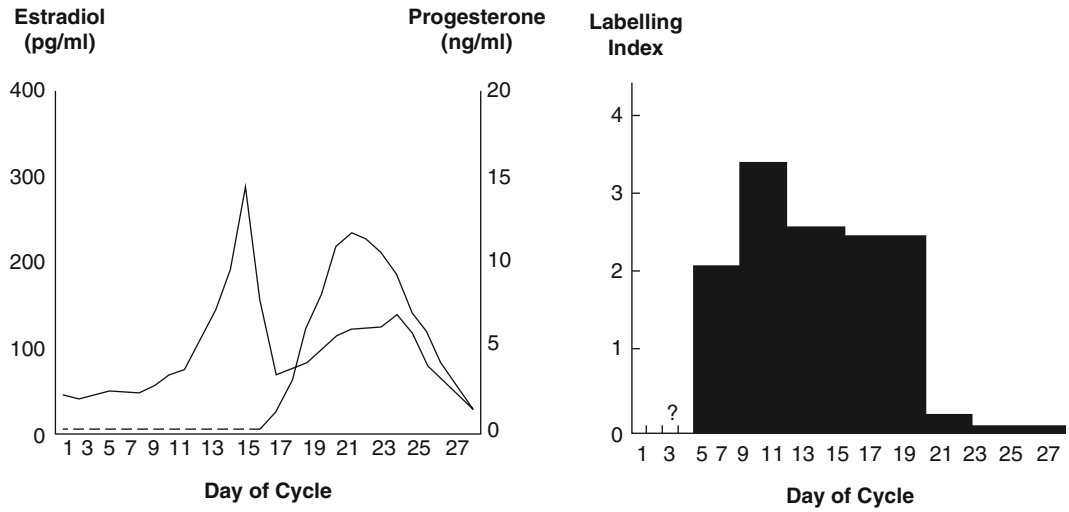

Fig. 2 Plasma concentrations of estradiol and progesterone and endometrial mitotic rate by day of cycle

The maximal mitotic rate is induced by the relatively low early follicular plasma E_2 concentration of ~50 pg/ml; later increases in E_2 levels do not appear to induce any further increase in mitotic rate. Thus, there appears to be an upper limit, no greater than ~50 pg/ml, to the effective plasma concentration of E_2.

The existence of a low ceiling of E_2 effect has important implications. In particular, this limit implies that, in premenopausal women, changes in E_2 will have little effect. Increases in E_2 concentration above normal will not increase endometrial cell division, while decreases in E_2 may, at most, only decrease mitotic activity for the few days of the cycle during which E_2 is normally close to the basal ~50 pg/ml level. In postmenopausal women, E_2 plasma levels are strongly correlated with increasing BMI—the average levels increase from ~7.5 pg/ml at a BMI of 20 kg/m^2 to ~13.2 pg/ml at a BMI of 30 kg/m^2 [13]. The E_2 plasma levels are well below the early follicular level of ~50 pg/ml even in women with a high BMI, and increases in E_2 may, therefore, increase the endometrial mitotic rate until the upper limit for E_2 effect is reached. We can refine this estimate of the upper limit by considering the effects of menopausal ET (see below).

Bioavailable E_2

Plasma E_2 is bound with high affinity to sex hormone-binding globulin (SHBG) and SHBG-bound E_2 is not bioavailable [14]. SHBG levels decrease significantly with increasing BMI, so that, for example, SHBG levels decrease ~43 % with a BMI change from 20 to 30 kg/m^2. The proportion of E_2 that is bioavailable increases from ~49 % at a BMI of 20 kg/m^2 to ~63 % at a BMI of 30 kg/m^2; the average bioavailable E_2 plasma levels increase from ~3.7 pg/ml at a BMI of 20 kg/m^2 to ~8.3 pg/ml at a BMI of 30 kg/m^2. (The above figures were calculated using the mass action approach of Södergard et al. [15] with the estimated association constants as given by Dunn et al. [16], and with the E_2 and SHBG values given by the Endogenous Hormones and Breast Cancer Collaborative Group [13].)

Body Mass Index

Increasing BMI is strongly associated with a greatly increasing risk of endometrial cancer, the risk approximately doubling between a BMI of 23 kg/m^2 and a BMI of 30 kg/m^2 [17]. This is evident both in premenopausal [18] and postmenopausal women [19]. At premenopausal ages, increasing BMI, especially obesity, is associated with an increased frequency of anovulatory cycles [20], in which in the absence of P_4, the endometrium is stimulated throughout the cycle. During the postmenopausal period, increasing BMI is associated with higher levels of E_2 from conversion of androgens to estrogens, as well as lower levels of SHBG, so that the estrogen is more bioactive [1, 21].

With increasing BMI, the protective effect of an earlier menopause will decrease until a situation is reached where there will be no effect at all as can be deduced from the results of several studies [22].

Menopausal Estrogen Therapy (ET)

The dose of menopausal ET most commonly used in the USA, that is, conjugated estrogens (CE) at 0.625 mg/day, results in endometrial cell proliferation approximately equal to that found during the follicular phase of the menstrual cycle [8]. Thus, it is to be expected that ET will substantially increase a woman's risk of developing endometrial cancer, and that this increase will be strongly dependent on the duration of use. In our study, an increased risk of ~16.8 % per year of use was found [22] and similar risks have been reported in other studies [23–25].

The increased risk from ET use is strongly dependent on BMI. In our study [22] the increased risk per year of use of ~16.8 % was

an average of 19.3 % for women with a BMI of <30 kg/m^2 and of 7.7 % for women with a BMI of ≥ 30 kg/m^2. Similar results were reported by Brinton and coworkers [26] with a relative risk of 3.8 for women with a BMI of <28 kg/m^2 and 1.05 for women with a BMI of ≥ 28 kg/m^2. The Million Women Study [27] found that ET use was associated with no increase in risk in women with a BMI of ≥ 30 kg/m^2. We conservatively estimate that there is no increased risk from ET use in women with a BMI ≥ 32 kg/m^2. Plasma E_2 is ~14.8 pg/ml in a 32 kg/m^2 woman [13], and it can be concluded that the ceiling of effective non-SHBG-bound plasma E_2 is ~9.7 pg/ml (calculated as described above).

All effective doses of ET are likely to result in plasma estrogen levels above this ceiling level. This can be seen most easily by considering the plasma estrogen levels of a woman on the 50 μg E_2 transdermal patch, which achieves roughly the same effects as a CE dose of 0.625 mg/day. A 50 μg E_2 patch increases plasma E_2 levels by ~30 pg/ml [28–30] and has little effect on SHBG [31, 32], so that non-SHBG-bound E_2 will increase from ~3.7 pg/ml to ~18.4 pg/ml in a 20 kg/m^2 woman. Thus, the steady-state plasma non-SHBG-bound E_2 level of all women on a 50 μg E_2 patch is well above the ceiling level of ~9.7 pg/ml. Even at only half the dose, i.e., a 25 μg E_2 patch, the non-SHBG-bound E_2 will be ~11.0 pg/ml in a 20 kg/m^2 woman, still above the ceiling. Thus, different doses of ET should have similar effects, as has been observed [25].

Menopausal Estrogen–Progestin Therapy

To reduce the increased endometrial cancer risk from menopausal ET, progestins were added to ET [estrogen–progestin therapy (EPT)] for between 10 and 13 days per month in a sequential fashion (sequential EPT).

Although there was some individual variation in response the increased endometrial cell proliferation associated with CE at 0.625 mg/day was generally reduced to the levels seen in the secretory phase of the cycle by the addition of a progestin equivalent to oral medroxyprogesterone acetate (MPA) at 5 mg/day [8, 33–37]. This and other findings [38–40] persuaded most prescribers that 10–13 days of progestin was sufficient to abolish any increased endometrial cancer risk, and this became standard practice [40].

Key and Pike [2] argued that if endometrial cell proliferation in the basalis layer was the key to increased risk from ET, there would still be an increased risk from sequential EPT even with 13 days of progestin use, since there would still be unopposed estrogen for around 15 days per treatment cycle. Moreover, Fig. 1 shows that endometrial cancer incidence is increasing rapidly in the premenopausal period, so that the notion that mimicking the progestin phase of the menstrual cycle would provide adequate protection was always suspect. Epidemiologic studies have consistently reported increased risks with sequential ET use and a meta-analysis shows a relative risk per year of use of 1.05 (95 % CI 1.02–1.08), clearly an increased risk although much smaller than was seen with ET.

Sequential EPT causes regular bleeding in many women and is associated with other negative side effects; as a result, continuous-combined EPT (ccEPT) regimens were prescribed in which the estrogen and progestin are always taken together. If the dose of progestin used in ccEPT is sufficient to block endometrial epithelial cell division, then one would predict that there should be no increased risk of endometrial cancer from use of ccEPT, and that there would be a decreased risk in heavier women as it would be expected that the progestin component would block endogenous estrogen in addition to blocking the action of the estrogen in the EPT. The Women's Health Initiative randomized trial of ccEPT found a decreased risk of endometrial cancer with a relative risk of 0.81 (95 % CI 0.48–1.36; based on 27 and 31 cases of endometrial cancer) during 5.6 years of use [41]. Similar results were observed in the much smaller HERS II randomized trial [42], and in a number of epidemiological studies [27, 43–45]; and the only two studies reporting effects by BMI found much larger protective effects in heavier women

[27, 44]. A number of these studies were done in Europe where higher doses of nor-testosterone-derived progestins were used [27, 36, 43, 45]. A number of other studies with MPA at 2.5 mg/day did not show a decreased risk with ccEPT [22, 46–48]: this would be in agreement with the results of studies that showed that endometrial epithelial cell proliferation is slightly increased with ccEPT with MPA at 2.5 mg/day [36, 49, 50]. It is clear that there is little risk from ccEPT, but whether there is a decreased risk with the low-dose 2.5 mg MPA ccEPT is unclear.

Parity

Endometrial cancer risk decreases significantly with increasing parity. A comprehensive meta-analysis found a relative risk per birth of 0.86, i.e., a 14 % reduction in risk per birth. Two and three births are therefore estimated to reduce risk by 26 % (relative risk of 0.86^2) and 36 % (relative risk of 0.86^3), respectively. A meta-analysis of epidemiological studies contributing data to the Epidemiology of Endometrial Cancer Consortium found that the relative risk (for a given number of births) was reduced by a factor of 0.88 for each 5 years later that the last birth took place. Compared to a woman who has her last birth under age 25, a woman who has the same number of births but has her last birth after age 35 has a 33 % lower risk of endometrial cancer and if she has her last birth after age 40 a 45 % lower risk. Women with only a single birth tend to have the birth late and this appears to be the reason that some earlier analyses had found the first birth to be more protective than subsequent births. A number of authors have suggested that these results support the hypothesis that the reduction in risk of endometrial cancer is related to a mechanical shed of malignant or premalignant cells at each delivery [51].

Hormonal Contraception

Combined Oral Contraceptives

The use of COCs is associated with a marked long-term reduction in endometrial cancer risk. The recently published comprehensive meta-analysis of epidemiological studies of COC use and endometrial cancer found that the reduction in risk increased with increasing duration of use: every 5 years of use was associated with a relative risk of 0.76 (i.e., a 24 % reduction in risk) [52]. Use of COCs for 10 years is associated with a 42 % reduction in risk (relative risk of 0.76^2). The reduction was still evident 30 years after use of COCs had stopped and there was no evidence of any change in the protective effect with changes in the doses and formulations of COCs over time. The reduction in risk will be somewhat higher at younger ages and lower at much older ages. Whether the extent of protection is greater with later age of COC use has not been investigated.

COCs are a mixture of an estrogen (ethinylestradiol) and a progestin. Their composition is such that they are progestin dominant for the endometrium, so that endometrial proliferation is much reduced during a COC cycle compared to a normal menstrual cycle. The observed reduction in risk with COC use is what we would predict from a mathematical model of incidence if the total endometrial proliferation over a 28-day cycle on a COC is reduced by a third compared to a normal cycle [53]. The common COCs have been packaged with 21 active and 7 placebo pills (21/7). Very recently, they have been packaged with 24 active and 4 placebo pills (24/4) or 84 active and 7 placebo pills (84/7). These COCs will be associated with less proliferation than the 21/7 OCs and should thus be associated with a greater protective effect against endometrial cancer.

Levonorgestrel Intrauterine System (LNG-IUS)

The use of the intrauterine system of delivery of the progestin, levonorgestrel, as a progestin-only contraceptive results in atrophy of the glandular epithelium [54]. The LNG-IUS used was designed for 5 years of use, and their use would thus be predicted to significantly reduce the risk of endometrial cancer. In the single epidemiological study of the effects of the LNG-IUS on endometrial cancer risk a 50 % reduction in risk was found with the purchase of a single LNG-IUS and a 75 % reduction in risk was found with the purchase of two or more LNG-IUSs. This study was done using the National Reimbursement Registry linked to the Finnish Cancer Registry and the LNG-IUS had been prescribed for treatment of menorrhagia. Comparison was made of the endometrial cancer rate in the LNG-IUS users to the rate in the general population. The study did not adjust for parity, BMI or COC use, or for the fact that the women were being treated with the LNG-IUS for menorrhagia. They also did not adjust the general population rate for the proportion of women in the general population who had been hysterectomized, but this would have made their figure for reduction in risk even greater. The study should be considered as providing strong suggestive evidence of a protective effect. As we noted above, the finding is what we would expect from the effect of the LNG-IUS on endometrial glandular proliferation, and from the substantial evidence that the use of the LNG-IUS in women with endometrial hyperplasia results in disease regression in the majority of cases [55] and use of LNG-IUS has been found to eradicate some early-stage endometrial cancers [56, 57]. Further studies are clearly needed.

Depot Medroxyprogesterone Acetate

Depot medroxyprogesterone acetate (DMPA) administered every 3 months at a 150 mg dose produces profound progestogenic effects on the endometrium; this is as expected, since the dose of progestin is sufficient to suppress ovulation throughout the 3 months, and the serum level of MPA soon after injection is some 25 times higher than is needed to suppress ovulation [58]. The single case-control study of DMPA and endometrial cancer was conducted in Thailand by the WHO in the late 1980s: the study found a 79 % lower risk (relative risk of 0.21; 95 % CI 0.06–0.79) of endometrial cancer for ever use of DMPA based on 3 cases and 84 controls [59]. No additional studies have been reported. Our understanding of the etiology of endometrial cancer strongly suggests that DMPA use will be associated with a lower risk of endometrial cancer with the effect being greater the longer the duration of use.

Non-hormonal Intrauterine Devices

The earliest epidemiological studies of the possible effects of non-hormonal intrauterine devices (IUDs) on endometrial cancer risk were made in the early 1990s. A comprehensive meta-analyses of the results of the published studies was reported by Beining et al. [60] and more recently Felix et al. [61] conducted a detailed analysis of the individual-level data on cases and controls included in the studies contributing to the Epidemiology of Endometrial Cancer Consortium (E2C2). Almost all individual studies found a reduction in risk with use of an IUD. The overall estimate of the reduction in risk found by Beining et al. was 46 % (95 % CI: 38–53 %) while the reduction in risk found by Felix et al. was 11 % (95 % CI: 34–21 % increase) for a copper-containing IUD and 31 % (95 % CI: 42–18 %) for an inert IUD. A majority of the studies included in the meta-analysis of Beining et al. were not members of E2C2 and these non-E2C2 studies contributed significantly to the greater protection they found for IUD use. For most studies Beining et al. did not have information on the type of IUD, and almost all of the studies did not adequately adjust for other endometrial cancer risk factors. Looking at the results as a whole it appears that more recent use is associated with a greater protective effect but a

protective effect is present for at least 10 years after stopping IUD use. It is not clear that there is a duration of use effect.

Although Felix et al. found only a small protective effect of the copper IUD, the single study investigating the effect of the copper IUD on endometrial glandular proliferation found an 80 % reduction in Ki67 comparing baseline to 6 months after IUD insertion (all comparisons made in the mid-follicular phase of the cycle) [62], so that we would have predicted a significantly reduced risk of endometrial cancer. In Table 2 in Felix et al. the crude relative risk for the copper IUD is 0.26; this becomes 0.89 after adjustment. This is in sharp contrast to the results for an inert IUD where the crude relative risk of 0.71 is hardly changed at all, becoming 0.69, after adjustment. It is not clear why there is such a difference in the effect of adjustment.

The protective effect of IUD use may be quite large and further analyses and possibly further studies are needed.

Smoking

Cigarette smoking has been consistently found to be associated with an approximately 25 % lower risk of endometrial cancer in postmenopausal women [63–65]. Risk was lower in current than in past smokers and some studies found a greater reduction in risk with increasing numbers of cigarettes smoked per day. There was no reduction in risk among premenopausal women. Smokers are known to have an earlier age at menopause and their average BMI is lower than that of nonsmokers, but adjustment for these factors did not explain the protective effect in postmenopausal women. Multiple studies have found no effect of smoking on serum estrogen levels in postmenopausal women but did find consistent elevations of androstenedione [66–69]. Although a number of investigators suggested that the elevated levels of androstenedione could be causally related to the protective effect of smoking, epidemiological studies of androgen levels as they relate to endometrial cancer risk have found no evidence for such an effect [70]. At present no viable hypothesis has been proposed that would explain the protective effect of smoking. Since the effect is quite large this area might benefit from direct study of the biological effect of smoking on endometrial cells.

Chemoprevention

The use of COCs is a most effective approach to chemoprevention of endometrial cancer. The protection is very long-lasting and should be further increased with the newer formulations of COCs with a higher ratio of active to placebo pills. DMPA, the progestin-containing IUS-LNG, and IUDs also provide protection against endometrial cancer, probably greater protection than is observed with COCs used for the same length of time.

The substantial reduction in risk of endometrial cancer seen with a late age at last birth suggests that endometrial sloughing may have a substantial protective effect. Further detailed studies of the endometrium—at or soon after delivery, at the end of the sloughing period while taking COCs with different ratios of active to placebo pills, and after varying periods of using DMPA, LNG-IUS, and IUDs—should lead to a deeper understanding of the basis of the protective effect of births and how we might hope to capitalize on the late age of births' protective effect.

Conclusions

- Proliferation of the endometrium is dependent on estrogen unopposed by a progestin.
- Maximum proliferation is achieved at a relatively low level of bioavailable estradiol.
- Basal estrogen levels in the postmenopausal age group are dependent on body mass index (BMI).
- Bioavailable estradiol levels are also dependent on BMI.
- The above facts explain many epidemiologic observations concerning the risk of developing

endometrial cancer in relation to age, obesity, and type of exogenous hormonal use.
- COCs, other hormonal contraceptives, and IUDs provide substantial long-lasting protective effects against endometrial cancer and newer formulations of COCs will in all likelihood provide even greater protection than has been seen with "traditional" COCs.

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References

1. Siiteri PK. Steroid hormones and endometrial cancer. Cancer Res. 1978;38:4360–6.
2. Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. Br J Cancer. 1988;57:205–12.
3. Cairns J. Somatic stem cells and the kinetics of mutagenesis and carcinogenesis. Proc Natl Acad Sci U S A. 2002;99:10567–70.
4. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE. Increased cell division as a cause of human cancer. Cancer Res. 1990;50:7415–21.
5. Waterhouse J, Muir C, Correa P, Powell J. Cancer incidence in five continents. IARC Sci Publ. 1976;15:1–583.
6. Ferenczy A. Studies on the cytodynamics of human endometrial regeneration. I. Scanning electron microscopy. Am J Obstet Gynecol. 1976;124:64–74.
7. Salamonsen LA. Tissue injury and repair in the female human reproductive tract. Reproduction. 2003;125:301–11.
8. Whitehead MI, Townsend PT, Pryse-Davies J, Ryder TA, King RJ. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. N Engl J Med. 1981;305:1599–605.
9. Tseng L, Gurpide E. Induction of human endometrial estradiol dehydrogenase by progestins. Endocrinology. 1975;97:825–33.
10. Ferenczy A, Bertrand G, Gelfand MM. Proliferation kinetics of human endometrium during the normal menstrual cycle. Am J Obstet Gynecol. 1979;133:859–67.
11. Goebelsmann UM, Mishell DR. The menstrual cycle. In: Mishell DR, Davajian V, editors. Reproductive endocrinology, infertility and contraception. Philadelphia: F.A. Davis Company; 1979. p. 67–89.
12. Thorneycroft IH, Mishell Jr DR, Stone SC, Kharma KM, Nakamura RM. The relation of serum 17-hydroxyprogesterone and estradiol-17-beta levels during the human menstrual cycle. Am J Obstet Gynecol. 1971;111:947–51.
13. Endogenous Hormones and Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst. 2003;95:1218–26.
14. Pardridge WM. Serum bioavailability of sex steroid hormones. Clin Endocrinol Metab. 1986;15:259–78.
15. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem. 1982;16:801–10.
16. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab. 1981;53:58–68.
17. Friedenreich C, Cust A, Lahmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control. 2007;18:399–413.
18. Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I, Duke A. The epidemiology of endometrial cancer in young women. Br J Cancer. 1983;47:749–56.
19. Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). Cancer Causes Control. 2000;11:185–92.
20. Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstrual abnormalities in women. Int J Obes. 1979;3:57–73.
21. Siiteri PK. Extraglandular oestrogen formation and serum binding of oestradiol: relationship to cancer. J Endocrinol. 1981;89:119–29.
22. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, Wan PC, et al. Estrogen-progestin replacement therapy and endometrial cancer. J Natl Cancer Inst. 1997;89:1110–6.
23. Beresford SAA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. Lancet. 1997;349:458–61.
24. Persson I, Weiderpass E, Bergkvist L, Bergstrom R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. Cancer Causes Control. 1999;10:253–60.
25. Cushing KL, Weiss NS, Voigt LF, McKnight B, Beresford SA. Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. Obstet Gynecol. 1998;91:35–9.

26. Brinton LA, Hoover RN. Estrogen replacement therapy and endometrial cancer risk: unresolved issues. Obstet Gynecol. 1993;81:265–71.
27. Beral V, Bull D, Reeves G, Collaborators MWS. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2005;365:1543–51.
28. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17B-estradiol: comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol. 1985;152:1099–106.
29. Schiff I, Sela HK, Cramer D, Tulchinskiy D, Ryan KJ. Endometrial hyperplasia in women on cyclic or continuous estrogen regimens. Fertil Steril. 1982;37:79–82.
30. Selby PL, Peacock M. Dose dependent response of symptoms, pituitary, and bone to transdermal oestrogen in postmenopausal women. BMJ. 1986;293:1337–9.
31. Nachtigall LE, Raju U, Banerjee S, Wan L, Levitz M. Serum estradiol-binding profiles in postmenopausal women undergoing three common estrogen replacement therapies: associations with sex hormone-binding globulin, estradiol, and estrone levels. Menopause. 2000;7:243–50.
32. Ropponen A, Aittomaki K, Vihma V, Tikkanen MJ, Ylikorkala O. Effects of oral and transdermal estradiol administration on levels of sex hormone-binding globulin in postmenopausal women with and without a history of intrahepatic cholestasis of pregnancy. J Clin Endocrinol Metab. 2005;90:3431–4.
33. Whitehead MI, Townsend PT, Pryse-Davies J, Ryder T, Lane G, Siddle N, et al. Actions of progestins on the morphology and biochemistry of the endometrium of postmenopausal women receiving low-dose estrogen therapy. Am J Obstet Gynecol. 1982;142:791–5.
34. King RJB, Townsend PT, Siddle N, Whitehead MI, Taylor RW. Regulation of estrogen and progesterone receptor levels in epithelium and stroma from pre- and postmenopausal endometrial. J Steroid Biochem. 1982;16:21–9.
35. Lane G, Siddle NC, Ryder TA, Pryse-Davies J, King RJB, Whitehead MI. Dose dependent effects of oral progesterone on the oestrogenised postmenopausal endometrium. BMJ. 1983;287:1241–5.
36. King RJB, Whitehead MI. Assessment of the potency of orally administered progestins in women. Fertil Steril. 1986;46:1062–6.
37. Lane G, Siddle NC, Ryder TA, Pryse-Davies J, King RJB, Whitehead MI. Is provera the ideal progestogen for addition to postmenopausal estrogen therapy? Fertil Steril. 1986;45:345–52.
38. Flowers CE, Wilborn WH, Hyde BM. Mechanisms of uterine bleeding in postmenopausal patients receiving estrogen alone or with a progestin. Obstet Gynecol. 1983;61:135–43.
39. Paterson MEL, Wade-Evans T, Sturdee DW, Thom MH, Studd JWW. Endometrial disease after treatment with oestrogens and progestogens in the climacteric. BMJ. 1980;22:822–4.
40. King RJB, Whitehead MI. Progestin action in relation to the prevention of endometrial abnormalities. In: Raynaud JP, Ojasoo T, Martini L, editors. Medical Management of Endometriosis. Raven Press: New York, 1984;67–77.
41. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA. 2003;290:1739–48.
42. Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002;288:58–66.
43. Weiderpass E, Baron JA, Adami HO, Magnusson C, Lindgren A, Bergstrom R, et al. Low-potency oestrogen and risk of endometrial cancer: a case-control study. Lancet. 1999;353:1824–8.
44. Doherty JA, Cushing-Haugen KL, Saltzman BS, Voigt LF, Hill DA, Beresford SA, et al. Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. Am J Obstet Gynecol. 2007;197:139.e1–7.
45. Allen NE, Tsilidis KK, Key TJ, Dossus L, Kaaks R, Lund E, et al. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. Am J Epidemiol. 2010;172:1394–403.
46. Newcomb PA, Trentham-Dietz A. Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). Cancer Causes Control. 2003;14:195–201.
47. Razavi P, Pike MC, Horn-Ross PL, Templeman C, Bernstein L, Ursin G. Long-term postmenopausal hormone therapy and endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2010;19:475–83.
48. Jain MG, Rohan TE, Howe GR. Hormone replacement therapy and endometrial cancer in Ontario, Canada. J Clin Epidemiol. 2000;53:385–91.
49. Langer RD, Landgren BM, Rymer J, Helmond FA, Investigators O. Effects of tibolone and continuous combined conjugated equine estrogen/medroxyprogesterone acetate on the endometrium and vaginal bleeding: results of the OPAL study. Am J Obstet Gynecol. 2006;195:1320–7.
50. Dahmoun M, Odmark IS, Risberg B, Karlsson MG, Pavlenko T, Backstrom T. Apoptosis, proliferation, and sex steroid receptors in postmenopausal endometrium before and during HRT. Maturitas. 2004;49:114–23.
51. Albrektsen G, Heuch I, Tretli S, Kvale G. Is the risk of cancer of the corpus uteri reduced by a recent

pregnancy? A prospective study of 765,756 Norwegian women. Int J Cancer. 1995;61:485–90.
52. Collaborative Group on Epidemiological Studies on Endometrial Cancer. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 2015;16:1061–70.
53. Pike MC. Age-related factors in cancers of the breast, ovary, and endometrium. J Chronic Dis. 1987;40 Suppl 2:59S–69.
54. Guttinger A, Critchley HO. Endometrial effects of intrauterine levonorgestrel. Contraception. 2007;75 (6 Suppl):S93–8.
55. Whiteman MK, Zapata LB, Tepper NK, Marchbanks PA, Curtis KM. Use of contraceptive methods among women with endometrial hyperplasia: a systematic review. Contraception. 2010;82:56–63.
56. Montz FJ, Bristow RE, Bovicelli A, Tomacruz R, Kurman RJ. Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol. 2002;186:651–7.
57. Orbo A, Rise CE, Mutter GL. Regression of latent endometrial precancers by progestin infiltrated intrauterine device. Cancer Res. 2006;66:5613–7.
58. Fotherby K, Koetsawang S, Mathrubutham M. Pharmacokinetic study of different doses of depo provera. Contraception. 1980;22:527–36.
59. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. Int J Cancer. 1991;49:186–90.
60. Beining RM, Dennis LK, Smith EM, Dokras A. Meta-analysis of intrauterine device use and risk of endometrial cancer. Ann Epidemiol. 2008;18:492–9.
61. Felix AS, Gaudet MM, La Vecchia C, Nagle CM, Shu XO, Weiderpass E, et al. Intrauterine devices and endometrial cancer risk: a pooled analysis of the Epidemiology of Endometrial Cancer Consortium. Int J Cancer. 2015;136:E410–22.
62. Guleria K, Agarwal N, Mishra K, Gulati R, Mehendiratta A. Evaluation of endometrial steroid receptors and cell mitotic activity in women using copper intrauterine device: can Cu-T prevent endometrial cancer? J Obstet Gynaecol Res. 2004;30:181–7.
63. Zhou B, Yang L, Sun Q, Cong R, Gu H, Tang N, et al. Cigarette smoking and the risk of endometrial cancer: a meta-analysis. Am J Med. 2008;121:501–8. e3.
64. Al-Zoughool M, Dossus L, Kaaks R, Clavel-Chapelon F, Tjonneland A, Olsen A, et al. Risk of endometrial cancer in relationship to cigarette smoking: results from the EPIC study. Int J Cancer. 2007;121:2741–7.
65. Felix AS, Yang HP, Gierach GL, Park Y, Brinton LA. Cigarette smoking and endometrial carcinoma risk: the role of effect modification and tumor heterogeneity. Cancer Causes Control. 2014;25:479–89.
66. Friedman AJ, Ravnikar VA, Barbieri RL. Serum steroid hormone profiles in postmenopausal smokers and nonsmokers. Fertil Steril. 1987;47:398–401.
67. Khaw K-T, Tazuke S, Barrett-Connor E. Cigarette smoking and levels of adrenal androgens in postmenopausal women. N Engl J Med. 1988;318:1705–9.
68. Cauley JA, Gutai JP, Kuller LH, LeDonne D, Powell JG. The epidemiology of serum sex hormones in postmenopausal women. Am J Epidemiol. 1989;129:1120–31.
69. Schlemmer A, Jensen J, Riis BJ, Christiansen C. Smoking induces increased androgen levels in early post-menopausal women. Maturitas. 1990;12:99–104.
70. Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer. 2008;15:485–97.

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Endometrial Cancer: Screening, Diagnosis, and Surgical Staging

Annekathryn Goodman

Abstract

Environmental and hereditary factors contribute to increased risk of developing endometrial cancer. An understanding of risk factors can guide screening modalities in premenopausal and postmenopausal women. Attention is drawn to certain anatomic abnormalities that prevent vaginal bleeding—the most common symptom related to cancer. Diagnostic tests that are available to pursue various aspects of the diagnosis in a sequential fashion are described, the most important of which is the endometrial biopsy. Recommendations for screening and diagnosis in the asymptomatic as well as the symptomatic patients are summarized. Surgical staging represents the final event in the diagnostic workup. Instances when such staging can be modified to deal with various comorbidities are delineated.

Keywords

Endometrial cancer • Heredity • Screening • Endometrial biopsy • Surgical staging

Screening

Case Report 1 *A 32-year-old thin, nulliparous woman presented with menorrhagia. The bleeding was unresponsive to birth control pill use. She had no other medical conditions. There was no family history of malignancies. She underwent an endometrial ablation. An endometrial biopsy was not performed prior to the ablation. Six months later, a hysterectomy was performed because of persistent bleeding. Her pathology showed a deeply invasive grade 2, endometrioid endometrial adenocarcinoma with metastases to a para-aortic lymph node.*

Endometrial cancer is the most common gynecologic malignancy in North America with an estimated 60,650 new cases and 10,470 deaths in 2016 and is the fourth most common cancer in women in the developed world [1, 2]. Routine

A. Goodman (✉)
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA 02114, USA
e-mail: agoodman@mgh.harvard.edu

screening is not recommended as symptoms of endometrial cancer develop at an early stage and the female genital tract allows easy access to the uterus for diagnostic evaluation. Therefore, the focus has been on efficient evaluation in the setting of symptoms.

There are certain groups of women who have an increased risk for the development of endometrial cancer. Evaluation of the endometrial cavity should be considered and a higher index of suspicion for the development of endometrial cancer should be entertained even in the absence of symptoms for these women. The decision to screen an individual, asymptomatic woman will be based on her risk factors, age, and physical examination findings.

Since the 1980s, two distinct types of endometrial cancers have been described, Type I and Type II [3]. Type I endometrial cancer makes up 80–90 % of all sporadic endometrial cancers [4]. Histologically, these tumors can be endometrioid adenocarcinoma with or without squamous differentiation and often are well differentiated. A multistep carcinogenic process of Type I endometrial malignancies starts with simple endometrial hyperplasia, then develops complex atypia hyperplasia followed by progression into the precursor lesion, endometrial intraepithelial neoplasia (EIN) [5]. The remaining 10–20 % of endometrial cancers, Type II, are mainly composed of two rarer histologies: uterine papillary serous carcinoma (UPSC) and clear-cell carcinoma. Both cancers appear to progress from an atrophic endometrium to the precursor lesion, endometrial glandular dysplasia [6].

Table 1 summarizes the groups of women who are at increased for the development of endometrial cancers. For this group, any factor that increases the exposure to unopposed estrogen increases the risk of endometrial cancer [7]. Premenopausal women who have had chronic anovulation will develop a buildup of the endometrial lining [8]. Women with polycystic ovarian syndrome will present with years of anovulation since their teenage years [9]. Other causes of anovulation include thyroid disease, hyperprolactinemia, and certain exogenous drugs such as antipsychotics [10]. Metabolic syndrome has been linked with endometrial cancer [11, 12]. Diabetes (both type 1 and type 2) has also been related to an increased risk of endometrial cancer [13]. Further, other metabolic risk factors, such as hypertension and hyperglycemia, have also been associated with increased endometrial cancer risk, especially among overweight and obese women. Estrogen-secreting ovarian tumors such as granulosa cell tumors and thecomas can lead to stimulation of the endometrial lining [14].

Morbid obesity is a risk factor at all ages as these women have higher endogenous estrogens

Table 1 Factors associated with increased risk of developing Type I endometrial cancer

Premenopausal women
Endogenous estrogen exposure
Anovulatory cycles
Polycystic ovarian syndrome
Morbid obesity
Estrogen secreting tumors
Sex cord stromal tumors Adrenal adenomas
Metabolic Syndrome
Hereditary syndromes
Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Lynch Syndrome
BRCA 1 mutation
Cowden syndrome
Li–Fraumeni syndrome
Peutz–Jeghers syndrome
Postmenopausal women
Endogenous estrogen exposure
Morbid obesity
Estrogen secreting tumors
Cirrhosis of the liver
Exogenous hormonal exposure
Exogenous estrogens without progestins
Tamoxifen
History of pelvic radiation
Hereditary syndromes
Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Lynch Syndrome
BRCA 1 mutation
Cowden syndrome
Li–Fraumeni syndrome
Peutz–Jeghers syndrome

due to aromatization of androgens to estradiol and the conversion of androstendione to estrone in peripheral adipose tissue [15]. The epidemic of obesity has led to a 50 % increase in the incidence of endometrial cancer [1, 16]. Use of exogenous estrogens without the balance of progesterone is associated with endometrial cancer [17]. Women with liver disease who cannot adequately metabolize their endogenous or exogenous estrogens are also at risk for the development of endometrial malignancies [18].

Tamoxifen increases the risk of endometrial cancer two- to threefold but the effects are not seen before 2 years of use [19]. However, the absolute risk of developing endometrial cancer while taking tamoxifen is 1.2/1000 per year. Currently, the American College of Obstetrician Gynecologists (ACOG) does not recommend routine screening in asymptomatic women taking tamoxifen [20]. Given the current obesity epidemic and factoring in long-term adverse effects, ACOG guidelines suggest consider of aromatase inhibitors instead of tamoxifen because of the reduced incidence of thrombosis, endometrial cancer, and vaginal bleeding.

Pelvic radiation for other malignancies such as lymphoma, cervical or rectal cancers will increase the risk of uterine corpus cancer. The most common post-radiation pelvic malignancy is adenocarcinoma of the endometrium [21].

Women with breast or colon cancer may have a higher genetic risk of gynecologic malignancies. A careful family history will help guide the decision to evaluate the endometrium. Hereditary nonpolyposis colon cancer (HNPCC) or Lynch syndrome, an autosomal dominant syndrome, confers a 40–60 % risk of endometrial cancer and makes up about 5 % of all cases of endometrial cancer [22]. The molecular basis for Lynch syndrome is a heritable functional deficiency in the DNA mismatch repair system, typically due to a germ line mutation. In contrast to the general population, the high lifetime risk of endometrial cancer in women with Lynch syndrome has led to consensus guidelines recommending annual or biennial endometrial sampling beginning at age 30–35 years and risk-reducing hysterectomy and bilateral salpingo-oophorectomy in women who have completed childbearing [23].

BRCA 1 gene mutation, in addition to the well-known risk of ovarian cancer, has been associated with an increased endometrial cancer risk [24]. Other genetic syndromes associated with endometrial cancer have now been identified [25]. Increased risk of endometrial cancer is caused by mutation in the phosphatase and tensin homolog (PTEN) gene in Cowden syndrome. Ovarian, uterine, and cervical cancers related to Peutz–Jeghers syndrome are due to liver kinase b1 (LKB1/STK11) gene mutation. Ovarian and endometrial cancers also occur excessively in patients with Li–Fraumeni syndrome, which has an inherited germ line mutation in p53.

Even in the absence of personal or family risk factors for endometrial cancer, all women with abnormal bleeding need to be evaluated for malignancy. Any vaginal bleeding in postmenopausal women regardless of the quantity needs to be evaluated. The risk of endometrial cancer in a 50-year-old woman with postmenopausal bleeding is 9 %, 16 % foe a woman in her sixties, 28 % for a woman in her seventies, and 60 % for a woman in her eighties [26]. Irregular bleeding in premenopausal women needs to be thoughtfully worked up. While hormone irregularities, complications of pregnancy, and pelvic infection are other causes of premenopausal bleeding; the possibilities of malignancy must be taken seriously. Twenty-five percent of all endometrial cancers occur in premenopausal women and 5 % are found in women less than 40 years old [27].

Table 2 lists certain anatomical changes that may prevent the development of the warning sign of vaginal bleeding or impair the examiner's ability to fully evaluate the pelvic tract. Women who have developed cervical stenosis because of postmenopausal atrophy, or previous cervical procedures such as cryotherapy, loop electrosurgical excision procedures (LEEP), or cervical cone biopsies may not have an open cervical canal. On physician inspection, the examiner will see that a cutip or cytobrush cannot pass

Table 2 Anatomic abnormalities that prevent vaginal bleeding

Abnormality	Causes
Agglutinated vagina	Dermatologic conditions
	Lichen planus
	Lichen sclerosis
	Postmenopausal atrophy
	Pelvic radiation
	Sequelae of infection
	Toxic shock syndrome
	Stevens–Johnson syndrome
	Use of exfoliating chemicals
	Intravaginal 5-fluoro-uracil cream
	Trauma
	Sexual assault
Cervical stenosis	Sequelae of therapy for CIN
	Cryotherapy
	LEEP
	Cone biopsy
Vaginal septum	Congenital
Intrauterine synechiae	Asherman's syndrome
	Endometrial ablation

CIN cervical intraepithelial neoplasia
LEEP loop electrosurgical excision procedure

through the cervical os. Some women develop agglutination of the upper vagina secondary to atrophy, radiation, trauma, or infection. Certain congenital duplications of the lower genital tract such as a vaginal septum can be a barrier to egress of blood from the uterus. Women who have had an endometrial ablation may develop a malignancy deep to the scar of ablation, which may not be amenable to detection by biopsy [28]. For all these women, it is important to evaluate the upper genital tract, especially if they also have other risk factors (Table 1).

Comment on Case Report 1

The 32-year-old woman had no known risk factors for endometrial cancer. However, she had unexplained abnormal bleeding that was not fully evaluated before the intervention of endometrial ablation. It is crucial to perform an endometrial biopsy when bleeding is unexplained [29]. Only 10 % of all gynecologic cancers are associated with a known genetic risk. Endometrial cancers that are not associated with hyperestrogenism have a more aggressive behavior.

Diagnostic Tests

Case Report 2 *A 49-year-old woman presented with mid-cycle spotting. She has had several abnormal pap smears showing atypical glandular cells over the past 5 years. Colposcopy and cervical biopsies had been normal. An endometrial biopsy showed a grade 2 endometrioid adenocarcinoma. She underwent a laparoscopic assisted hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic node dissection. Her final pathology showed a superficially invasive endometrioid adenocarcinoma. All staging biopsies were negative.*

Evaluation of the uterus occurs with physical examination, which includes a visual inspection of the vagina and cervix and palpation of the uterus by vaginal and rectovaginal digital examination, cervical cytology, endometrial tissue sampling, and radiologic imaging. Table 3 summarizes the different diagnostic tests that are available to study the uterus.

Physical examination includes visual inspection of the external genitalia. In the setting of abnormal bleeding, it is important to rule out the possibility of an extrauterine lesion. The vulva, periurethral region, and anus are examined. The vagina and cervix are evaluated. The cervix is assessed for stenosis, friability, and gross lesions. The vagina should also be palpated circumferentially to make sure that there are no nodules that may have been missed on visual examination. Palpation of the uterus gives information about uterine size, tenderness, and irregularities of shape. A rectovaginal examination can evaluate the cul-de-sac, back wall of the uterus, adnexa, and the pelvic floor compartments: parametrial and uterosacral ligaments and the pelvic sidewall. There are some women who will be unable to tolerate an

Table 3 Diagnostic tests for uterine corpus disease

Office procedure	*Type of information*
Physical examination	Origin of bleeding
	Cervical stenosis
	Uterine size
	Pelvic mass
Pap smear	Cytologic abnormalities of cervix, vagina
	Occasional information about upper genital tract
Endometrial biopsy	Endometrial lining
Hysteroscopy	Endometrial lining
Radiologic Procedures	*Type of Information*
Transvaginal ultrasound	Endometrial stripe
	Uterine size
	Adnexal size, presence of cysts, masses
Sonohysterogram	Endometrial stripe
	Submucosal fibroids
	Endometrial polyps, masses
Pelvic MRI	Myometrial abnormalities, fibroids
	Depth of myometrial invasion
	Adnexal structures
	Invasion into parametria, vagina, bladder
	Pelvic lymphadenopathy
Abdominopelvic CT scan	Ascites
	Lymphadenopathy
	Intraparenchymal organ abnormalities
	Peritoneal and omental disease
PET CT scan	Same as CT scan
	Metabolic activity suggestive of metastatic disease
Operative procedures	*Type of information*
Examination under anesthesia	Same as physical examination
Dilation and curettage	Endometrial lining
Hysteroscopy	Endometrial lining
Hysterectomy	Full pathologic analysis of the uterus
Sentinel Node Biopsy	Identification of first lymphatic bed from uterus
Lymphadenectomy	Lymphatic involvement by cancer

office exam due to discomfort or due to psychological reasons such as a history of past sexual assault [30].

While Papanicolaou (Pap) smears were developed for screening lower genital tract neoplasia, an occasional asymptomatic woman with endometrial carcinoma will present with abnormal cytology. Cervical cytology is not a reliable screening test for endometrial cancer. In a recent review of 54,179 women who underwent pap smear screening, 14 were identified as having endometrial cancer based on abnormal glandular cytology [31]. However, endometrial cells identified on cervical cytology in women over 40 years of age can signify endometrial cancer [32]. Human papillomavirus (HPV) testing for high-risk subtypes can be a triage test to determine a cervical or endometrial origin to atypical glandular cytology [33]. HPV is not associated with endometrial neoplasia and therefore a positive HPV test will indicate a premalignant or malignant cervical glandular lesion.

Any abnormal uterine bleeding needs to be evaluated by endometrial biopsy. The accuracy of an office biopsy will depend on the size of the endometrial lesion, the examiner's skills, the anatomy of the patient, and patient comfort. A lesion that occupies less than 10 % of the uterine cavity, cervical stenosis with inability to enter the uterine cavity, distorting uterine fibroids, and patient factors such as vaginismus will all reduce the yield of an office biopsy. Premedication with a nonsteroidal anti-inflammatory drug, and the use of a paracervical block can help facilitate an office evaluation. An office hysteroscopy can also increase the yield for diagnostic abnormalities. Many different types of office biopsy devices are thought to be effective for diagnosis of endometrial pathology [34]. Currently, the office Pipelle biopsy device is thought to be as accurate as a dilation and curettage when the previously mentioned challenges are not a factor [35].

If it is not possible to obtain an adequate sampling in the office due to patient distress, anatomic factors, or a discrepancy between normal office biopsy results and an abnormal imaging study (see below), an outpatient surgical procedure should be scheduled. Under

anesthesia, vaginal adhesions can be gently opened up. If cervical stenosis is present, an ultrasound-guided dilation can prevent uterine perforation. Hysteroscopy in combination with endometrial curettage is recommended to avoid missing small lesions.

Imaging studies are a useful adjunct in the evaluation of endometrial pathology. In asymptomatic women, a transvaginal ultrasound finding of an abnormally thickened endometrial lining will guide the practitioner to performing a biopsy. Endometrial stripe width will vary with the menstrual cycle in premenopausal women. Thickness varies between the proliferative phase (4–8 mm) and the secretory phase (8–14 mm); the 8-mm cutoff value is used for recommending a biopsy in perimenopausal women unless they present with other risk factors [36]. After menopause, an endometrial stripe thickness greater than 4 mm is considered abnormal [37]. Tamoxifen can increase the incidence of a falsely thickened endometrial stripe due to tamoxifen-induced subendometrial edema [38]. In addition, about 30 % of women taking tamoxifen will develop endometrial polyps [39]. A sonohysterogram is a more sensitive and specific than transvaginal ultrasound in detection of intra cavity abnormalities [40]. Sterile saline is instilled into the endometrial cavity and then a transvaginal ultrasound is performed. The saline will reveal subtle irregularities such as small polyps and will reduce inaccuracies of endometrial stripe measurement.

A pelvic MRI is useful preoperatively to help determine depth of myometrial invasion in a known invasive endometrial cancer. When compared to the findings of surgical pathology, there was concordance on the depth of myometrial invasion and pathology 64 % of the time [41]. CT scan and PET CT scans can help evaluate for intraperitoneal and nodal metastatic disease and is recommended for women with high risk features such as poorly differentiated tumors and serous and clear cell subtypes [42]. Table 4 summarizes screening and diagnostic recommendations.

Table 4 Endometrial cancer: Recommendations for screening and diagnosis

Asymptomatic patient
No risk factors and normal physical examination: routine yearly follow-up
Risk factors for estrogen excess: transvaginal ultrasound
Tamoxifen use for greater than 2 years: annual sonohysterogram
Genetic risk factors: annual endometrial biopsy; consideration of risk reducing hysterectomy after completion of family
Cervical stenosis, enlarged uterus: transvaginal ultrasound
Symptomatic patient
Office endometrial biopsy and transvaginal ultrasound
Dilation and curettage and hysteroscopy if unable to perform office biopsy

Comment on Case Report 2

This patient had repetitively abnormal glandular cells of cytology. She also had unexplained mid-cycle bleeding. When her cervical evaluation with colposcopy and cervical biopsies was normal, she should have undergone an endometrial biopsy and transvaginal ultrasound.

Surgical Staging

Case Report 3 *A 35-year-old G3P3 woman with menorrhagia underwent a total vaginal hysterectomy. The final pathology revealed a grade 3 endometrioid adenocarcinoma of the endometrium with inner one half myometrial invasion. She is taken back to surgery and undergoes a laparoscopic bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection. All staging biopsies are negative for cancer. She has a stage Ia Grade 3 endometrioid endometrial cancer.*

The staging of a cancer serves three main purposes. An internationally agreed upon numeric classification of extent of disease allows the collection of statistics and

worldwide interpretation of treatment outcome and survival. A stage assignment for a particular cancer gives information about prognosis. Third, a particular evidence-based treatment by staging and risk factors can be assigned. A stage is assigned for the cancer at initial presentation and this stage assignment never changes. For instance, a woman who develops lung metastases after an initial diagnosis of stage II endometrial cancer does not now have stage IV endometrial cancer. Her cancer is described as stage II with lung metastases.

The endometrial cancer is staged surgically and the most recent revision of the International Federation of Gynecology and Obstetrics (FIGO) staging system was published in 2009 [43]. Table 5 summarizes surgically staged categories for endometrial cancer. The endometrioid adenocarcinoma, the degree of differentiation is included in staging information. A grade 1 or well-differentiated tumor has less than 5 % solid growth pattern of the glandular component. A grade 2 or moderately differentiated tumor has between 6 and 50 % solid growth pattern. Grade 3 or poorly differentiated tumors have greater than 50 % solid component. Endometrioid adenocarcinomas of the endometrium usually spread in a predictable pattern [44]. At first there is direct extension into the myometrium. Spread can also progress into the cervix and vagina. Tumor cells can migrate trans-tubally with implantation on the ovaries and uterine serosa. Involvement of lymphovascular spaces can lead to lymphatic spread and distant metastases to the upper abdomen, inguinal nodes, and lungs. Surgical staging reflects this predictable behavior. While the rare histologic subtypes have less predictable behavior, they are included in the FIGO endometrial cancer staging system. Clear cell and serous histologies commonly spread by trans-tubal route and follow the peritoneal fluid circulation in a manner similar to epithelial ovarian cancers [45]. Spread frequently occurs with serous tumors while the primary cancer is small and noninvasive.

Operative Techniques for Staging

Laparoscopic Hysterectomy

The surgical approach chosen for removal of the uterus, tubes, and ovaries will be based on many factors. If a patient has had multiple prior surgeries, a history of peritonitis, diverticulitis, or abdominal radiation, an open laparotomy approach may be judicious. However, laparoscopic removal either by conventional laparoscopic techniques or with the robotic platform has become the standard of care [46]. Usually, a central port in the periumbilical is placed for the camera. The abdomen is insufflated with carbon dioxide gas. Two ports on the right and left sides of the mid to lower abdomen are placed for instrumentation. A uterine manipulator is placed transvaginally into the uterus to allow manipulation of the uterus during the surgical dissection. After all the pedicles have been developed, a colpotomy is made and the uterus, cervix, fallopian tubes, and ovaries are delivered through the vagina. The vagina cuff is then sutured using laparoscopic suturing techniques. Minimally invasive hysterectomy techniques, as described here, do not appear to compromise long-term survival for women with endometrial cancer [47]. Uterine morcellation should not be performed because of the theoretical risk of seeding and spread of viable cancer cells [48].

Laparotomy

The choice of an incision can be based on the patient's body habitus, previous incisions, and what surgery is planned. The classic incision for abdominal exploration is the low vertical incision, which can be extended into the upper abdomen as needed for greater surgical exposure. A modification to the low vertical is a paramedian incision, which avoids compromising the structural integrity of the umbilicus. A low transverse incision is reasonable for grade I cancers when high para-aortic nodal dissection is not planned. The transverse incision can be modified by the

muscle splitting Maylard incision if more exposure is needed. It is important not to compromise the blood supply to the skin by making a parallel incision to an old incision. As the skin and subcutaneous tissue is supplied by the superficial epigastric vessels that come in from the lateral position, a skin bridge between two old incisions has a risk of necrosis. Preoperative knowledge of previous breast reconstruction with a myofascial flap is important. Commonly, a mesh is placed after a TRAM (transverse rectus abdominus muscle) flap. It is helpful to obtain advice about where to place the new fascial incision from the plastic surgeon, who has performed the flap, to reduce postoperative devascularization of the abdominal wall and hernia formation. This information is also important for the laparoscopic approach.

Vaginal Approach

For patients who have multiple comorbidities, a simple vaginal hysterectomy without comprehensive surgical staging should be considered. The purpose of this surgery is to remove the uterus and stop bleeding. This surgery can be performed under spinal anesthesia. Vaginal hysterectomy with bilateral salpingo-oophorectomy is also appropriate for women with grade 1 minimally invasive tumors. It is not always technically possible to remove the ovaries through the transvaginal approach. As synchronous primary cancers of endometrium and ovaries can be found in up to 10 % of women, it is important to remove the ovaries if technically feasible and surgically safe to do [49].

Lymphadenectomy

Most patients with endometrial cancer present at an early clinical stage with low risk for nodal metastases, estimated at 3–5 % for well-differentiated tumors with only superficial invasion of the myometrium [44]. Therefore, performing routine lymphadenectomy (LND) on all women with endometrial cancer may lead to a large number of patients being "surgically overstaged" despite having disease confined to the uterus. Consequently, no consensus has been reached as to the role of LND in the management of early-stage cases. The different approaches range from omission of LND under most circumstances to routine LND for all patients.

Practices opting for a selective LND approach typically rely on algorithms to identify patients in which LND may be safely omitted. The most commonly used algorithm for lymphadenectomy, the "Mayo algorithm", exempts from full staging all patients with International Federation of Gynecology and Obstetrics (FIGO) grade 1–2 tumors of endometrioid histology, with greatest surface dimension $\leq$2 cm, myometrial invasion $\leq$50 % and no intraoperative evidence of macroscopic disease [50]. Current studies on the use of sentinel node biopsy suggest that this minimally invasive nodal evaluation may be another useful tool in surgical staging [51].

Comment on Case Report 3

The gynecologic oncology group demonstrated that 22 % of women with clinical stage I disease but high risk features had extrauterine spread of disease [44]. The patient had undergone a vaginal hysterectomy because of menorrhagia but without a preoperative endometrial biopsy. With the discovery of grade 3 cancer, it was crucial to perform a second surgery to remove her adnexa and evaluate her lymph nodes. Her final surgical stage of stage Ia grade was reassuring and she did not need postoperative adjuvant therapy with chemotherapy or whole pelvic radiation. She still was at higher risk for vaginal cuff recurrence and vaginal brachytherapy was recommended.

Conclusions

- An endometrial biopsy is the key diagnostic test for abnormal bleeding.
- Any positive findings on biopsy should be pursued further beyond physical examination and

Table 5 Surgical staging of endometrial cancer

Stage	Site of tumor involvement	Substages
I	uterine corpus	Ia: no or < one half myometrial invasion
		Ib: > one half myometrial invasion
II	cervix	II: cervical stromal invasion
III	pelvic structures	IIIa: invades serosa or adnexa
		IIIb: vaginal and/or parametrial involvement
	Lymph nodes	IIIc1: pelvic node involvement
		IIIc2: para-aortic node involvement
IV	Pelvic viscera	Iva : invades bladder and/or bowel mucosa
	Distant structures	IVb: abdominal metastases, inguinal nodes Lung, brain

cytologic evaluation, selecting from a number of radiologic and operative procedures.

– With a diagnosis of invasive endometrial cancer, treatment includes the surgical removal of uterus, cervix, and adnexa. Surgical staging requires a lymphadenectomy. Algorithms have been developed to determine which patients are at highest risk for lymph node metastases. Another approach is to consider sentinel node biopsies on all patents (Table 5).

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics 2016. CA Cancer J Clin. 2016;66(1):7–30.
2. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and mortality worldwide: IARC CancerBase No. 10 [Internet] Lyon. France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr.
3. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10–7.
4. Doll A, Abal M, Rigau M, et al. Novel molecular profiles of endometrial cancer-new light through old windows. J Steroid Biochem Mol Biol. 2008;108 (3–5):221–9.
5. Mutter GL, Zaino RJ, Baak JP, et al. Benign endometrial hyperplasia sequence and endometrial intraepithelial neoplasia. Int J Gynecol Pathol. 2007;26(2):103–14.
6. Felix AS, Weissfeld JL, Stone RA, et al. Factors associated with Type I and Type II endometrial cancer. Cancer Causes Control. 2010;21(11):1851–6.
7. Hale GE, Hughes CL, Cline JM. Endometrial cancer: hormonal factors, the perimenopasual "window at risk", and isoflavones. J Clin Endocrinol Metab. 2002;87:3–15.
8. Salilew-Wondim D, Wang Q, Tesfaye D, et al. Polycystic ovarian syndrome is accompanied by repression of gene signatures associated with biosynthesis and metabolism of steroids, cholesterol and lipids. J Ovarian Res. 2015;8:24.
9. Ezeh U, Yildiz BO, Azziz R. Referral bias in defining the phenotype and prevalence of obesity in polycystic ovary syndrome. J Clin Endocrinol Metab. 2013;98 (6):E1088–96.
10. Schlechte J, Sherman B, Halmi N, et al. Prolactin-secreting pituitary tumors in amenorrheic women: a comprehensive study. Endocr Rev. 1980;1 (3):295–308.
11. Rosato V, Zucchetto A, Bosetti C, et al. Metabolic syndrome and endometrial cancer risk. Ann Oncol. 2011;22:884–9.
12. Trabert B, Wentzensen N, Felix AS, et al. Metabolic syndrome and risk of endometrial cancer in the United States: a study in the SEER-Medicare linked database. Cancer Epidemiol Biomarkers Prev. 2015;24 (1):261–7.
13. Lindemann K, Vatten LJ, Ellstrom-Engh M, et al. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer. 2008;98:1582–5.
14. Haroon S, Zia A, Idrees R, et al. Clinicopathological spectrum of ovarian sex cord-stromal tumors; 20 years' retrospective study in a developing country. J Ovarian Res. 2013;6:87.
15. Silva KR, Liechocki S, Carneiro JR, et al. Stromal-vascular fraction content and adipose stem cell behavior are altered in morbid obese and post bariatric surgery ex-obese women. Stem Cell Res Ther. 2015;6(1):72.
16. Park SL, Goodman MT, Zhang ZF, et al. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. Int J Cancer. 2010;126(2):490–9.
17. Weiderpass E, Adami H-O, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. J Natl Cancer Inst. 1999;91(13):1131–7.
18. Zacharias BT, Coelho JC, Parolin MB, et al. Hypothalamic-pituitary-gonadal function in men with liver cirrhosis before and after liver transplantation. Rev Col Bras Cir. 2014;41(6):421–5.
19. Rydén L, Heibert Arnlind M, Vitols S, et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast

cancer compared with tamoxifen or placebo - meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast. 2016;26:106–14.
20. ACOG. American College of Obstetrician Gynecologists. Committee opinion no. 663: aromatase inhibitors in gynecologic practice. Obstet Gynecol. 2016;127(6):e170–4.
21. Lowry KP, Turan EA, Eisenberg J, et al. Projected effects of radiation-induced cancers on life expectancy in patients undergoing CT surveillance for limited-stage Hodgkin lymphoma: a Markov model. AJR Am J Roentgenol. 2015;204(6):1228–33.
22. Mills AM, Longacre TA. Lynch syndrome: female genital tract cancer diagnosis and screening. Surg Pathol Clin. 2016;9(2):201–14.
23. ACOG American College of Obstetrician Gynecologists. Committee on practice bulletins-gynecology and society of gynecologic oncology. ACOG practice bulletin No. 147: lynch syndrome. Obstet Gynecol. 2014;124:1042–54.
24. Levine DA, Lin O, Barakat RR, et al. Risk of endometrial cancer associated with BRCA mutation. Gynecol Oncol. 2001;80:395–8.
25. Neto N, Cunha TM. Do hereditary syndrome-related gynecologic cancers have any specific features? Insights Imaging. 2015;6(5):545–52.
26. Anderson B. Diagnosis of endometrial cancer. Clin Obstet Gynecol. 1986;13:739–50.
27. Pellerin GP, Finan MA. Endometrial cancer in women 45 years of age or younger: a clinicopathological analysis. Am J Obstet Gynecol. 2005;193(5):1640–4.
28. Argall E, Jovanovic A, Figueroa R, et al. Effects of endometrial ablation on treatment planning in women with endometrial cancer. J Minim Invasive Gynecol. 2016;23(2):281–5.
29. ACOG. American College of Obstetrician Gynecologists. Committee Opinion No. 557. Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Obstet Gynecol. 2013;121(4):891–6.
30. Havig K. The health care experiences of adult survivors of child sexual abuse: a systematic review of evidence on sensitive practice. Trauma Violence Abuse. 2008;9(1):19–33.
31. Kingnate C, Tangiitgamol S, Khunnarong J, et al. Abnormal uterine cervical cytology in a large tertiary hospital in Bangkok metropolis: Prevalence, management, and outcomes. Indian J Cancer. 2016;53:67–73.
32. Serdy K, Yildiz-Aktas I, Li Z, et al. The value of papanicolaou tests in the diagnosis of endometrial carcinoma: a large study cohort from an academic medical center. Am J Clin Pathol. 2016;145(3):350–4.
33. Goodman A. Human papillomavirus infection and cervical cancer. BMJ. 2015;350:h2372.
34. Clark TJ, Mann CH, Shah N, et al. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systemic quantitative review. BJOG. 2002;109:313–21.
35. Gungorduk K, Asicioglu O, Ertas IE, et al. Comparison of the histopathological diagnoses of preoperative dilatation and curettage and Pipelle biopsy. Eur J Gynaecol Oncol. 2014;35(5):539–43.
36. Bredella MA, Feldstein VA, Filly RA, et al. Measurement of endometrial thickness at US in multicenter drug trials: value of central quality assurance reading. Radiology. 2000;217:516–20.
37. Kim M-J, Kim J-J, Kim SM. Endometrial evaluation with transvaginal ultrasonography for the screening of endometrial hyperplasia or cancer in premenopausal and perimenopausal women. Obstet Gynecol Sci. 2016;59(3):192–200.
38. Love CD, Muir BB, Scrimgeour JB, et al. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J Clin Oncol. 1999;17:2050–4.
39. Schwartz LB, Snyder J, Horan C, et al. The use of transvaginal ultrasound and saline infusion sonohysyerography for the evaluation of aymptomatic postmenopausal breast cancer patients on tamoxifen. Ultrasound Obstet Gynecol. 1998;11:48–53.
40. Chawla I, Tripathi S, Vohra P, et al. To evaluate the accuracy of saline infusion sonohysterography (SIS) for evaluation of uterine cavity abnormalities in patients with abnormal uterine bleeding. J Obstet Gynaecol India. 2014;64(3):197–201.
41. Arnaiz J, Muñoz AB, Verna V, et al. Magnetic resonance imaging for the pre-surgical assessment of endometrial cancer: results in a routine clinical setting, outside dedicated trials; a cross-sectional study. Anticancer Res. 2016;36(4):1891–4.
42. Signorelli M, Crivellaro C, Buda A, et al. Staging of high-risk endometrial cancer with PET/CT and sentinel lymph node mapping. Clin Nucl Med. 2015;40 (10):780–5.
43. Mutch DG. The new FIGO staging system for cancers of the vulva, cervix, endometrium, and sarcomas. Gynecol Oncol. 2009;115:325–8.
44. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. Cancer. 1987;60:2035–41.
45. Liang LW, Perez AR, Cangemi NA, et al. An assessment of prognostic factors, adjuvant treatment, and outcomes of stage IA polyp-limited versus endometrium-limited type II endometrial carcinoma. Int J Gynecol Cancer. 2016;26(3):497–504.
46. Mäenpää MM, Nieminen K, Tomás EI, et al. Robotic-assisted versus traditional laparoscopic surgery for endometrial cancer: A Randomized Controlled Trial. Am J Obstet Gynecol. 2016; pii: S0002–9378(16) 30314–3.
47. Wright JD, Burke WM, Tergas AI, et al. Comparative effectiveness of minimally invasive hysterectomy for endometrial cancer. J Clin Oncol. 2016;34 (10):1087–96.
48. Hall TR, Lee S, Boruta DM, Goodman A. Medical device safety and surgical dissemination of

unrecognized uterine malignancy: morcellation in minimally invasive gynecologic surgery. Oncologist. 2015;20(11):1274–82.
49. Soliman PT, Slomovitz BM, Broaddus RR, et al. Synchronous primary cancers of the endometrium and ovary: a single institution review of 84 cases. Gynecol Oncol. 2004;94:456–62.
50. Convery PA, Cantrell LA, Santo ND, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma. Gynecol Oncol. 2011;123:65–70.
51. Clark LH, Soper JT (2016) Endometrial cancer and the role of lymphadenectomy. Obstet Gynecol Surv 71(6):353–360

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Imaging in the Diagnosis and Treatment of Endometrial Cancer

Jessica J. Kraeft and Susanna I. Lee

Abstract

Ultrasound, sonohysterography (SHG), magnetic resonance imaging, computed tomography (CT), and 18-2-fluorodeoxy-2-deoxy-D-glucose fusion positron emission tomography CT (FDG-PET CT) are tools available for diagnosis, treatment planning, and detection of recurrences post-primary therapy of EC. Transvaginal ultrasound has an established role in screening for cancer in women presenting with postmenopausal bleeding. Sonohysterography allows for diagnosis of focal endocavitary lesions and hysteroscopy planning. For treatment planning, magnetic resonance imaging (MRI) provides the best definition of tumor extent in the central soft tissue pelvis whereas FDG-PET CT is the most accurate modality for detecting lymphadenopathy and distant metastases. Post-primary therapy, CT and FDG-PET CT are both useful in evaluating recurrences with the latter being more sensitive.

Keywords

Female pelvic imaging • Gynecologic cancer imaging • Lymph node imaging • Cancer staging • Pelvic ultrasound

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J.J. Kraeft (✉)
Department of Radiology, Tufts Medical Center, 800 Washington St., #299, Floating 4, Boston, MA 02111, USA
e-mail: jkraeft@tuftsmedicalcenter.org

S.I. Lee
Department of Radiology Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

Introduction

Imaging is employed in the many steps during the diagnosis and treatment of endometrial cancer. Evaluation of abnormal uterine bleeding for tumor detection, defining tumor extent following diagnosis, and post-treatment surveillance, all require imaging. This chapter provides an overview of various imaging modalities used in the

evaluation of endometrial cancer highlighting the strengths and limitations of the various applications.

Ultrasound

Ultrasound has long been known as an effective tool in the evaluation of women with postmenopausal bleeding (PMB) [1–4]. Although transabdominal ultrasound can be used to detect endometrial pathology, limited spatial resolution, patient body habitus, uterine retroflexion, and coexisting conditions such as leiomyomas can make transabdominal endometrial evaluation challenging. The improved resolution afforded by the high-frequency transvaginal ultrasound probe has led to the establishment of transvaginal ultrasound (TVUS) as the initial noninvasive study of choice in evaluating women presenting with postmenopausal bleeding. TVUS demonstrates better image quality than transabdominal ultrasound in 72 % of patients [5] and performs significantly better in evaluating the endometrium in the retroverted uterus [6].

Cancer Detection

In a postmenopausal patient with abnormal vaginal bleeding, the primary role of TVUS is to identify women who need further evaluation for cancer in the form of endometrial biopsy. Endometrial appearance on TVUS is evaluated by thickness and morphology. Normal postmenopausal endometrium is $\leq$5 mm and is homogenous in thickness and echotexture (Fig. 1a). As TVUS demonstrates very high sensitivity and negative predictive value [7] for cancer comparable to other more invasive techniques [8–10] (Table 1), it identifies women who are highly unlikely to have endometrial cancer. Thus, a normal TVUS study can be used to triage patients to diagnostic algorithms that are effective in detecting benign focal causes of PMB, e.g., endometrial polyps or submucosal fibroids.

Endometrial Thickness

Endometrial thickness measurement is an integral part of a TVUS endometrial evaluation. Numerous studies have attempted to establish a size threshold below which endometrial pathology can be excluded with measurements ranging

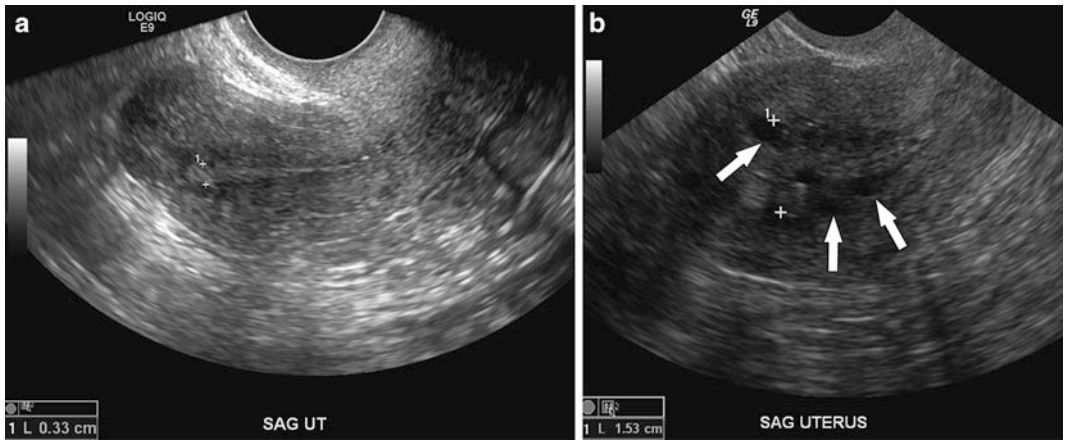

Fig. 1 Transvaginal ultrasound of normal postmenopausal endometrium. Endometrial thicknesses of a patient not on hormone replacement therapy (**a**) and on tamoxifen therapy (**b**) are measured on sagittal images of the uterus. Note that the patient on tamoxifen demonstrates subendometrial cysts (*arrows*) and apparent thickening of the endometrium

Table 1 Diagnostic modalities for endometrial cancer detection

Modality	Sensitivity (%)	Specificity (%)	PPV[a] (%)	NPV[b] (%)
TVUS not on hormone replacement therapy [7]	96	99	57	99
TVUS on hormone replacement therapy [7]	96	77	31	99
Nonfocal biopsy [8]	87	99	82	99
Hysteroscopy [9]	86	99	72	99
Sonohysterography [10]	89	46	16	97

[a]Positive predictive value
[b]Negative predictive value

from 4 to 7 mm [6, 7, 11]. A large meta-analysis including 35 studies with 5,892 women demonstrated that, using a 5 mm threshold to define endometrial thickening, 96 % of women with endometrial cancer had an abnormal TVUS result whereas 92 % of women with any endometrial disease such as cancer, polyp, or hyperplasia had an abnormal TVUS. This threshold of 5 mm is particularly accurate in excluding endometrial disease in symptomatic women on tamoxifen (Table 1). In postmenopausal women with vaginal bleeding, a 10 % pretest probability of endometrial cancer was reduced to a 1 % posttest probability after a normal TVUS [7]. Thus, TVUS is a powerful tool for identifying patients with PMB who are highly unlikely to have endometrial pathology.

While a threshold of $\leq$5 mm endometrial thickness is highly sensitive for detecting endometrial cancer, it is not very specific. Seventy percent of women with postmenopausal bleeding and endometrial thickness >5 mm demonstrate benign pathology [12]. Multiple etiologies for PMB have been reported [13] (Table 2), some of which result in a thickened endometrium. Postmenopausal women on hormonal replacement therapy have a thickened endometrium at baseline as opposed to those who are not on hormone replacement. Patients on sequential hormonal therapy demonstrate greater endometrial thickness than in those on continuous hormonal replacement [14]. Patients on tamoxifen with cystic subendometrial atrophy can also demonstrate apparent abnormal thickening of the endometrium [15] (Fig. 1b).

It is important to note that normal endometrial thickness does not exclude endometrial cancer as a cause for postmenopausal bleeding. A study of women with PMB not on tamoxifen showed that half the patients with endometrial cancer had an endometrial thickness between 3 and 4 mm [12]. Thus, even in patients with normal endometrial thickness, persistent or recurrent bleeding should be further evaluated to definitively identify the cause of the symptoms.

Table 2 Common causes of postmenopausal bleeding [13]

Polyps	30 %
Submucosal fibroids	30 %
Endometrial atrophy	8 %
Hyperplasia	4–8 %
Endometrial carcinoma	10 %

Endometrial Morphology

In addition to endometrial thickness, TVUS assesses endometrial morphology. Endometrial morphology can be classified as either focal or diffuse. Diffuse endometrial thickening is often due to hyperplasia or carcinoma (Fig. 2a) and biopsy will usually be adequate to establish a histologic diagnosis. Focal thickening is usually due to "endometrial polyps", which could be benign or malignant (Fig. 2b), and hysteroscopic tissue sampling is often required to establish the diagnosis.

Morphologic features of the endometrium associated with malignancy have been described. They include heterogeneous echotexture, hyperechoic echotexture with irregular borders, and a heterogeneous intraluminal mass. Using these criteria, Weigel et al. concluded that a combined assessment of endometrial thickness and morphology improves detection of endometrial pathology on TVUS [16].

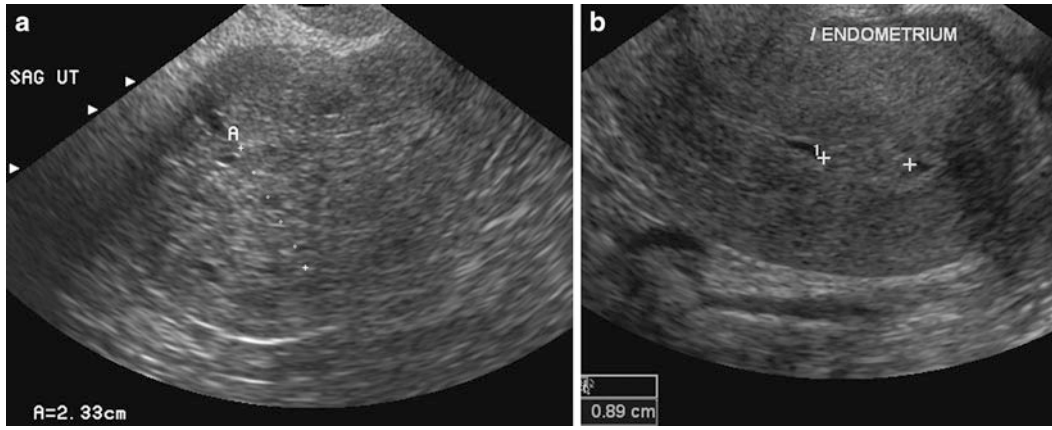

Fig. 2 Transvaginal ultrasound of abnormally thickened endometrium. Sagittal images of the uterus demonstrate diffuse (**a**) and focal (**b**) endometrial thickening (calipers) pathologically confirmed to be endometrial cancer and a benign endometrial polyp respectively

Color Doppler is used in conjunction with TVUS in the evaluation of women with PMB. Presence of Doppler signal within an endometrial lesion eliminates blood clot as a possible etiology. Color Doppler can also assess the pattern of vascularity of an endometrial mass. Malignant lesions are usually broad based with diffuse high level vascularity (Fig. 3a, b) whereas a single feeding vessel in a lesion of relatively low overall vascularity is associated with benign polyps on a stalk (Fig. 3c, d) [16].

As TVUS is used as a first step to triage patients with PMB for tissue sampling, criteria for an abnormal endometrium should be optimized to maximize sensitivity for cancer detection. Thus, all patients with PMB with abnormal endometrial thickness or morphology on TVUS should undergo histological sampling.

Cancer Staging

FIGO staging for endometrial cancer is based on surgery and pathology (Table 3) [17]. Imaging is frequently used for preoperative treatment planning and to estimate prognosis. The high resolution afforded by TVUS readily allows for assessment of the extent of tumor spread within the uterus. However, due to limitations in tissue penetration, neither transabdominal nor transvaginal ultrasound can accurately assess extrauterine spread or nodal involvement by tumor.

To assess the utility of TVUS for tumor staging, accuracies of TVUS in detecting deep myometrial invasion (>50 % myometrial thickness) and cervical extension have been studied [18–23]. In a series of 69 patients, Artner et al. reported high levels of accuracy in detecting deep myometrial invasion (99 %) and cervical extension (96 %) using TVUS [19], although in the latter, TVUS was noted to have missed 3/9 cases of cervical extension. In a study of 90 patients, Sawicki et al. reported slightly lower accuracies of 84 % for myometrial invasion and 86 % for cervical extension [22]. Studies comparing TVUS and magnetic resonance imaging (MRI) have not found comparable TVUS performance in tumor staging with reported accuracies of 68 % [21] and 69 % [20]. This wide range in reported accuracies, likely explained in part by variations in patient body habitus and operator expertise, results in TVUS being a modality whose reliability in tumor staging is difficult to assess.

The technical factors limiting TVUS performance as a staging tool are well understood. TVUS can both under- and overestimate the extent of myometrial tumor invasion. Overestimation can occur when coexisting myometrial

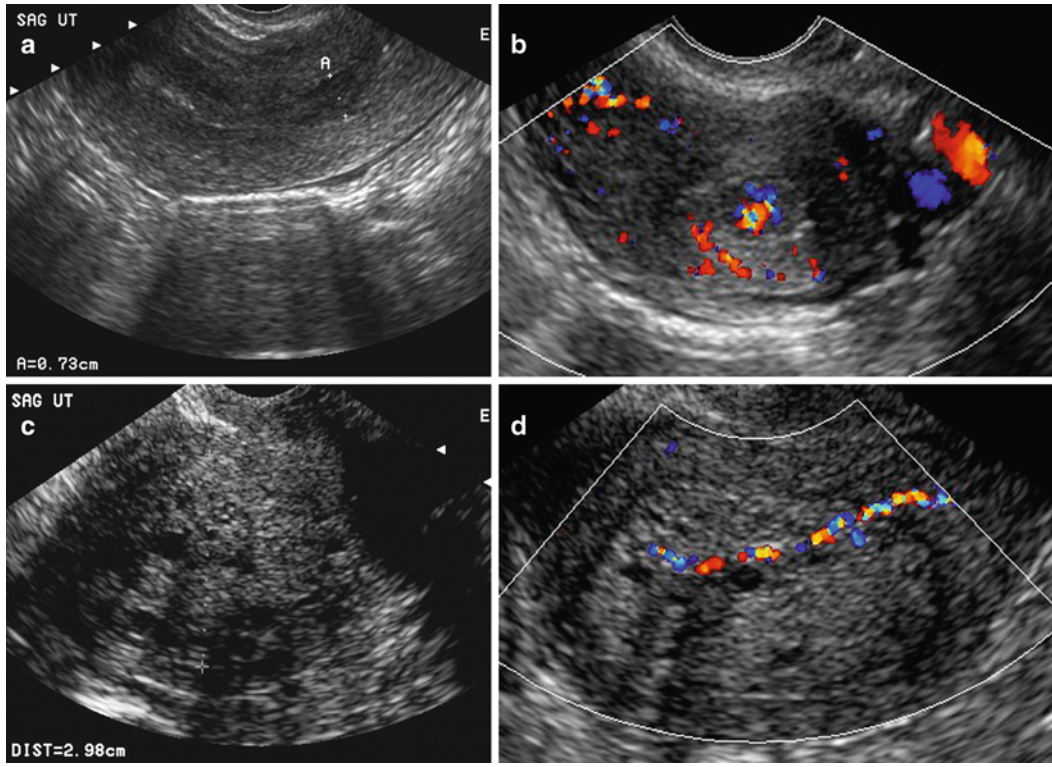

Fig. 3 Doppler ultrasound of abnormally thickened endometrium. Grey scale (**a** and **c**) and color Doppler (**b** and **d**) transvaginal ultrasound evaluation demonstrate a diffusely elevated vascularity of the thickened endometrium typical for cancer (**a** and **b**) and a single feeding vessel in an endometrium of overall low vascularity characteristic of a polyp (**c** and **d**)

Table 3 FIGO staging of endometrial cancer

Stage I			Tumor confined to the corpus uteri
	IA		No or less than half myometrial invasion
	IB		Invasion equal to or more than half of the myometrium
Stage II			Tumor invades the cervical stroma, but does not extend beyond the uterus
Stage III			Local and/or regional spread of the tumor
	IIIA		Tumor invades the serosa of the corpus uteri and/or adnexae
	IIIB		Vaginal and/or parametrial involvement
	IIIC		Metastases to pelvic and/or para-aortic lymph nodes
		IIIC1	Positive pelvic nodes
		IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV			Tumor invades bladder and/or bowel mucosa, and/or distant metastases
	IVA		Tumor invasion of bladder and/or bowel mucosa
	IVB		Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

processes, e.g., adenomyosis, leiomyomas, or endometrial cavity distension from tumor or hematometra, are present. Underestimation is usually seen in cases of microscopic invasion or lymphovascular invasion.

Intrauterine sonography involving transcervical insertion of a high-frequency microtip probe has also been used as a staging tool. Probe placement does not require cervical dilatation or anesthesia. Improved accuracies for depth of

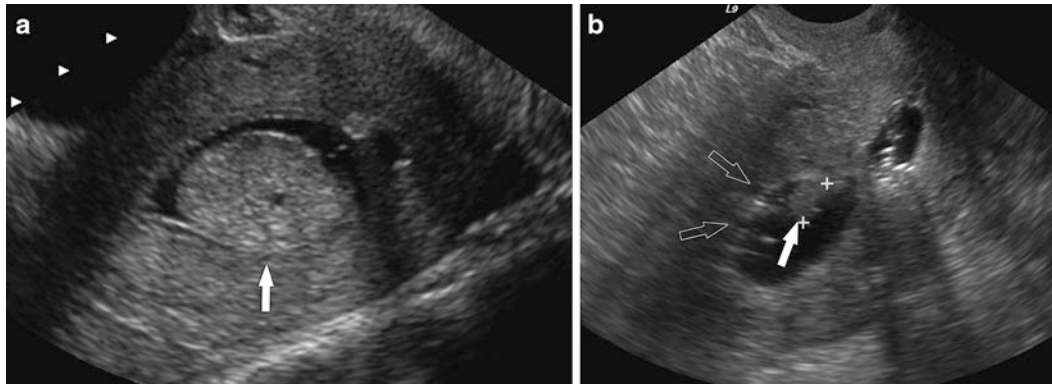

Fig. 4 Sonohysterography of abnormally thickened endometrium. Sagittal images of the uterus after intracavitary saline infusion delineate a polyp (**a**) with a narrow base of attachment (*arrow*) to the posterior fundal wall. Evaluation of the tamoxifen endometrium (**b**), same patient as in Fig. 1b demonstrates a polyp (*solid arrow*) originating from the anterior uterine body and the subendometrial location of the cysts (*clear arrows*) both accounting for the apparent thickening seen on transvaginal ultrasound

tumor invasion when compared to TVUS have been reported [23] in a single series of 48 patients.

Sonohysterography

Sonohysterography (SHG) is a minimally invasive procedure in which saline is instilled in the uterine cavity prior to TVUS through a catheter positioned in the cervical canal. The saline separates the two walls of the uterus facilitating sonographic evaluation of the endometrium. Endometrium suspicious for hypertrophy or malignancy demonstrates irregularities in thickness or echotexture or a broad-based poorly marginated endoluminal mass. Benign endometrium is characterized as either normal, i.e., homogeneous echotexture or uniform thickness, or demonstrating a polyp, i.e., a smoothly marginated pedunculated endoluminal mass (Fig. 4a).

SHG is recommended when TVUS cannot adequately assess the endometrium. In patients with non- or poor visualization of the endometrium with TVUS, usually due to fibroids or adenomyosis, SHG can delineate the endometrial cavity. It is also extremely useful in assessing patients with postmenopausal bleeding on tamoxifen, many of whom demonstrate apparent endometrial thickening on TVUS due to cystic subendometrial atrophy [24]. As SHG can discriminate between endometrial and subendometrial processes, an endometrial lesion, e.g., polyp or cancer, can be visualized separate from the subendometrial tamoxifen-related changes after the instillation of saline (Fig. 4b).

SHG accurately identifies endometrial pathology with reported sensitivities of 89–98 % and specificities of 46–88 % (Table 1) [10, 25]. As with TVUS, SHG demonstrates higher sensitivity than specificity, thereby a highly reliable negative predictive value. While SHG is more sensitive than TVUS in detecting focal endometrial pathology, there is no data to suggest that SHG is more sensitive in cancer detection when the endometrium has been adequately visualized with TVUS. Thus, based on the current evidence, the primary role of SHG in evaluating patients with postmenopausal bleeding should be to identify etiologies other than cancer (Table 2).

SHG is recommended in patients with abnormal endometrial thickness on TVUS or with persistent PMB only after a nonfocal endometrial biopsy has proven negative for cancer [26]. As SHG demonstrates a sensitivity for endometrial pathology comparable to that reported for hysteroscopy (Table 1), and it represents a less invasive alternative in evaluating patients with a negative biopsy.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is primarily used for defining tumor extent for treatment planning and estimation of prognosis. The inherent soft tissue resolution and multiplanar imaging capability of MRI make this technique an effective modality for assessing disease extent within the pelvis. MRI plays only a limited role in cancer detection to evaluate patients with cervical or vaginal stenosis where adequate assessment of the endometrium is precluded with TVUS or biopsy.

Technique

MRI protocols for imaging patients with endometrial cancer include triplane T2-weighted fast spin echoimages of the pelvis, axial sagittal dynamic gadolinium-enhanced fat-saturated T1-weighted images, and triplane post-contrast fat-saturated T1-weighted images. For purposes of tumor staging, gadolinium should be routinely administered as it is necessary to accurately define the extent of tumor spread in the uterus and adjacent organs [27]. Diffusion-weighted imaging is increasingly being adopted as it aids in delineating the primary tumor and in detecting lymphadenopathy [28, 29]. Finally, as uterine cancer may present with para-aortic adenopathy in the absence of pelvic adenopathy, one sequence of a staging exam, typically an axial T1-weighted or a single shot fast spin echo coronal T2-weighted, should be dedicated to evaluate retroperitoneal adenopathy and to assess hydronephrosis. The study is performed with a phased array body coil in either a 1.5 T or 3.0 T magnet. To decrease artifact from bowel motion, patients may be asked to fast for 4–6 hours prior to imaging and glucagon may be administered.

Cancer Detection

The normal endometrium is isointense on T1-weighted images, very hyperintense on T2-weighted images, and enhances more slowly than the myometrium after dynamic gadolinium administration. Endometrial pathology, including cancer, appears as intermediate signal (between bright endometrium and dark myometrium) on T2-weighted images (Fig. 5a) and, after dynamic gadolinium administration, enhances faster than normal endometrium but slower than the

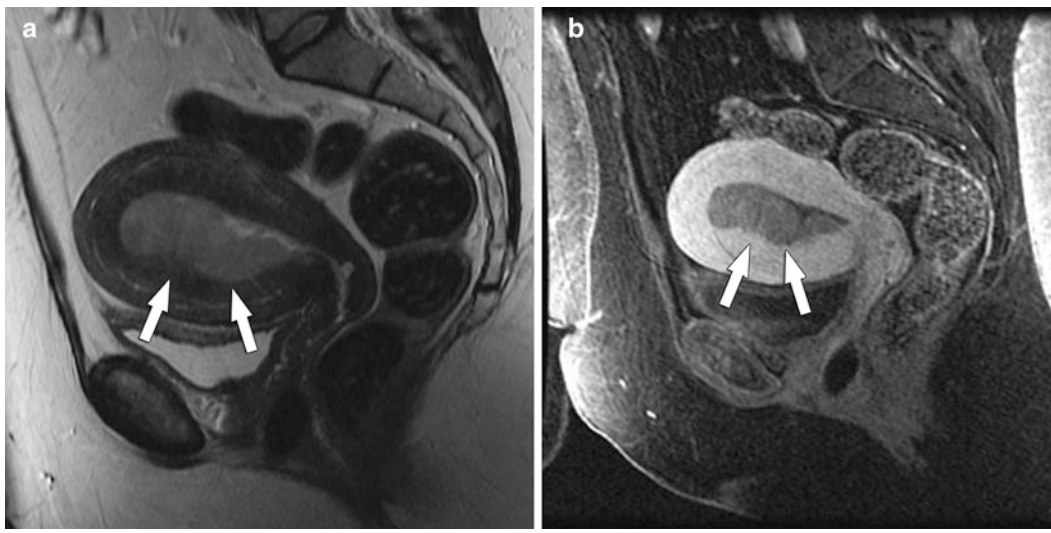

Fig. 5 Magnetic resonance imaging (MRI) of endometrial cancer. Sagittal FSE (fast spin echo) T2-weighted (**a**) and post-gadolinium T1-weighted fat-saturated (**b**) images of the uterus demonstrate a mass (*arrows*) extending throughout the endometrial cavity, which is of intermediate grey T2 signal and enhances with gadolinium more avidly than normal endometrium. Note that the cancer does not enhance as avidly as normal myometrium

hypervascular myometrium (Fig. 5b). Blood clots can be distinguished from endometrial pathology as they often demonstrate portions that are T1 hyperintense and minimal or no enhancement with gadolinium. However, in the absence of tumor extension outside the endometrial cavity, MRI cannot discriminate cancer from other endometrial pathologies such as hyperplasia or polyps [30]. Thus, endometrial lesions identified on MRI require histology for definitive diagnosis.

Cancer Staging

The initial step in endometrial cancer therapy is usually hysterectomy and bilateral salpingo-oophorectomy for those patients with presumed stages I–III disease. Surgery can also include resection of the pelvic and para-aortic lymph nodes to assess for metastases, which is only performed in patients with a primary tumor demonstrating high-risk features for lymph. These are high-grade histology (grade 3 endometrioid, serous papillary or clear cell adenocarcinomas), tumor size >2 cm, deep (>50 % thickness) myometrial invasion, or cervical stromal invasion [31]. The latter three features are best assessed preoperatively with MRI. Meta-analysis has demonstrated that contrast-enhanced MRI performs better than noncontrast MRI, CT, or US in detecting myometrial invasion [27]. In a multicenter audit of 775 cases over a 12-month period in the UK, MRI demonstrated sensitivity and specificity of 77 % and 88 %, respectively, in detecting deep myometrial invasion; 42 % and 97 %, respectively, in detecting cervical stromal invasion; and 64 % and 96 % in diagnosing pelvic lymphadenopathy [32].

As MRI is the most effective imaging modality to define the extent of tumor, it is used to evaluate endometrial cancer patients for lymphadenectomy, radical hysterectomy, and medical hormonal therapy for fertility preservation. In patients with comorbidities that preclude surgery, MRI is used to both stage and plan fields for primary radiotherapy.

Myometrial Invasion

Assessment of myometrial invasion with MRI requires evaluation of both T2-weighted and post-gadolinium administration images. Any disruption or irregularity of the myometrial junctional zone by an isointense mass on T2-weighted images is diagnostic of myometrial invasion. An intact junctional zone with a sharp tumor-myometrium interface suggests a non-invasive malignancy. MRI detects deep myometrial invasion with reported accuracies of 74–91 % (Fig. 6) [33, 34]. When compared side-by-side to TVUS, MRI demonstrates similar

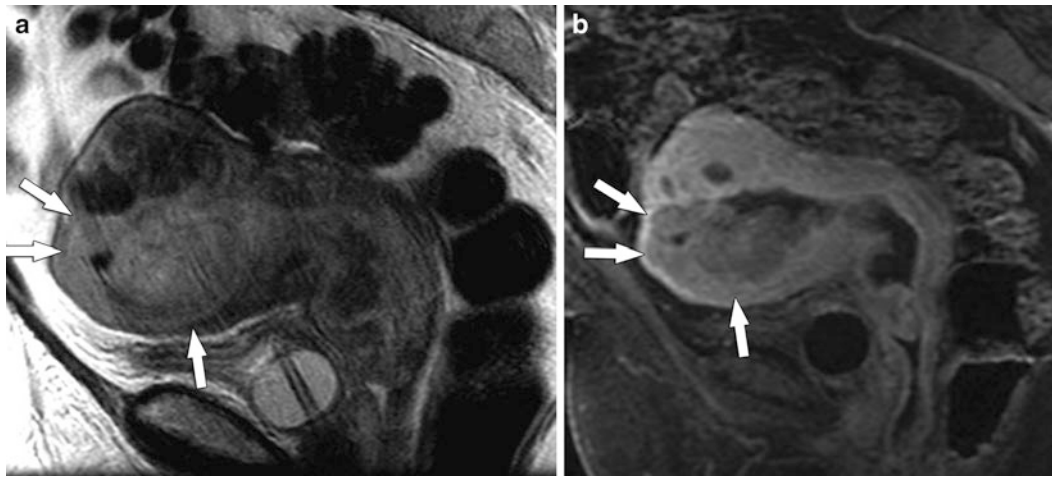

Fig. 6 MRI evaluation of the depth of myometrial invasion. Sagittal FSE T2-weighted (**a**) and post-gadolinium T1-weighted fat-saturated (**b**) images of the uterus demonstrate a cancer with invasion of >50 % myometrial depth (*arrows*). Imaging findings were confirmed by pathologic examination

accuracies with noncontrast imaging [33] but higher accuracies when gadolinium is administered [35].

Typically, errors occur in over- rather than underestimating the extent of myometrial tumor invasion [36]. Coexisting myometrial conditions, such as leiomyomas or thinned myometrium due to atrophy or endometrial canal distention, can decrease the accuracy of MRI in assessing tumor invasion. In patients with adenomyosis who demonstrate a thickened junctional zone, an indistinct junctional zone on T2-weighted images corresponds to myometrial invasion only in 22 % of cases. With gadolinium administration, accuracy is reported to increase considerably to 92 % [37].

Cervical Invasion

Tumor extending into the cervix appears as widening of the internal os and the endocervical canal. Disruption of the cervical stroma is seen as loss of the "fibrous" black line around the cervix seen on T2-weighted images (Fig. 7). While accuracies using MRI are reported to be as high as 92 % [38], sensitivity may be lower as microscopic cervical invasion can be missed.

Extrauterine Spread

Disruption or irregularity of the outer layer of the myometrium indicates extrauterine spread. There may be direct extension of the tumor to serosa or adnexa (Stage IIIA) (Fig. 8a). The ovaries can also be involved by discrete metastases. While gross tumor extension into the vaginal tissue (Stage IIIB) can be seen on gadolinium-enhanced images, mucosal vaginal involvement is more readily established by direct visualization and biopsy.

Extension into the bladder or rectum is best determined on gadolinium-enhanced sagittal images and can be corroborated on axial imaging (Fig. 8b). Loss of the normal fat plane between the tumor and the bladder or rectum indicates invasion (Stage IVA). While this finding signifies tumor invasion of the bladder or rectal serosa, it does not necessary imply mucosal involvement, which is more accurately assessed by endoscopic visualization and biopsy.

Lymph Nodes

As a cross-sectional imaging modality, MRI enables detection of pelvic and retroperitoneal lymphadenopathy (Stage IIIC). Typically endometrial cancer spreads to regional pelvic nodes,

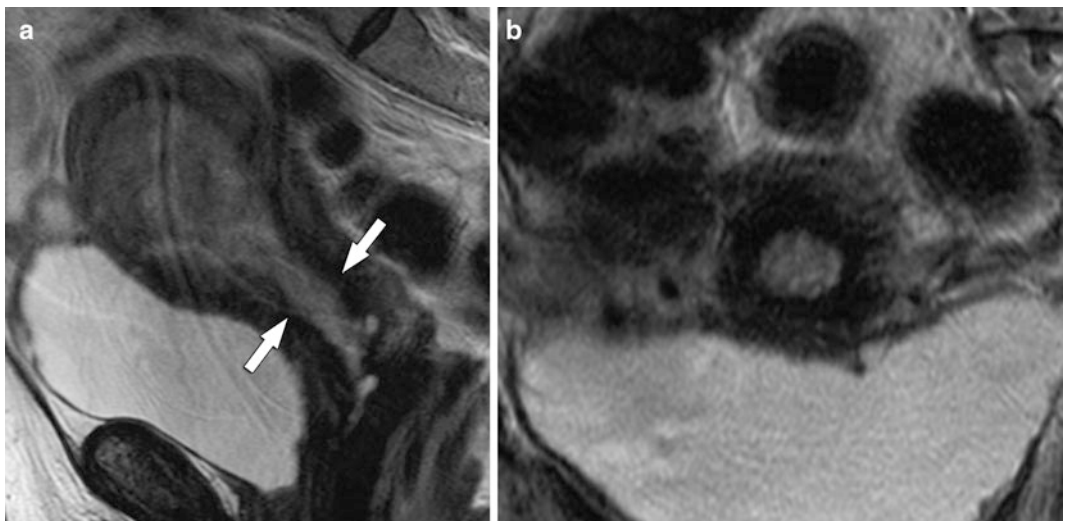

Fig. 7 MRI evaluation of cervical invasion. Sagittal FSE T2-weighted image of the uterus (**a**) demonstrates a mass involving the endometrial cavity and the endocervical canal (*arrows*). A long-axis oblique FSE T2-weighted image of the cervix (**b**) reveals no evidence of gross stromal or parametrial invasion by tumor. Imaging findings were confirmed by pathologic examination

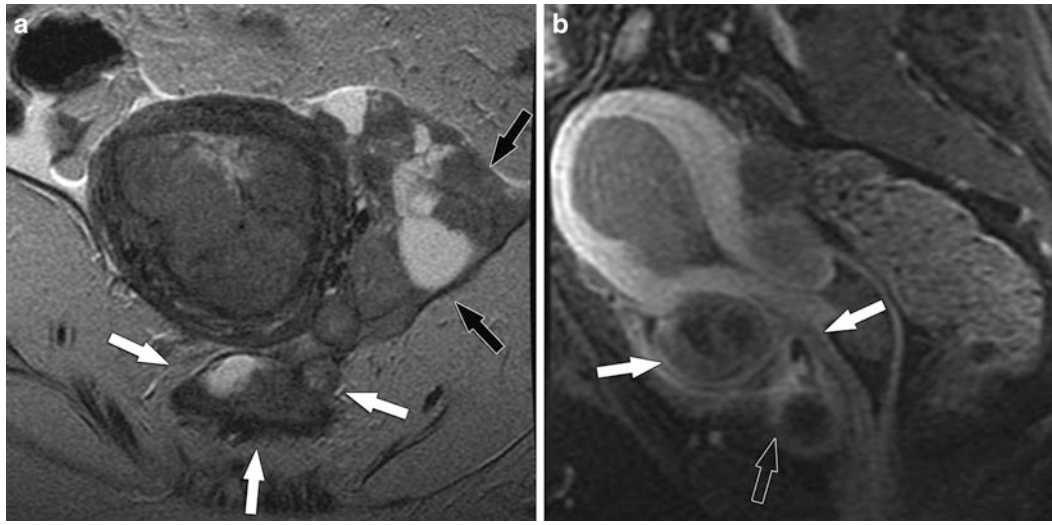

Fig. 8 MRI evaluation of extrauterine spread. Axial FSE T2-weighted image of the uterus (**a**) shows cancer involving the endometrial cavity with metastasis to the left ovary (*black arrows*). Tumor implants in the cul-de-sac (*white arrows*) are also noted. Sagittal post-gadolinium T1-weighted image with fat saturation (**b**) illustrates a Foley catheter balloon in a collapsed bladder (*black arrow*) and tumor involving the bladder dome and trigone, respectively (*white arrows*). Imaging findings were confirmed by pathologic examination biopsy

Table 4 Imaging for nodal metastases

	Sensitivity (%)	Specificity (%)
CT endometrial [41]	28–64	78–94
MRI endometrial [40, 41]	59–72	93–97
PET-CT endometrial [41, 53]	74–77	93–100

but it can metastasize to abdominal nodes without involvement of pelvic nodes. Consequently, pelvic MRI for endometrial cancer staging includes view images from the pelvic floor to the renal hilum to assess for retroperitoneal as well as pelvic sidewall lymphadenopathy. Size and morphology have traditionally been used as criteria for suscipious lymphadenopathy with oval nodes greater than 1 cm in the short axis labeled as concerning for malignant disease [39]. These morphologic criteria yield moderate sensitivity (59–72 %) but very high specificity (93–97 %) in detecting lymph node metastases (Table 4) [40, 41]. Diffusion-weighted imaging, an MRI technique that improves lesion detection, clearly aids in detection of positive nodes (Fig. 9). However, whether the technique improves differentiation of benign from malignant nodes beyond the more conventional size criteria is still under investigation [29, 42].

Computed Tomography

Computed tomography (CT) does not play a role in primary tumor detection or in defining tumor spread in early stage intrauterine disease. In patients with suspected advanced disease, it can be used to evaluate nodal (Stage IIIC) and distant metastases (Stage IVB) should integrated 2-[18F]-fluoro-2-deoxyglucose positron emission tomography-CT (FDG-PET CT), a more accurate modality for this purpose, not be available. Compared to MRI, with a resolution sometimes compromised by bowel or patient motion, contrast-enhanced CT more reliably detects distant parenchymal metastases, peritoneal implants, and malignant ascites [43] (Fig. 10). CT performs comparably to MRI in detecting lymphadenopathy, as both modalities rely on morphologic criteria of >1 cm short axis diameter for a lymph node to be considered positive.

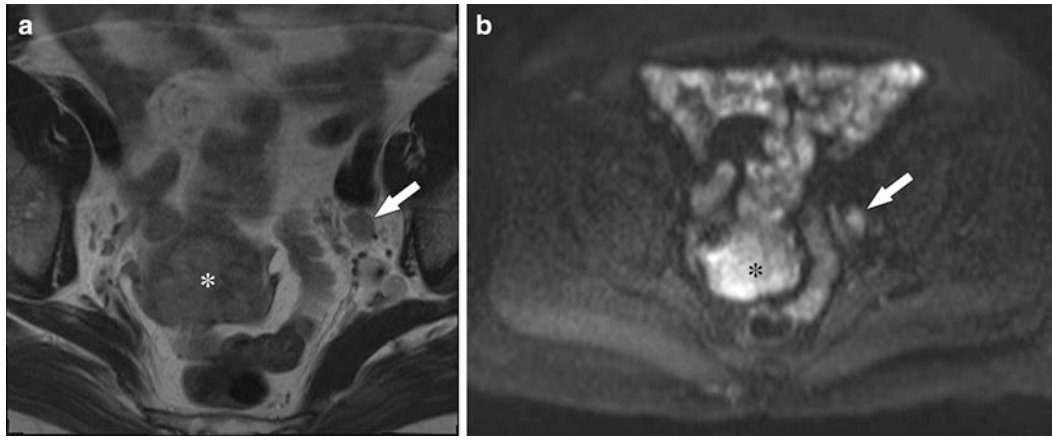

Fig. 9 MRI evaluation of nodal involvement. Axial FSE T2-weighted (**a**) and diffusion-weighted images (**b**) of the pelvis reveal an abnormally enlarged 1.8 × 1.1 cm left obturator node (*arrow*) shown to be involved by tumor by pathologic examination

Reported ranges of sensitivity and specificity of CT in detecting lymph node metastases are 28–64 % and 78–94 %, respectively (Table 4) [41].

Because of its multiplanar and greater tissue-specific imaging capabilities, MRI performs better than CT in staging early disease (Stages I and II) and in evaluating tumor invasion into adjacent organs (Stage IVA) [27, 44–46]. A side-by-side comparison of both modalities found that CT demonstrates 83 % sensitivity and 42 % specificity while MR demonstrates 92 % sensitivity and 90 % specificity in detecting myometrial invasion. Moreover CT demonstrates 25 % sensitivity and 70 % specificity while MR demonstrates 86 % sensitivity and 97 % specificity in detecting cervical invasion [47].

Integrated 2-[18F]-Fluoro-2-Deoxyglucose Positron Emission Tomography and Computed Tomography

Imaging Technique

Positron emission tomography (PET) with the radioactive glucose analog 18-2-fluorodeoxy-2-deoxy-D-glucose (18-FDG) has proven to be a powerful tool for cancer staging and detection of tumor recurrence. Cells with elevated glycolysis avidly take up this glucose analog. 18-FDG is phosphorylated to 18-FDG-6P, which is trapped in tumor cells that are relatively deficient in glucose-6-phosphatase during the time interval in which images are acquired. Following a $\geq$6 h fast, patients are injected with the 18-FDG (average dose, 555 MBq [15 mCi]). A low radiation dose CT is first obtained for attenuation correction of the PET scan. PET images from the neck to the pelvis are then obtained 45–60 min after intravenous injection of the tracer, followed by a diagnostic quality CT exam with or without the administration of intravenous contrast. Increased 18-FDG uptake can be detected on PET images corresponding to tissue with increased metabolic activity, such as in neoplastic or inflammatory conditions.

Concurrent FDG-PET and diagnostic CT scanning are necessary for accurate staging of endometrial cancer. Analysis of fused PET-CT images minimizes errors in lesion detection and localization. As FDG physiologically localizes to bowel and urine, and as endometrial cancer metastasizes to retroperitoneal lymph nodes and peritoneal surfaces, normal tracer can be reliably distinguished from tumor only with precise anatomic mapping on CT images. When PET images

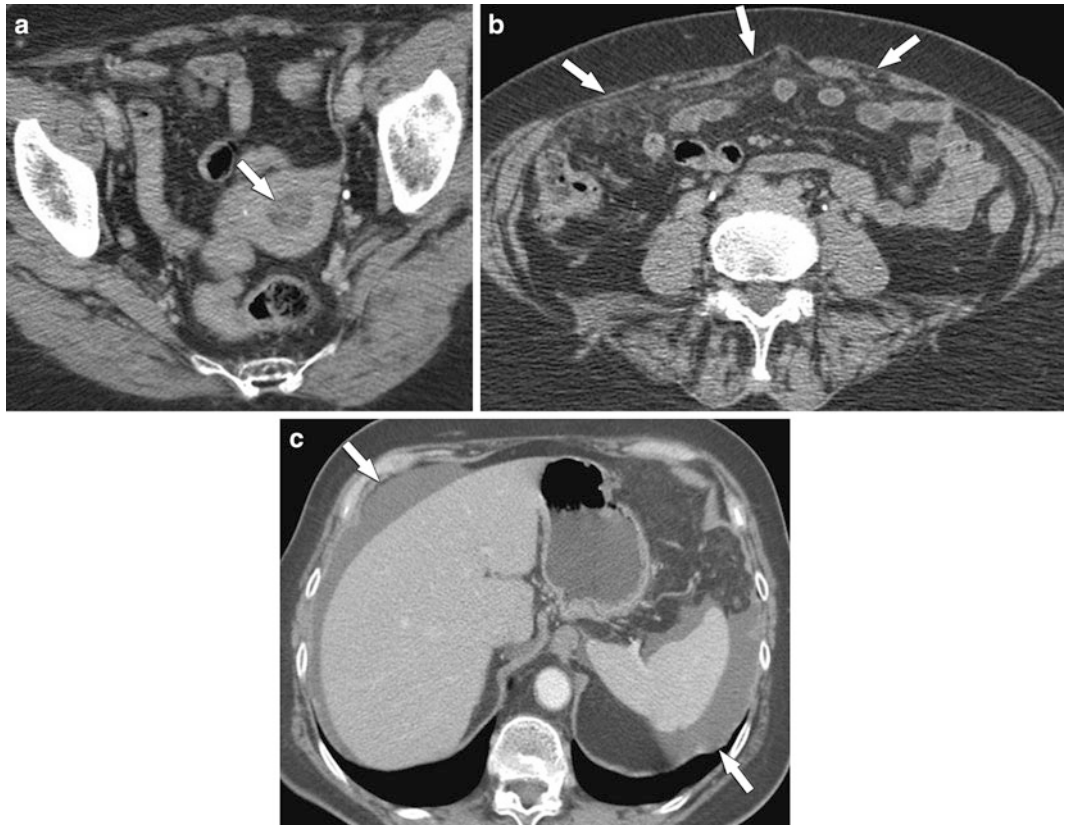

Fig. 10 Computed tomography (CT) of advanced endometrial cancer. Axial contrast-enhanced image through the pelvis (**a**) demonstrates an enhancing mass (*arrow*) enlarging the endometrial cavity. Image through the mid-abdomen above the iliac crests (**b**) reveals omental carcinomatosis (*arrows*). Image of the upper abdomen at the level of the liver (**c**) shows ascites (*arrows*). Pathologic evaluation demonstrated a clear cell endometrial cancer

are interpreted in the absence of a concurrent diagnostic CT, physiologic tracer activity can be mistaken for pathology, resulting in false positive (Fig. 11), and tumor can be misinterpreted as normal physiologic activity, resulting in false negative [48, 49]. Finally small metastases below the threshold of resolution of PET (approximately <8 mm) such as peritoneal carcinomatosis are missed if only PET images are evaluated.

Cancer Detection

Most endometrial cancers are abnormally hypermetabolic on PET-CT; low grade endometrial cancers can demonstrate little to no FDG uptake [50]. Most importantly, nonmalignant endometrium can demonstrate increase tracer avidity and be mistaken for cancer. In premenopausal patients, endometrial evaluation on PET-CT should be correlated with menstrual history, as the endometrium can exhibit FDG uptake during the proliferative phase and menses. In addition, infection (e.g., endometritis) and benign processes (e.g., polyps) can also exhibit tracer avidity [51]. However, in postmenopausal patients, increased endometrial tracer uptake should elicit clinical evaluation and, if appropriate, biopsy to exclude cancer.

Cancer Staging

In patients with known high-grade cancer or suspected extrauterine disease, FDG-PET CT and MRI represent complementary imaging tools for staging. While MRI is the best modality to assess extent of tumor spread in soft tissues of

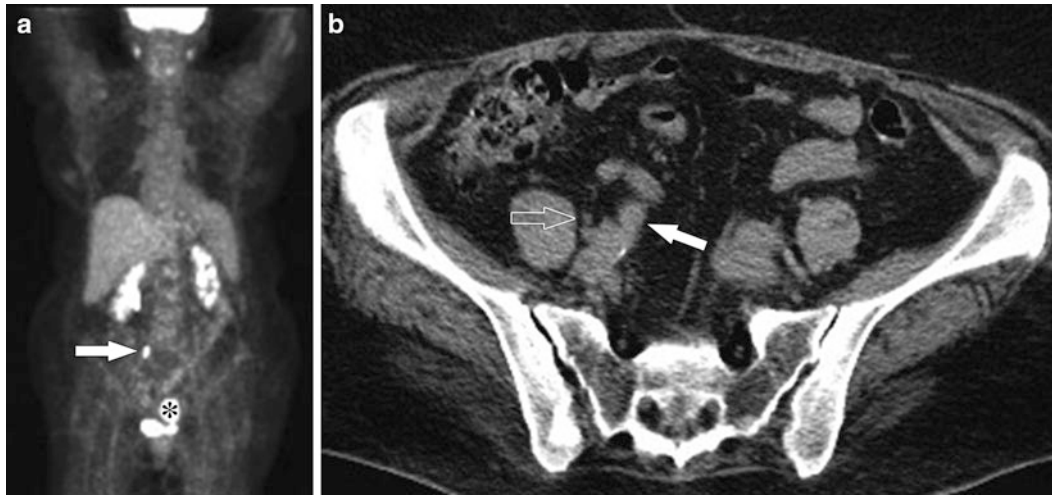

Fig. 11 PET-CT without diagnostic CT resulting in false positive lymphadenopathy. Coronal PET image demonstrates FDG avid uterine tumor (*asterisk*) and a right pelvic focus of tracer (*arrow*) interpreted as a lymphadenopathy (**a**). Diagnostic CT performed 5 days later demonstrates a 1.2 × 1.0 cm right common iliac node (*arrow*) thought to correspond to the FDG-avid right pelvic focus located adjacent to the ureter (**b**). Surgical resection of the node, confirmed on postoperative CT (not shown), revealed no tumor. The FDG-avid focus likely represented urine in the ureter

the central pelvis, PET-CT is preferred to assess for lymphadenopathy and distant metastases [52].

PET-CT demonstrates 74–77 % sensitivity and 93–100 % specificity in the detection of lymphadenopathy from endometrial cancer [40, 53]. PET-CT allows for the detection of tumor involvement in lymph nodes that measure <1 cm in short axis, i.e., the size threshold for morphologic assessment of lymphadenopathy (Fig. 12). Thus, in lymph node evaluation, PET-CT demonstrates increased sensitivity when compared to CT or MRI without loss of specificity. Detection of FDG-avid nodes allows for surgical planning and histologic confirmation. Nevertheless, because PET-CT is still suboptimal to detect micrometastases, staging lymphadenectomy is performed in patients with primary tumors with high-risk features even when PET-CT is negative.

In patients with high-grade histology, PET-CT is the most accurate imaging test to determine the complete extent of tumor spread. It images the whole body and detects lymph node and osseous metastases with greater sensitivity than CT. Thus, it is the preferred exam to evaluate stage IV disease that would triage a patient away from the unnecessary morbidity of a large-scale staging operation [54].

Imaging Post-primary Therapy

Most patients are cured following primary treatment. However, 20–25 % of patients develop recurrence, usually within the first 3 years. Most common sites are lymph nodes and vagina. Recommended algorithms for postoperative surveillance include clinical history, pelvic examination, and vaginal cytology. However, detection of recurrence based on clinical and laboratory findings is suboptimal as 20 % of patients present with asymptomatic metastases [55]. Hence, imaging is used as an adjunct to evaluate for clinically occult recurrence.

FDG-PET CT is the preferred modality to evaluate recurrence post-therapy. Whole-body PET or integrated PET-CT demonstrate 92–93 % sensitivity and 93–100 % specificity in detecting recurrent disease [56, 57]. A study measuring the added value of FDG-PET in addition to CT or MRI for

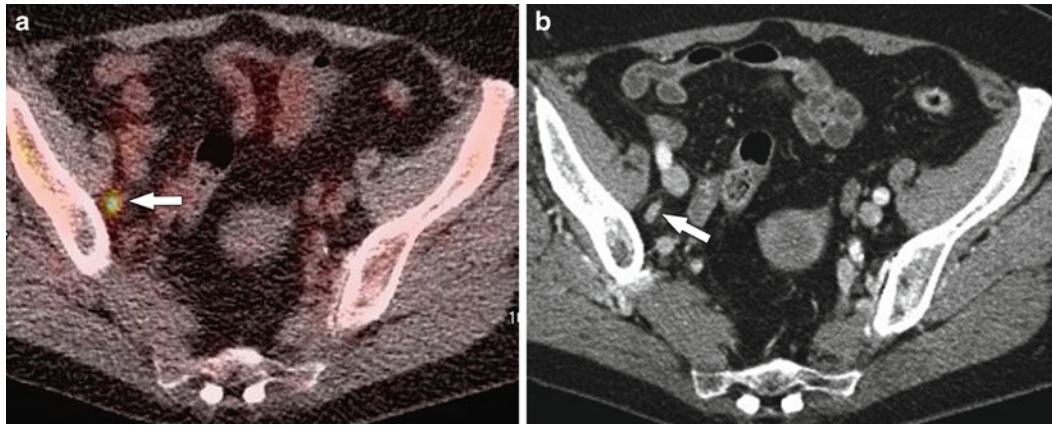

Fig. 12 Fusion PET-CT of endometrial cancer detecting lymphadenopathy. Fusion FDG-PET image (**a**) of a patient with endometrial cancer demonstrates abnormal tracer uptake (*arrow*) in the right pelvic sidewall which on concurrent diagnostic CT (**b**) corresponds to a 1.0 × 0.9 cm right obturator (*arrow*) node. Tumor involvement of the node was confirmed with surgical resection and pathologic evaluation

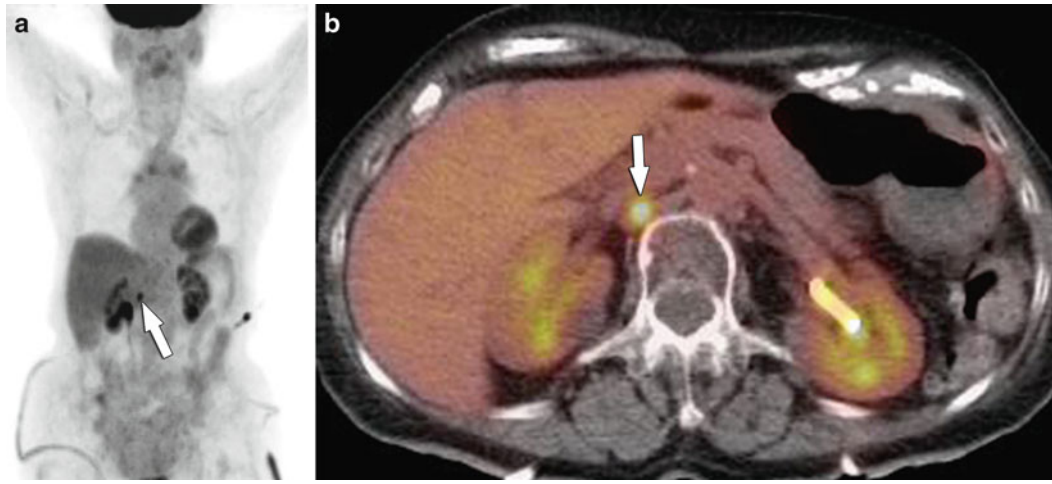

Fig. 13 Fusion PET-CT detecting endometrial cancer recurrence. Coronal FDG-PET image (**a**) of a patient with a history of Grade 2 endometrial cancer and primary therapy 1 year ago demonstrates a focus of abnormal tracer uptake (*arrow*) medial to the right kidney. Fusion PET-CT image (**b**) reveals a corresponding 1.0 × 0.8 cm retrocaval node which was not identified as abnormal on a standard CT examination 7 days before. Tumor involvement of the node was confirmed with a biopsy

post-therapy surveillance found that FDG-PET had better diagnostic performance (accuracy 93.3 %) compared to combined conventional imaging (accuracy 85 %) and tumor markers (accuracy 83.3 %) [57] (Fig. 13). Additionally, as PET-CT affords whole-body evaluation of metastases, it serves to identify patients who would not be candidates for loco-regional therapy. In patients with recurrent tumor confined to the pelvis, MRI is used to plan salvage surgery or radiotherapy.

Conclusions

- In detecting endometrial cancer, TVUS has a well-defined role in the evaluation of patients presenting with postmenopausal bleeding. It

is recommended as the initial test to select patients for biopsy as it demonstrates a high negative predictive value.
- Once the diagnosis of endometrial cancer is confirmed, MRI is the best modality to delineate the intrauterine tumor and its spread into adjacent pelvic organs.
- In patients with suspected extrauterine disease, integrated FDG-PET CT is more accurate than MRI or CT to detect lymph node, intraperitoneal, thoracic, and bony metastases.
- Optimal test performance for PET-CT requires that diagnostic quality CT images be acquired concurrently with the PET scan.
- Following treatment, PET-CT is the most accurate modality to assess for recurrence.

References

1. Fleischer AC, Kalemeris GC, Machin JE, Entman SS, James AE Jr (1986) Sonographic depiction of normal and abnormal endometrium with histopathologic correlation. J Ultrasound Med 5:445–452
2. Fleischer AC, Mendelson EB, Bohm-Velez M, Entman SS (1988) Transvaginal and transabdominal sonography of the endometrium. Semin Ultrasound CT MR 9:81–101
3. Johnson MA, Graham MF, Cooperberg PL (1982) Abnormal endometrial echoes: sonographic spectrum of endometrial pathology. J Ultrasound Med 1:161–166
4. Mendelson EB, Bohm-Velez M, Neiman HL, Russo J (1988) Transvaginal sonography in gynecologic imaging. Semin Ultrasound CT MR 9:102–121
5. Guy RL, King E, Ayers AB (1988) The role of transvaginal ultrasound in the assessment of the female pelvis. Clin Radiol 39:669–672
6. Coleman BG, Arger PH, Grumbach K et al (1988) Transvaginal and transabdominal sonography: prospective comparison. Radiology 168:639–643
7. Smith-Bindman R, Kerlikowske K, Feldstein VA et al (1998) Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA 280:1510–1517
8. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK (2002) Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG 109:313–321
9. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS (2002) Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA 288:1610–1621
10. Dubinsky TJ, Stroehlein K, Abu-Ghazzeh Y, Parvey HR, Maklad N (1999) Prediction of benign and malignant endometrial disease: hysterosonographic-pathologic correlation. Radiology 210:393–397
11. Sheth S, Hamper UM, Kurman RJ (1993) Thickened endometrium in the postmenopausal woman: sonographic-pathologic correlation. Radiology 187:135–139
12. Phillip H, Dacosta V, Fletcher H, Kulkarni S, Reid M (2004) Correlation between transvaginal ultrasound measured endometrial thickness and histopathological findings in Afro-Caribbean Jamaican women with postmenopausal bleeding. J Obstet Gynaecol 24:568–572
13. Critchley HO, Warner P, Lee AJ, Brechin S, Guise J, Graham B (2004) Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status. Health Technol Assess 8:iii–iv
14. Affinito P, Palomba S, Pellicano M et al (1998) Ultrasonographic measurement of endometrial thickness during hormonal replacement therapy in postmenopausal women. Ultrasound Obstet Gynecol 11:343–346
15. Weaver J, McHugo JM, Clark TJ (2005) Accuracy of transvaginal ultrasound in diagnosing endometrial pathology in women with post-menopausal bleeding on tamoxifen. Br J Radiol 78:394–397
16. Weigel M, Friese K, Strittmatter HJ, Melchert F (1995) Measuring the thickness is that all we have to do for sonographic assessment of endometrium in postmenopausal women? Ultrasound Obstet Gynecol 6:97–102
17. Pecorelli S (2009) Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105:103–104
18. Gordon AN, Fleischer AC, Reed GW (1990) Depth of myometrial invasion in endometrial cancer: preoperative assessment by transvaginal ultrasonography. Gynecol Oncol 39:321–327
19. Artner A, Bosze P, Gonda G (1994) The value of ultrasound in preoperative assessment of the myometrial and cervical invasion in endometrial carcinoma. Gynecol Oncol 54:147–151
20. DelMaschio A, Vanzulli A, Sironi S et al (1993) Estimating the depth of myometrial involvement by endometrial carcinoma: efficacy of transvaginal sonography vs MR imaging. AJR Am J Roentgenol 160:533–538
21. Yamashita Y, Mizutani H, Torashima M et al (1993) Assessment of myometrial invasion by endometrial carcinoma: transvaginal sonography vs contrast-enhanced MR imaging. AJR Am J Roentgenol 161:595–599
22. Sawicki W, Spiewankiewicz B, Stelmachow J, Cendrowski K (2003) The value of ultrasonography in preoperative assessment of selected prognostic factors in endometrial cancer. Eur J Gynaecol Oncol 24:293–298

23. Gruessner SE (2004) Intrauterine versus transvaginal sonography for benign and malignant disorders of the female reproductive tract. Ultrasound Obstet Gynecol 23:382–387
24. Davis PC, O'Neill MJ, Yoder IC, Lee SI, Mueller PR (2002) Sonohysterographic findings of endometrial and subendometrial conditions. Radiographics 22:803–816
25. Bree RL, Bowerman RA, Bohm-Velez M et al (2000) US evaluation of the uterus in patients with postmenopausal bleeding: a positive effect on diagnostic decision making. Radiology 216:260–264
26. Reinhold C, Khalili I (2002) Postmenopausal bleeding: value of imaging. Radiol Clin North Am 40:527–562
27. Kinkel K, Kaji Y, Yu KK, Segal MR, Lu Y, Powell CB, Hricak H (1999) Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology 212:711–718
28. Lin G, Ng KK, Chang CJ et al (2009) Myometrial invasion in endometrial cancer: diagnostic accuracy of diffusion-weighted 3.0-T MR imaging–initial experience. Radiology 250:784–792
29. Lin G, Ho KC, Wang JJ et al (2008) Detection of lymph node metastasis in cervical and uterine cancers by diffusion-weighted magnetic resonance imaging at 3T. J Magn Reson Imaging 28:128–135
30. Hricak H, Stern JL, Fisher MR, Shapeero LG, Winkler ML, Lacey CG (1987) Endometrial carcinoma staging by MR imaging. Radiology 162:297–305
31. Mariani A, Dowdy SC, Cliby WA et al (2008) Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 109:11–18
32. Duncan KA, Drinkwater KJ, Frost C, Remedios D, Barter S (2012) Staging cancer of the uterus: a national audit of MRI accuracy. Clin Radiol 67:523–530
33. Sironi S, Taccagni G, Garancini P, Belloni C, DelMaschio A (1992) Myometrial invasion by endometrial carcinoma: assessment by MR imaging. AJR Am J Roentgenol 158:565–569
34. Ascher SM, Reinhold C (2002) Imaging of cancer of the endometrium. Radiol Clin North Am 40:563–576
35. Nasi F, Fiocchi F, Pecchi A, Rivasi F, Torricelli P (2005) MRI evaluation of myometrial invasion by endometrial carcinoma. comparison between fast-spin-echo T2W and coronal-FMPSPGR gadolinium-dota-enhanced sequences. Radiol Med (Torino) 110:199–210
36. Ben-Shachar I, Vitellas KM, Cohn DE (2004) The role of MRI in the conservative management of endometrial cancer. Gynecol Oncol 93:233–237
37. Tanaka YO, Nishida M, Tsunoda H, Ichikawa Y, Saida Y, Itai Y (2003) A thickened or indistinct junctional zone on T2-weighted MR images in patients with endometrial carcinoma: pathologic consideration based on microcirculation. Eur Radiol 13:2038–2045
38. Manfredi R, Mirk P, Maresca G et al (2004) Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning. Radiology 231:372–378
39. Jager GJ, Barentsz JO, Oosterhof GO, Witjes JA, Ruijs SJ (1996) Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR imaging with a three-dimensional TI-weighted magnetization-prepared-rapid gradient-echo sequence. AJR Am J Roentgenol 167:1503–1507
40. Antonsen SL, Jensen LN, Loft A et al (2013) MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer—a multicenter prospective comparative study. Gynecol Oncol 128:300–308
41. Selman TJ, Christopher H, Mann CH, Zamora J, Khan KS (2008) A systematic review of tests for lymph node status in primary endometrial cancer. BMC Women's Health 8:8
42. Nakai G, Matsuki M, Inada Y et al (2008) Detection and evaluation of pelvic lymph nodes in patients with gynecologic malignancies using body diffusion-weighted magnetic resonance imaging. J Comput Assist Tomogr 32:764–768
43. Russell AH, Anderson M, Walter J, Kinney W, Smith L, Scudder S (1992) The integration of computed tomography and magnetic resonance imaging in treatment planning for gynecologic cancer. Clin Obstet Gynecol 35:55–72
44. Pete I, Godeny M, Toth E, Rado J, Pete B, Pulay T (2003) Prediction of cervical infiltration in stage II endometrial cancer by different preoperative evaluation techniques (D&C, US, CT, MRI). Eur J Gynaecol Oncol 24:517–522
45. Kim SH, Kim HD, Song YS, Kang SB, Lee HP (1995) Detection of deep myometrial invasion in endometrial carcinoma: comparison of transvaginal ultrasound, CT, and MRI. J Comput Assist Tomogr 19:766–772
46. Zerbe MJ, Bristow R, Grumbine FC, Montz FJ (2000) Inability of preoperative computed tomography scans to accurately predict the extent of myometrial invasion and extracorporeal spread in endometrial cancer. Gynecol Oncol 78:67–70
47. Hardesty LA, Sumkin JH, Hakim C, Johns C, Nath M (2001) The ability of helical CT to preoperatively stage endometrial carcinoma. AJR Am J Roentgenol 176:603–606
48. Prabhakar HB, Kraeft JJ, Schorge JO, et al. (2015) FDG PET-CT of gynecologic cancers: pearls and pitfalls. *Abdominal Imaging* [Epub ahead of print]
49. Gorospe L, Jover-Diaz R, Vicente-Bartulos A (2012) Spectrum of PET-CT pelvic pitfalls in patients with gynecologic malignancies. Abdom Imaging 37 (6):1041–1065
50. Nakamura K, Kodama J, Okumura Y, Hongo A, Kanazawa S, Hiramatsu Y (2010) The SUVmax of

18F-FDG PET correlates with histological grade in endometrial cancer. Int J Gynecol Cancer 20:110–115
51. Liu Y (2009) Benign ovarian and endometrial uptake on FDG PET-CT: patterns and pitfalls. Ann Nucl Med 23:107–112
52. Lee SI, Catalano OA, Dehdashti F (2015) Gynecologic cancer imaging with MRI,FDG PET-CT and PET-MR. *J Nucl Med* [Epub ahead of print]
53. Signorelli M, Guerra L, Buda A et al (2009) Role of the integrated FDG PET/CT in the surgical management of patients with high risk clinical early stage endometrial cancer: detection of pelvic nodal metastases. Gynecol Oncol 115:231–235
54. Picchio M, Mangili G, Samanes Gajate AM et al (2010) High-grade endometrial cancer: value of (18)F)FDG PET/CT in preoperative staging. Nuc Med Commun 31:506–512
55. Berchuck A, Anspach C, Evans AC et al (1995) Post-surgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol 59 (1):20–24
56. Kitajima K, Murakami K, Yamasaki E et al (2008) Performance of FDG-PET/CT in the diagnosis of recurrent endometrial cancer. Ann Nucl Med 22:103–109
57. Sironi S, Picchio M, Landoni C et al (2007) Post-therapy surveillance of patients with uterine cancer: value of integrated FDG PET/CT in the detection of recurrence. Eur J Nucl Med Mol Imaging 34:472–479

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Erratum to: Imaging in the Diagnosis and Treatment of Endometrial Cancer

Jessica J. Kraeft and Susanna I. Lee

Erratum to:
Chapter "Imaging in the Diagnosis and Treatment of Endometrial Cancer" in:
J. J. Kraeft, S. I. Lee, Current Clinical Oncology,
DOI 10.1007/7631_2015_3

Page 1
Abstract: 'recurrence' should be 'recurrences'.
Section "Introduction"
(1st paragraph), 5th line: hyphen missing in 'post-treatment'.

Page 2
Section "**Cancer Detection"**
(First paragraph), 3rd line: Deleted 'because'.

Page 3
Section **"Endometrial Morphology"**
(1st paragraph), 6th line: deleted 'nonfocal'.

Page 4
Section "**Cancer Staging"**
(1st paragraph): Replaced 'because of the' with 'due to'.
(2nd paragraph), 9th line: deleted 'case'.
(3rd paragraph), 9th line: Inserted 'invasion'

The updated online version of this chapter can be found at
https://doi.org/10.1007/7631_2015_3

Page 6
Section "**Sonohysterography"**
(4th paragraph)
5th line: Replaced 'Because' with 'As'. Inserted 'a' after 'demonstrates'
8th line: Replaced 'for' with 'in'.

Page 7
Section "**Magnetic Resonance Imaging"**, last line: '. . .with TVUS or biopsy is precluded.' was replaced with '. . .is precluded with TVUS or biopsy.'

Section **"Technique"** (1st paragraph), 14th line: inserted 'may' after 'cancer'. Changed 'presents' to 'present'.

Section "**Cancer Detection"** (1st paragraph), 6th line: Inserted 'as' after 'appears'.

Page 8
Section "**Cancer Staging"** (1st paragraph):
Throughout this section "MR" has been corrected to "MRI".
1st line: Insert 'The' at beginning of sentence.
3rd line: insert 'patients' after 'those'. Revise 'stage' with 'stages'.
6th line: Delete 'lymph node'
7th line: Replace 'on those' with 'in patients'.
8th line: Replace 'extrauterine metastases' with 'lymph'.
23rd line: Replace 'for' with in'. Replace 'diagnosis' with diagnosing'.
(2nd paragraph), line 1: Replace 'Because' with "As".

Section "**Myometrial Invasion"**: (2nd paragraph)
1st line: Replaced 'are' with 'occur'.
2nd line: Replaced 'to' with 'of'
8th line: Revised 'demonstrates' to 'demonstrate'

Section **"Cervical Invasion"**: (1st paragraph): Delete the last sentence.

(2nd paragraph):
1st line: Replace 'of up to' with 'using MRI are reported to be as high as'.
2nd line: Delete 'reported'. Replace 'because' with 'as'.

Page 9
Fig. 6: In caption 'with surgical pathology' was replaced with 'by pathologic examination'.
Fig.7.: In caption 'with surgical pathology' was replaced with 'by pathologic examination'.

Section "**Extrauterine Spread'**: (1st paragraph), lines 3-4: 'into parametrial fat' was replaced with 'to serosa'.

Page 10
Fig. 8: In caption "with surgical evaluation and' was replace with 'by pathologic examination'.

Page 11
Fig. 9: In caption 'on surgical pathology' was replaced with ' by pathologic examination'.
Section '**Computed Tomography'**: (1st paragraph):
8th line: 'whose' was replaced with 'with a'.

13th line: ‘In detecting lymphadenopathy’ was moved to 14th line after word ‘MRI’.
16th line: ‘for a lymph node to be’ was inserted after the word ‘diameter’.
18th line: ‘detecting’ was inserted before word ‘lymph’.

(2nd paragraph)
10th line: ‘For detecting cervical invasion’ was replaced with ‘in detecting myometrial invasion,’
13th line: ‘in detecting cervical invasion’ was inserted after ‘specifity’.

Page 14
Fig. 12: In caption ‘pathologically’ was deleted. At end of caption ‘and pathologic evaluation’ was inserted.

Section **‘Imaging Post-primary Therapy’**: (1st paragraph), 4th line: ‘for recurrent tumor’ and ‘the’ were deleted.

Section ‘**Conclusion’**: 7th line: ‘made’ was replaced with ‘confirmed’.

Page 15
Fig. 13: In caption ‘pathologically’ was deleted.

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Uterine Cancer: Pathology

Robert A. Soslow and Esther Oliva

Abstract

Endometrioid adenocarcinoma is the most common type of endometrial carcinoma (approximately 85 %). By definition, it should resemble, at least focally, proliferative-type endometrium with tubular glands lined by mitotically active columnar cells. Common problems in diagnosis involve its distinction from complex atypical hyperplasia, endocervical adenocarcinoma, serous carcinoma, clear cell carcinoma, and carcinosarcoma. Pure serous carcinomas comprise about 10 % of endometrial cancers. The term "serous" refers to shared characteristics with cells lining the fallopian tube, particularly the tumor cells' columnar shape, eosinophilic cytoplasm, and tendency to form papillae. However, some serous carcinomas are not papillary but glandular. Importantly, all serous carcinomas exhibit marked nuclear pleomorphism and most demonstrate discrepancies between architectural differentiation and cytologic features. Clear cell carcinoma is the third most common endometrial carcinoma subtype, even though it represents <5 % of all endometrial cancers. Epidemiologic characteristics of patients with clear cell carcinoma are obscure because of this tumor's rarity, difficulties in diagnostic reproducibility, and accumulating evidence that there are perhaps several subtypes of clear cell carcinoma. Most clear cell carcinomas are composed of cells

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R.A. Soslow
Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

E. Oliva (✉)
Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Professor of Pathology, Harvard Medical School, Boston, MA, USA
e-mail: eoliva@mgh.harvard.edu

with clear cytoplasm, but this feature is not restricted to clear cell carcinoma and some clear cell carcinomas contain cells with eosinophilic cytoplasm. Other subtypes of endometrial carcinoma are rare and include squamous, transitional, small cell, undifferentiated/dedifferentiated, and mixed cell types. Among pure mesenchymal tumors of the uterus, leiomyosarcoma is the most common. Microscopic criteria to establish the diagnosis of leiomyosarcoma include the combination of two of the following: cytologic atypia, mitotic activity, and tumor cell necrosis. The threshold for mitotic activity varies for spindled, epithelioid, and myxoid subtypes and a variety of uterine tumors enter in the differential diagnosis, including several variants of leiomyoma (mitotically active, apoplectic, with bizarre nuclei, highly cellular, and hydropic). Low-grade endometrial stromal sarcomas are composed of a homogenous population of small cells with scant cytoplasm resembling proliferative-type endometrial stroma. They show a diffuse growth and infiltrate the uterine wall in a permeative (not destructive) fashion and may have prominent intravascular growth. High-grade endometrial stromal sarcomas do not resemble proliferative stroma, are composed of small rounds cells with brisk mitotic activity and are more aggressive than low-grade tumors. Undifferentiated uterine sarcoma is a very poorly differentiated sarcoma and a diagnosis of exclusion. Carcinosarcomas (malignant mixed müllerian tumors) are biphasic tumors typically composed of highly malignant epithelial and stromal/mesenchymal elements. The histogenesis of these tumors has evolved in recent years and it is now accepted that they either arise from a common pluripotential cell with divergent differentiation or that the sarcomatous component develops from the carcinomatous component by a metaplastic process. Other rare low-grade or clinically aggressive mesenchymal tumors include: (1) low-grade müllerian adenosarcoma (composed of benign-appearing glands and malignant stroma); (2) PEComa, which is composed of epithelioid cells that are typically positive for HMB-45 and may be associated with tuberous sclerosis; and (3) intravenous leiomyomatosis which shows a proliferation of smooth muscle cells within vascular spaces. Even though the latter smooth muscle proliferation is considered benign it can behave aggressively from the clinical point of view.

Keywords

Endometrioid • Serous • Clear cell • Mixed carcinomas • Leiomyosarcoma • Endometrial stromal sarcoma • Carcinosarcoma • Low-grade müllerian adenosarcoma • PEComa • Intravenous leiomyomatosis

Endometrial Carcinoma and Precursor Lesions

Endometrioid Carcinoma

Endometrioid adenocarcinoma is the most common type of endometrial carcinoma (~85 %). They are considered type I endometrial cancers according to the Bokhman classification [1] because of their epidemiologic association with estrogen excess. Recent work indicates that low-grade endometrioid carcinomas segregate into three subcategories, defined by the number of mutations [2]. Slightly more than one-half of

these tumors have low numbers of mutations, mostly restricted to the PTEN/PI3K pathway. These are probably the prototypical type I carcinomas. The remaining low-grade tumors are either microsatellite instability-high, with high numbers of additional mutations, or have mutations in the hotspot region of *POLE*, leading to enormous numbers of additional mutations. High-grade endometrioid carcinomas segregate not only into these groups, but also into a serous-like group, characterized by extensive DNA insertions and deletions and *TP53* mutations. This signifies that some high-grade endometrioid carcinomas are more akin to Bokhman type II than to type I tumors [3]. The current model of estrogen-dependent endometrial carcinogenesis involves progression from hyperplasia with increasing degrees of architectural and cytologic atypia (complex atypical hyperplasia). The development of an invasive neoplasm heralds the emergence of "adenocarcinoma" in this context.

Gross Features

The typical endometrioid adenocarcinoma forms a grossly visible mass that protrudes into the endometrial cavity or causes a diffuse thickening of the endometrial stripe, making it difficult to appreciate a dominant mass. Most tumors arise in the fundus; less commonly, they are found in one of the cornua or in the lower uterine segment, and in some cases, the lesion is centered in an endometrial polyp. Endometrioid adenocarcinomas are usually tan in color and soft in consistency. A good gross description will include an estimate of the depth of invasion into the myometrium as well as involvement of the cervix, uterine serosa, fallopian tubes, or ovaries. The latter three tissues may be involved by direct extension or metastasis.

Histologic Features

Endometrioid adenocarcinomas by definition should resemble, at least focally, proliferative-type endometrium showing tubular glands with smooth luminal surfaces, lined by mitotically active columnar cells (Fig. 1). Based on the degree of glandular differentiation, these tumors are divided into three Federation International Gynecologic Oncologists (FIGO) categories: grade 1 shows $\leq$5 % of solid non-glandular growth (Figs. 1, 2, 3, and 4), grade 2 is defined by finding between 6 and 50 % of solid non-glandular growth, and grade 3 contains $>$50 % of solid growth (Fig. 5). The presence of marked cytologic atypia increases the grade by one. Solid components showing overt squamous differentiation are not counted as "solid" for the purposes of tumor grading. Several binary

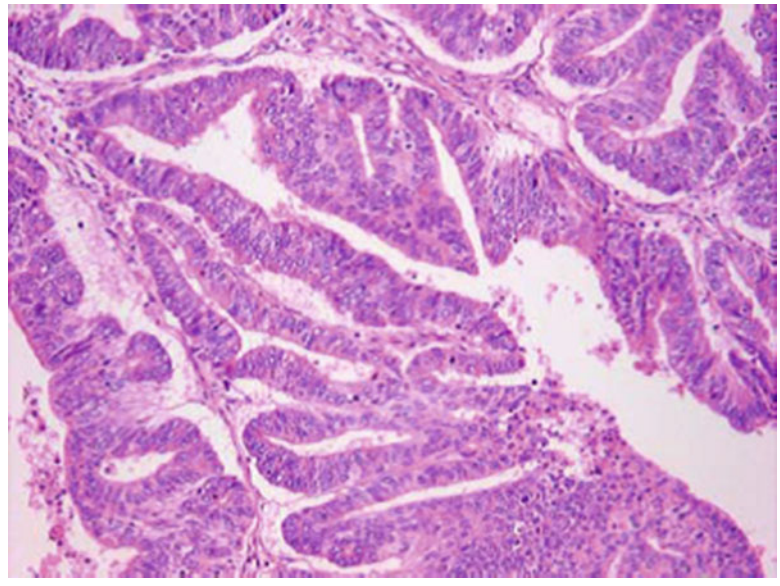

Fig. 1 Endometrioid adenocarcinoma. This typical well-differentiated adenocarcinoma (FIGO grade 1) is composed of well-formed endometrioid glands

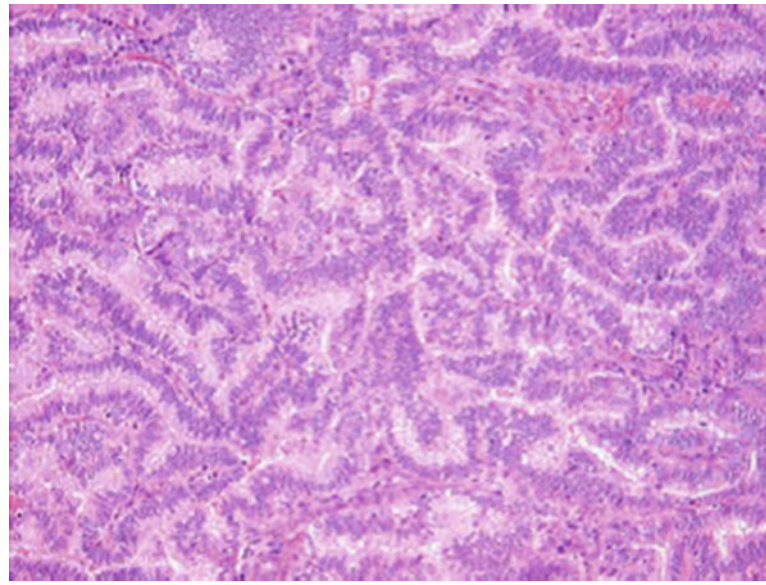

Fig. 2 Endometrioid adenocarcinoma. This well-differentiated adenocarcinoma (FIGO grade 1) features a highly complex proliferation of fused and branched glands that excludes endometrial stroma

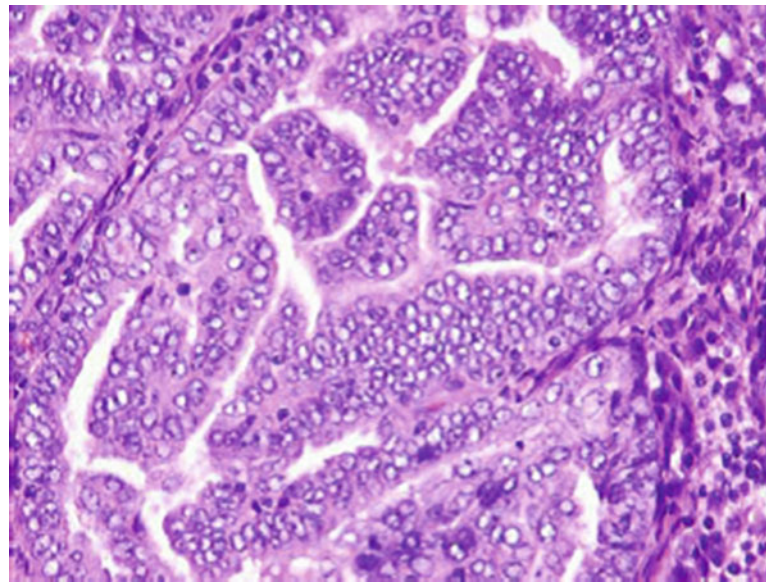

Fig. 3 Endometrioid adenocarcinoma, well differentiated (FIGO grade 1), displaying papillary architecture. Note the smooth luminal contours and low-grade cytologic appearance of the tumor cells

grading schemes have been proposed in an effort to improve interobserver variability in grade assignment, but none is currently in routine use [4–6]. Histologic features considered typical of endometrioid carcinoma include keratinizing squamous metaplasia or morular metaplasia (nonkeratinizing). Additional features commonly encountered in both nonneoplastic and neoplastic endometrium include tubal and/or mucinous metaplasia, and secretory/clear cell change (with subnuclear or supranuclear cytoplasmic vacuoles) (Fig. 4).

There are three typical endometrioid growth patterns that on occasion elicit concern for serous carcinoma or carcinosarcoma. Villoglandular architecture is typified by long and thin, finger-like papillae lined by cells with cytologically low-grade nuclei. Endometrioid carcinomas

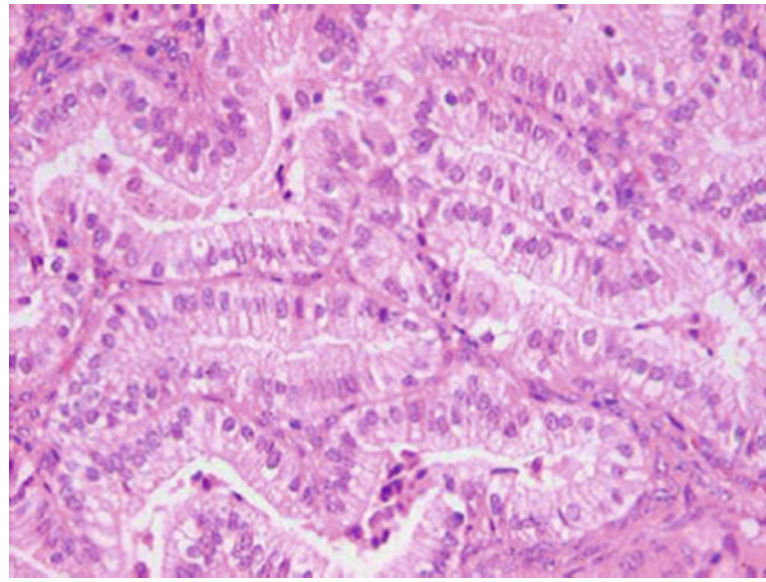

Fig. 4 Endometrioid adenocarcinoma, well differentiated (FIGO grade 1), displaying secretory changes (cytoplasmic clearing). Note the absence of hobnail change and the low-grade cytologic appearance of the tumor cells

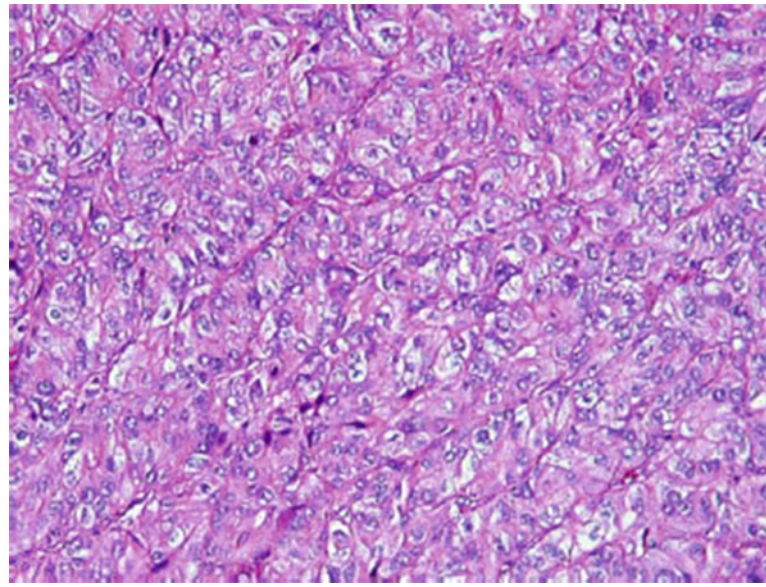

Fig. 5 Endometrioid adenocarcinoma, poorly differentiated (FIGO grade 3). In contrast to FIGO grade 1 tumors, these neoplasms are predominantly solid

with "small non-villous" papillae demonstrate typical endometrioid cytomorphology along with small papillae [7]. Last, the corded and hyalinized variant of endometrioid carcinoma "CHEC pattern" [8] displays corded growth and hyalinized stroma at a minimum, but many examples also show cytologically bland spindle cell proliferations, sex cord-like growth, and chondroid or osseous metaplasia lacking atypia.

Endometrioid adenocarcinomas display different patterns of myometrial invasion, some of which appear to have prognostic significance. Standard myometrial invasion is manifested by irregular infiltration of myometrium with a surrounding desmoplastic response. Less commonly encountered patterns include "pushing" [9], "adenoma malignum" [10], and "microcystic elongated and fragmented" (MELF) [11]. The

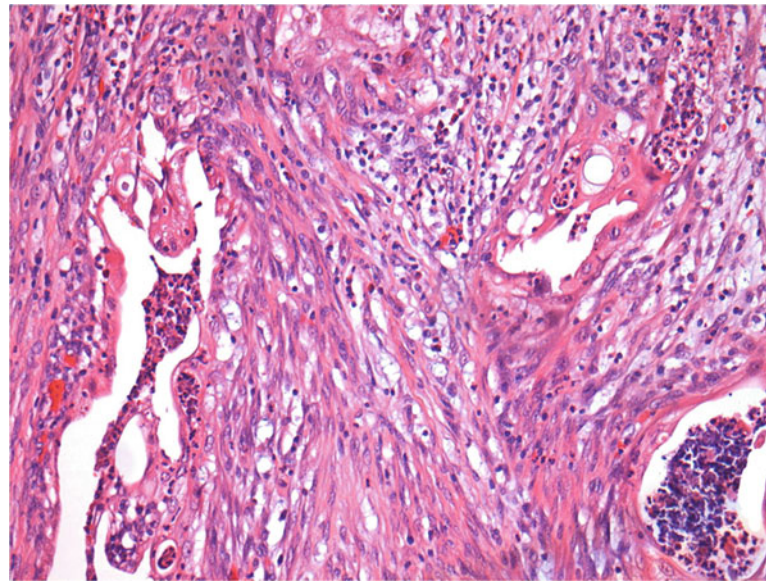

Fig. 6 Endometrioid carcinoma with MELF pattern of invasion with elongated and fragmented glands associated with fibromyxoid stromal response and abundant acute inflammatory infiltrate

pushing pattern demonstrates extension into myometrium over a broad front without irregular infiltration. The pattern is recognized as invasive only when a stromal reaction is found at the advancing invasive edge. The adenoma malignum pattern shows myometrial infiltration by well-formed glands lacking a stromal response. It is distinguished from adenomyosis by its diffuse infiltration and lack of endometrial stroma. MELF pattern of invasion is characterized by microcystic and elongate invasive glands, frequently showing squamous metaplasia with attenuation of epithelium lining the microcysts. Single neoplastic cells can be found adjacent to these foci, leading to the impression of gland fragmentation. Single and clustered neoplastic cells may be found in the microcysts' lumens, leading to the erroneous impression of lymphovascular invasion. Probably most striking about MELF invasion is the almost invariable presence of an exaggerated fibromyxoid and fibroinflammatory stromal reaction surrounding the invasive foci. MELF invasion is treacherous because it may be discontinuous with the endomyometrial junction and present deep in myometrium. MELF pattern invasion is statistically associated with the presence of lymphovascular invasion (Fig. 6).

Differential Diagnosis

The differential diagnosis of uterine endometrioid adenocarcinoma includes other uterine carcinomas such as serous and clear cell carcinomas. Strategies for distinguishing between these entities are summarized in Table 1. Other common problems in diagnosis involve the distinction of complex atypical hyperplasia from endometrioid adenocarcinoma (Table 2), endocervical from endometrial adenocarcinoma (Table 3), and carcinosarcoma from endometrioid adenocarcinoma, which will be discussed subsequently in this chapter.

Since complex atypical hyperplasia and well-differentiated (FIGO grade 1) endometrial endometrioid carcinoma are both differentiated neoplasms, endometrioid tubular glands generally predominate in both. Conceptually, hyperplasia is separated from adenocarcinoma by the absence of endometrial stromal invasion (Fig. 7) [12–14]. Squamous metaplasia may be seen in both (Fig. 8). In practice, the presence of extensive confluent papillary growth, macroglands, and cribriform architecture is sufficient to categorize a lesion as adenocarcinoma [12–14]. Marked cytologic atypia also disqualifies the diagnosis of hyperplasia

Table 1 Histologic and immunohistochemical summary useful in the differential diagnosis of endometrial carcinoma subtypes

Endometrioid adenocarcinoma:
Endometrial hyperplasia
Squamous, morular, mucinous metaplasia
Smooth luminal contours
ER, PR, vimentin positive; p53, p16, CEA negative (FIGO grades 1 and 2)
Serous carcinoma:
No squamous, morular, mucinous metaplasia
Jagged luminal contours
Slit-like spaces
Cytologic pleomorphism
p53 overexpression, p16 and vimentin positive; ER, PR, CEA negative or weakly positive
Clear cell carcinoma:
Hobnail cells
Hyaline stroma
Classic growth patterns
Vimentin positive; ER, PR, CEA negative or weakly positive; variable p16, p53, napsin A, and hepatocyte nuclear factor-1 beta positivity

Table 2 Features favoring adenocarcinoma over complex atypical hyperplasia

Extensive papillary architecture
Extensive gland fusion with exclusion of endometrial stroma
Extensive macroglands with internal complexity and exclusion of endometrial stroma
Marked cytologic atypia

Table 3 Endometrioid endometrial adenocarcinoma versus endocervical adenocarcinoma[a]

Endometrial adenocarcinoma:
Postmenopausal patient
Imaging and clinical examination favor corpus primary
More tissue in endometrial than in endocervical curettage
Endometrial hyperplasia
Stromal foam cells
Squamous metaplasia
Expression of ER, PR, and vimentin
Endocervical adenocarcinoma:
Pre- or perimenopausal patient
Imaging and clinical examination favor cervical primary
History of abnormal pap smears
More tissue in endocervical than in endometrial curettage
Endocervical adenocarcinoma in situ or squamous dysplasia
Large, elongated, pseudostratified darkly stained nuclei
Abundant mitotic activity, including forms toward the apical portion of the cells
Abundant apoptotic bodies
Diffuse expression of CEA and p16

[a]The phenotypes described pertain only to FIGO grades 1 and 2 endometrioid adenocarcinoma and endocervical adenocarcinoma of the usual type. These guidelines do *not* pertain to high-grade endometrial carcinomas (FIGO grade 3 endometrioid, serous, and clear cell) and unusual types of endocervical adenocarcinomas (adenoma malignum, intestinal mucinous, clear cell, mesonephric, and serous carcinoma)

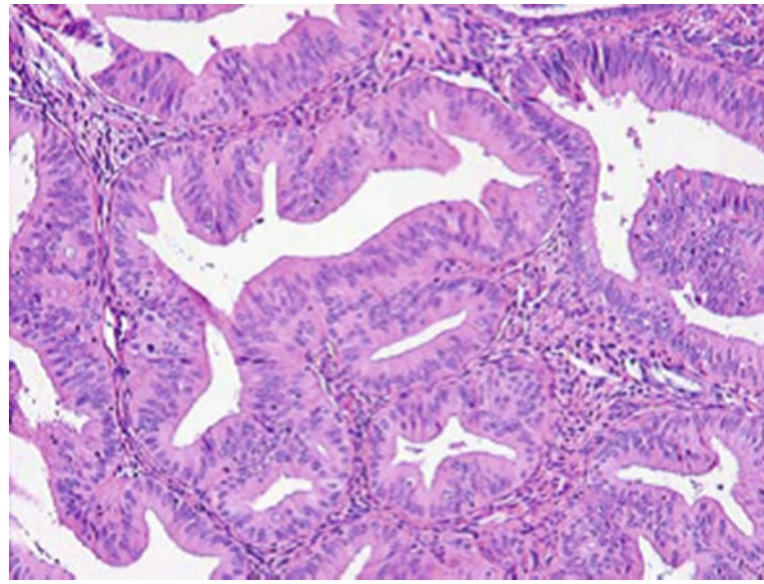

Fig. 7 Complex atypical hyperplasia. Note the preserved endometrial stroma between abnormal endometrioid glands

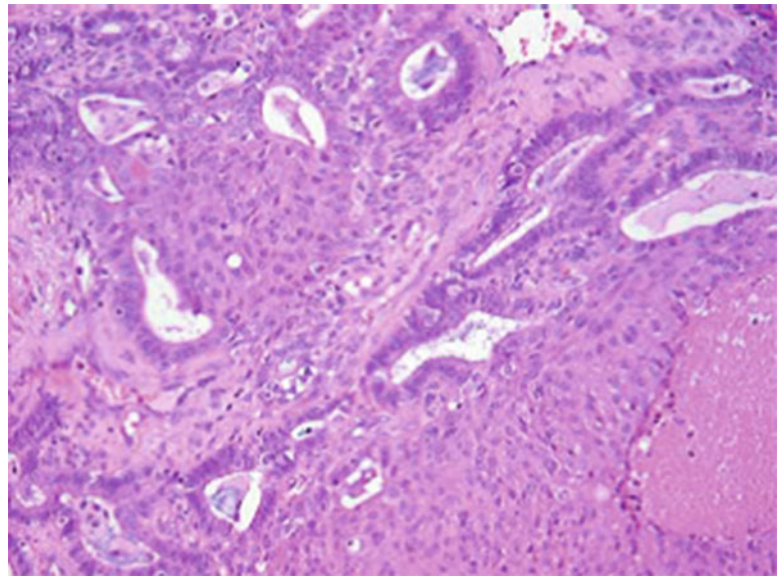

Fig. 8 Complex atypical hyperplasia exhibiting squamous metaplasia. Squamous metaplasia is typical of neoplastic endometrioid proliferations, either hyperplasia or carcinoma

[13]. Another challenge concerns the differential diagnosis with endocervical adenocarcinoma. The latter may demonstrate features that resemble those of endometrial endometrioid adenocarcinoma, but there are usually subtle histologic differences. Clinical presentation, precursor lesions (endocervical adenocarcinoma in situ versus endometrial hyperplasia), and immunophenotype differ and can be used to establish the correct diagnosis (Table 3).

Related Carcinomas

As mentioned earlier, endometrioid adenocarcinomas can demonstrate mucinous differentiation and can contain ciliated cells and cells with secretory features. When mucinous differentiation predominates (intracytoplasmic but not luminal mucin; present in >50 % of cells), the tumor is referred to as "mucinous carcinoma" [15, 16]. Likewise, "ciliated carcinoma" [17] and "secretory carcinoma" [18] have been described but are rare. Endometrioid adenocarcinomas may also feature papillary architecture. The tumor is referred to as "villoglandular carcinoma" [19] when the papillae are long, slender with delicate fibrovascular cores, and lined by pseudostratified columnar cells perpendicular to the basement membrane. Other findings that can be seen in endometrioid adenocarcinomas include psammomatous calcifications [20], cells with clear cytoplasm, spindled cells, trabeculae resembling sex cord ovarian tumors, hyalinized and myxoid stroma, and, exceptionally, heterologous elements [8] such as osteoid and lobules of cartilage.

Immunophenotype

The immunophenotype of endometrioid carcinoma tends to vary with degrees and types of differentiation. In general, endometrioid adenocarcinomas coexpress pan-cytokeratin and vimentin [21, 22] and they rarely show diffuse cytoplasmic staining with carcinoembryonic antigen (CEA) [23–25]. Almost all endometrioid neoplasms express CK7 and are largely negative for CK20 [26, 27]. Other commonly expressed antigens include CA125 [28], BerEP4 [29], and B72.3 [30]. The expression of estrogen and progesterone receptors (ER, PR) is ubiquitous among FIGO grade 1 adenocarcinomas, but this feature is present in <50 % of FIGO grade 3 tumors [31, 32]. Overexpression of p53 (expression in >50–75 % of nuclei) is seen in about one-third of FIGO grade 3 adenocarcinomas, but almost never in FIGO grade 1 tumors [33, 34].

The expression of p16 also tends to accumulate with increasing histological grade [31]. High-molecular-weight cytokeratins, p63, and nuclear β-catenin are preferentially expressed in areas demonstrating squamous differentiation [35, 36].

Serous Carcinoma

Pure serous carcinomas comprise about 10 % of endometrial cancers. They are epidemiologically, biologically, histologically, and clinically distinct. The mean age of women with serous carcinoma is approximately one decade older than those with endometrioid adenocarcinoma. Instead of being related to hyperestrinism, serous carcinomas arise in the setting of atrophy and, as such, correspond to Bokhman's type II endometrial cancers [1]. Other associations with serous carcinoma include a personal history of breast cancer [37, 38], treatment with tamoxifen [39, 40], and pelvic radiation therapy [41, 42]. Serous carcinomas are aggressive neoplasms that have a tendency to present at high stage [43, 44].

Gross Features

Uteri harboring serous carcinomas tend to be small and lack the endometrial thickening that is more characteristic of endometrioid adenocarcinomas. Instead, many serous carcinoma uteri contain endometrial polyps. When carcinomas are confined to the polyp, the tumor itself may not be grossly apparent. More advanced tumors frequently demonstrate obvious myometrial permeation and either extension or metastasis to tissues included in the resection. Uterine serous carcinomas have a predilection for peritoneal dissemination as seen in their ovarian counterpart.

Histologic Features

The term "serous" refers to shared characteristics with cells lining the fallopian tube, particularly the tumor cells' columnar shape, eosinophilic cytoplasm, and tendency to form papillae (Fig. 9). However, not all serous carcinomas are papillary and not all papillary carcinomas are serous. Essentially, all serous carcinomas exhibit marked nuclear pleomorphism and most demonstrate discrepancies between architectural differentiation and cytologic features. Serous carcinoma cells have high nuclear to cytoplasmic ratio with enlarged nuclei that tend to be irregularly shaped. They may be hyperchromatic or contain large, red macronucleoli (Fig. 10). Brisk mitotic activity and atypical mitoses are

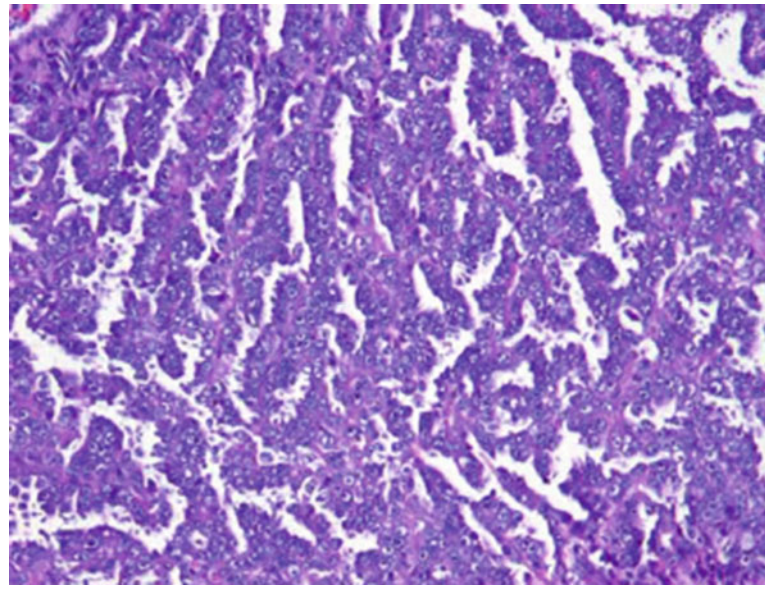

Fig. 9 Serous carcinoma. Typical low-power appearance demonstrating papillary architecture and slit-like spaces

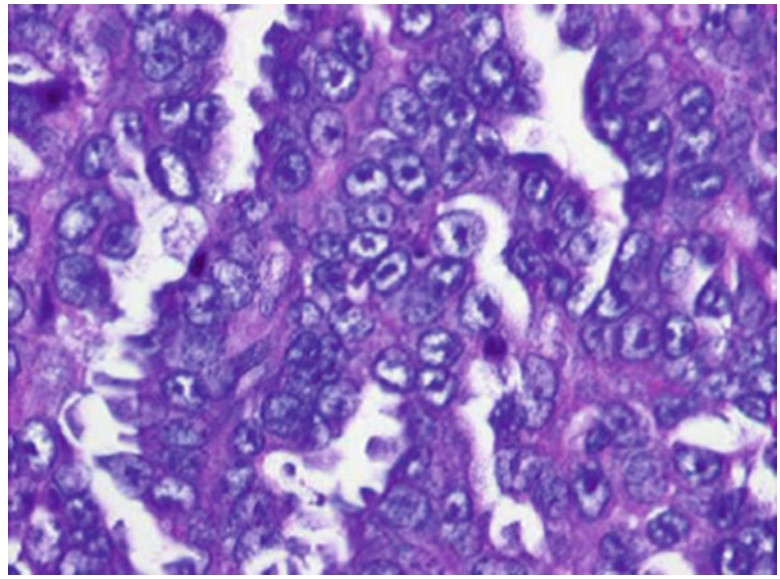

Fig. 10 Serous carcinoma. This high power shows the ragged luminal profiles and highly atypical nuclei

common. In contrast to endometrioid carcinoma, the luminal surfaces are irregular and jagged (Fig. 9), and the cells are less cohesive with frequent cellular tufting, and detached small cell aggregates. Unlike endometrioid adenocarcinomas, serous carcinomas do not show squamous or mucinous metaplasia, or ciliated cells.

The earliest serous carcinoma may consist solely of neoplastic epithelium colonizing preexisting atrophic endometrium, particularly on the surface of endometrial polyps [45, 46]. This has been referred to as intraepithelial serous carcinoma or endometrial intraepithelial carcinoma [45, 46]. Importantly, intraepithelial serous carcinoma can metastasize despite the absence of myometrial invasion. At low power, these minimal carcinomas appear hyperchromatic and display abrupt transition with the nonneoplastic epithelium. Serous carcinomas may be difficult to diagnose when they replace preexisting atrophic endometrial glands and papillary architecture is not apparent [47]. Correct classification as serous carcinoma centers on appreciation of the cytologic features, jagged luminal profiles, absence of confirmatory endometrioid characteristics (including squamous and mucinous metaplasia), and background atrophy. Architectural patterns encountered in established serous carcinomas include papillae, tubular glands, slit-like glands, and solid nests and sheets. Since these patterns are not specific for serous carcinoma, attention directed to the cytologic characteristics is essential to make the correct diagnosis.

Immunophenotype

Like endometrioid adenocarcinomas, serous carcinomas coexpress pan-cytokeratins and vimentin and rarely express diffuse cytoplasmic CEA. They also are positive for CK7, CA125, BerEP4, and B72.3 and are largely negative for CK20. The expression of ER and PR is less common than in endometrioid adenocarcinomas and is found in <50 % of tumors [31, 32, 48]. Overexpression of p53 (>50–75 % of nuclei) is seen in nearly 90 % of serous carcinomas and is related to the near-universal presence of *p53* mutations [34, 49], while p16 expression is also very common [31].

Clear Cell Carcinoma

This subtype of endometrial carcinoma is the third most common, even though it represents <5 % of all carcinomas at this site. The epidemiologic characteristics of patients with clear cell

carcinoma are obscure because of this tumor's rarity, difficulties in diagnostic reproducibility, and accumulating evidence that there are perhaps several subtypes of clear cell carcinoma. The subtypes include (1) tumors admixed with endometrioid adenocarcinoma; (2) those mixed with or histologically resembling serous carcinoma; and (3) pure clear cell carcinoma [50, 51]. There are emerging data that suggest that clear cell carcinomas might be overrepresented in patients with Lynch syndrome [52].

Gross Features

Clear cell carcinoma has no distinctive gross features. Tumors combined with endometrioid adenocarcinomas may be associated with a thickened endometrium. Pure clear cell carcinomas as well as those mixed with serous carcinomas are often associated with endometrial polyps and deep myometrial invasion.

Histologic Features

Most clear cell carcinomas are composed of cells with clear cytoplasm, but this feature is not restricted to this subtype of endometrial cancer (*see* "Discussion" of endometrioid adenocarcinomas). Furthermore, some clear cell carcinomas may contain cells with eosinophilic cytoplasm. As with other endometrial carcinoma subtypes, the combination of low-power architectural features and cytologic characteristics permits its diagnosis. These tumors classically demonstrate varied architectural patterns that include papillary, tubular, tubulocystic, solid, and mixtures thereof. The papillae of clear cell carcinoma are small and round in comparison to those of either serous carcinoma or villoglandular endometrioid adenocarcinomas. Characteristically, the stroma of the papillae is densely hyalinized (Fig. 11). The lining epithelium is only one or two cells thick, without prominent tufting. The cells are large, generally contain ample clear cytoplasm filled with glycogen, and show sharply defined cytoplasmic boundaries. Hobnail cells may be seen lining papillae or glands. The nuclei are cytologically malignant, sometimes containing macronucleoli, although overt pleomorphism is found only infrequently (Fig. 11). Like serous carcinoma, clear cell carcinoma usually arises in the setting of atrophic endometrium and in endometrial polyps [45].

Immunophenotype

Most clear cell carcinomas coexpress pancytokeratins and vimentin and rarely show diffuse cytoplasmic CEA positivity. They also express CK7 and are largely negative for CK20. Data

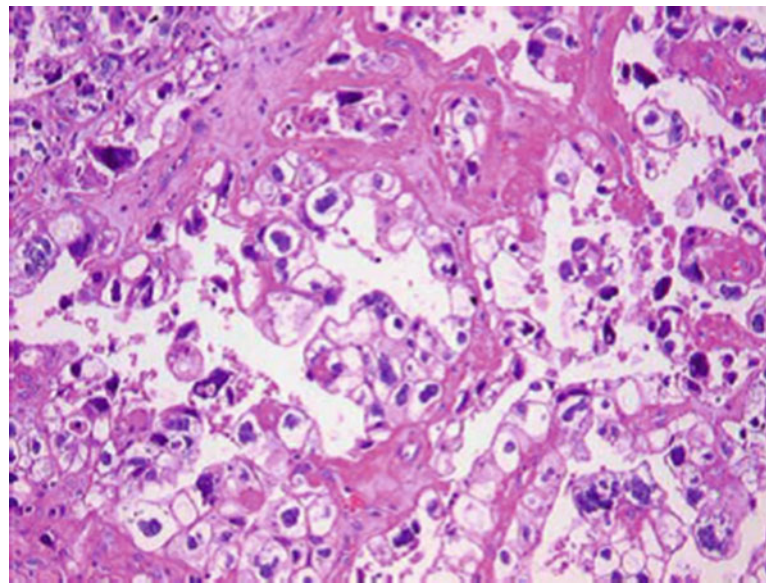

Fig. 11 Clear cell carcinoma. The tumor cells have cytoplasmic clearing, hobnail features, and striking cytologic atypia, and hyalinized stroma is seen

regarding expression of ER, PR, and p53 are contradictory, while results of p16 expression are now just emerging. ER and PR expression is uncommon and, when present, is weak and focal [31, 51, 53]. p53 overexpression can be seen, but with a rate (approximately at the 50 % level) significantly lower than in serous carcinoma [50, 51, 53]. The degree of ER, PR, and p53 expression might be related to an individual tumor's pathogenesis [50, 51, 53]. For example, clear cell carcinomas associated with endometrioid adenocarcinomas might preferentially express ER and PR, while those resembling or associated with serous carcinomas might overexpress p53. p16, expression of which may also be found in pure clear cell carcinomas, is more common than in endometrioid adenocarcinomas but less frequent than in serous carcinomas [31]. Expression of napsin A [54] and hepatocyte nuclear factor 1 beta [55] has been reported in both ovarian and endometrial clear cell carcinomas, but the sensitivity and specificity of these markers tend to be stronger in ovarian tumors with clear cytoplasm than in endometrial tumors.

Mixed (Mixed Epithelial) Carcinomas

With only one exception (mucinous carcinoma), mixed epithelial carcinomas are diagnosed when at least two endometrial carcinoma subtypes are present and the minor component(s) constitute 5 % of the tumor. Because mucinous differentiation is so commonly encountered in endometrioid adenocarcinomas, there is less enthusiasm now than in the past to diagnose "mixed endometrioid and mucinous carcinoma." The 2014 World Health Organization classification of gynecologic tumors [56] now specifies that mixed epithelial tumors must contain one component that is high grade or "type II." The term "mixed carcinoma" should not be used for tumors that contain areas with subtle differences. For example, a serous carcinoma with glandular architecture should not be considered a mixed serous and endometrioid adenocarcinoma unless two distinctive morphologies are present. Emerging data suggest that most carcinomas historically interpreted as "mixed epithelial" are instead monoclonal tumors with intratumoral heterogeneity, with one possible exception being those tumors that arise in the setting of Lynch Syndrome.

Squamous Cell Carcinoma

Primary squamous cell carcinoma of the endometrium is very rare and should only be diagnosed in the absence of hyperplasia or any endometrioid glandular differentiation [57]. They are histologically similar to squamous cell carcinomas of the cervix and most are cytologically high grade. Extension from a cervical squamous carcinoma or a history of a previous cervical squamous cell carcinoma excludes a diagnosis of primary squamous carcinoma of the endometrium.

Transitional Cell Carcinoma

This extraordinarily rare tumor is by definition composed of cells resembling those of urothelial transitional cell carcinoma [58, 59]. The architecture is papillary or trabecular, just like the urothelial counterparts. Extension and metastasis from a urothelial primary carcinoma should always be excluded. These tumors can occur in pure form or be mixed with other carcinoma subtypes. Many cases may, indeed, represent morphological variants of endometrioid carcinoma.

Small Cell Carcinoma

The histologic appearance of this tumor is essentially identical to that of small-cell neuroendocrine carcinomas of other organs [60]. These tumors can occur in pure form or be mixed with other carcinoma subtypes.

Undifferentiated Carcinoma

Undifferentiated carcinomas by definition lack any evidence of differentiation. As such, their appearance may simulate high-grade sarcoma, lymphoma, melanoma, and metastases to the

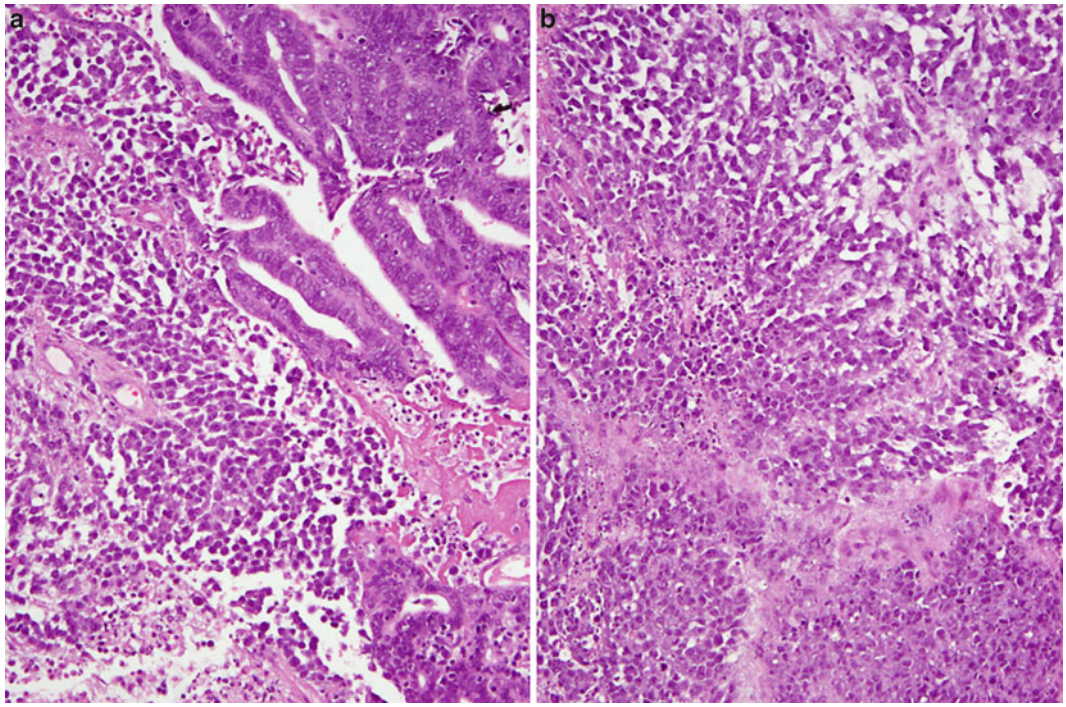

Fig. 12 Dedifferentiated carcinoma. A well-differentiated endometrioid carcinoma is juxtaposed to an undifferentiated carcinoma (**a**), which is composed of non-cohesive poorly differentiated epithelial cells without gland formation (**b**)

uterus. Universal but frequently only focal expression of cytokeratins and epithelial membrane antigen (EMA) is seen [60, 61]. Many examples coexist with differentiated endometrioid carcinoma, in which case the tumors may be diagnosed as "dedifferentiated endometrial carcinoma" or "mixed undifferentiated and endometrioid carcinoma." (Fig. 12).

Uterine Sarcomas and Mixed Müllerian Tumors

Leiomyosarcoma

Uterine leiomyosarcoma constitutes 1 % of all uterine malignancies; it is the most common uterine sarcoma, and represents approximately 40 % of all sarcomas at this site, and 40 % of leiomyosarcomas among women at all sites [62] (Table 4). The incidence of uterine leiomyosarcoma is approximately 0.67/100,000 women per year [63]. Even though uterine leiomyomas are the most common tumor of the female genital tract, the incidence of leiomyosarcoma originating from leiomyoma is very low, ranging between 0.13 and 0.80 [64], but some authors believe that leiomyosarcoma may have areas closely resembling classic leiomyoma or its variants but do not really arise from leiomyoma as when evaluating both leiomyoma-like areas and leiomyosarcoma areas both have nearly the same genetic aberrations by CGH array [65]. As occurs with

Table 4 Classification of malignant mesenchymal tumors of the uterus

Leiomyosarcoma
Spindled
Epithelioid
Myxoid
Low-grade endometrial stromal sarcoma High-grade endometrial stromal sarcoma
Undifferentiated uterine sarcoma
Low-grade müllerian adenosarcoma Malignant mixed müllerian tumor (carcinosarcoma)
Perivascular epithelioid tumor (PEComa)[a]
Others

[a]Not all tumors in this category behave in a malignant fashion

leiomyomas, uterine leiomyosarcomas are more frequent among black women [62]. There is at least one familial cancer syndrome characterized by retinoblastoma, hereditary leiomyomatosis, and renal cell cancer which has an increased incidence of uterine leiomyosarcoma [66].

Gross Features

Leiomyosarcoma occurs most commonly as a single nodule in almost 90 % of cases and if multiple nodules are present in the uterus, it is usually the largest [67, 68]. Leiomyosarcoma typically forms an intramyometrial mass with either well-circumscribed or irregular infiltrative growth into the surrounding myometrium. On sectioning, the tumors appear fleshy, gray to pink, and are frequently associated with areas of hemorrhage and necrosis [67, 69]. If the tumor has a prominent gelatinous cut surface, it should raise suspicion for a myxoid leiomyosarcoma [69].

Histologic Features

The diagnosis of malignancy in a smooth muscle tumor is based on three histologic features: (1) tumor cell necrosis; (2) moderate-to-severe cytologic atypia; and (3) mitotic activity [70]. Tumor cell necrosis is defined by the finding of an abrupt transition between the nonviable and viable tumor. The viable tumor frequently grows around vessels (perivascular distribution) and pleomorphic cells may still be identified in the devitalized areas. However, it is often difficult to distinguish tumor cell necrosis from infarct-type necrosis [71] and interobserver agreement amongst gynecologic pathologists is only fair in making a diagnosis of tumor cell necrosis [72]. In most cases, tumor cell necrosis is accompanied by tumor cells showing increased mitotic activity and marked cellular atypia. The latter is defined by cellular pleomorphism, nuclear enlargement and/or irregular outlines, hyperchromatism, as well as prominent nucleolus. Cytologic atypia should be identified at medium power (10×) and typically is diffuse in leiomyosarcomas. Finally, it may be difficult to count mitotic activity in smooth muscle tumors as not infrequently apoptotic cells are misinterpreted as mitoses. Apoptotic cells are typically characterized by refractile dense eosinophilic cytoplasm and coarse clumped chromatin, which contrasts with the hairy chromatin extending from a central dense mass of chromosomes with discernible cytoplasm and absent nuclear membrane in a true mitoses. Immunohistochemical markers including PHH3 and MPM-2 have been used to increase interobserver reproducibility in the assessment of mitotic activity and appear helpful in this distinction although they are not used universally [73, 74]. Even though mitotic activity had been considered the most important criterion to establish a diagnosis of malignancy in a smooth muscle tumor in the past, it has been demonstrated that mitotic activity in the absence of one of the other two histologic features previously described is insufficient to establish the diagnosis of leiomyosarcoma. Furthermore, it is important to keep in mind that the threshold for mitotic activity is higher in smooth muscle tumors of the uterus than that used in soft tissue tumors [75]. This is due to the mitogenic effect of estrogen and progesterone on gynecologic tumors and in particular on spindle cell smooth muscle tumors of the uterus. It is also important to be aware that the diagnostic mitotic threshold varies among the different subtypes of leiomyosarcoma, being $\geq$10 in spindle, $\geq$5 in epithelioid, and $\geq$2 in myxoid leiomyosarcomas [71].

Leiomyosarcomas can be classified into grades 1, 2, and 3 or low and high grade based on the degree of cellular differentiation, mitotic activity, and tumor cell necrosis, but these classifications are subjective. A tumor showing marked cytologic atypia associated with brisk mitotic activity and tumor cell necrosis is classified as high grade while a tumor that at low power displays mild cytologic atypia but has brisk mitotic activity and focal tumor necrosis can be classified as low-grade leiomyosarcoma. However, based on the available diagnostic criteria, most malignant smooth muscle tumors are high grade while the majority of leiomyosarcomas diagnosed as low grade in the past can be reclassified as leiomyoma variants or other low-grade mesenchymal tumors of the uterus [76].

Leiomyosarcomas are divided into three main categories depending on their morphologic

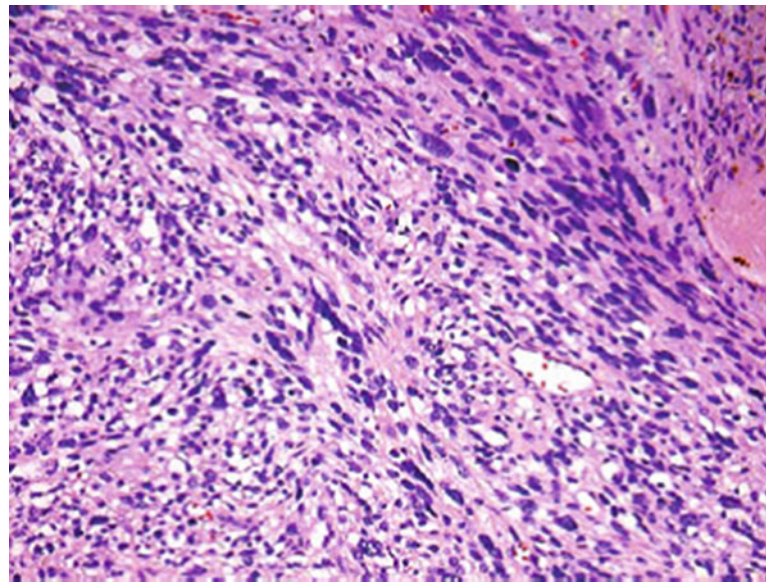

Fig. 13 Spindle cell leiomyosarcoma. The neoplastic cells form intersecting fascicles and display pleomorphic and hyperchromatic nuclei

appearance: (a) spindled, (b) epithelioid, and (c) myxoid; and not infrequently, they show more than one component. Rarely, leiomyosarcomas can contain xanthomatous or giant cells.

1. Spindle cell leiomyosarcoma is composed of fusiform cells showing central elongated nuclei with blunted ends occasionally indented by a clear vacuole (Fig. 13). The cytoplasm is deeply eosinophilic due to the presence of myofilaments that are disposed parallel to the cell axis (best seen in a Masson trichrome stain). The cells form long well-oriented intersecting fascicles [77]. The combination of any two of the following three features establishes the diagnosis of spindled leiomyosarcoma: diffuse moderate-to-severe cytologic atypia, $\geq$10 mitoses/10 high-power fields (HPFs), and tumor cell necrosis (Fig. 14; Table 5) [75]. Vascular invasion is detected in approximately 20 % of leiomyosarcomas and some tumors may have a prominent intravascular growth ("intravenous leiomyosarcomatosis") [78, 79].
2. Epithelioid leiomyosarcoma is composed of sheets, nests, or cords of cells with abundant cytoplasm. To establish the diagnosis of epithelioid leiomyosarcoma, at least 50 % of the cells should display epithelioid features. The cells show a centrally located round nucleus and eosinophilic cytoplasm (Fig. 15) but in up to 25 % of the tumors, the cytoplasm is clear. Variable amounts of collagen deposition may be seen. The criteria to establish the diagnosis of malignancy in epithelioid smooth muscle tumors are not well established. However, as a general rule, the diagnosis of epithelioid leiomyosarcoma is warranted when there are $\geq$5 mitoses/10 HPFs and diffuse moderate-to-severe cytologic atypia or tumor cell necrosis (Table 5) [80–82].
3. Myxoid leiomyosarcoma is rare and it is characterized by the presence of abundant myxoid matrix that is positive for Alcian Blue or colloidal iron histochemical stains. The tumors are often hypocellular in contrast to most spindled and epithelioid leiomyosarcomas. Most tumors show an infiltrative growth into the surrounding myometrium (Fig. 16a). At higher magnification, the degree of cytologic atypia and mitotic activity is quite variable [83–88]. The diagnosis of myxoid leiomyosarcoma is made when either marked cytologic atypia or tumor cell necrosis is identified. In their absence, the finding of $\geq$2 mitoses/10 HPFs separates myxoid leiomyosarcoma from myxoid leiomyoma (Fig. 16b; Table 5) [83].

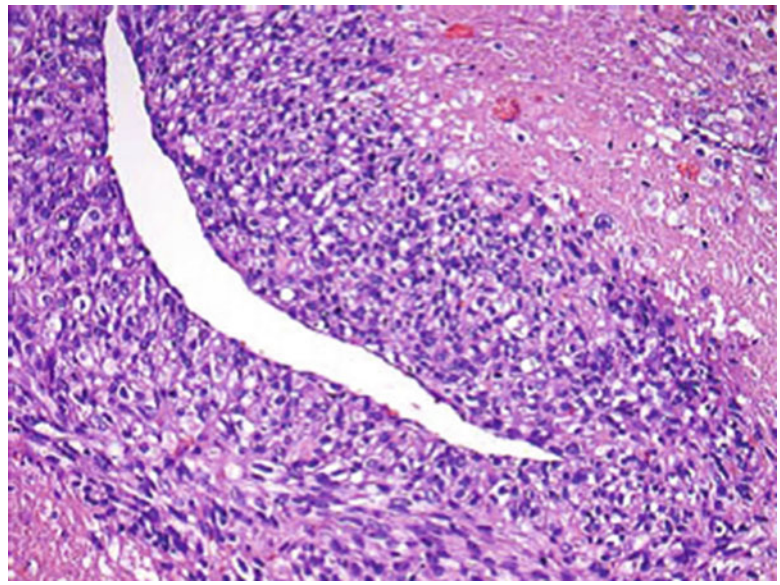

Fig. 14 Spindle cell leiomyosarcoma. There is an abrupt transition from viable to nonviable tumor (tumor cell necrosis) and the tumor cells typically grow around vessels. Notice that scattered atypical cells are seen in the necrotic foci

Table 5 Diagnostic criteria for the different subtypes of leiomyosarcoma

	Cytologic atypia		Tumor cell necrosis		Mitoses
Spindled	+	and/or	+	and/or	≥10/10HPFs[a]
Epithelioid	+	and/or	+	or	≥5/10HPFs
Myxoid	+	or	+	or	≥2/10HPFs

[a]In spindled leiomyosarcomas, two of the three features need to be present

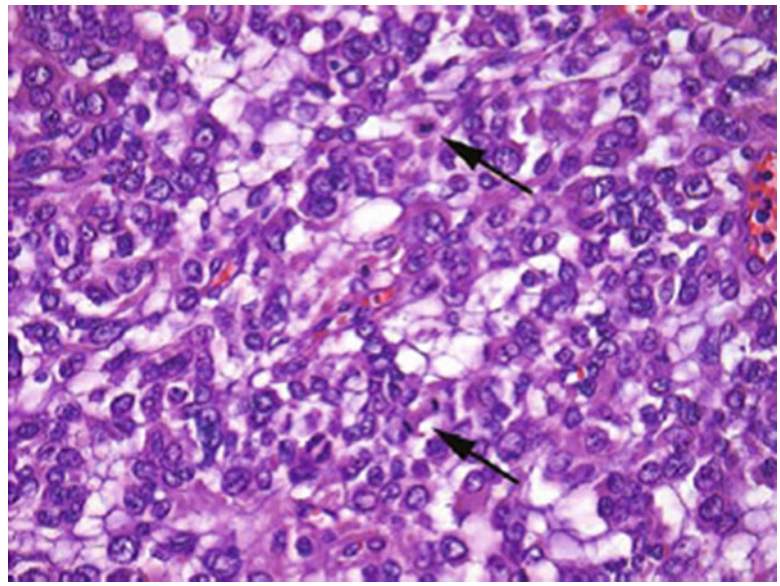

Fig. 15 Epithelioid leiomyosarcoma. The tumor cells grow in sheets. They have abundant eosinophilic cytoplasm and focal moderate nuclear atypia and mitoses are easy to identify (*arrows*)

Immunophenotype

Leiomyosarcomas are typically positive for actin, desmin, and h-caldesmon. They also frequently express CD10 [89], oxytocin [90], ER, PR, and androgen receptor [91]. Epithelioid leiomyosarcomas frequently express keratin and EMA [92], and both epithelioid and myxoid leiomyosarcomas are less frequently positive for smooth

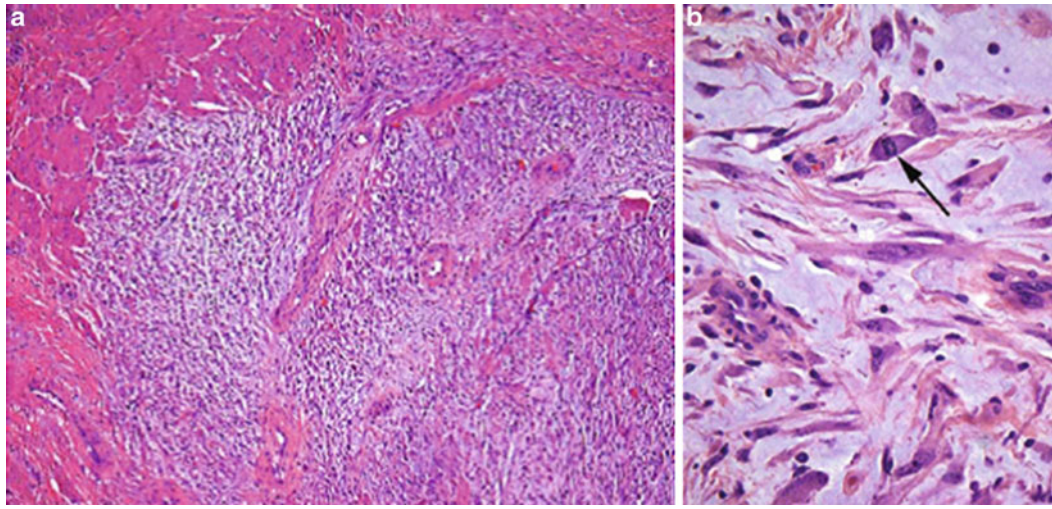

Fig. 16 Myxoid leiomyosarcoma. The tumor has an infiltrative margin into surrounding myometrium. It is hypocellular with a prominent myxoid background 9 (**a**) and the tumor cells show nuclear pleomorphism and mitotic activity (*arrow*) (**b**)

muscle markers. Leiomyosarcomas display p53 and c-kit positivity; however, no associated c-kit mutations have been reported [93–95]. They also express strongly and diffusely p16 [96] while they show variable expression of bcl-2 [97] and rare-to-absent Med12 mutations [98–100].

Differential Diagnosis

Spindle cell leiomyosarcoma should be distinguished from leiomyoma variants including mitotically active leiomyoma, apoplectic leiomyoma, and leiomyoma with bizarre nuclei. Mitotically active leiomyoma displays brisk mitotic activity; however, it lacks cytologic atypia and tumor cell necrosis [101, 102]. Leiomyoma with apoplectic change may show areas of hypercellularity associated with slight cytologic atypia and brisk mitotic activity surrounding the areas of hemorrhage, thus causing concern for malignancy. However, away from these areas, the tumor has the appearance of a conventional leiomyoma [103, 104]. It is important to keep in mind that areas close to the apoplectic change frequently show an increased ki-67 index as well as p16 positivity increasing the concern for malignancy. Positivity becomes imperceptible away from these areas which is helpful in establishing the diagnosis of leiomyoma with apoplectic change [105]. Finally, worrisome features associated with leiomyoma with bizarre nuclei include the presence of mono- or multinucleated cells which may show prominent nuclei, nuclear pseudoinclusions, karyorrhectic nuclei (that may mimic atypical mitotic figures), and some degree of mitotic activity. It is important to notice that in most cases, the bizarre cells have a patchy distribution in the tumor, mitotic activity is low, and there is no tumor cell necrosis [106, 107]. This leiomyoma variant is frequently p16 and p53 strongly and diffusely positive and shows variable ki67 expression, an immunoprofile that overlaps with that observed in leiomyosarcoma. Other rare malignant tumors in the differential diagnosis include spindle cell rhabdomyosarcoma [108] and undifferentiated uterine sarcoma [109]. The former may be very difficult to distinguish from a spindle cell leiomyosarcoma. The finding of cytoplasmic cross striations and positivity for skeletal muscle markers (myoglobin, myoD1, and myogenin) are helpful in this differential diagnosis. Undifferentiated uterine sarcoma is a diagnosis of exclusion based on histologic and immunohistochemical findings [77].

Epithelioid leiomyosarcoma should be distinguished from a poorly differentiated carcinoma, trophoblastic tumors (placental site trophoblastic tumor and epithelioid trophoblastic tumor) [110],

PEComa (discussed below) [111–113], uterine tumor resembling an ovarian sex cord stromal tumor [114–116], the rare alveolar soft part sarcoma [117, 118], and metastatic melanoma [119]. In order to establish the correct diagnosis, it is important to consider the patient's clinical history and to sample the tumor extensively. In difficult cases, the use of a battery of immunohistochemical markers including those for epithelial, smooth muscle, sex cord, and intermediate trophoblast differentiation may be helpful.

Myxoid leiomyosarcoma must be distinguished from its benign counterpart, the myxoid leiomyoma. The latter is an extremely rare tumor that typically is small (<5 cm), shows well-circumscribed margins, no cytologic atypia, absent tumor cell necrosis, and mitotic count <2/10 HPFs [80]. Leiomyoma with hydropic change may also be considered in the differential diagnosis of a myxoid leiomyosarcoma; however, the background matrix is composed of edema fluid which is Alcian Blue and colloidal iron negative [120a]. Rarely an inflammatory myofibroblastic tumor may mimic a myxoid leiomyosarcoma. It is frequently associated with a lymphoplasmatic unfiltrate and it is ALK positive, showing ALK rearrangement by FISH [120b]

Low-Grade Endometrial Stromal Sarcoma

Endometrial stromal neoplasms are divided into three main groups based on the latest WHO classification: (a) endometrial stromal nodule, (b) low-grade endometrial stromal sarcoma, and (c) high-grade endometrial stromal sarcoma. Low-grade endometrial stromal sarcoma accounts for approximately 80 % of all stromal neoplasms and it represents the second most common pure uterine sarcoma of the homologous type following leiomyosarcoma. A new category of high-grade endometrial stromal sarcoma has been established as it is associated with an intermediate prognosis between low-grade endometrial stromal sarcoma and undifferentiated endometrial/uterine sarcoma and it is characterized by distinctive morphology, immunophenotype, and chromosomal translocation [121]. The term undifferentiated uterine sarcoma includes tumors of stromal derivation but these tumors (either arising from the endometrial stroma or the myometrium) are very aggressive with a behavior similar to that of any high-grade sarcomas in the soft tissues [121].

Gross Features

Low-grade endometrial stromal sarcomas commonly appear as multiple coalescent tan to yellow soft nodules involving the endometrium and myometrium. The tumors typically show a permeative growth into the myometrial wall and myometrial veins and, not infrequently, may be identified grossly, outside the uterus in parametrial veins. They may show areas of necrosis and hemorrhage [122].

Histologic Features

These tumors infiltrate the myometrium as irregular islands without any associated stromal response (Fig. 17). The tumor cells are small, uniform with scant cytoplasm and round-to-oval nuclei with indistinct nucleoli. The tumor cells may whorl around the vessels, which are small and reminiscent of endometrial-type arterioles (Fig. 18). Histiocytes, single or in groups, collagen plaques, and cholesterol clefts are common associated findings [123]. Low-grade endometrial stromal sarcomas may show morphologic variations or unusual features including smooth muscle [124], skeletal muscle [125] or adipose differentiation [125], fibrous and/or myxoid background [126, 127], endometrioid glandular [128, 129] and sex cord-like differentiation [130], cells with granular eosinophilic or clear cytoplasm [131, 132], cells with a rhabdoid phenotype [133], cells with bizarre nuclei [125] or osteoclast-like cells [134], and finally pseudopapillary architecture [135].

To establish the diagnosis of low-grade endometrial stromal sarcoma, the tumor must resemble proliferative-type endometrial stroma regardless of the mitotic index. A diagnosis of high-grade endometrial stromal sarcoma could be made when a tumor with high-grade cytologic atypia (undifferentiated) arises in the context of a low-grade endometrial stromal sarcoma [77].

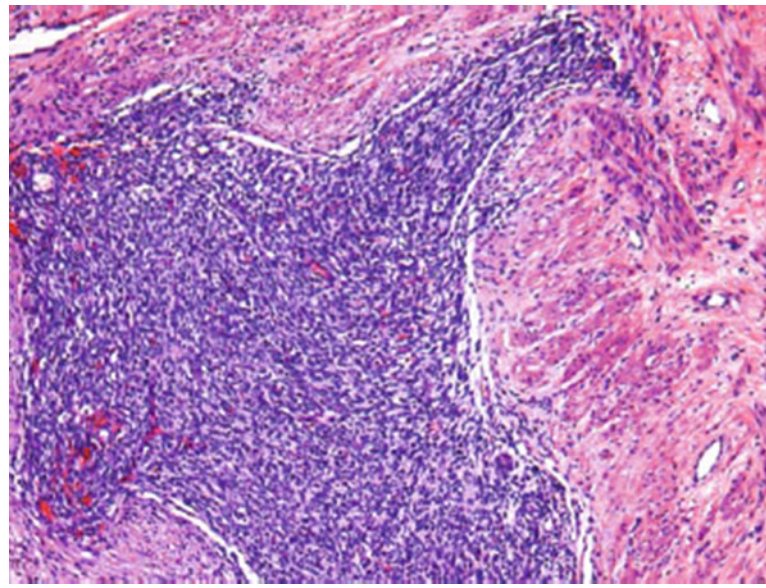

Fig. 17 Low-grade endometrial stromal sarcoma. The tumor is hypercellular and infiltrates the myometrium as irregular tongues

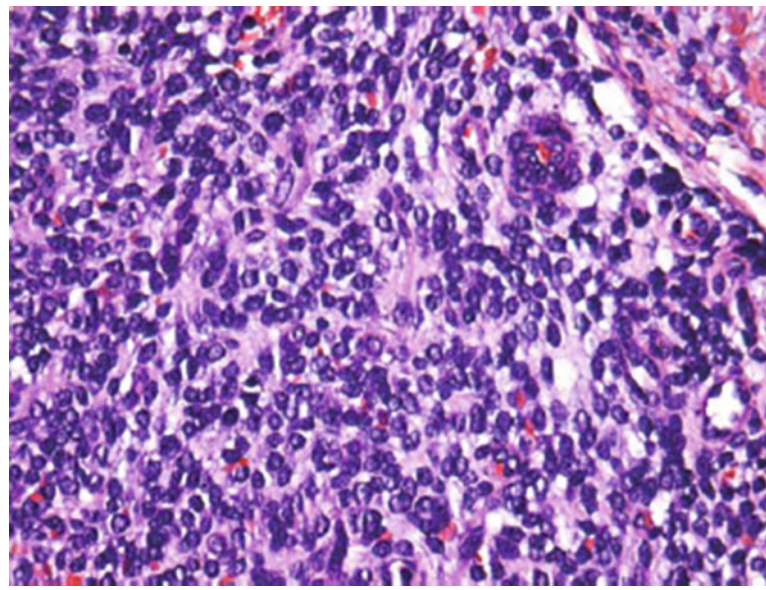

Fig. 18 Low-grade endometrial stromal sarcoma. The tumor cells are small and uniform and focally whorl around arterioles

Immunophenotype

The neoplastic endometrial stromal cells are typically immunoreactive for vimentin, muscle-specific and smooth muscle actin, keratin, and CD10 [136–138]. However, it is important to note that CD10 staining can be seen in other uterine tumors. They typically express ER and PR [139] and may express androgen receptors [140]. Some degree of positivity for desmin and caldesmon may be seen particularly if the tumor shows smooth muscle differentiation [89, 137, 138, 141–143]. Areas of sex cord-like differentiation may be positive for inhibin, calretinin, CD99, WT1, and melan A as well as demonstrate positivity for epithelial and smooth muscle markers [115, 144, 145]. Areas of

rhabdomyoblastic differentiation are positive for myoD1, myoglobin, and myogenin [125]. C-kit has been reported to be positive in low-grade endometrial stromal sarcomas; however, no associated mutations have been noted [146]. Some low-grade endometrial stromal sarcomas express β-catenin [109, 147] and some may show aromatase expression which may be used for therapeutic purposes [148].

Molecular Genetics

Low-grade endometrial stromal sarcomas are genetically heterogeneous and often harbor recurrent chromosomal translocations resulting in specific gene rearrangements. The most common genetic alteration is the *t*(7;17)(p15;q21) translocation resulting in *JAZF1–SUZ12* gene fusion. However, other chromosomal translocations and their corresponding gene fusions have been identified: *t*(7;17)(p15;q21), *t*(6;7)(p21;p15), *t*(6;10;10)(p21;q22;p11), and *t*(1;6)(p34;p21), resulting in *JAZF1–SUZ12, PHF1–JAZF1*, *EPC1–PHF1*, and *MEAF6–PHF1* rearrangements, respectively [149, 150].

Differential Diagnosis

The main entities in the differential diagnosis of low-grade endometrial stromal sarcoma include endometrial stromal nodule and highly cellular leiomyoma. An endometrial stromal nodule shares the same cytologic features described in low-grade endometrial stromal sarcoma. The main difference is the finding of a well-defined tumor-myometrium interface. Focal irregularities in the form of small finger-like projections or small islands not exceeding 3 mm are allowed; however, no vascular invasion should be seen [151]. It is important to extensively sample the tumor–myometrium interface in order to identify subtle permeation into the myometrium that may escape the naked eye [151]. Clinicians should be made aware that the pathologist cannot distinguish between an endometrial stromal nodule and a low-grade endometrial stromal sarcoma in a curettage specimen in most instances, as it is not possible to assess the entire margin, which is the most important feature in this differential diagnosis. The other important differential diagnosis is with a highly cellular leiomyoma. This benign smooth muscle tumor is characterized by dense uniform cellularity, prominent vascularity, and sometimes a pseudoinfiltrative growth into the surrounding myometrium, features that overlap with those described in endometrial stromal tumors. However, the tumor cells frequently form fascicles, the vessels are typically large with thick walls, and there is transition from the tumor to the myometrium, features that are lacking in a low-grade endometrial stromal sarcoma. The distinction is important, as it has prognostic implications, especially in a curettage specimen from a young woman. If the diagnosis is that of highly cellular leiomyoma, the patient may retain her uterus, whereas if the diagnosis is that of endometrial stromal neoplasm, the patient requires a hysterectomy in most cases [152, 153]. Other neoplastic and nonneoplastic processes that rarely enter into the differential diagnosis include gland poor adenomyosis [154] and cellular intravenous leiomyomatosis [155]. When low-grade endometrial stromal sarcomas show unusual features, the differential diagnosis is broader including endometrioid adenomyoma (if there is prominent smooth muscle differentiation) [156], myxoid smooth muscle tumor (if there is prominent myxoid change) [123], uterine tumor resembling an ovarian sex cord tumor (if there is prominent sex cord-like differentiation) [114], and finally adenomyosis and low-grade müllerian adenosarcoma (if there is glandular differentiation) [157].

High-Grade Endometrial Stromal Sarcoma

These are tumors that often show a pattern of myometrial infiltration similar to that seen in low-grade endometrial stromal sarcomas. They are composed of small round cells that either grow in diffuse or vaguely nested patterns. In the latter, the nests are separated by a delicate capillary network. Cells have a high nuclear to cytoplasmic ratio and the cytoplasm is scant to moderate at most and faintly eosinophilic.

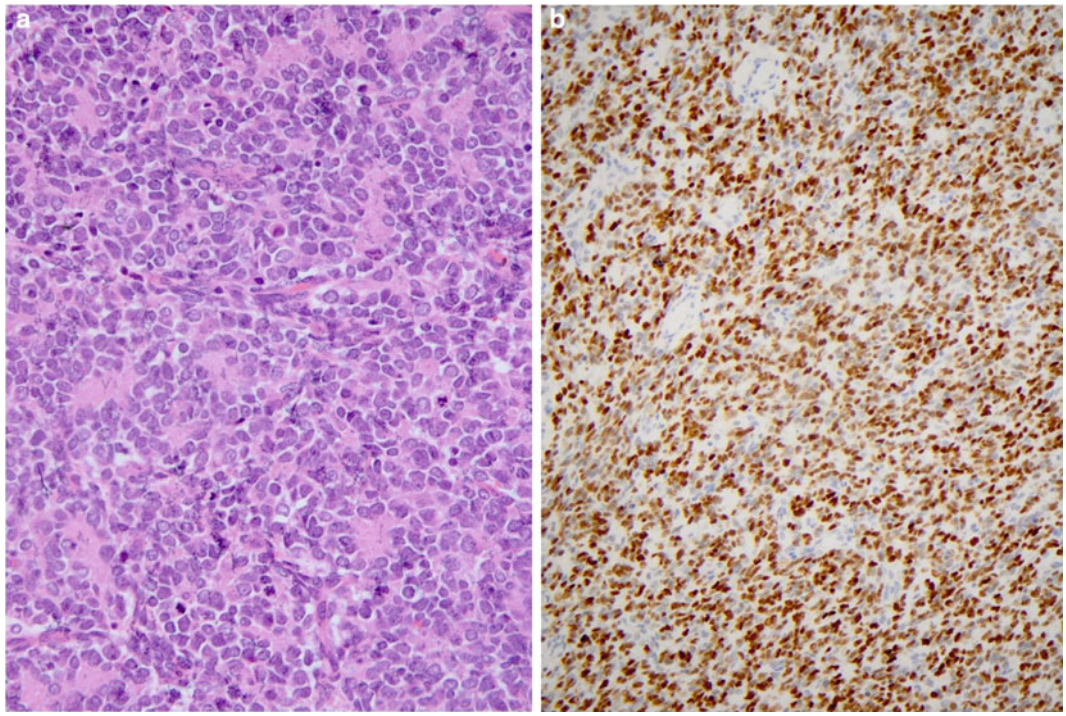

Fig. 19 High-grade endometrial stromal sarcoma. Small epithelioid cells with brisk mitotic activity grow in sheets (**a**). The tumor cells are strongly and diffusely cyclin D1 positive (**b**)

Mitotic activity is typically high (>10/10 HPFs), and tumor cell necrosis and vascular invasion are often present (Fig. 19a). In approximately 50 % of the tumors, a component of low-grade endometrial stromal sarcoma is present, typically the fibromyxoid variant where monomorphic, fusiform to spindled cells are set in a fibrocollagenous or fibromyxoid background [158].

Patients with these tumors typically present with advance stage and have a prognosis that is intermediate between low-grade endometrial stromal sarcoma and undifferentiated endometrial/uterine sarcoma [158].

A diagnosis of high-grade endometrial stromal sarcoma can also be made when a high-grade sarcoma is associated with a second component that can be diagnosed as a low-grade endometrial stromal sarcoma. The prognosis of these tumors is similar to that reported for undifferentiated endometrial/uterine sarcomas [121].

Immunophenotype and Molecular Genetics

These tumors, in contrast to low-grade endometrial stromal sarcomas, are typically negative for CD10, ER, and PR but strongly and diffusely positive for CyclinD1 (Fig. 19b) and show a characteristic *t*(10,17) with *YWHAE–FAM22* rearrangement [158].

Undifferentiated Uterine Sarcoma

This is a high-grade sarcoma without specific histologic features. In the 2014 WHO classification, the term undifferentiated uterine sarcoma replaces undifferentiated endometrial sarcoma as not all these tumors have an endometrial stromal origin [121]. This diagnosis should only be made after poorly differentiated carcinoma, leiomyosarcoma, rhabdomyosarcoma, adenosarcoma with sarcomatous overgrowth, and

malignant mixed müllerian tumor have been excluded by extensive sampling, careful histologic examination, and use of immunohistochemical stains if needed [77].

As mentioned earlier, a diagnosis of high-grade endometrial stromal sarcoma can be applied only in cases in which a component of low-grade endometrial stromal sarcoma is identified. Otherwise, the diagnosis is that of undifferentiated uterine sarcoma. This nomenclature conveys the highly aggressive nature of the tumor which contrasts with the much better prognosis associated with a low-grade endometrial stromal sarcoma [77].

Low-Grade Müllerian Adenosarcoma

This tumor belongs to the biphasic müllerian category of tumors (Table 6). It is typically composed of benign-appearing glands and a low-grade malignant mesenchymal component. It has been reported to represent approximately 7 % of all uterine sarcomas in a large series [159]. It most commonly affects perimenopausal women and has a similar incidence in white and black women. These tumors have been reported in women receiving tamoxifen therapy or after pelvic radiation therapy [160].

Gross Features

Most low-grade müllerian adenosarcomas appear as large polypoid masses filling the endometrial cavity, but rarely arise in the myometrium, within adenomyosis [161]. On sectioning, they may be predominantly solid or have a spongy appearance with cysts of different sizes. The cysts are filled with clear fluid or hemorrhage and are separated by variable amounts of tan to brown tissue [157].

Table 6 Mixed müllerian tumors of the uterus

Adenofibroma
Low-grade adenosarcoma
Homologous
Heterologous
With sarcomatous overgrowth
Malignant Mixed Tumor (Carcinosarcoma)
Homologous
Heterologous
Adenomyoma
Endometrioid type
Endocervical type
Atypical polypoid adenomyoma

Histologic Features

On low-power examination, the key histologic features include the finding of marked condensation of the low-grade malignant stromal component around glands that may be cystically dilated (Fig. 20a) or a phyllodes-type morphology. In the latter, the finding of intraluminal protrusions of the neoplastic stroma is also characteristic. The malignant mesenchymal component is commonly a low-grade homologous sarcoma reminiscent of low-grade endometrial stromal sarcoma or fibrosarcoma. The greatest degree of cytologic atypia (at most moderate) and mitotic activity is seen in the areas of stromal condensation. The glandular component is commonly of endometrioid-type although mucinous or tubal-type epithelium and squamous differentiation may be found. The epithelium is typically benign, but it may on occasion appear atypical. The diagnosis of adenosarcoma is generally established by the finding of the typical architectural and cytologic features accompanied by any degree of mitotic activity in the hypercellular stromal component surrounding the glands. Even though in the past a threshold of 4 mitoses/10 HPFs was used for the diagnosis of adenosarcoma, it has been shown that tumors showing prominent periglandular condensation, stromal atypia, and < 4 mitoses/10 HPFs frequently recur and, thus, should be diagnosed as adenosarcoma [157]. It is important to keep in mind that endometrial polyps may sometimes show focal architectural and/or cytologic features that overlap with that described in adenosarcoma including phyllodes-like architecture, intraglandular polypoid projections, altered periglandular stroma, and stromal cytologic atypia [162]. However, as mentioned earlier, these findings are focal and these polyps appear to be associated with a benign outcome [162]. It is also important to be aware that the diagnosis of

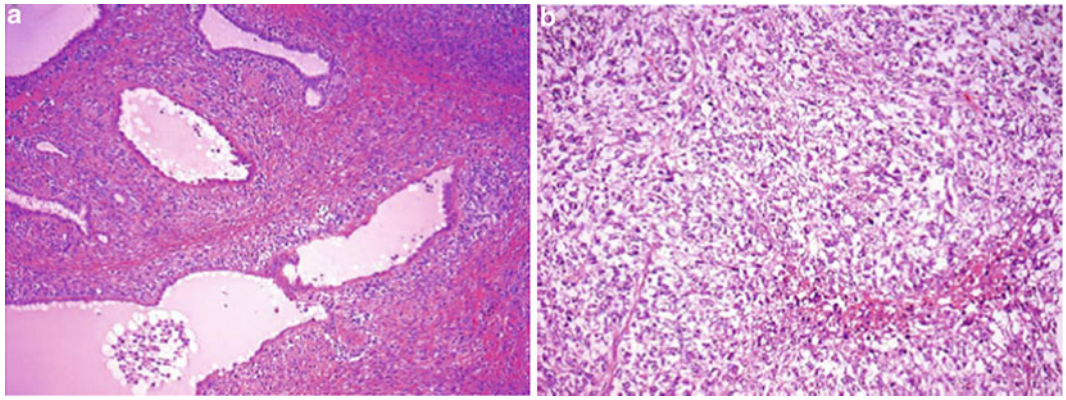

Fig. 20 Low-grade müllerian adenosarcoma. The neoplastic stromal cells condensate around the müllerian-type glands ("collaring") (**a**). Sarcomatous overgrowth. A high-grade sarcoma is associated with focal necrosis and has overgrown areas of conventional low-grade müllerian adenosarcoma (**b**)

müllerian adenofibroma should be only rendered with extreme caution. Adenofibroma is the benign counterpart of adenosarcoma, and although it is common in the ovary it is exceedingly rare in the uterus. It has been shown that tumors diagnosed as uterine adenofibromas may in fact represent very low-grade adenosarcomas as they have recurred multiple times and have been associated with an adverse outcome [163]. The mesenchymal component of an adenosarcoma may show bizarre nuclei, foamy histiocytes, smooth muscle, and sex cord-like differentiation [157, 160, 164]. Rhabdomyoblastic, cartilaginous, or fatty differentiation is more commonly seen outside the uterine corpus and is present in 10–15 % of cases [157, 165]. Finally, 10 % of these tumors show sarcomatous overgrowth, defined by the presence of pure sarcoma involving approximately 25 % of the tumor (Fig. 20b) [166]. In most cases, the sarcomatous overgrowth is composed of a high-grade sarcoma but it has also been reported as a low-grade sarcoma [167]. Sarcomatous overgrowth is associated with destructive invasion of the myometrium by sarcoma not accompanied by glands. This is in contrast to typical low-grade müllerian adenosarcomas which show a low incidence of myometrial invasion with both epithelial and stromal components forming part of the invasive tumor [157].

Immunophenotype and Molecular Genetics

The low-grade malignant stromal component is typically positive for vimentin, WT1, CD10, ER, and PR with variable expression of cytokeratin, muscle actin, and androgen receptor. This immunohistochemical profile overlaps with that reported in low-grade endometrial stromal sarcomas. Areas of sarcomatous overgrowth show decreased or absent CD10, ER, and PR expression [168]. The most frequent abnormalities in low-grade müllerian adenosarcomas include MDM2 and CDK4 amplifications but alterations in PIK3CA/AKT/PTEN pathway members are also common while MYBL1 amplification and p53 mutations are uncommon and typically seen in areas of sarcomatous overgrowth [169].

Malignant Mixed Müllerian Tumor (Carcinosarcoma)

Even though it represents <5 % of all malignant uterine tumors, this highly malignant mixed tumor was previously considered the most common uterine sarcoma [170]. The histogenesis of these tumors has evolved in recent years. It is now widely accepted that carcinosarcomas

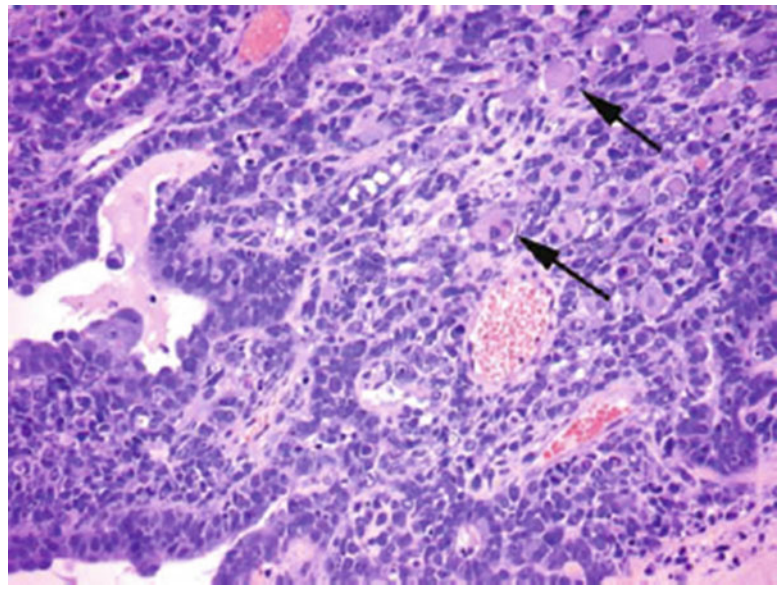

Fig. 21 Malignant mixed müllerian tumor. The epithelial and sarcomatous components of the tumor are intimately admixed. The sarcomatous component shows rhabdomyoblastic differentiation (*arrows*)

either arise from a common pluripotential cell with divergent differentiation or that the sarcomatous component develops from the carcinomatous component by a metaplastic process or dedifferentiation [171, 172]. These tumors occur typically in postmenopausal women and have a higher incidence in black women [170].

Gross Features

These are typically large, bulky polypoid tumors filling and distending the endometrial cavity. On sectioning, they show a fleshy heterogeneous cut surface with extensive areas of hemorrhage and necrosis. Deep and destructive infiltration of the myometrium is easily identified in most cases. While most tumors originate in the uterine corpus, approximately 5 % arise in the cervix [173–175].

Histologic Features

These tumors are characterized by an intimate admixture of high-grade malignant epithelial and mesenchymal elements. However, in some cases, the two elements do not appear admixed but they are juxtaposed. The high-grade carcinoma is more frequently either of serous or endometrioid type (with or without squamous differentiation) (Fig. 21), although any type of endometrial carcinoma can be seen. If the tumor arises in the cervix, the epithelial component is typically squamous and can be found adjacent to high-grade squamous dysplasia. The high-grade sarcoma is often of the homologous type, resembling high-grade leiomyosarcoma, malignant fibrous histiocytoma, or undifferentiated endometrial sarcoma. Heterologous differentiation [including in order of frequency rhabdomyosarcoma (Fig. 21), chondrosarcoma, liposarcoma, and rarely osteosarcoma and neuroectodermal differentiation] is seen in approximately 50 % of cases [173, 176–178].

Immunophenotype

The high-grade carcinoma typically coexpresses epithelial markers (keratin and EMA) and vimentin. The high-grade sarcoma is positive for vimentin and frequently for smooth muscle actin and epithelial markers. This overlapping profile of epithelial and mesenchymal components supports a common histogenesis. Synaptophysin, neuron-specific enolase, Leu-7, and CD10 may be expressed in the mesenchymal as well as in the epithelial component. The rhabdomyosarcomatous component is positive for myoglobin, myogenin, and MyoD1. p53 is frequently positive in both components [173, 179, 180]. These tumors

are an excellent example of the epithelial-mesenchymal transition with loss of epithelial characteristics, including cadherin switching and acquisition of a mesenchymal phenotype. Typically E-cadherin is drastically diminished in the mesenchymal component while CDH11, SPARC, TGFβ1, and TGFβ2 are augmented in the mesenchymal areas [181].

Perivascular Epithelioid Cell Tumor (PEComa)

These are rare uterine tumors that belong to the family of neoplasms thought to originate from the perivascular epithelioid cell (PEC). The latter cell type is defined by the presence of abundant clear to eosinophilic granular cytoplasm, positive staining for HMB-45 or other melanocytic markers including melan A, microphthalmia transcription factor, cathepsinK, or TFE3, as well as frequent expression of muscle markers [182, 183]. Other tumors that belong to this family include clear cell "sugar" tumors of the lung and pancreas, some forms of angiomyolipoma, and the clear cell myelomelanocytic tumor of ligamentum teres/falciform ligament [184–187]. These tumors show a particular association with lymphangiomyomatosis as well as tuberous sclerosis [113, 185]. PEComa (sporadic or syndromic) frequently harbors mutation and loss of heterozygosity (LOH) of TSC2 and much more rarely TSC1 [188].

Gross Features

Most tumors are solitary and can be well circumscribed with a white and whorled cut surface or show poorly defined margins, often with a fleshy and soft, gray-white to tan or yellow cut surface [111–113, 189].

Histologic Features

On low-power examination, some tumors have a tongue-like infiltrative growth similar to that seen in a low-grade endometrial stromal sarcoma, while in others, the interface between the tumor and the surrounding tissue is smooth [111, 112]. The tumor cells grow in sheets or small nests with scant intervening stroma but prominent sinusoidal vasculature. The cells have abundant clear or eosinophilic cytoplasm and oval-to-round nuclei (Fig. 22a). Tumors with pure clear cell morphology are much less frequently associated with *TSC* mutations [188]. PEComas not infrequently show, at least focally, a fascicular growth and in these areas, the cells have elongated nuclei with an appearance similar to that described in smooth muscle tumors. The degree of nuclear atypia is variable and the mitotic rates are low in most cases [111–113, 189, 190]. Tumors with $\geq$2 of the following criteria are typically associated with a malignant behavior including gross size $>$5 cm, infiltrative growth, high-grade nuclear features, necrosis, vascular invasion, or a mitotic index $\geq$1/50 HPFs [188]. Unusual forms of PEComa have been reported including PEComatosis (multiple PEComas) [191–193] sclerosing PEComa (striking hyalinizing background stroma) [194] and TFE-3 mutated PEComas characterized by prominence of clear cells [188].

Immunophenotype

The tumors are characteristically positive for HMB-45 (Fig. 22b), melanA, microphthalmia transcription factor (MiTF), cathepsinK, and TFE3 although the degree of positivity is variable and may be minimal for HMB45 and melan A [188] and are typically negative for S-100. They frequently express muscle markers, more often smooth muscle actin and desmin and much less commonly h-caldesmon, and may be positive for CD10, but they are negative for inhibin and keratin. In contrast to most PEComas, tumors composed predominantly of clear cells show diffuse TFE3, HMB45, and cathepsinK positivity with either focal or no melan A expression [188]. The coexpression of two melanocytic markers (HMB-45, melan A, microphthalmia transcription factor, cathepsinK, or TFE3) +/− muscle markers is diagnostic of this tumor [111, 113, 183, 189].

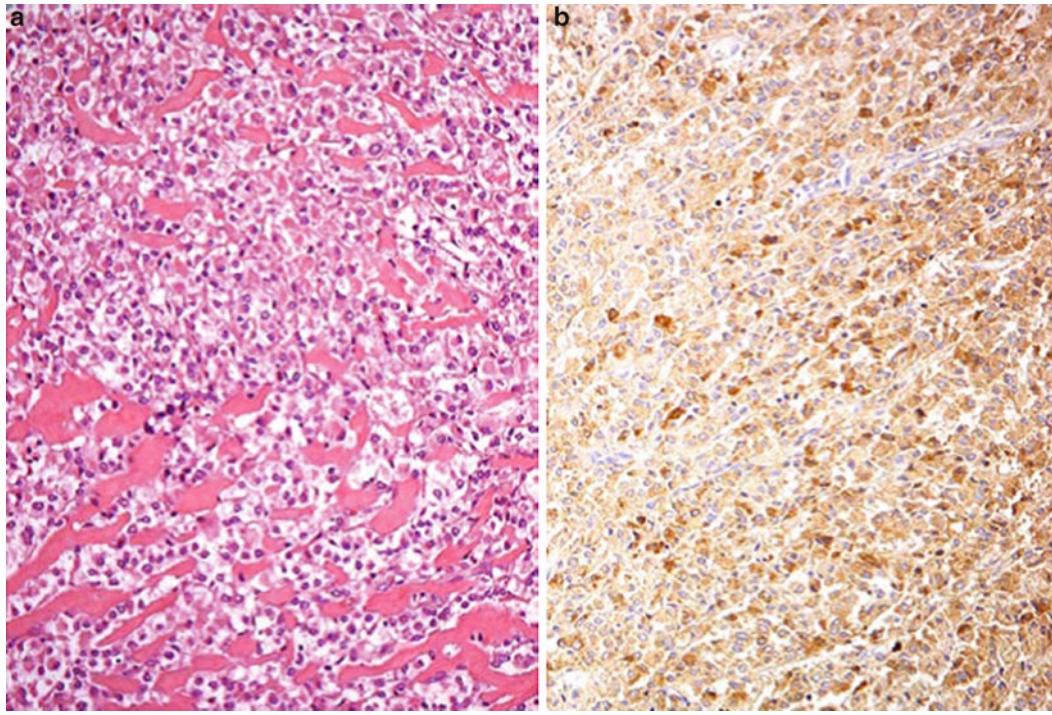

Fig. 22 PEComa. The tumor cells have abundant pale cytoplasm and grow in sheets and cords (**a**) and are diffusely positive for HMB-45 (**b**)

Intravenous Leiomyomatosis

Although this is a rare, histologically benign condition, characterized by a predominant intravascular proliferation of smooth muscle cells, it is included in this chapter because it may pursue an aggressive behavior, growing along the inferior vena cava into the right heart [195–199]. As intravenous leiomyomatosis is frequently associated with uterine leiomyomas, a diagnosis of intravenous leiomyomatosis should only be made when the intravascular growth is present beyond the confines or in the absence of a leiomyoma [155]. Extrauterine extension is most common within the broad ligament veins (up to 80 % of cases) and into the right heart (up to 40 % of cases) [155, 197]. This condition may occur at any age, but it is more common in middle-aged women.

Gross Features

In some occasions, the gross appearance is similar to that seen in a leiomyoma being more often multinodular [200]. White to yellow and firm to soft worm-like plugs of tumor may be seen filling and distending the myometrial veins, sometimes with extrauterine extension; however, not infrequently, it is not appreciated on initial gross examination of the uterus [155, 200, 201].

Histologic Features

On low-power examination, intravenous leiomyomatosis shows a prominent growth into vascular spaces. On high power, its appearance closely overlaps with that seen in typical leiomyomas [155]. The bland tumor cells form intersecting fascicles and display elongated nuclei with "blunt ends," eosinophilic cytoplasm, and rare-to-absent mitotic activity [155,

200–202]. Leiomyoma variants have also been described including hydropic change, myxoid, epithelioid, highly cellular, lipoleiomyoma, and with bizarre nuclei [203–205].

Cytogenetics

It has been recently shown that recurrent loss of 22q12.3-q13.1 is common in intravenous leiomyomatosis, followed by losses of 22q11.23-q13.31, 1p36.13-p33, 2p25.3-p23.3, and 2q24.2-q32.2 and gains of 6p22.2, 2q37.3 and 10q22.2-q22.3, in decreasing order of frequency [206].

Conclusions

- Endometrioid adenocarcinomas resemble, at least focally, proliferative-type endometrium showing tubular glands with smooth luminal surfaces, lined by mitotically active columnar cells
- Based on the degree of glandular differentiation, endometrioid carcinomas are divided into three FIGO categories: grade 1: $\leq$5 % of solid non-glandular growth; grade 2: 6–50 % of solid non-glandular growth; and grade 3: >50 % of solid growth. The presence of marked cytologic atypia increases the grade by one.
- The presence of extensive confluent papillary growth, macroglands, or cribriform architecture as well as marked cytologic atypia is diagnostic of adenocarcinoma and excludes endometrial hyperplasia.
- The distinction between endometrial carcinoma and endocervical carcinoma or between high-grade endometrioid- carcinoma and serous carcinoma may be very difficult on a curettage specimen.
- Mucinous, ciliated, secretory, and villoglandular carcinomas are related to endometrioid carcinomas.
- Serous carcinomas may be very small or even confined to a polyp or the endometrium but they are always of high grade and frequently have extrauterine spread. They typically show p53 overexpression and they are ER and PR positive in <50 % of cases.
- Clear cell carcinoma is uncommonly ER and PR positive and p53 overexpression is significantly less frequent than in serous carcinoma.
- The specific diagnostic criteria for the different subtypes of leiomyosarcomas differ.
- A combination of any two of the following three features establishes the diagnosis of spindled leiomyosarcoma: diffuse moderate-to-severe atypia, $\geq$10 mitoses/10 HPFs, and tumor cell necrosis.
- The criteria to establish the diagnosis of malignancy are not well established in epithelioid smooth muscle tumors. As a general rule, this diagnosis is warranted when there are $\geq$5 mitoses/10 HPFs and diffuse moderate-to-severe cytologic atypia or tumor cell necrosis.
- The diagnosis of myxoid leiomyosarcoma is warranted when either marked cytologic atypia or tumor cell necrosis is identified. In their absence, the finding of $\geq$2 mitoses/10 HPFs separates myxoid leiomyosarcoma from myxoid leiomyoma.
- Clinicians should be made aware that pathologists cannot distinguish between endometrial stromal nodule and low-grade endometrial stromal sarcoma in a curettage specimen in most instances; the most important feature in this differential diagnosis, the status of the tumor myometrial interface, cannot be assessed in this setting.
- A new category of high-grade endometrial stromal sarcoma has been included in the latest WHO classification which is defined by relatively small epithelioid cells growing in sheets or nests associated with cytologic atypia and brisk mitotic activity. The tumor is typically CD10, ER, and PR negative and CyclinD1 positive and shows a $t(10,17)$ in contrast to the $t(7,17)$ observed in >50 % of low-grade endometrial stromal sarcomas.
- A diagnosis of high-grade endometrial stromal sarcoma can also be applied when the tumor has arisen in the context of a low-grade endometrial stromal sarcoma. However, it is important to be aware that these tumors behave in a very aggressive fashion.

- The diagnosis of undifferentiated uterine sarcoma is a diagnosis of exclusion as this is a high-grade sarcoma without specific histologic features.
- The most important histologic parameters in the prognosis of low-grade müllerian adenosarcoma are myometrial invasion and sarcomatous overgrowth.
- Malignant mixed müllerian tumors arise either from a common pluripotential cell with divergent differentiation or by progression from the carcinomatous component by a metaplastic process or dedifferentiation, coexpressing epithelial and mesenchymal markers.
- PEComas are rare uterine tumors that belong to the family of neoplasms thought to originate from the perivascular epithelioid cell (PEC), which is defined by the presence of abundant clear to eosinophilic granular cytoplasm, positivity for melanocytic markers (HMB-45, melan A, microphthalmia transcription factor, cathepsinK, and TFE3) with or without expression of muscle markers.
- Intravenous leiomyomatosis is a proliferation of histologically benign smooth muscle growing in vascular spaces. It may be seen in the absence of leiomyomas or outside the confines of leiomyomas. It has commonly extrauterine extension which may be responsible of an aggressive behavior.

References

1. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10–7.
2. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73.
3. Alvarez T, Miller E, Duska L, Oliva E. Molecular profile of grade 3 endometrioid endometrial carcinoma: is it a type I or type II endometrial carcinoma? Am J Surg Pathol. 2012;36(5):753–61.
4. Alkushi A, Abdul-Rahman ZH, Lim P, et al. Description of a novel system for grading of endometrial carcinoma and comparison with existing grading systems. Am J Surg Pathol. 2005;29 (3):295–304.
5. Conlon N, Leitao Jr MM, Abu-Rustum NR, Soslow RA. Grading uterine endometrioid carcinoma: a proposal that binary is best. Am J Surg Pathol. 2014;38 (12):1583–7.
6. Lax SF, Kurman RJ, Pizer ES, Wu L, Ronnett BM. A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. Am J Surg Pathol. 2000;24(9):1201–8.
7. Murray SK, Young RH, Scully RE. Uterine endometrioid carcinoma with small nonvillous papillae: an analysis of 26 Cases of a favorable-prognosis tumor to be distinguished from serous carcinoma. Int J Surg Pathol. 2000;8(4):279–89.
8. Murray SK, Clement PB, Young RH. Endometrioid carcinomas of the uterine corpus with sex cord-like-formations, hyalinization, and other unusual morphologic features: a report of 31 cases of a neoplasm that may be confused with carcinosarcoma and other uterine neoplasms. Am J Surg Pathol. 2005;29(2):157–66.
9. Quick CM, May T, Horowitz NS, Nucci MR. - Low-grade, low-stage endometrioid endometrial adenocarcinoma: a clinicopathologic analysis of 324 cases focusing on frequency and pattern of myoinvasion. Int J Gynecol Pathol. 2012;31 (4):337–43.
10. Longacre TA, Hendrickson MR. Diffusely infiltrative endometrial adenocarcinoma: an adenoma malignum pattern of myoinvasion. Am J Surg Pathol. 1999;23(1):69–78.
11. Murray SK, Young RH, Scully RE. Unusual epithelial and stromal changes in myoinvasive endometrioid adenocarcinoma: a study of their frequency, associated diagnostic problems, and prognostic significance. Int J Gynecol Pathol. 2003;22 (4):324–33.
12. Kurman RJ, Norris HJ. Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma. Cancer. 1982;49 (12):2547–59.
13. Longacre TA, Chung MH, Jensen DN, Hendrickson MR. Proposed criteria for the diagnosis of well-differentiated endometrial carcinoma. A diagnostic test for myoinvasion. Am J Surg Pathol. 1995;19 (4):371–406.
14. Norris HJ, Tavassoli FA, Kurman RJ. Endometrial hyperplasia and carcinoma. Diagnostic considerations. Am J Surg Pathol. 1983;7(8):839–47.
15. Melhem MF, Tobon H. Mucinous adenocarcinoma of the endometrium: a clinico-pathological review of 18 cases. Int J Gynecol Pathol. 1987;6(4):347–55.
16. Ross JC, Eifel PJ, Cox RS, Kempson RL, Hendrickson MR. Primary mucinous adenocarcinoma of the endometrium. A clinicopathologic and histochemical study. Am J Surg Pathol. 1983;7 (8):715–29.

17. Hendrickson MR, Kempson RL. Ciliated carcinoma--a variant of endometrial adenocarcinoma: a report of 10 cases. Int J Gynecol Pathol. 1983;2 (1):1–12.
18. Tobon H, Watkins GJ. Secretory adenocarcinoma of the endometrium. Int J Gynecol Pathol. 1985;4 (4):328–35.
19. Chen JL, Trost DC, Wilkinson EJ. Endometrial papillary adenocarcinomas: two clinicopathological types. Int J Gynecol Pathol. 1985;4(4):279–88.
20. Parkash V, Carcangiu ML. Endometrioid endometrial adenocarcinoma with psammoma bodies. Am J Surg Pathol. 1997;21(4):399–406.
21. Hedrick Ellenson L, Ronnett BM, Soslow RA, Zaino RJ, Kurman RJ. Endometrial carcinoma. In: Kurman RJ, Hedrick Ellenson L, Ronnett BM, editors. Blaustein's Pathology of the Female Genital Tract. New York:Springer; 2011. p. 407–8.
22. Dabbs DJ, Geisinger KR, Norris HT. Intermediate filaments in endometrial and endocervical carcinomas. The diagnostic utility of vimentin patterns. Am J Surg Pathol. 1986;10(8):568–76.
23. Dabbs DJ, Sturtz K, Zaino RJ. The immunohistochemical discrimination of endometrioid adenocarcinomas. Hum Pathol. 1996;27 (2):172–7.
24. Dallenbach-Hellweg G, Lang-Averous G, Hahn U. The value of immunohistochemistry in the differential diagnosis of endometrial carcinomas. APMIS Suppl. 1991;23:91–9.
25. McCluggage WG, Sumathi VP, McBride HA, Patterson A. A panel of immunohistochemical stains, including carcinoembryonic antigen, vimentin, and estrogen receptor, aids the distinction between primary endometrial and endocervical adenocarcinomas. Int J Gynecol Pathol. 2002;21 (1):11–5.
26. Castrillon DH, Lee KR, Nucci MR. Distinction between endometrial and endocervical adenocarcinoma: an immunohistochemical study. Int J Gynecol Pathol. 2002;21(1):4–10.
27. Wang NP, Zee S, Zarbo RJ, Bacchi CE, Gown AM. Coordinate expression of cytokeratins 7 and 20 defines unique subsets of carcinomas. Appl Immunohistochem. 1995;3(2):99–107.
28. Ginath S, Menczer J, Fintsi Y, Ben-Shem E, Glezerman M, Avinoach I. Tissue and serum CA125 expression in endometrial cancer. Int J Gynecol Cancer. 2002;12(4):372–5.
29. Cherchi PL, Bosincu L, Dessole S, et al. Immunohistochemical expression of BerEP4, a new epithelial antigen, in endometrial carcinoma: correlation with clinical parameters. Eur J Gynaecol Oncol. 1999;20(5–6):393–5.
30. Katari RS, Fernsten PD, Schlom J. Characterization of the shed form of the human tumor-associated glycoprotein (TAG-72) from serous effusions of patients with different types of carcinomas. Cancer Res. 1990;50(16):4885–90.
31. Reid-Nicholson M, Iyengar P, Hummer AJ, Linkov I, Asher M, Soslow RA. Immunophenotypic diversity of endometrial adenocarcinomas: implications for differential diagnosis. Mod Pathol. 2006;19(8):1091–100.
32. Soslow RA, Shen PU, Chung MH, Isacson C, Baergen RN. Cyclin D1 expression in high-grade-endometrial carcinomas--association with histologic subtype. Int J Gynecol Pathol. 2000;19(4):329–34.
33. Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. Cancer. 2000;88 (4):814–24.
34. Sherman ME, Bur ME, Kurman RJ. p53 in endometrial cancer and its putative precursors: evidence for diverse pathways of tumorigenesis. Hum Pathol. 1995;26(11):1268–74.
35. Brachtel EF, Sanchez-Estevez C, Moreno-Bueno G, Prat J, Palacios J, Oliva E. Distinct molecular alterations in complex endometrial hyperplasia (CEH) with and without immature squamous metaplasia (squamous morules). Am J Surg Pathol. 2005;29(10):1322–9.
36. Schlosshauer PW, Ellenson LH, Soslow RA. Beta-catenin and E-cadherin expression patterns in high-grade endometrial carcinoma are associated with histological subtype. Mod Pathol. 2002;15 (10):1032–7.
37. Gehrig PA, Bae-Jump VL, Boggess JF, Groben PA, Fowler Jr WC, Van Le L. Association between uterine serous carcinoma and breast cancer. Gynecol Oncol. 2004;94(1):208–11.
38. Geisler JP, Sorosky JI, Duong HL, et al. Papillary serous carcinoma of the uterus: increased risk of subsequent or concurrent development of breast carcinoma. Gynecol Oncol. 2001;83(3):501–3.
39. Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. J Clin Oncol. 1993;11(3):485–90.
40. Olson SH, Finstad CL, Harlap S, Kurian L, Saigo PE, Barakat RR. A case-case analysis of factors related to overexpression of p53 in endometrial cancer following breast cancer. Cancer Epidemiol Biomarkers Prev. 1997;6(10):815–7.
41. Parkash V, Carcangiu ML. Uterine papillary serous carcinoma after radiation therapy for carcinoma of the cervix. Cancer. 1992;69(2):496–501.
42. Pothuri B, Ramondetta L, Martino M, et al. Development of endometrial cancer after radiation treatment for cervical carcinoma. Obstet Gynecol. 2003;101(5 Pt 1):941–5.
43. Carcangiu ML, Chambers JT. Uterine papillary serous carcinoma: a study on 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and

concomitant ovarian carcinoma. Gynecol Oncol. 1992;47(3):298–305.
44. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982;6(2):93–108.
45. Ambros RA, Sherman ME, Zahn CM, Bitterman P, Kurman RJ. Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. Hum Pathol. 1995;26(11):1260–7.
46. Spiegel GW. Endometrial carcinoma in situ in postmenopausal women. Am J Surg Pathol. 1995;19 (4):417–32.
47. Darvishian F, Hummer AJ, Thaler HT, et al. Serous endometrial cancers that mimic endometrioid adenocarcinomas: a clinicopathologic and immunohistochemical study of a group of problematic cases. Am J Surg Pathol. 2004;28(12):1568–78.
48. Demopoulos RI, Mesia AF, Mittal K, Vamvakas E. Immunohistochemical comparison of uterine papillary serous and papillary endometrioid carcinoma: clues to pathogenesis. Int J Gynecol Pathol. 1999;18 (3):233–7.
49. Tashiro H, Isacson C, Levine R, Kurman RJ, Cho KR, Hedrick L. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. Am J Pathol. 1997;150 (1):177–85.
50. An HJ, Logani S, Isacson C, Ellenson LH. Molecular characterization of uterine clear cell carcinoma. Mod Pathol. 2004;17(5):530–7.
51. Lax SF, Pizer ES, Ronnett BM, Kurman RJ. Clear cell carcinoma of the endometrium is characterized by a distinctive profile of p53, Ki-67, estrogen, and progesterone receptor expression. Hum Pathol. 1998;29(6):551–8.
52. Carcangiu ML, Dorji T, Radice P, Bertario L, Sala P. HNPCC-related endometrial carcinomas show a high frequency of non-endometrioid types and of high FIGO grade endometrioid carcinomas. Mod Pathol. 2006;19(1S):173A.
53. Vang R, Whitaker BP, Farhood AI, Silva EG, Ro JY, Deavers MT. Immunohistochemical analysis of clear cell carcinoma of the gynecologic tract. Int J Gynecol Pathol. 2001;20(3):252–9.
54. Fadare O, Desouki MM, Gwin K, et al. Frequent expression of napsin A in clear cell carcinoma of the endometrium: potential diagnostic utility. Am J Surg Pathol. 2014;38(2):189–96.
55. Fadare O, Liang SX. Diagnostic utility of hepatocyte nuclear factor 1-beta immunoreactivity in endometrial carcinomas: lack of specificity for endometrial clear cell carcinoma. Appl Immunohistochem Mol Morphol. 2012;20(6):580–7.
56. Zaino R, Carinelli SG, Ellenson LH, et al. Epithelial tumours and precursors. Chapter 5, Tumours of the uterine corpus. In: Kurman R, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. Lyon: IARC Press; 2014. p. 125–35.
57. Goodman A, Zukerberg LR, Rice LW, Fuller AF, Young RH, Scully RE. Squamous cell carcinoma of the endometrium: a report of eight cases and a review of the literature. Gynecol Oncol. 1996;61 (1):54–60.
58. Lininger RA, Ashfaq R, Albores-Saavedra J, Tavassoli FA. Transitional cell carcinoma of the endometrium and endometrial carcinoma with transitional cell differentiation. Cancer. 1997;79 (10):1933–43.
59. Spiegel GW, Austin RM, Gelven PL. Transitional cell carcinoma of the endometrium. Gynecol Oncol. 1996;60(2):325–30.
60. Abeler VM, Kjorstad KE, Nesland JM. Undifferentiated carcinoma of the endometrium. A histopathologic and clinical study of 31 cases. Cancer. 1991;68 (1):98–105.
61. Altrabulsi B, Malpica A, Deavers MT, Bodurka DC, Broaddus R, Silva EG. Undifferentiated carcinoma of the endometrium. Am J Surg Pathol. 2005;29 (10):1316–21.
62. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: an analysis of 26,758 cases. Int J Cancer. 2006;119(12):2922–30.
63. Harlow BL, Weiss NS, Lofton S. The epidemiology of sarcomas of the uterus. J Natl Cancer Inst. 1986;76(3):399–402.
64. Schwartz PE, Kelly MG. Malignant transformation of myomas: myth or reality? Obstet Gynecol Clin North Am. 2006;33(1):183–98. xii.
65. Mittal KR, Chen F, Wei JJ, et al. Molecular and immunohistochemical evidence for the origin of uterine leiomyosarcomas from associated leiomyoma and symplastic leiomyoma-like areas. Mod Pathol. 2009;22(10):1303–11.
66. Launonen V, Vierimaa O, Kiuru M, et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci U S A. 2001;98 (6):3387–92.
67. Rammeh-Rommani S, Mokni M, Stita W, et al. [Uterine smooth muscle tumors: retrospective epidemiological and pathological study of 2760 cases]. J Gynecol Obstet Biol Reprod (Paris). 2005;34 (6):568–71.
68. Schwartz LB, Diamond MP, Schwartz PE. Leiomyosarcomas: clinical presentation. Am J Obstet Gynecol. 1993;168(1 Pt 1):180–3.
69. Oliva ECP, Young RH. Mesenchymal tumors of the uterus: selected topics emphasizing potential pitfalls. Curr Diagn Pathol. 2002;8:268–82.
70. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms. A clinicopathologic study of 213 cases. Am J Surg Pathol. 1994;18(6):535–58.

71. Chiang S, Oliva E. Recent developments in uterine mesenchymal neoplasms. Histopathology. 2013;62 (1):124–37.
72. Lim D, Alvarez T, Nucci MR, et al. Interobserver variability in the interpretation of tumor cell necrosis in uterine leiomyosarcoma. Am J Surg Pathol. 2013;37(5):650–8.
73. Tapia C, Kutzner H, Mentzel T, Savic S, Baumhoer D, Glatz K. Two mitosis-specific antibodies, MPM-2 and phospho-histone H3 (Ser28), allow rapid and precise determination of mitotic activity. Am J Surg Pathol. 2006;30(1):83–9.
74. Veras E, Malpica A, Deavers MT, Silva EG. - Mitosis-specific marker phospho-histone H3 in the assessment of mitotic index in uterine smooth muscle tumors: a pilot study. Int J Gynecol Pathol. 2009;28(4):316–21.
75. Hornick JL, Fletcher CD. Criteria for malignancy in nonvisceral smooth muscle tumors. Ann Diagn Pathol. 2003;7(1):60–6.
76. Veras E, Zivanovic O, Jacks L, Chiappetta D, Hensley M, Soslow R. "Low-grade leiomyosarcoma" and late-recurring smooth muscle tumors of the uterus: a heterogenous collection of frequently misdiagnosed tumors associated with an overall favorable prognosis relative to conventional uterine leiomyosarcomas. Am J Surg Pathol. 2011;35 (11):1626–37.
77. Tavassoli F. World Health Organization classification of tumours. In: Tavassoli F, Devilee P, editors. Pathology and genetics of tumors of breast and female genital organs. Lyon: IARC Press; 2003.
78. Burns B, Curry RH, Bell ME. Morphologic features of prognostic significance in uterine smooth muscle tumors: a review of eighty-four cases. Am J Obstet Gynecol. 1979;135(1):109–14.
79. Coard KC, Fletcher HM. Leiomyosarcoma of the uterus with a florid intravascular component ("intravenous leiomyosarcomatosis"). Int J Gynecol Pathol. 2002;21(2):182–5.
80. Kurman RJ, Norris HJ. Mesenchymal tumors of the uterus. VI. Epithelioid smooth muscle tumors including leiomyoblastoma and clear-cell leiomyoma: a clinical and pathologic analysis of 26 cases. Cancer. 1976;37(4):1853–65.
81. Prayson RA, Goldblum JR, Hart WR. Epithelioid smooth-muscle tumors of the uterus: a clinicopathologic study of 18 patients. Am J Surg Pathol. 1997;21 (4):383–91.
82. Oliva E, Nielsen GP, Clement PB, et al. Epithelioid smooth muscle tumors of the uterus: a clinicopathologic analysis of 80 cases. Mod Pathol. 1997;10:107A.
83. Atkins K, Bell SW, Kempson RL. Myxoid smooth muscle tumors of the uterus. Mod Pathol. 2001;14:132A.
84. Burch DM, Tavassoli FA. Myxoid leiomyosarcoma of the uterus. Histopathology. 2011;59(6):1144–55.
85. Chen KT. Myxoid leiomyosarcoma of the uterus. Int J Gynecol Pathol. 1984;3(4):389–92.
86. King ME, Dickersin GR, Scully RE. Myxoid leiomyosarcoma of the uterus. A report of six cases. Am J Surg Pathol. 1982;6(7):589–98.
87. Pounder DJ, Iyer PV. Uterine leiomyosarcoma with myxoid stroma. Arch Pathol Lab Med. 1985;109 (8):762–4.
88. Salm R, Evans DJ. Myxoid leiomyosarcoma. Histopathology. 1985;9(2):159–69.
89. Oliva E, Young RH, Amin MB, Clement PB. An immunohistochemical analysis of endometrial stromal and smooth muscle tumors of the uterus: a study of 54 cases emphasizing the importance of using a panel because of overlap in immunoreactivity for individual antibodies. Am J Surg Pathol. 2002;26 (4):403–12.
90. Loddenkemper C, Mechsner S, Foss HD, et al. Use of oxytocin receptor expression in distinguishing between uterine smooth muscle tumors and endometrial stromal sarcoma. Am J Surg Pathol. 2003;27 (11):1458–62.
91. Leitao MM, Soslow RA, Nonaka D, et al. Tissue microarray immunohistochemical expression of estrogen, progesterone, and androgen receptors in uterine leiomyomata and leiomyosarcoma. Cancer. 2004;101(6):1455–62.
92. Iwata J, Fletcher CD. Immunohistochemical detection of cytokeratin and epithelial membrane antigen in leiomyosarcoma: a systematic study of 100 cases. Pathol Int. 2000;50(1):7–14.
93. Anderson SE, Nonaka D, Chuai S, et al. p53, epidermal growth factor, and platelet-derived growth factor in uterine leiomyosarcoma and leiomyomas. Int J Gynecol Cancer. 2006;16(2):849–53.
94. Leath 3rd CA, Straughn Jr JM, Conner MG, et al. Immunohistochemical evaluation of the c-kit proto-oncogene in sarcomas of the uterus: a case series. J Reprod Med. 2004;49(2):71–5.
95. Raspollini MR, Pinzani P, Simi L, et al. Uterine leiomyosarcomas express KIT protein but lack mutation(s) in exon 9 of c-KIT. Gynecol Oncol. 2005;98 (2):334–5.
96. Mills AM, Ly A, Balzer BL, et al. Cell cycle regulatory markers in uterine atypical leiomyoma and leiomyosarcoma: immunohistochemical study of 68 cases with clinical follow-up. Am J Surg Pathol. 2013;37(5):634–42.
97. D'Angelo E, Espinosa I, Ali R, et al. Uterine leiomyosarcomas: tumor size, mitotic index, and biomarkers Ki67, and Bcl-2 identify two groups with different prognosis. Gynecol Oncol. 2011;121 (2):328–33.
98. Bertsch E, Qiang W, Zhang Q, et al. MED12 and HMGA2 mutations: two independent genetic events in uterine leiomyoma and leiomyosarcoma. Mod Pathol. 2014;27(8):1144–53.
99. Matsubara A, Sekine S, Yoshida M, et al. Prevalence of MED12 mutations in uterine and extrauterine

smooth muscle tumours. Histopathology. 2013;62 (4):657–61.
100. Schwetye KE, Pfeifer JD, Duncavage EJ. MED12 exon 2 mutations in uterine and extrauterine smooth muscle tumors. Hum Pathol. 2014;45(1):65–70.
101. Perrone T, Dehner LP. Prognostically favorable "mitotically active" smooth-muscle tumors of the uterus. A clinicopathologic study of ten cases. Am J Surg Pathol. 1988;12(1):1–8.
102. Prayson RA, Hart WR. Mitotically active leiomyomas of the uterus. Am J Clin Pathol. 1992;97(1):14–20.
103. Myles JL, Hart WR. Apoplectic leiomyomas of the uterus. A clinicopathologic study of five distinctive hemorrhagic leiomyomas associated with oral contraceptive usage. Am J Surg Pathol. 1985;9 (11):798–805.
104. Norris HJ, Hilliard GD, Irey NS. Hemorrhagic cellular leiomyomas ("apoplectic leiomyoma") of the uterus associated with pregnancy and oral contraceptives. Int J Gynecol Pathol. 1988;7 (3):212–24.
105. Lim D, Ip PP, Cheung AN, Kiyokawa T, Oliva E. Immunohistochemical comparison of ovarian and uterine endometrioid carcinoma, endometrioid carcinoma with clear cell change and clear cell carcinoma. Am J Surg Pathol. 2015;39:1061–9.
106. Croce S, Young RH, Oliva E. Uterine leiomyomas with bizarre nuclei: a clinicopathologic study of 59 cases. Am J Surg Pathol. 2014;38(10):1330–9.
107. Downes KA, Hart WR. Bizarre leiomyomas of the uterus: a comprehensive pathologic study of 24 cases with long-term follow-up. Am J Surg Pathol. 1997;21(11):1261–70.
108. McCluggage WG, Lioe TF, McClelland HR, Lamki H. Rhabdomyosarcoma of the uterus: report of two cases, including one of the spindle cell variant. Int J Gynecol Cancer. 2002;12(1):128–32.
109. Kurihara S, Oda Y, Ohishi Y, et al. Endometrial stromal sarcomas and related high-grade sarcomas: immunohistochemical and molecular genetic study of 31 cases. Am J Surg Pathol. 2008;32(8): 1228–38.
110. Baergen RN, Rutgers JL, Young RH, Osann K, Scully RE. Placental site trophoblastic tumor: a study of 55 cases and review of the literature emphasizing factors of prognostic significance. Gynecol Oncol. 2006;100(3):511–20.
111. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol. 2005;29(12):1558–75.
112. Schoolmeester JK, Howitt BE, Hirsch MS, Dal Cin P, Quade BJ, Nucci MR. Perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: clinicopathologic and immunohistochemical characterization of 16 cases. Am J Surg Pathol. 2014;38 (2):176–88.
113. Vang R, Kempson RL. Perivascular epithelioid cell tumor ('PEComa') of the uterus: a subset of HMB-45-positive epithelioid mesenchymal neoplasms with an uncertain relationship to pure smooth muscle tumors. Am J Surg Pathol. 2002;26 (1):1–13.
114. Clement PB, Scully RE. Uterine tumors resembling ovarian sex-cord tumors. A clinicopathologic analysis of fourteen cases. Am J Clin Pathol. 1976;66 (3):512–25.
115. Irving JA, Carinelli S, Prat J. Uterine tumors resembling ovarian sex cord tumors are polyphenotypic neoplasms with true sex cord differentiation. Mod Pathol. 2006;19(1):17–24.
116. Krishnamurthy S, Jungbluth AA, Busam KJ, Rosai J. Uterine tumors resembling ovarian sex-cord tumors have an immunophenotype consistent with true sex-cord differentiation. Am J Surg Pathol. 1998;22(9):1078–82.
117. Nielsen GP, Oliva E, Young RH, Rosenberg AE, Dickersin GR, Scully RE. Alveolar soft-part sarcoma of the female genital tract: a report of nine cases and review of the literature. Int J Gynecol Pathol. 1995;14(4):283–92.
118. Roma AA, Yang B, Senior ME, Goldblum JR. TFE3 immunoreactivity in alveolar soft part sarcoma of the uterine cervix: case report. Int J Gynecol Pathol. 2005;24(2):131–5.
119. Giordano G, Gnetti L, Ricci R, Merisio C, Melpignano M. Metastatic extragenital neoplasms to the uterus: a clinicopathologic study of four cases. Int J Gynecol Cancer. 2006;16 Suppl 1:433–8.
120a. Clement PB, Young RH, Scully RE. Diffuse, perinodular, and other patterns of hydropic degeneration within and adjacent to uterine leiomyomas. Problems in differential diagnosis. Am J Surg Pathol. 1992;16(1):26–32.
120b. Parra-Herran C et al. Am J Surg Pathol 2015; 39:157–68
121. Oliva E, Carcangiu ML, Carinelli S, et al. Mesenchymal tumours. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. Lyon: IARC Press; 2014. p. 135–47.
122. Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. Am J Surg Pathol. 1990;14(5):415–38.
123. Oliva E, Clement PB, Young RH. Endometrial stromal tumors: an update on a group of tumors with a protean phenotype. Adv Anat Pathol. 2000;7 (5):257–81.
124. Oliva E, Clement PB, Young RH, Scully RE. Mixed endometrial stromal and smooth muscle tumors of the uterus: a clinicopathologic study of 15 cases. Am J Surg Pathol. 1998;22(8):997–1005.
125. Baker PM, Moch H, Oliva E. Unusual morphologic features of endometrial stromal tumors: a report of 2 cases. Am J Surg Pathol. 2005;29(10):1394–8.

126. Oliva E, Young RH, Clement PB, Scully RE. Myxoid and fibrous endometrial stromal tumors of the uterus: a report of 10 cases. Int J Gynecol Pathol. 1999;18(4):310–9.
127. Yilmaz A, Rush DS, Soslow RA. Endometrial stromal sarcomas with unusual histologic features: a report of 24 primary and metastatic tumors emphasizing fibroblastic and smooth muscle differentiation. Am J Surg Pathol. 2002;26(9):1142–50.
128. Clement PB, Scully RE. Endometrial stromal sarcomas of the uterus with extensive endometrioid glandular differentiation: a report of three cases that caused problems in differential diagnosis. Int J Gynecol Pathol. 1992;11(3):163–73.
129. Levine PH, Abou-Nassar S, Mittal K. Extrauterine low-grade endometrial stromal sarcoma with florid endometrioid glandular differentiation. Int J Gynecol Pathol. 2001;20(4):395–8.
130. McCluggage WG, Date A, Bharucha H, Toner PG. Endometrial stromal sarcoma with sex cord-like areas and focal rhabdoid differentiation. Histopathology. 1996;29(4):369–74.
131. Lifschitz-Mercer B, Czernobilsky B, Dgani R, Dallenbach-Hellweg G, Moll R, Franke WW. Immunocytochemical study of an endometrial diffuse clear cell stromal sarcoma and other endometrial stromal sarcomas. Cancer. 1987;59(8):1494–9.
132. Oliva E, Clement PB, Young RH. Epithelioid endometrial and endometrioid stromal tumors: a report of four cases emphasizing their distinction from epithelioid smooth muscle tumors and other oxyphilic uterine and extrauterine tumors. Int J Gynecol Pathol. 2002;21(1):48–55.
133. Kim YH, Cho H, Kyeom-Kim H, Kim I. Uterine endometrial stromal sarcoma with rhabdoid and smooth muscle differentiation. J Korean Med Sci. 1996;11(1):88–93.
134. Fadare O, McCalip B, Mariappan MR, Hileeto D, Parkash V. An endometrial stromal tumor with osteoclast-like giant cells. Ann Diagn Pathol. 2005;9(3):160–5.
135. McCluggage WG, Young RH. Endometrial stromal sarcomas with true papillae and pseudopapillae. Int J Gynecol Pathol. 2008;27(4):555–61.
136. Chu P, Arber DA. Paraffin-section detection of CD10 in 505 nonhematopoietic neoplasms. Frequent expression in renal cell carcinoma and endometrial stromal sarcoma. Am J Clin Pathol. 2000;113 (3):374–82.
137. Farhood AI, Abrams J. Immunohistochemistry of endometrial stromal sarcoma. Hum Pathol. 1991;22 (3):224–30.
138. Lillemoe TJ, Perrone T, Norris HJ, Dehner LP. Myogenous phenotype of epithelial-like areas in endometrial stromal sarcomas. Arch Pathol Lab Med. 1991;115(3):215–9.
139. Wu TI, Chou HH, Yeh CJ, et al. Clinicopathologic parameters and immunohistochemical study of endometrial stromal sarcomas. Int J Gynecol Pathol. 2013;32(5):482–92.
140. Moinfar F, Regitnig P, Tabrizi AD, Denk H, Tavassoli FA. Expression of androgen receptors in benign and malignant endometrial stromal neoplasms. Virchows Arch. 2004;444(5):410–4.
141. de Leval L, Waltregny D, Boniver J, Young RH, Castronovo V, Oliva E. Use of histone deacetylase 8 (HDAC8), a new marker of smooth muscle differentiation, in the classification of mesenchymal tumors of the uterus. Am J Surg Pathol. 2006;30(3):319–27.
142. Franquemont DW, Frierson Jr HF, Mills SE. An immunohistochemical study of normal endometrial stroma and endometrial stromal neoplasms. Evidence for smooth muscle differentiation. Am J Surg Pathol. 1991;15(9):861–70.
143. Rush DS, Tan J, Baergen RN, Soslow RA. -h-Caldesmon, a novel smooth muscle-specific antibody, distinguishes between cellular leiomyoma and endometrial stromal sarcoma. Am J Surg Pathol. 2001;25(2):253–8.
144. Baker RJ, Hildebrandt RH, Rouse RV, Hendrickson MR, Longacre TA. Inhibin and CD99 (MIC2) expression in uterine stromal neoplasms with sex-cord-like elements. Hum Pathol. 1999;30(6):671–9.
145. Sumathi VP, Al-Hussaini M, Connolly LE, Fullerton L, McCluggage WG. Endometrial stromal neoplasms are immunoreactive with WT-1 antibody. Int J Gynecol Pathol. 2004;23(3):241–7.
146. Geller MA, Argenta P, Bradley W, et al. Treatment and recurrence patterns in endometrial stromal sarcomas and the relation to c-kit expression. Gynecol Oncol. 2004;95(3):632–6.
147. Hrzenjak A, Tippl M, Kremser ML, et al. Inverse correlation of secreted frizzled-related protein 4 and beta-catenin expression in endometrial stromal sarcomas. J Pathol. 2004;204(1):19–27.
148. Reich O, Regauer S. Aromatase expression in low-grade endometrial stromal sarcomas: an immunohistochemical study. Mod Pathol. 2004;17 (1):104–8.
149. Chiang S, Oliva E. Cytogenetic and molecular aberrations in endometrial stromal tumors. Hum Pathol. 2011;42(5):609–17.
150. Sandberg AA. The cytogenetics and molecular biology of endometrial stromal sarcoma. Cytogenet Genome Res. 2007;118(2–4):182–9.
151. Dionigi A, Oliva E, Clement PB, Young RH. Endometrial stromal nodules and endometrial stromal tumors with limited infiltration: a clinicopathologic study of 50 cases. Am J Surg Pathol. 2002;26(5):567–81.
152. Oliva E. Cellular mesenchymal tumors of the uterus: a review emphasizing recent observations. Int J Gynecol Pathol. 2014;33(4):374–84.
153. Oliva E, Young RH, Clement PB, Bhan AK, Scully RE. Cellular benign mesenchymal tumors of the uterus. A comparative morphologic and immunohistochemical analysis of 33 highly cellular leiomyomas and six endometrial stromal nodules, two frequently confused tumors. Am J Surg Pathol. 1995;19(7):757–68.

154. Goldblum JR, Clement PB, Hart WR. Adenomyosis with sparse glands. A potential mimic of low-grade endometrial stromal sarcoma. Am J Clin Pathol. 1995;103(2):218–23.
155. Clement PB. Intravenous leiomyomatosis of the uterus. Pathol Annu. 1988;23(Pt 2):153–83.
156. Gilks CB, Clement PB, Hart WR, Young RH. Uterine adenomyomas excluding atypical polypoid adenomyomas and adenomyomas of endocervical type: a clinicopathologic study of 30 cases of an underemphasized lesion that may cause diagnostic problems with brief consideration of adenomyomas of other female genital tract sites. Int J Gynecol Pathol. 2000;19(3):195–205.
157. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum Pathol. 1990;21 (4):363–81.
158. Lee CH, Marino-Enriquez A, Ou W, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: a histologically high-grade and clinically aggressive tumor. Am J Surg Pathol. 2012;36(5):641–53.
159. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993;71(4 Suppl):1702–9.
160. Clement PB, Oliva E, Young RH. Mullerian adenosarcoma of the uterine corpus associated with tamoxifen therapy: a report of six cases and a review of tamoxifen-associated endometrial lesions. Int J Gynecol Pathol. 1996;15(3):222–9.
161. Clarke BA, Mulligan AM, Irving JA, McCluggage WG, Oliva E. Mullerian adenosarcomas with unusual growth patterns: staging issues. Int J Gynecol Pathol. 2011;30(4):340–7.
162. Howitt BE, Quade BJ, Nucci MR. Uterine polyps with features overlapping with those of Mullerian adenosarcoma: a clinicopathologic analysis of 29 cases emphasizing their likely benign nature. Am J Surg Pathol. 2015;39(1):116–26.
163. Gallardo A, Prat J. Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. Am J Surg Pathol. 2009;33(2):278–88.
164. Clement PB, Scully RE. Mullerian adenosarcomas of the uterus with sex cord-like elements. A clinicopathologic analysis of eight cases. Am J Clin Pathol. 1989;91(6):664–72.
165. Ramos P, Ruiz A, Carabias E, Pinero I, Garzon A, Alvarez I. Mullerian adenosarcoma of the cervix with heterologous elements: report of a case and review of the literature. Gynecol Oncol. 2002;84(1):161–6.
166. Clement PB. Mullerian adenosarcomas of the uterus with sarcomatous overgrowth. A clinicopathological analysis of 10 cases. Am J Surg Pathol. 1989;13 (1):28–38.
167. Wu RI, Schorge JO, Dal Cin P, Young RH, Oliva E. Mullerian adenosarcoma of the uterus with low-grade sarcomatous overgrowth characterized by prominent hydropic change resulting in mimicry of a smooth muscle tumor. Int J Gynecol Pathol. 2014;33(6):573–80.
168. Soslow RA, Ali A, Oliva E. Mullerian adenosarcomas: an immunophenotypic analysis of 35 cases. Am J Surg Pathol. 2008;32(7):1013–21.
169. Howitt BE, Sholl LM, Dal Cin P, et al. Targeted genomic analysis of Mullerian adenosarcoma. J Pathol. 2015;235(1):37–49.
170. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecol Oncol. 2004;93(1):204–8.
171. McCluggage WG. Malignant biphasic uterine tumours: carcinosarcomas or metaplastic carcinomas? J Clin Pathol. 2002;55(5):321–5.
172. Zelmanowicz A, Hildesheim A, Sherman ME, et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors. Gynecol Oncol. 1998;69(3):253–7.
173. Costa MJ, Khan R, Judd R. Carcinoma (malignant mixed mullerian [mesodermal] tumor) of the uterus and ovary. Correlation of clinical, pathologic, and immunohistochemical features in 29 cases. Arch Pathol Lab Med. 1991;115(6):583–90.
174. Grayson W, Taylor LF, Cooper K. Carcinosarcoma of the uterine cervix: a report of eight cases with immunohistochemical analysis and evaluation of human papillomavirus status. Am J Surg Pathol. 2001;25(3):338–47.
175. Clement PB, Zubovits JT, Young RH, Scully RE. Malignant mullerian mixed tumors of the uterine cervix: a report of nine cases of a neoplasm with morphology often different from its counterpart in the corpus. Int J Gynecol Pathol. 1998;17(3):211–22.
176. Ferguson SE, Tornos C, Hummer A, Barakat RR, Soslow RA. Prognostic features of surgical stage I uterine carcinosarcoma. Am J Surg Pathol. 2007;31 (11):1653–61.
177. Fukunaga M, Nomura K, Endo Y, Ushigome S, Aizawa S. Carcinosarcoma of the uterus with extensive neuroectodermal differentiation. Histopathology. 1996;29(6):565–70.
178. Kempson RL, Hendrickson MR. Smooth muscle, endometrial stromal, and mixed Mullerian tumors of the uterus. Mod Pathol. 2000;13(3):328–42.
179. George E, Manivel JC, Dehner LP, Wick MR. Malignant mixed mullerian tumors: an immunohistochemical study of 47 cases, with histogenetic considerations and clinical correlation. Hum Pathol. 1991;22(3):215–23.
180. Meis JM, Lawrence WD. The immunohistochemical profile of malignant mixed mullerian tumor. Overlap with endometrial adenocarcinoma. Am J Clin Pathol. 1990;94(1):1–7.
181. Castilla MA, Moreno-Bueno G, Romero-Perez L, et al. Micro-RNA signature of the epithelial-mesenchymal transition in endometrial carcinosarcoma. J Pathol. 2011;223(1):72–80.
182. Pea M, Martignoni G, Zamboni G, Bonetti F. Perivascular epithelioid cell. Am J Surg Pathol. 1996;20(9):1149–53.

183. Conlon N, Soslow RA, Murali R. Perivascular epithelioid tumours (PEComas) of the gynaecological tract. J Clin Pathol. 2015;68(6):418–26.
184. Bonetti F, Pea M, Martignoni G, et al. Clear cell ("sugar") tumor of the lung is a lesion strictly related to angiomyolipoma--the concept of a family of lesions characterized by the presence of the perivascular epithelioid cells (PEC). Pathology. 1994;26(3):230–6.
185. Folpe AL, Goodman ZD, Ishak KG, et al. Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. Am J Surg Pathol. 2000;24(9):1239–46.
186. Pea M, Bonetti F, Zamboni G, et al. Melanocyte-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney. Pathology. 1991;23(3):185–8.
187. Zamboni G, Pea M, Martignoni G, et al. Clear cell "sugar" tumor of the pancreas. A novel member of the family of lesions characterized by the presence of perivascular epithelioid cells. Am J Surg Pathol. 1996;20(6):722–30.
188. Schoolmeester JK, Dao LN, Sukov WR, et al. TFE3 translocation-associated perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: morphology, immunophenotype, differential diagnosis. Am J Surg Pathol. 2015;39(3):394–404.
189. Fukunaga M. Perivascular epithelioid cell tumor of the uterus: report of four cases. Int J Gynecol Pathol. 2005;24(4):341–6.
190. Bosincu L, Rocca PC, Martignoni G, et al. Perivascular epithelioid cell (PEC) tumors of the uterus: a clinicopathologic study of two cases with aggressive features. Mod Pathol. 2005;18(10):1336–42.
191. Fang CL, Lin YH, Chen WY. Microscopic endometrial perivascular epithelioid cell nodules: a case report with the earliest presentation of a uterine perivascular epithelioid cell tumor. Diagn Pathol. 2012;7:117.
192. Froio E, Piana S, Cavazza A, Valli R, Abrate M, Gardini G. Multifocal PEComa (PEComatosis) of the female genital tract associated with endometriosis, diffuse adenomyosis, and endometrial atypical hyperplasia. Int J Surg Pathol. 2008;16(4):443–6.
193. Liang SX, Pearl M, Liu J, Hwang S, Tornos C. "Malignant" uterine perivascular epithelioid cell tumor, pelvic lymph node lymphangioleiomyomatosis, and gynecological pecomatosis in a patient with tuberous sclerosis: a case report and review of the literature. Int J Gynecol Pathol. 2008;27(1):86–90.
194. Lim GS, Oliva E. The morphologic spectrum of uterine PEC-cell associated tumors in a patient with tuberous sclerosis. Int J Gynecol Pathol. 2011;30(2):121–8.
195. Burke M, Opeskin K. Death due to intravenous leiomyomatosis extending to the right pulmonary artery. Pathology. 2004;36(2):202–3.
196. Carr RJ, Hui P, Buza N. Intravenous leiomyomatosis revisited: an experience of 14 cases at a single medical center. Int J Gynecol Pathol. 2015;34(2):169–76.
197. To WW, Ngan HY, Collins RJ. Intravenous leiomyomatosis with intracardiac involvement. Int J Gynaecol Obstet. 1993;42(1):37–40.
198. Topcuoglu MS, Yaliniz H, Poyrazoglu H, et al. Intravenous leiomyomatosis extending into the right ventricle after subtotal hysterectomy. Ann Thorac Surg. 2004;78(1):330–2.
199. Virzi G, Ragazzi S, Bussichella F, et al. Intravenous leiomyomatosis extending from the inferior caval vein to the pulmonary artery. J Thorac Cardiovasc Surg. 2007;133(3):831–2.
200. Mulvany NJ, Slavin JL, Ostor AG, Fortune DW. Intravenous leiomyomatosis of the uterus: a clinicopathologic study of 22 cases. Int J Gynecol Pathol. 1994;13(1):1–9.
201. Nogales FF, Navarro N, Martinez de Victoria JM, et al. Uterine intravascular leiomyomatosis: an update and report of seven cases. Int J Gynecol Pathol. 1987;6(4):331–9.
202. Norris HJ, Parmley T. Mesenchymal tumors of the uterus. V. Intravenous leiomyomatosis. A clinical and pathologic study of 14 cases. Cancer. 1975;36(6):2164–78.
203. Clement PB, Young RH, Scully RE. Intravenous leiomyomatosis of the uterus. A clinicopathological analysis of 16 cases with unusual histologic features. Am J Surg Pathol. 1988;12(12):932–45.
204. Han HS, Park IA, Kim SH, Lee HP. The clear cell variant of epithelioid intravenous leiomyomatosis of the uterus: report of a case. Pathol Int. 1998;48(11):892–6.
205. Jordan LB, Al-Nafussi A, Beattie G. Cotyledonoid hydropic intravenous leiomyomatosis: a new variant leiomyoma. Histopathology. 2002;40(3):245–52.
206. Buza N, Xu F, Wu W, Carr RJ, Li P, Hui P. Recurrent chromosomal aberrations in intravenous leiomyomatosis of the uterus: high-resolution array comparative genomic hybridization study. Hum Pathol. 2014;45(9):1885–92.

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Erratum to: Uterine Cancer: Pathology

Robert A. Soslow and Esther Oliva

Erratum to:
Chapter "Uterine Cancer: Pathology" in:
R. A. Soslow, E. Oliva, Current Clinical Oncology,
DOI 10.1007/7631_2015_7

Page 2
Abstract: 12th line: 'tumors' was replaced with 'sarcomas'.

Page 3
Section '**Endometrioid Carcinoma':** 24th line: 'tumors' was deleted.

Page 11
Section '**Clear Cell Carcinoma':** (1st paragraph), 3rd line: 'cases' was replaced with 'all carcinomas at this site'.

Page 15
Section '**Histologic Features':** (5th paragraph), last line: '[80-83]' was replaced with '[80-82]'.

Page 17
Caption for figure 16 was revised from:
'Myxoid leiomyosarcoma. The tumor has an infiltrative margin into the surrounding myometrium (a). It is hypocellular with a prominent myxoid background and the tumor cells show nuclear pleomorphism andmitotic activity (arrow) (**b**)'
to:
'Myxoid leiomyosarcoma. The tumor has an infiltrative margin into surrounding myometrium. It is hypocellular with a prominent myxoid background 9 (**a**) and the tumor cells show nuclear pleomorphism and mitotic activity (**b**).'

The updated online version of this chapter can be found at
https://doi.org/10.1007/7631_2015_7

Page 23
Image for figure 20 was replaced with correct version.

Page 31
Numbering of references 80, 81, 82, and 83 needed to be corrected. ‘80’ changed to ‘83’; ‘81’ changed to ‘80’; ‘82’ changed to ‘81’; and ‘83’ changed to ‘82’.

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Molecular Pathology and Cytogenetics of Endometrial Carcinoma, Carcinosarcoma, and Uterine Sarcomas

Jose Palacios and Paola Dal Cin

Abstract

Molecular pathology and genetics are the subjects of increasing focus since they are providing a link between etiologic factors and the heterogeneity of clinicopathologic manifestations that have been covered in the preceding chapters. In endometrial cancer, two divergent pathways have been delineated that may be thought as analogous to the hormone-dependent and -independent subtypes in cancers of breast and prostate. Most hormone dependent EC are EEC, which from a molecular point of view can be classified into different subgroups: (a) ultramutated, due to POLE mutations; (b) hypermutated tumors with MSI, most frequently due to MLH1 promoter, but also seen in Lynch syndrome; and (c) MSS EC with low mutation rate, the most frequent subgroup of EEC. Hormone-independent tumors are represented by serous carcinomas, characterized by a high rate of mutations in p53 that produce genomic instability with extensive somatic copy number alterations. Knowledge on alterations in sarcomas will hopefully lead to advances in diagnosis and therapy that are urgently needed in women where spread beyond the uterus has occurred.

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J. Palacios
Servicio de Anatomía Patológica, Hospital Universitario Ramón y Cajal, Carretera de Colmenar, Km 9.100, Madrid 28034, Spain
e-mail: jose.palacios@salud.madrid.org

P. Dal Cin (✉)
Department of Pathology, CAMD, Brigham and Women's Hospital, 25 Francis St., Shapiro, 5-058, Boston, MA 02115, USA
e-mail: pdalcin@partners.org

Keywords
Molecular pathways • Microsatellite instability • PTEN inactivation • β-catenin • Cytogenetics

Endometrial Carcinoma

Molecular Abnormalities

During the last few years, it has been demonstrated that endometrioid (EEC) (type I) and non-endometrioid (type II) endometrial carcinomas (NEEC) not only differed from epidemiologic, clinical, and morphologic viewpoints but also regarding molecular alterations implicated in their initiation and progression. Several different molecular pathways are involved in EEC development, including DNA mismatch repair (MMR), phosphoinositide 3-kinase (PI3K)/Akt, RAS-RAF-MEK-ERK, fibroblast growth factor (FGF), and WNT pathways. Alterations in some of these pathways have also been found in atypical endometrial hyperplasia, indicating their role in tumor initiation, but they are infrequent in NECC. In contrast, *TP53* mutations occur in a high percentage of NEEC, mainly in serous carcinomas and in its precursor lesion, endometrial intraepithelial carcinoma, but are detected only in a subset of grade 3 EECs. In addition, it has been suggested that *TP53* inactivation may be implicated in the phenotypic change from EEC to NEEC as observed in some mixed carcinomas [1, 2] (Table 1).

Recently, the Cancer Genome Atlas Research Network (TCGA) [2] proposed a new molecular classification of endometrial cancer (EC). Based on a combination of somatic mutations, microsatellite instability (MSI), and somatic copy number variations, the endometrial tumors were classified into four groups: (1) an ultra-mutated group with unusually high mutation rates; (2) a hypermutated group with microsatellite instability (MSI), most with MLH1 promoter methylation; (3) a group with lower mutation frequency and most of the microsatellite stable (MSS) endometrioid cancers; and (4) a group that consists primarily of serous-like cancers with extensive somatic copy number alterations and a low mutation rate. Groups 1, 2, and 3 included predominantly endometrioid carcinomas, whereas group 4 included serous carcinomas and some grade 3 endometrioid carcinomas.

POLE Mutations

The ultra-mutated group of EC is characterized by mutations in the exonuclease domain of POLE, which is a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair [3]. Seventy five percent of mutations are located at hot-spots P286R and V411L. Ultra-mutated tumors represented 7 %

Table 1 Most frequently mutated genes in histological types of endometrial cancer

GENE	Endometrioid carcinoma (%)	Serous carcinoma (%)	Carcinosarcoma (%)
PTEN	52	<5	19
PIK3CA	35	36	35
PIK3R1	25	<5	10
CTNNB1	24	<5	<5
ARID1A	25	7	14
KRAS	17	<5	12
CTCF	14	<5	5
FGFR2	9	7	<5
TP53	9	74	91
FBXW7	7	26	38
PPP2R1A	<5	23	28
CHD4	<5	13	17

of EC in the TCGA series and showed an increased C → A transversion frequency [2]. The majority demonstrated defining morphological features of endometrioid differentiation, they were frequently high grade (60 %) and rich in tumor-infiltrating lymphocytes and/or peritumoral lymphocytes (84 %); many tumors showed morphological heterogeneity (52 %) and ambiguity (16 %). Foci demonstrating severe nuclear atypia led to concern for serous carcinoma in 28 % of the tumors [4].

At the molecular level, the majority of the TCGA *POLE*-mutated tumors were microsatellite stable (65 %), and *TP53* mutations were present in 35 % of them. They also harbored mutations in *PTEN* (94 %), *FBXW7* (82 %), *ARID1A* (76 %), and *PIK3CA* (71 %). Since all patients in TCGA and other cohorts [4, 5] were alive without disease, it has been suggested that ultra-mutated tumors have an excellent prognosis despite of adverse molecular and pathological features. However, other authors have not found *POLE* mutations as prognostic factor in EC [6]. Some studies have demonstrated that *POLE* mutations may induce MSI by generating somatic mutations in DNA mismatch repair genes, most frequently in *MSH6*, in a subset of tumors. Thus, *POLE* testing in MSI ECs could serve as a marker of somatic disease origin and therefore, may be a valuable exclusionary criterion for Lynch syndrome gene testing [6, 7].

DNA Mismatch Repair Deficiency

Microsatellite instability represents a pattern of mutations in cells with a replication error phenotype due to deficient DNA MMR. Microsatellite loci contain repetitive elements of 1–6 nucleotides in length and are most commonly (CA) or poly A/T sequences. MSI status can be detected by using a standard panel of five microsatellite markers. When at least two of the five markers show MSI, tumors are classified as MSI-high (MSI-H). In contrast, tumors without size alteration in microsatellites or those with only one altered marker are classified as microsatellite stable (MSS) and MSI-low (MSI-L), respectively. From a clinicopathologic point of view, MSI-L tumors should be included with MSS tumors [8]. Microsatellite instability was first reported in colorectal adenocarcinomas of patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC). This status of high-frequency mutagenesis is caused by mutations in the main DNA MMR genes, such as *hMLH1* and *hMSH2* and less frequently *hMSH6*, *hPMS1*, and *hPMS2*. MSI is also seen in approximately 15 % of sporadic colorectal carcinomas, usually reflecting loss of expression of hMLH1 associated with gene silencing by *hMLH1* promoter methylation [9].

Available data indicate that EC is the most common extracolonic tumor in Lynch syndrome, with lifetime risk estimates ranging from 40 to 60 % in female mutation carriers [10]. As a result, the original Amsterdam criteria for Lynch syndrome were revised in 1999 to include EC among the diagnostic criteria [11]. It has been suggested that EC is the most common malignancy among women carrying hMSH6 germ line mutations [12].

MSI is seen in approximately 15–45 % of sporadic EEC [13], usually reflecting loss of expression of hMLH1 associated with gene silencing by *hMLH1* promoter methylation. This change has been reported in 69–92 % of EC with MSI [14, 15]. In addition, it has been shown that the *hMLH1* promoter is frequently methylated in the histologically normal endometrium [15] and atypical endometrial hyperplasia [14] of patients with ECs and that the methylation status is similar to that in the carcinoma. These findings support the notion that, in a subset of tumors, epigenetic changes in DNA MMR genes might be the initial events that trigger the genetic alterations involved in endometrial carcinogenesis.

Immunohistochemistry can be used to explore MMR gene inactivation in EC. Currently, there are antibodies available to study the expression of the most important MMR proteins, such as hMLH1, hMSH2, hMSH6, and hPMS2. In colon cancer, large studies comparing immunohistochemistry and MSI genotyping have demonstrated a 93–100 % sensitivity to detect MSI by immunohistochemistry analysis. Although there are not such large series in EC, different

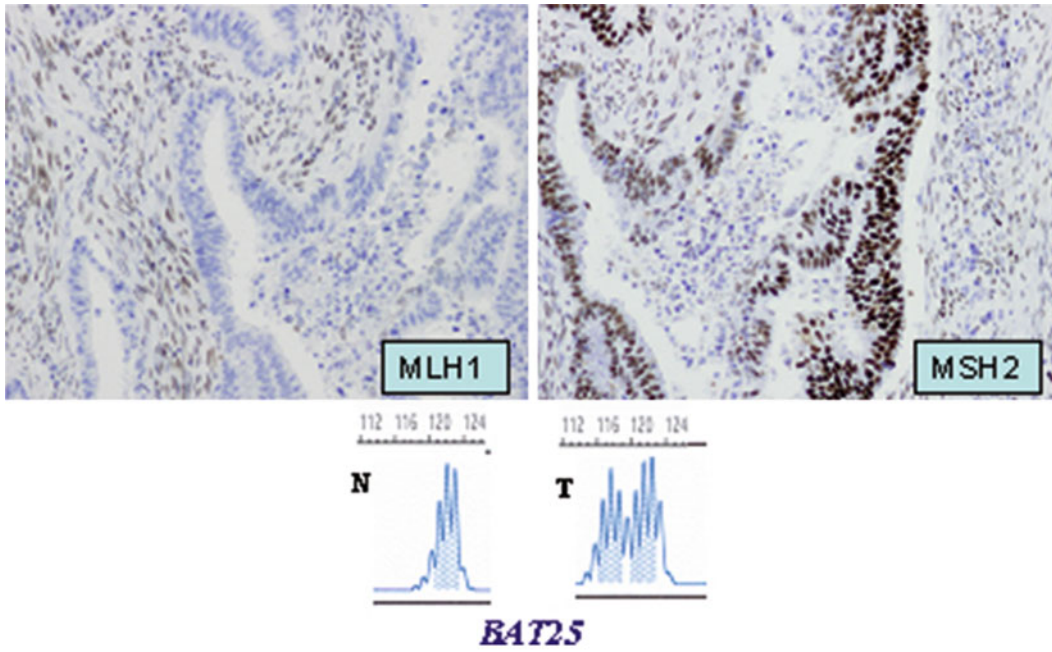

Fig. 1 Absence of MLH1 expression and preserved MSH2 expression in an EEC with microsatellite instability. Note abnormal size of BAT25 microsatellite in tumor tissue (T) with respect to normal tissue (N)

studies have reported a 70–100 % sensitivity when using immunohistochemistry (Fig. 1) [16, 17].

MMR deficiency in cancer produces instability not only in microsatellites that are located in noncoding sequences, such as those used for MSI genotyping, but also in mononucleotide tract repeats located in coding sequences of different genes. The proteins encoded by these genes participate in a variety of essential cellular processes like signal transduction (TGFβRII, IGFIIR, PTEN), apoptosis (BAX), DNA repair (hMSH3, hMSH6, MBD4), transcriptional regulation (TCF-4), protein translocation and modification (SEC63, OGT), or immune surveillance (β2M). It is generally believed that this subset of critical targets specifically promotes MSI carcinogenesis in a large proportion of tumors. Moreover, several studies have demonstrated that selection of target gene mutations in MSI cancers is a tissue-specific process. Whereas some of the genes were proposed to be real target genes for mutation in the most common types of cancers with MSI (colon, gastric, and endometrial cancer) (*TGFβRII*, *BAX*, *IGFIIR*, *MSH3*, *MSH6*, and *GRB14*), selection of other genes for mutation appeared to be dependent on the primary site of the tumor. ECs with MSI accumulate significantly fewer mutations at coding repeats compared to gastrointestinal MSI tumors. For example, the almost systematic *TGFβRII* gene mutation in MSI gastrointestinal tumors was observed in only 0–10 % of the MSI EC in different series [18–20].

Although MSI occurs in a substantial fraction of sporadic EC, data on whether these endometrial tumors differ from their MSI-negative counterparts in clinical characteristics, pathologic features, and survival is controversial; although some studies have reported favorable survival associated with MSI EEC, other series did not find differences in grade, recurrence rate, and survival between MSI-positive and -negative EC [13].

Several studies have analyzed the morphological features associated with MSI, irrespective of the sporadic or hereditary nature of the tumors. MSI EEC tumors frequently have peritumoral lymphocytic infiltration and tumor-infiltrating

lymphocytes (40/10 high-power fields), and some MSI ECs exhibit areas of dedifferentiation [21].

Alterations in the Phosphoinositide 3-Kinase (PI3K)/Akt Pathway

In EEC, the constitutive PI3K-AKT pathway is frequently activated in response to alterations of certain genes, such as those inactivating *PTEN*, mutations or amplifications of *PIK3CA* and somatic missense mutations within AKT kinases.

PTEN gene is located in 10q23, a region undergoing frequent somatic deletion in tumors. It encodes a 403-amino acid dual-specificity phosphatase containing a region of homology to tensin and auxilin, which are two cytoskeletal proteins. Among other activities, PTEN antagonizes the PI3K/AKT pathway, which results in downregulation of AKT phosphorylation activation. Thus, decreased expression of PTEN leads to increased levels of phospho-AKT, which results in both suppression of apoptosis and induction of cell cycle. *PTEN* is mutated in the germ line of patients with Cowden's disease, a rare autosomal dominant cancer syndrome, which occasionally may be associated with EC. However, *PTEN* is also frequently somatically mutated in tumors from various tissues. *PTEN* may be also inactivated by deletion, as shown by the elevated frequency of loss of heterozygosity in different tumor types. Finally, a third proposed mechanism for *PTEN* inactivation is promoter hypermethylation. However, the true significance of *PTEN* promoter methylation is still under discussion.

Loss of heterozygosity at chromosome 10q23 occurs in 40 % of EECs [22]. Moreover, *PTEN* is the most frequently mutated gene in EEC (Fig. 2). The frequency of *PTEN* mutations in EEC varies between 24 and 50 % [2, 23–25] in different series, although one study has reported an incidence as high as 83 % [26]. In addition, *PTEN* silencing may occur not only in EEC and endometrial hyperplasia [25–28] but also in isolated glands in up to 40 % of premenopausal women [29], indicating a major role of this alteration in the initiation of some EEC.

PTEN mutations may occur throughout the entire coding region, but are more frequent in exons 5, 7, and 8. A high percentage of mutations in exon 5 (around 60 %) are single base substitution, being more common in codon 130 (Fig. 2).

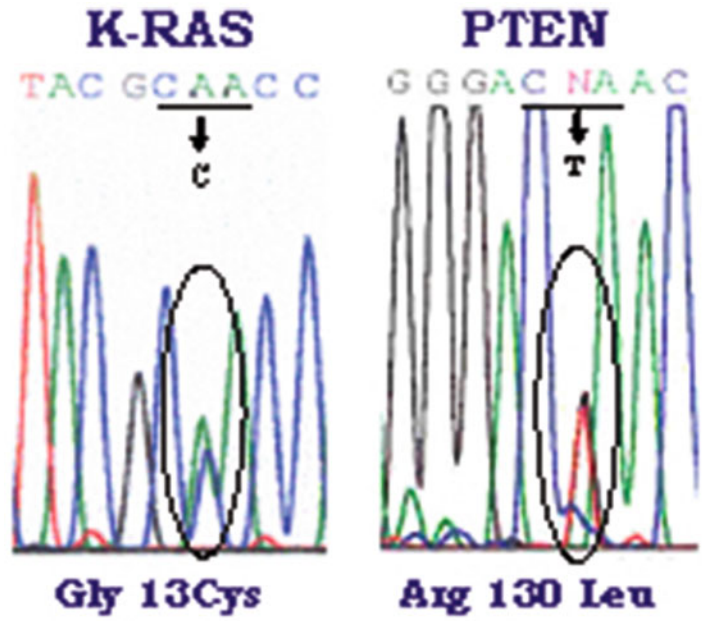

Fig. 2 Common single point mutations in *PTEN* and *K-RAS* genes

In contrast, frameshift mutations are more frequent in exons 7 and 8, where two hot spot deletions or insertions have been identified: two (A)6 sequences in codons 265–267 and codons 321–323. Mutations in those sites are characteristic of MSI tumors and suggest that some mutations in the *PTEN* gene are consequence of loss of DNA repair mechanism. Opinions differ, however, on the relationship between occurrence of *PTEN* gene mutations and the presence of MSI in EC. Thus, most series [24, 30, 31] have demonstrated that *PTEN* gene mutations occur more frequently in EC with MSI (65–86 %) than in those without it (20–36 %). However, other authors failed to find any relationship between high frequency of *PTEN* gene mutations and MSI in EC [26].

PTEN mutations have been detected more frequently in Caucasians relative to African-Americans, and have been correlated with young age, low FIGO-stage, low grade, and favorable prognosis in some studies [32–34]. However, other series have reported higher incidences of *PTEN* in advanced tumors (72 % of PTEN mutations in FIGO stage Ic as opposed to 56 % in FIGO stage Ia), as well as in less differentiated versus well-differentiated carcinomas (81 % in G2 vs. 44 % in G1 ECs) [35].

It has been suggested that PTEN immunostaining may be an effective method to screen for abnormal PTEN expression in tumors and premalignant lesions. However, some variability has been observed with different antibodies and techniques, particularly when correlating the immunohistochemical results with the presence of molecular alterations. Some studies have suggested that the monoclonal antibody 6.H2.1 is the only antibody that recognizes a pattern of PTEN expression that correlates with the presence of molecular alterations in *PTEN* (mutations, deletions, or promoter hypermethylation) [36, 37].

The PI3K pathway can be activated in EC not only by PTEN inactivating mutations but also by mutations in other genes. PI3K is a heterodimer composed of a catalytic subunit (p110α) encoded by *PIK3CA*, which is located at chromosome 3q26.32, and a regulatory subunit (p85α) encoded by *PIK3R1*. A high prevalence of mutations in the *PIK3CA* gene has been reported in EECs (up to 36 %) [2, 38–43], with most studies focusing on exons 9 and 20, as these two exons account for >80 % of mutations in other tumor types, and they encode the C-terminal helical and kinase domains of p110α [41, 42]. A significant association between *PIK3CA* and *PTEN* mutations has also been observed, suggesting an additive effect of these alterations in the activation of the PI3K/AKT pathway [41–43]. *PIK3CA* and *KRAS* mutations appear to be mutually exclusive [40, 43, 44]. However, their association with other genetic defects, such as *CTNNB1* mutations or MSI, remains to be established [41, 42]. A link between *PIK3CA* mutations and adverse clinicopathologic parameters such as grade and stage has been described in some studies [42, 43]. Moreover, mutations in exon 20 are observed more frequently in high-grade than low-grade EECs (67 % vs. 33 %), while grade 1 ECCs are more frequently associated with exon 9 mutations (up to 57 %) [41]. *PI3KCA* amplification has also been reported in 12 % of EECs, occurring independently of mutational events at the same locus, and they are strongly associated with age, suggesting a role of *PIK3CA* amplification in the initiation and progress of ECs in older women [43].

More recently, mutations within the *PI3K* regulatory subunit (*PIK3R1)* have been reported in up to 43 % of EECs, preferentially localized in the p85α-iSH2 domain that mediates binding to p110α [2, 44]. These mutations are mutually exclusive with those affecting *PIK3CA*.

The AKT serine/threonine kinases regulate diverse cellular processes (survival, proliferation, invasion, and metabolism) and they are activated by direct recruitment to the plasma membrane via the pleckstrin homology (PH) domain. A missense mutation in the PH domain of *AKT1* (E17K) previously described in other tumors [45], was demonstrated in 2 % of EECs [46]. Interestingly, the two tumors that displayed *AKT1* mutations did not exhibit any mutations or LOH in *PTEN*, nor mutations in *PIK3CA* or *KRAS*. Subsequently, *AKT1* mutations were demonstrated in 4–12 % of EECs [47, 48], while additional mutations in

other AKT family members (*AKT2* and *AKT3*) have been also described.

Alterations in the WNT Signaling Pathway

The Wnt signaling pathway plays an important role in normal and tumor cells. In the absence of an extracellular Wnt signal in normal cells, the free (cytoplasmic) β-catenin (coded by *CTNNB1*) level is low since the protein is targeted for destruction in the ubiquitin–proteasome system after phosphorylation by glycogen synthase kinase-3β(GSK-3β). The latter forms a complex with the adenomatous polyposis coli (APC) protein and other proteins, such as AXIN1, AXIN2, and protein phosphatase 2A. The most common molecular alterations in tumor cells leading to disruption of β-catenin degradation are mutations that inactivate APC or activate β-catenin itself. These alterations produce an accumulation of cytoplasmic β-catenin that translocates into the nucleus and, interacting with members of the lymphoid enhancer factor-1/T-cell factor (Lef-1/Tcf), activates transcription of various genes, such as *CNDD1* and *MYC*.

Regarding EC, the Wnt signaling pathway is altered only in EEC. In these tumors, mutations of APC have not been detected [49, 50], but *CTNNB1* mutations occurred in approximately 15–36 % of EEC (Fig. 3) [2, 49–53], and in 14 % of endometrial atypical hyperplasias [24]. Most mutations affect the aminoacids implicated in the downregulation of β-catenin through phosphorylation by this serine/threonine kinase (serine 33, serine 37, threonine 41, and serine 45) and two adjacent residues. Mutations in these residues render a fraction of cellular β-catenin insensitive to APC-mediated downregulation and are responsible for upregulation of cytoplasmic β-catenin and its accumulation in the nuclei of tumor cells, which can be detected by immunohistochemistry.

From a morphologic point of view, several studies have stressed the association between nuclear β-catenin accumulation and squamous metaplasia in EEC. Although nuclear β-catenin may be associated with usual squamous metaplasia, it is more characteristically associated with morular metaplasia and *CTNNB1* mutations are found in 50 % of atypical endometrial hyperplasias with squamous morules [28] (Fig. 3).

Some series have not found significant relationship between *CTNNB1* gene mutations and clinicopathologic features, such as age, tumor grade, and stage. However, in the TCGA series, *CTNNB1* mutations were observed in 47 %, 36 %, and 17 % of grade 1, 2, and 3 EECs, respectively [2]. One study has shown an association with low-grade tumors and absence of lymph node metastases [53], suggesting that *CTNNB1* mutations might occur in a subset of less aggressive ECs. In contrast, a recent study has found that *CTNNB1* exon 3 mutations characterize an aggressive subset of low-grade and low-stage EEC occurring in younger women [52].

Mutations in *SOX17* gene, which mediates proteasomal degradation of β-catenin, occur in 8 % EEC without MSI at recurrent positions

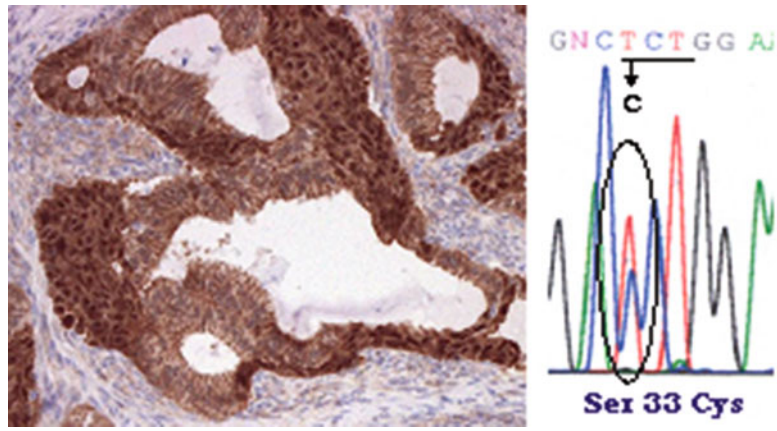

Fig. 3 β-catenin nuclear accumulation in areas of squamous metaplasia in an EEC, which carry a single point mutation in codon 33

(A96G and S403I) and are mutually exclusive with *CTNNB1* mutations [2].

Alterations in the RAS-RAF-MEK-ERK Signaling Pathway

The RAS-RAF-MEK-ERK signaling pathway plays an important role in the development and progression of ECs. The *RAS* gene family consists of three closely related genes (*KRAS*, *NRAS*, and *HRAS*) that encode proteins with GTPase activity, which are localized at the inner plasma cellular membrane and involved in several signal transduction pathways.

KRAS mutations in codons 12 and 13 have been identified in 10–30 % of ECs (Fig. 2) [2, 50, 54–56]. Although some authors have failed to demonstrate a correlation between *KRAS* mutations and stage, grade, depth of invasion, age, or clinical outcome in EC, others have reported associations between *KRAS* mutations and presence of coexistent endometrial atypical hyperplasia, lymph node metastases, and clinical outcome in postmenopausal patients above 60 years [57]. An association between *KRAS* mutations and mucinous differentiation has also been reported [56, 58]. Several studies have tried to correlate *KRAS* mutations and MSI in EC, but results are contradictory.

Other *RAS* genes are infrequently mutated in EC. In the TCGA series, about 3 % of EECs carried point mutations at *NRAS* [2].

BRAF, which encodes a *RAF* family member that functions downstream of RAS, has been reported to be somatically mutated in a number of human cancers. Activating mutations of *BRAF* have been frequently observed in MSI colorectal carcinomas, in which mutations of *BRAF* and *KRAS* have been reported to be mutually exclusive [59]. Several series have analyzed the frequency of *BRAF* mutations in EC. Although one of these studies reported a 21 % incidence of *BRAF* mutations in EEC suggesting an association with MSI status [60], and another study reported 10 % of *BRAF* mutations in EEC [61], most studies have found a very low incidence of *BRAF* alterations [2, 62, 63], indicating a minor role of this gene in endometrial carcinogenesis.

In 10–12 % of EECs, somatic mutations in the tyrosine kinase receptor *FGFR2* have been reported that are identical to the germline mutations associated with craniosynostosis and skeletal dysplasia syndromes [2, 64–66], the most common being S252W and N549K. *FGFR2* mutations are associated with enhanced FGF signaling and downstream activity, predominantly through the RAS-MAPK pathway. Interestingly, while mutations in *KRAS* and *FGFR2* are mutually exclusive events, *FGFR2* and *PTEN* mutations frequently coexist [67].

ARID1A Gene Alterations

ARID1A is a recently identified tumor suppressor gene located at chromosome 1p36 that encodes a large nuclear protein (BAF 250A). This protein is a key component of the multi-protein SWI/SNF complex involved in chromatin remodeling that plays an integral role in controlling gene expression and regulating widely diverse cellular processes, from differentiation during development and proliferation, to DNA repair and tumor suppression [68, 69].

ARID1A mutations were recently described in ovarian clear cell carcinomas, 30 % of ovarian low-grade endometrioid carcinomas and in some cases of atypical endometriosis, a putative precursor of ovarian clear cell and endometrioid carcinomas, suggesting that *ARID1A* loss is a relatively specific event in the genesis of these tumors [70, 71]. Interestingly, most *ARID1A* mutations are insertion/deletion mutations, leading to generation of premature stop codons due to a frameshift, and giving rise to truncated proteins prone to degradation.

A number of studies have demonstrated that the loss of BAF250A protein is correlated with *ARID1A* mutation status [71, 72] (Fig. 4) and a high incidence of *ARID1A* mutations has been reported in both low-grade (up to 40 %) and high-grade (up to 60 %) EECs [73, 74]. Interestingly, in both grade 1 and grade 3 EECs, *ARID1A* mutations are significantly associated with concurrent mutations in *PTEN* and *PIK3CA*, suggesting a cooperative role of these pathways in EEC tumorigenesis [75]. In addition, *ARID1A* mutations seem to be mutually exclusive with

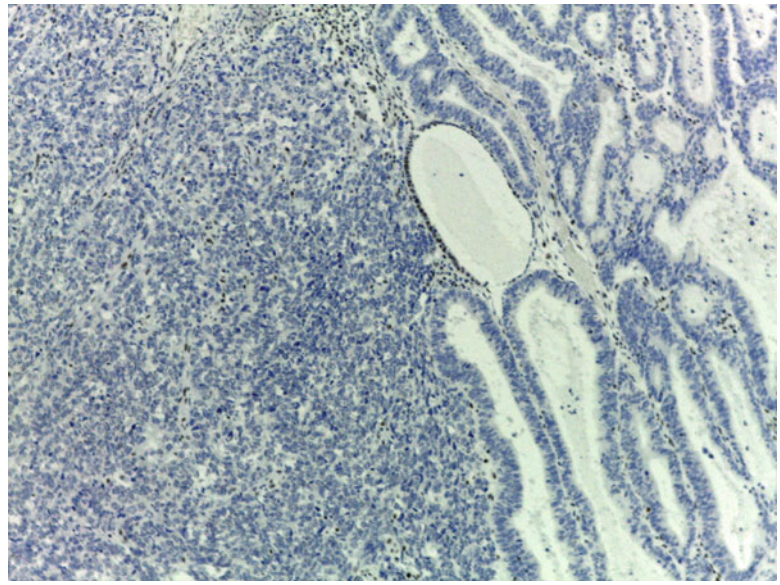

Fig. 4 Endometrioid carcinoma showing loss of ARID-1A expression in both components (dedifferentiated (left) and well-differentiated (right) endometrioid carcinoma). Notice preserved expression in preexistent normal endometrial gland

TP53 mutations, but are associated with MSI [76, 77]. Interestingly, whereas near 75 % of sporadic EECs with MSI also carried *ARID1A* mutations, only 15 % of Lynch-associated EECs did, suggesting that *ARIDIA* is a causative gene instead of a target gene of MSI [77].

TP53 Gene Alterations

The *TP53* tumor suppressor gene was initially identified as being essential for DNA damage checkpoint, but it was subsequently found to have a broader function after cellular stress, such as oncogene activation or hypoxia. The p53 protein is found at very low levels in normal cells. After stress, different pathways lead to posttranslational modification of the protein and its stabilization. This accumulation activates the transcription of a wide range of genes involved in various activities, including cell cycle inhibition and apoptosis depending on cellular context, extent of damage, or other unknown parameters.

Inactivation of *TP53* is essentially due to small mutations (missense and nonsense mutations or insertions/deletions of several nucleotides), which lead to either expression of (90 %) or absence of expression (10 %) of the mutant protein. Thus, there is no a complete concordance between genotyping and immunohistochemistry in tumors with *TP53* mutations. No inactivation of *p53* gene expression by hypermethylation of transcription promoters has been demonstrated. In many instances, these mutations are associated with loss of the wild-type allele of the *TP53* gene located on the short arm of chromosome 17.

TP53 mutations have been detected in approximately 10 % of EECs, being more frequent among grade 3 or advanced stage EECs [2, 78–82]. In contrast, 50–80 % of serous carcinomas carry *TP53* mutations, more frequently associated with protein overexpression (Fig. 5) [2, 83, 84]. For this reason, p53 immunohistochemistry may help in the differential diagnosis of uterine serous carcinoma when it exhibits glands without papillary architecture from EEC [85] although it is important to note that EEC may have *TP53* mutations.

TP53 mutation and expression have been reported to be an adverse prognostic factor in EC in some studies, but not in others. It has been proposed that the functional activity of mutant p53 protein is a strong predictor of survival in these patients [82]. Thus, the presence of dominant-negative *p53* mutations, those that produce mutated proteins that complex with and inactivate wild-type protein, are associated with poor prognosis in advanced EEC.

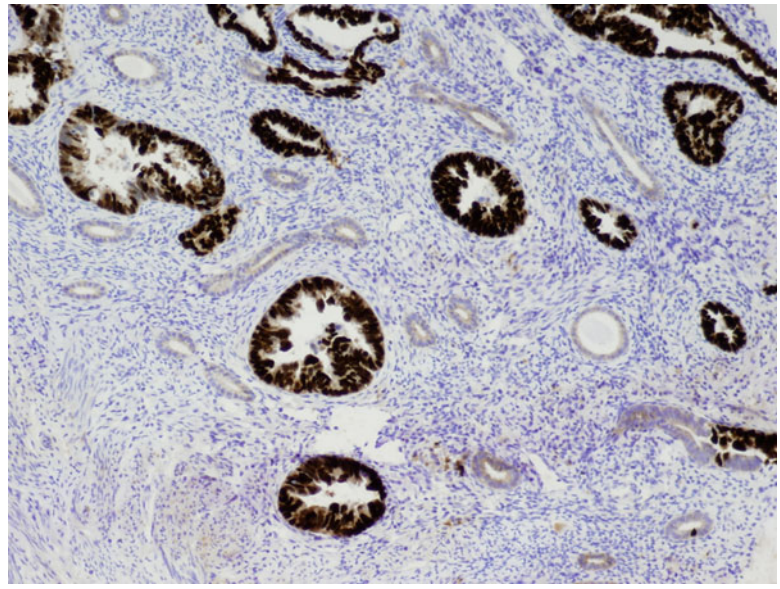

Fig. 5 p53 positive immunostaining in endometrial intraepithelial carcinoma. Note the admixture of atrophic (p53-wild-type) and neoplastic (p53-diffusely and strongly positive) glands

Table 2 Most frequent amplified genes in histological types of endometrial cancer

GENE	Endometrioid carcinoma (%)	Serous carcinoma (%)	Carcinosarcoma (%)
MECOM	4	28	21
CCNE1	1	26	42
ERBB2	1	26	10
PIK3CA	3	22	14
MYC	5	22	21

One of the principal features of tumors with *TP53* mutations is the high level of chromosomal instability that produces losses and gains that involve large chromosomal regions and specific genes. For this reason, serous carcinomas frequently carry amplification of genes like *CCNE1*, *HER2*, *MYC*, and *PIK3CA* [86, 87] (Table 2). Regarding *HER2*, although previous studies found inconsistencies regarding HER2 overexpression and amplification, the Gynaecological Oncology Group (GOG) phase II trial of trastuzumab in advanced and recurrent EC found that *HER2* was amplified in 28 % of serous carcinomas as opposed to 7 % of EECs, demonstrating a correlation between HER2 overexpression and *HER2* amplification [88]. However, no objective responses to trastuzumab therapy alone were reported in tumors displaying either *HER2* overexpression or amplification. Marked heterogeneity of *HER2* gene amplification has been described in endometrial serous carcinoma [89].

Cytogenetic Abnormalities

Cytogenetic studies have shown that most ECs have hyperdiploid karyotypes with relatively simple abnormalities, both numerical and structural, although cases also exist with complex chromosomal rearrangements [90]. Although aberrations of chromosome 1 leading to trisomy/tetrasomy 1q are the most frequent abnormalities reported, no specific karyotypic changes have been detected. A recent comparative genomic hybridization (CGH) study revealed more complex chromosomal imbalances in hormone-independent, type II ECs than in hormone-related, type I carcinomas. Moreover, the same

study showed increased karyotypic complexity in relation to tumor grade in type I ECs, supporting the idea that tumor-phenotype is altered with accumulation of genomic imbalances [91]. Recently the same group compared DNA ploidy status with karyotypic and comparative genomic hybridization data on 51 ECs [92]. They found that gains of material from chromosomes 8 and 7 might be specifically correlated with DNA aneuploidy in ECs, The most frequent CGH findings in the DNA diploid tumors were gains of 1q and of parts of chromosome 10, suggesting that such gains could be an early event in ECs. In contrast, aberrations on chromosome 7 and 8 were rare in DNA diploid tumors but frequent in DNA aneuploid tumors. Of interest, none of the typical genes known to be altered in ECs, like *PTEN*, *KRAS*, and *CTNNB1*, are located on chromosomes 7 and 8.

Carcinosarcomas (Malignant Mixed Müllerian Tumors)

Molecular Abnormalities

A number of immunohistochemical and molecular studies support the monoclonal nature of uterine carcinosarcomas (CSs) [93]. For example, immunohistochemical studies have documented the expression of epithelial markers in the sarcomatous components of a large proportion of tumors. Moreover, X-chromosomal inactivation assays, mutational analyses, and LOH studies have all shown the carcinomatous and sarcomatous elements to share common genetic alterations [94, 95]. Provisional TCGA data (Tables 1 and 2) demonstrated a molecular profile more similar to serous than endometrioid carcinomas. However, a recent study including 17 uterine and 5 ovarian carcinosarcomas demonstrated that molecular alterations typical of EEC are also found in CSs. Thus, 40 % and 32 % of these tumors carried *PTEN* and *ARID1A* mutations respectively [96]. Mutations in *PIK3CA* are also frequent in uterine carcinosarcoma [96, 97]. More than 70 % of uterine CSs overexpressed EGFR, mainly in the sarcomatous component, but only about 20 % of them also carried *EGFR* amplification [97].

Uterine carcinosarcomas differ in their mutational profile from Müllerian adenosarcomas. These mixed tumors with a benign epithelial component frequently carry alterations of the PIK3CA/AKT/PTEN pathway (72 %), but infrequent *TP53* mutations (17 %). In addition, the most frequent amplified genes in Müllerian adenosarcomas are *CDK4* and *MDM2* (28 %), and *MYBL1* (22 %) if sarcomatous overgrowth is present [98].

Cytogenetic Abnormalities

It has been reported that karyotypes and CGH profiles of CSs are very similar to uterine carcinomas and different from sarcomas. Genetic imbalance profiles of CSs frequently mirror those of the epithelial component present in the tumor [91].

Uterine Sarcomas

Leiomyosarcoma

Molecular Abnormalities

Several series, including a relatively low number of tumors, have reported a 13–37 % frequency of *TP53* mutations in these tumors [99–101]. *PTEN* mutational status has been studied in uterine sarcomas since these tumors frequently show loss of heterozygosity of 10q23.3 [102]; however, the incidence of *PTEN* mutations seems to be very low since only one mutation has been detected among 33 leiomyosarcomas analyzed in two different series [103, 104].

MED12 exon 2 mutations are frequently identified in uterine leiomyomas [105] but are mutually exclusive with uterine leiomyomas carrying a 12q14-15 (*HMGA2*) rearrangement [106]. However, *MED12* mutation is a less frequently oncogenetic mechanism in uterine leiomyosarcoma and in extrauterine leiomyomas [107–109].

Table 3 Most frequent/characteristic cytogenetic abnormalities in mesenchymal uterine tumors

Tumor type	Characteristic cytogenetic abnormality	Molecular event
Endometrial stromal tumor	*t*(7;17)(p15;q21)	*JAZF1–JJAZ1* fusion
	t(6;7)(p21;p15)	*JAZF1–PHF1* fusion
	6p21 translocations	*PHF1* rearrangement
	t(10;17)(q22;p13)	*YWHAE- NUTM2AB* fusion
	t(X;22) (p11;q13)	*ZC3H7B- BCOR* fusion
	t(X ;17) (p11.2;q21.33)	*MBTD1-CXorf67* fusion
Intravenous leiomyomatosis	der(14)*t*(12;14)(q15;q24)	*HMGA2* rearrangement
		22q deletion
Leiomyosarcoma	complex karyotype	

Cytogenetic Abnormalities

Most reported karyotypes in uterine leiomyosarcomas are complex without consistent numerical and structural aberrations (Table 3). In addition, CGH studies have confirmed a high frequency of gains and losses of several chromosomal regions [110]. This large number of nonrandom aberrations suggests that increased genetic instability plays a role in the origin of these tumors. The majority of molecular and cytogenetic data do not support an origin of leiomyosarcoma from its benign counterpart. A study of a series of smooth muscle tumors showed different gene expression profiles for leiomyosarcoma and leiomyoma [111]. However, MED12 mutation has been recently detected in a small subgroup of uterine leiomyosarcomas and in extrauterine leiomyomas [108, 109].

The transcriptional profile of a small group of cellular leiomyomas with a specific chromosome abnormality, e.g., del(1)(p11p36), is more similar to that seen in leiomyosarcoma than to profiles of normal myometrium and conventional leiomyoma [112]. A recent study demonstrated that 1p deletion occurs in approximately 25 % of cellular leiomyomas potentially associated with clinicopathologic features that are present with uterine sarcomas [113].

Several uterine smooth muscle proliferations, i.e., intravenous leiomyomatosis (IVL), disseminated peritoneal leiomyomatosis (DPL), and benign metastasizing leiomyoma (BML) are unusual because of their "aggressive" clinical behavior but they do not belong to the malignant category of smooth muscle tumors. However, several cytogenetic alterations have been detected that are worth discussing. A nonrandom pathogenetic event in IVL is the finding of a karyotype showing a der(14)*t*(12;14)(q15;q24) in addition to two normal copies of chromosome 12 (Table 3). The presence of *t*(12;14) in IVL, which is the most frequent abnormality in conventional leiomyomas, suggests a pathogenetic relationship between these two smooth muscle proliferations [114]. Recently an aCGH study in 9 IVL, reveled several losses and gains, including large deletions of 22q chromosome region in 6 [115]. Deletion at 22q is also a frequent aberration observed in BML by karyotyping [116] and aCGH [117]. Finally, DPL, a rare condition presenting with multiple benign smooth muscle proliferations throughout omental and peritoneal surfaces, has been suggested to have a common pathogenesis with conventional leiomyoma because of similar chromosome aberrations involving chromosomes 1, 3, 7, and 12 [118, 119].

Low-Grade Endometrial Stromal Sarcoma

Molecular Abnormalities

No mutations in *TP53*, *PTEN*, *KRAS*, or *CTNNB1* have been described in low-grade endometrial stromal sarcomas (LG-ESS); however, nuclear β-catenin expression is seen in up to 40 % of these tumors [120]. This immunohistochemical pattern might be related to the downregulation of SFRP4, a negative modulator of the Wnt pathway [121].

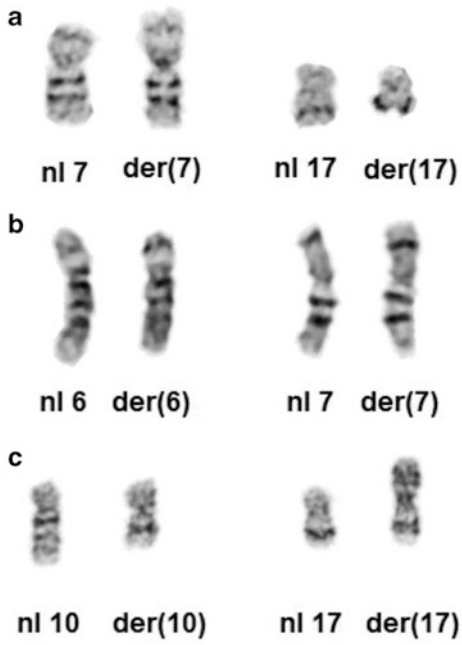

Fig. 6 Partial GTG-banding karyotype showing the most frequent translocations seen in a low-grade ESS: *t*(7;17)(p15;q21) (**a**) and *t*(6;7)(p21;p15) (**b**), and in high-grade ESS *t*(10;17)(q22;p13) (**c**)

Cytogenetic Abnormalities

Cytogenetic abnormalities reported in LG-ESSs demonstrate wide karyotypic heterogeneity. The most common abnormality is a *t*(7;17)(p15;q21) (Fig. 6a) resulting in the fusion of *JAZF1* and *SUZ12(JJAZ1)* genes at 7p15 and 17q21, respectively [122]. *JAZF1-SUZ12* fusion has been detected mostly in endometrial stromal nodules (~65 %), in ~48 % of low-grade (LG)-ESS and in ~12 % of undifferentiated ESSs [123, 124].

The second most frequent abnormality in these tumors is a *t*(6;7) (p21;p15) (Fig. 6b), a so-called variant translocation of the *t*(7;17), because of the involvement of 7p15 and 6p21 instead of the 17q21. [125]. At molecular level, this translocation resulted in a fusion gene between the *PHD* finger protein 1 (*PHF1*) gene, located in chromosome 6, band p21 and the JAZF1 at 7p15. Recently, the same authors expanded our knowledge of the 6p21 rearrangements in ESS. The *PHF1* gene can fuse with *JAZF1* at 7p15, with *EPC1* at 10p11 and *MEAF6* at 1p34 [126]. Moreover, it seems that there is a correlation in ESSs showing sex cord-like differentiation having *PHF1* genetic rearrangement [127].

Two additional translocations have been described in ESSs, a *t*(X;22) (p11;q13) and *t*(X;17) (p11.2;q21.33) associated with a *ZC3H7B-BCOR* fusion and *MBTD1-CXorf67* fusion, respectively [128, 129]. Gene expression profile showed that the *t*(X;17)/*ZC3H7B-BCOR* fusion clustered together with the *t*(7;17)/JAZF1-SUZ12.

Although endometrial stromal tumors are genetically heterogeneous, the different genes involved in stromal nodules and low-grade ESS are functionally related (*PHF1, SUZ12*, *EPC1*, *MBTD1*), being members of the polycomb gene family. Of interest, *ZC3H7B-BCOR*, *MEAF6-PHF1*, and *EPC1-PHF1* fusions were also identify in ossifying fibromyxoid tumors [130] and *JAZ1-PFH1* in an ossifying sarcoma of the heart [131].

High-Grade Endometrial Stromal Sarcomas

Cytogenetic Abnormalities

The most common cytogenetic alteration reported in high-grade ESS is a *t*(10;17)(q22;p13) associated with a *YWHAE-NUTM2AB* (aka FAM22A/B) fusion [132]. Tumors with *YWHAE-NUTM2AB* rearrangements constitute a distinct group of ESS, which is associated with small epithelioid cells, frequent necrosis, and more aggressive clinical behavior compared to JAZF1-LG-ESS but less aggressive than undifferentiated uterine sarcoma [133] (Fig. 6c). Thus, their distinction from undifferentiated uterine sarcoma is important for prognostic and therapeutic purposes, and standardized FISH analysis may be used in this setting [134, 135]. HG-ESSs with *t*(10;17) typically show strong and diffuse nuclear positivity for cyclinD1, Therefore, this can be used as a surrogate screening marker for these tumors [136]. Of interest, the same *t*(10;17)/YWHAE-NUTM2AB has been also reported in clear cell sarcoma, a subgroup of childhood renal tumors [137].

Other Sarcomas

Other sarcomas rarely occur in the uterus, e.g., embryonal rhabdomyosarcoma, primitive neuroectodermal tumor, or liposarcoma among others [138]. Inflammatory myofibroblastic tumors of the female genital tract are rare but characteristically show *ALK* rearrangement [139].

Conclusions

- From a molecular point of view, endometrial cancer is classified into four groups: ultra-mutated, hypermutated, with low mutation frequency and microsatellite stable, and serous-like.
- Ultra-mutated endometrial carcinoma is characterized by mutations in the exonuclease domain of POLE that produces an unusually high mutation rate.
- Tumors with POLE mutations seem to have an excellent prognosis in spite of adverse molecular and pathological features.
- The hypermutated endometrial carcinomas are tumors with microsatellite instability (MSI), most with MLH1 promoter methylation. Immunohistochemistry is a sensitive tool to detect MSI.
- EC is the most common extracolonic tumor in patients with Lynch syndrome.
- There are no differences in grade, recurrence rate, and survival between MSI-positive and -negative EC in most studies.
- Most EECs are MSS EC with low mutation rate. In this group, the most frequently mutated genes are in the PI3K-AKT pathway (*PTEN, PIK3CA, PIK3R1*).
- *CTNNB1* mutations occur more frequently in grade 1 EEC and correlate with immunohistochemical nuclear expression of b-catenin. From a morphologic point of view, nuclear b-catenin accumulation is frequently seen in association with squamous morular metaplasia in EECs.
- *ARID1A* mutations occur in 20–40 % of EEC depending on grade, are more frequent in MSI tumors, and are associated with BAF250A protein expression loss.
- 90 % of EC with extensive somatic copy number alterations and low mutation rates are serous carcinomas, although 10 % of high-grade EEC may have this molecular signature.
- Genomic instability in serous carcinoma is secondary to p53 mutations.
- HER-2 amplification/overexpression is more characteristic of serous carcinomas. However, overexpression of HER-2-neu is not a well-established prognostic marker in EC.
- Molecular-genetic studies support the monoclonal nature of CSs, as they have shown that the carcinomatous and sarcomatous elements share common genetic alterations.
- CSs more frequently have a molecular profile similar to serous carcinomas (TP53 mutations); however, up to 30–40 % have molecular alterations that are more typical of EEC (*PTEN*, *ARID1A*).
- The most common chromosome translocations observed in LG-ESS are *t*(7;17)(p15;q21) associated with *JAZF1-SUZ12* fusion, and translocation involving *PHF1* gene at 6p21, which can frequently fuse with *JAZF1* at 7p15, with *EPC1* at 10p11 and *MEAF6* at 1p34. Rarely, *t*(X;22) (p11;q13) and *t*(X;17) (p11.2;q21.33) associated with a *ZC3H7B-BCOR* fusion and *MBTD1-CXorf67* fusion, respectively, can be also observed.
- High-grade endometrial stromal sarcomas are characterized by the *t*(10;17)(q22;p13) associated with *YWHAE-NUTM2AB*.

References

1. Yeramian A, Moreno-Bueno G, Dolcet X, et al. Endometrial carcinoma: molecular alterations involved in tumor development and progression. Oncogene. 2013;32(4):403–13.
2. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73.
3. Church DN, Stelloo E, Nout RA, et al. Prognostic significance of POLE proofreading mutations in

endometrial cancer. J Natl Cancer Inst. 2014;107 (1):402.
4. Hussein YR, Weigelt B, Levine DA, et al. Clinicopathological analysis of endometrial carcinomas harboring somatic POLE exonuclease domain mutations. Mod Pathol. 2015;28(4):505–14.
5. Meng B, Hoang LN, McIntyre JB, et al. POLE exonuclease domain mutation predicts long progression-free survival in grade 3 endometrioid carcinoma of the endometrium. Gynecol Oncol. 2014;134 (1):15–9.
6. Billingsley CC, Cohn DE, Mutch DG, Stephens JA, Suarez AA, Goodfellow PJ. Polymerase ε (POLE) mutations in endometrial cancer: clinical outcomes and implications for Lynch syndrome testing. Cancer. 2015;121(3):386–94.
7. Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. Gastroenterology. 2014;147 (6):1308–1316.e1.
8. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998;58 (22):5248–57.
9. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96(4):261–8.
10. Tafe LJ, Riggs ER, Tsongalis GJ. Lynch syndrome presenting as endometrial cancer. Clin Chem. 2014;60(1):111–21.
11. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology. 1999;116(6):1453–6.
12. Wijnen J, de Leeuw W, Vasen H, et al. Familial endometrial cancer in female carriers of MSH6 germline mutations. Nat Genet. 1999;23(2):142–4.
13. Karamurzin Y, Rutgers JK. DNA mismatch repair deficiency in endometrial carcinoma. Int J Gynecol Pathol. 2009;28(3):239–55.
14. Esteller M, Catasus L, Matias-Guiu X, et al. hMLH1 promoter hypermethylation is an early event in human endometrial tumorigenesis. Am J Pathol. 1999;155(5):1767–72.
15. Kanaya T, Kyo S, Maida Y, et al. Frequent hypermethylation of MLH1 promoter in normal endometrium of patients with endometrial cancers. Oncogene. 2003;22(15):2352–60.
16. Hardisson D, Moreno-Bueno G, Sanchez L, et al. Tissue microarray immunohistochemical expression analysis of mismatch repair (hMLH1 and hMSH2 genes) in endometrial carcinoma and atypical endometrial hyperplasia: relationship with microsatellite instability. Mod Pathol. 2003;16(11):1148–58.
17. McConechy MK, Talhouk A, Li-Chang HH, et al. Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol. 2015; pii: S0090-8258(15)00584-3.
18. Schwartz S, Yamamoto H, Navarro M, Maestro M, Reventos J, Perucho M. Frameshift mutations at mononucleotide repeats in caspase-5 and other target genes in endometrial and gastrointestinal cancer of the microsatellite mutator phenotype. Cancer Res. 1999;59(12):2995–3002.
19. Catasus L, Matias-Guiu X, Machin P, et al. Frameshift mutations at coding mononucleotide repeat microsatellites in endometrial carcinoma with microsatellite instability. Cancer. 2000;88(10):2290–7.
20. Furlan D, Casati B, Cerutti R, et al. Genetic progression in sporadic endometrial and gastrointestinal cancers with high microsatellite instability. J Pathol. 2002;197(5):603–9.
21. Shia J, Black D, Hummer AJ, Boyd J, Soslow RA. Routinely assessed morphological features correlate with microsatellite instability status in endometrial cancer. Hum Pathol. 2008;39(1):116–25.
22. Peiffer SL, Herzog TJ, Tribune DJ, Mutch DG, Gersell DJ, Goodfellow PJ. Allelic loss of sequences from the long arm of chromosome 10 and replication errors in endometrial cancers. Cancer Res. 1995;55 (9):1922–6.
23. Risinger JI, Hayes AK, Berchuck A, Barrett JC. PTEN/MMAC1 mutations in endometrial cancers. Cancer Res. 1997;57(21):4736–8.
24. Moreno-Bueno G, Hardisson D, Sarrio D, et al. Abnormalities of E- and P-cadherin and catenin (beta-, gamma-catenin, and p120ctn) expression in endometrial cancer and endometrial atypical hyperplasia. J Pathol. 2003;199(4):471–8.
25. Sun H, Enomoto T, Fujita M, et al. Mutational analysis of the PTEN gene in endometrial carcinoma and hyperplasia. Am J Clin Pathol. 2001;115(1):32–8.
26. Mutter GL, Lin MC, Fitzgerald JT, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924–30.
27. Orbo A, Kaino T, Arnes M, Kopp M, Eklo K. Genetic derangements in the tumor suppressor gene PTEN in endometrial precancers as prognostic markers for cancer development: a population-based study from northern Norway with long-term follow-up. Gynecol Oncol. 2004;95(1):82–8.
28. Brachtel EF, Sanchez-Estevez C, Moreno-Bueno G, Prat J, Palacios J, Oliva E. Distinct molecular alterations in complex endometrial hyperplasia (CEH) with and without immature squamous metaplasia (squamous morules). Am J Surg Pathol. 2005;29(10):1322–9.
29. Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res. 2001;61(11):4311–4.

30. Bussaglia E, del Rio E, Matias-Guiu X, Prat J. PTEN mutations in endometrial carcinomas: a molecular and clinicopathologic analysis of 38 cases. Hum Pathol. 2000;31(3):312–7.
31. Koul A, Willen R, Bendahl PO, Nilbert M, Borg A. Distinct sets of gene alterations in endometrial carcinoma implicate alternate modes of tumorigenesis. Cancer. 2002;94(9):2369–79.
32. Risinger JI, Hayes K, Maxwell GL, et al. PTEN mutation in endometrial cancers is associated with favorable clinical and pathologic characteristics. Clin Cancer Res. 1998;4(12):3005–10.
33. Maxwell GL, Risinger JI, Hayes KA, et al. Racial disparity in the frequency of PTEN mutations, but not microsatellite instability, in advanced endometrial cancers. Clin Cancer Res. 2000;6 (8):2999–3005.
34. Salvesen HB, Stefansson I, Kretzschmar EI, et al. Significance of PTEN alterations in endometrial carcinoma: a population-based study of mutations, promoter methylation and PTEN protein expression. Int J Oncol. 2004;25(6):1615–23.
35. Konopka B, Paszko Z, Janiec-Jankowska A, Goluda M. Assessment of the quality and frequency of mutations occurrence in PTEN gene in endometrial carcinomas and hyperplasias. Cancer Lett. 2002;178(1):43–51.
36. Pallares J, Bussaglia E, Martinez-Guitarte JL, et al. Immunohistochemical analysis of PTEN in endometrial carcinoma: a tissue microarray study with a comparison of four commercial antibodies in correlation with molecular abnormalities. Mod Pathol. 2005;18(5):719–27.
37. Eritja N, Santacana M, Maiques O, Gonzalez-Tallada X, Dolcet X, Matias-Guiu X. Modeling glands with PTEN deficient cells and microscopic methods for assessing PTEN loss: endometrial cancer as a model. Methods. 2015;77–78:31–40.
38. Rudd ML, Price JC, Fogoros S, Godwin AK, Sgroi DC, Merino MJ, Bell DW. A unique spectrum of somatic PIK3CA (p110alpha) mutations within primary endometrial carcinomas. Clin Cancer Res. 2011;17(6):1331–40.
39. Oda K, Stokoe D, Taketani Y, McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. Cancer Res. 2005;65(23):10669–73.
40. Velasco A, Bussaglia E, Pallares J, et al. PIK3CA gene mutations in endometrial carcinoma: correlation with PTEN and K-RAS alterations. Hum Pathol. 2006;37(11):1465–72.
41. Catasus L, Gallardo A, Cuatrecasas M, Prat J. Concomitant PI3K-AKT and p53 alterations in endometrial carcinomas are associated with poor prognosis. Mod Pathol. 2009;22(4):522–9.
42. Kang S, Seo SS, Chang HJ, Yoo CW, Park SY, Dong SM. Mutual exclusiveness between PIK3CA and KRAS mutations in endometrial carcinoma. Int J Gynecol Cancer. 2008;18(6):1339–43.
43. Konopka B, Janiec-Jankowska A, Kwiatkowska E, et al. PIK3CA mutations and amplification in endometrioid endometrial carcinomas: relation to other genetic defects and clinicopathologic status of the tumors. Hum Pathol. 2011;42(11):1710–9.
44. Urick ME, Rudd ML, Godwin AK, Sgroi D, Merino M, Bell DW. PIK3R1 (p85alpha) is somatically mutated at high frequency in primary endometrial cancer. Cancer Res. 2011;71(12):4061–7.
45. Carpten JD, Faber AL, Horn C, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. Nature. 2007;448 (7152):439–44.
46. Shoji K, Oda K, Nakagawa S, et al. The oncogenic mutation in the pleckstrin homology domain of AKT1 in endometrial carcinomas. Br J Cancer. 2009;10(1):145–8.
47. Cohen Y, Shalmon B, Korach J, Barshack I, Fridman E, Rechavi G. AKT1 pleckstrin homology domain E17K activating mutation in endometrial carcinoma. Gynecol Oncol. 2010;116(1):88–91.
48. Dutt A, Salvesen HB, Greulich H, Sellers WR, Beroukhim R, Meyerson M. Somatic mutations are present in all members of the AKT family in endometrial carcinoma. Br J Cancer. 2009;101 (7):1218–9.
49. Schlosshauer PW, Pirog EC, Levine RL, Ellenson LH. Mutational analysis of the CTNNB1 and APC genes in uterine endometrioid carcinoma. Mod Pathol. 2000;13(10):1066–71.
50. Moreno-Bueno G, Hardisson D, Sanchez C, et al. Abnormalities of the APC/beta-catenin pathway in endometrial cancer. Oncogene. 2002;21(52):7981–90.
51. Fukuchi T, Sakamoto M, Tsuda H, Maruyama K, Nozawa S, Hirohashi S. Beta-catenin mutation in carcinoma of the uterine endometrium. Cancer Res. 1998;58(16):3526–8.
52. Liu Y, Patel L, Mills GB, Lu KH, et al. Clinical significance of CTNNB1 mutation and Wnt pathway activation in endometrioid endometrial carcinoma. J Natl Cancer Inst. 2014;106(9). pii: dju245.
53. Saegusa M, Hashimura M, Yoshida T, Okayasu I. Beta-catenin mutations and aberrant nuclear expression during endometrial tumorigenesis. Br J Cancer. 2001;84(2):209–17.
54. Sasaki H, Nishii H, Takahashi H, et al. Mutation of the Ki-ras protooncogene in human endometrial hyperplasia and carcinoma. Cancer Res. 1993;53 (8):1906–10.
55. Garcia-Dios DA, Lambrechts D, Coenegrachts L, et al. High-throughput interrogation of PIK3CA, PTEN, KRAS, FBXW7 and TP53 mutations in primary endometrial carcinoma. Gynecol Oncol. 2013;128(2):327–34.
56. Lagarda H, Catasus L, Arguelles R, Matias-Guiu X, Prat J. K-ras mutations in endometrial carcinomas with microsatellite instability. J Pathol. 2001;193 (2):193–9.

57. Ito K, Watanabe K, Nasim S, et al. K-ras point mutations in endometrial carcinoma: effect on outcome is dependent on age of patient. Gynecol Oncol. 1996;63(2):238–46.
58. Alomari A, Abi-Raad R, Buza N, Hui P. Frequent KRAS mutation in complex mucinous epithelial lesions of the endometrium. Mod Pathol. 2014;27 (5):675–80.
59. Rajagopalan H, Bardelli A, Lengauer C, Kinzler KW, Vogelstein B, Velculescu VE. Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. Nature. 2002;418(6901):934.
60. Feng YZ, Shiozawa T, Miyamoto T, et al. BRAF mutation in endometrial carcinoma and hyperplasia: correlation with KRAS and p53 mutations and mismatch repair protein expression. Clin Cancer Res. 2005;11(17):6133–8.
61. He M, Breese V, Hang S, Zhang C, Xiong J, Jackson C. BRAF V600E mutations in endometrial adenocarcinoma. Diagn Mol Pathol. 2013;22(1):35–40.
62. Salvesen HB, Kumar R, Stefansson I, et al. Low frequency of BRAF and CDKN2A mutations in endometrial cancer. Int J Cancer. 2005;115 (6):930–4.
63. Pappa KI, Choleza M, Markaki S, et al. Consistent absence of BRAF mutations in cervical and endometrial cancer despite KRAS mutation status. Gynecol Oncol. 2006;100(3):596–600.
64. Byron SA, Gartside M, Powell MA, et al. FGFR2 point mutations in 466 endometrioid endometrial tumors: relationship with MSI, KRAS, PIK3CA, CTNNB1 mutations and clinicopathological features. PLoS One. 2012;7(2):e30801.
65. Gatius S, Velasco A, Azueta A, et al. FGFR2 alterations in endometrial carcinoma. Mod Pathol. 2011;24(11):1500–10.
66. Pollock PM, Gartside MG, Dejeza LC, et al. Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. Oncogene. 2007;26(50):7158–62.
67. Byron SA, Gartside MG, Wellens CL, et al. Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation. Cancer Res. 2008;68(17):6902–7.
68. Sif S, Saurin AJ, Imbalzano AN, Kingston RE. Purification and characterization of mSin3A-containing Brg1 and hBrm chromatin remodeling complexes. Genes Dev. 2001;15(5):603–18.
69. Reisman D, Glaros S, Thompson EA. The SWI/SNF complex and cancer. Oncogene. 2009;28 (14):1653–68.
70. Jones S, Wang TL, Shih IM, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. Science. 2010;330 (6001):228–31.
71. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med. 2010;363(16):1532–43.
72. Maeda D, Mao TL, Fukayama M, Nakagawa S, et al. Clinicopathological significance of loss of ARID1A immunoreactivity in ovarian clear cell carcinoma. Int J Mol Sci. 2010;11(12):5120–8.
73. Guan B, Mao TL, Panuganti PK, et al. Mutation and loss of expression of ARID1A in uterine low-grade endometrioid carcinoma. Am J Surg Pathol. 2011;35 (5):625–32.
74. Wiegand KC, Lee AF, Al-Agha OM, et al. Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas. J Pathol. 2011;224(3):328–33.
75. McConechy MK, Ding J, Cheang MC, et al. Use of mutation profiles to refine the classification of endometrial carcinomas. J Pathol. 2012;228(1):20–30.
76. Allo G, Bernardini MQ, Wu RC, et al. ARID1A loss correlates with mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas. Mod Pathol. 2014;27(2):255–61.
77. Bosse T, ter Haar NT, Seeber LM, et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer. Mod Pathol. 2013;26(11):1525–35.
78. Risinger JI, Dent GA, Ignar-Trowbridge D, et al. p53 gene mutations in human endometrial carcinoma. Mol Carcinog. 1992;5(4):250–3.
79. Enomoto T, Fujita M, Inoue M, et al. Alterations of the p53 tumor suppressor gene and its association with activation of the c-K-ras-2 protooncogene in premalignant and malignant lesions of the human uterine endometrium. Cancer Res. 1993;53 (8):1883–8.
80. Kihana T, Hamada K, Inoue Y, et al. Mutation and allelic loss of the p53 gene in endometrial carcinoma. Incidence and outcome in 92 surgical patients. Cancer. 1995;76(1):72–8.
81. Swisher EM, Peiffer-Schneider S, Mutch DG, et al. Differences in patterns of TP53 and KRAS2 mutations in a large series of endometrial carcinomas with or without microsatellite instability. Cancer. 1999;85(1):119–26.
82. Sakuragi N, Watari H, Ebina Y, et al. Functional analysis of p53 gene and the prognostic impact of dominant-negative p53 mutation in endometrial cancer. Int J Cancer. 2005;116(4):514–9.
83. Tashiro H, Blazes MS, Wu R, et al. Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. Cancer Res. 1997;57(18):3935–40.
84. Kovalev S, Marchenko ND, Gugliotta BG, Chalas E, Chumas J, Moll UM. Loss of p53 function in uterine papillary serous carcinoma. Hum Pathol. 1998;29 (6):613–9.
85. Darvishian F, Hummer AJ, Thaler HT, et al. Serous endometrial cancers that mimic endometrioid adenocarcinomas: a clinicopathologic and immunohistochemical study of a group of problematic cases. Am J Surg Pathol. 2004;28(12):1568–78.
86. Le Gallo M, O'Hara AJ, Rudd ML, et al. Exome sequencing of serous endometrial tumors identifies

recurrent somatic mutations in chromatin-remodeling and ubiquitin ligase complex genes. Nat Genet. 2012;44(12):1310–5.
87. Zhao S, Choi M, Overton JD, et al. Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. Proc Natl Acad Sci U S A. 2013;110(8):2916–21.
88. Fleming GF, Sill MW, Darcy KM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2010;116(1):15–20.
89. Buza N, English DP, Santin AD, Hui P. Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice. Mod Pathol. 2013;26(12):1605–12.
90. Mitelman F, Johansson B, Mertens F, editors. (2008). Mitelman database of chromosome aberrations in cancer. http://cgap.nci.nih.gov/Chromosomes/Mitelman.
91. Micci F, Teixeira MR, Haugom L, Kristensen G, Abeler VM, Heim S. Genomic aberrations in carcinomas of the uterine corpus. Genes Chromosomes Cancer. 2004;40(3):229–46.
92. Kildal W, Micci F, Risberg B, et al. Genomic imbalances in endometrial adenocarcinomas - comparison of DNA ploidy, karyotyping and comparative genomic hybridization. Mol Oncol. 2012;6(1):98–107.
93. Lopez-Garcia MA, Palacios J. Pathologic and molecular features of uterine carcinosarcomas. Semin Diagn Pathol. 2010;27(4):274–86.
94. Wada H, Enomoto T, Fujita M, et al. Molecular evidence that most but not all carcinosarcomas of the uterus are combination tumors. Cancer Res. 1997;57(23):5379–85.
95. Fujii H, Yoshida M, Gong ZX, et al. Frequent genetic heterogeneity in the clonal evolution of gynecological carcinosarcoma and its influence on phenotypic diversity. Cancer Res. 2000;60(1):114–20.
96. Jones S, Stransky N, McCord CL, et al. Genomic analyses of gynaecologic carcinosarcomas reveal frequent mutations in chromatin remodelling genes. Nat Commun. 2014;5:5006. doi:10.1038/ncomms6006.
97. Biscuola M, Van de Vijver K, Castilla MÁ, et al. Oncogene alterations in endometrial carcinosarcomas. Hum Pathol. 2013;44(5):852–9.
98. Howitt BE, Sholl LM, Dal Cin P, et al. Targeted genomic analysis of Müllerian adenosarcoma. J Pathol. 2015;235(1):37–49.
99. de Vos S, Wilczynski SP, Fleischhacker M, Koeffler P. p53 alterations in uterine leiomyosarcomas versus leiomyomas. Gynecol Oncol. 1994;54(2):205–8.
100. Jeffers MD, Farquharson MA, Richmond JA, McNicol AM. p53 immunoreactivity and mutation of the p53 gene in smooth muscle tumours of the uterine corpus. J Pathol. 1995;177(1):65–70.
101. Teneriello MG, Taylor RR, et al. Analysis of Ki-ras, p53, and MDM2 genes in uterine leiomyomas and leiomyosarcomas. Gynecol Oncol. 1997;65(2):330–5.
102. Quade BJ, Pinto AP, Howard DR, Peters 3rd WA, Crum CP. Frequent loss of heterozygosity for chromosome 10 in uterine leiomyosarcoma in contrast to leiomyoma. Am J Pathol. 1999;154(3):945–50.
103. Lancaster JM, Risinger JI, Carney ME, Barrett JC, Berchuck A. Mutational analysis of the PTEN gene in human uterine sarcomas. Am J Obstet Gynecol. 2001;184(6):1051–3.
104. Amant F, Vloeberghs V, Woestenborghs H, et al. ERBB-2 gene overexpression and amplification in uterine sarcomas. Gynecol Oncol. 2004;95(3):583–7.
105. Mehine M, Mäkinen N, Heinonen HR, Aaltonen LA, Vahteristo P. Genomics of uterine leiomyomas: insights from high-throughput sequencing. Fertil Steril. 2014;102(3):621–9.
106. Markowski DN, Bartnitzke S, Löning T, Drieschner N, Helmke BM, Bullerdiek J. MED12 mutations in uterine fibroids--their relationship to cytogenetic subgroups. Int J Cancer. 2012;131(7):1528–36.
107. Pérot G, Croce S, Ribeiro A, et al. MED12 alterations in both human benign and malignant uterine soft tissue tumors. PLoS One. 2012;7(6):e40015.
108. Ravegnini G, Mariño-Enriquez A, Slater J, et al. MED12 mutations in leiomyosarcoma and extrauterine leiomyoma. Mod Pathol. 2013;26(5):743–9.
109. Bertsch E, Qiang W, Zhang Q, et al. MED12 and HMGA2 mutations: two independent genetic events in uterine leiomyoma and leiomyosarcoma. Mod Pathol. 2014;27(8):1144–53.
110. Levy B, Mukherjee T, Hirschhorn K. Molecular cytogenetic analysis of uterine leiomyoma and leiomyosarcoma by comparative genomic hybridization. Cancer Genet Cytogenet. 2000;121(1):1–8.
111. Quade BJ, Wang TY, Sornberger K, Dal Cin P, Mutter GL, Morton CC. Molecular pathogenesis of uterine smooth muscle tumors from transcriptional profiling. Genes Chromosomes Cancer. 2004;40(2):97–108.
112. Christacos NC, Quade BJ, Dal Cin P, Morton CC. Uterine leiomyomata with deletions of Ip represent a distinct cytogenetic subgroup associated with unusual histologic features. Genes Chromosomes Cancer. 2006;45(3):304–12.
113. Hodge JC, Pearce KE, Clayton AC, Taran FA, Stewart EA. Uterine cellular leiomyomata with chro mosome 1p deletions represent a distinct entity. Am J Obstet Gynecol. 2014; 210(6):572.e1–7.
114. Dal Cin P, Quade BJ, Neskey DM, Kleinman MS, Weremowicz S, Morton CC. Intravenous leiomyomatosis is characterized by a der(14)*t*

(12;14)(q15;q24). Genes Chromosomes Cancer. 2003;36(2):205–6.
115. Buza N, Xu F, Wu W, Carr RJ, Li P, Hui P. Recurrent chromosomal aberrations in intravenous leiomyomatosis of the uterus: high-resolution array comparative genomic hybridization study. Hum Pathol. 2014;45(9):1885–92.
116. Nucci MR, Drapkin R, Dal Cin P, Fletcher CD, Fletcher JA. Distinctive cytogenetic profile in benign metastasizing leiomyoma: pathogenetic implications. Am J Surg Pathol. 2007;31(5):737–43.
117. Bowen JM, Cates JM, Kash S, et al. Genomic imbalances in benign metastasizing leiomyoma: characterization by conventional karyotypic, fluorescence in situ hybridization, and whole genome SNP array analysis. Cancer Genet. 2012;205(5):249–54.
118. Quade BJ, McLachlin CM, Soto-Wright V, Zuckerman J, Mutter GL, Morton CC. Disseminated peritoneal leiomyomatosis. Clonality analysis by X chromosome inactivation and cytogenetics of a clinically benign smooth muscle proliferation. Am J Pathol. 1997;150(6):2153–66.
119. Ordulu Z, Dal Cin P, Chong WW, et al. Disseminated peritoneal leiomyomatosis after laparoscopic supracervical hysterectomy with characteristic molecular cytogenetic findings of uterine leiomyoma. Genes Chromosomes Cancer. 2010;49 (12):1152–60.
120. Ng TL, Gown AM, Barry TS, et al. Nuclear beta-catenin in mesenchymal tumors. Mod Pathol. 2005;18(1):68–74.
121. Hrzenjak A, Tippl M, Kremser ML, et al. Inverse correlation of secreted frizzled-related protein 4 and beta-catenin expression in endometrial stromal sarcomas. J Pathol. 2004;204(1):19–27.
122. Koontz JI, Soreng AL, Nucci M, et al. Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci U S A. 2001;98 (11):6348–53.
123. Nucci MR, Harburger D, Koontz J, Dal Cin P, Sklar J. Molecular analysis of the JAZF1-JJAZ1 gene fusion by RT-PCR and fluorescence in situ hybridization in endometrial stromal neoplasms. Am J Surg Pathol. 2007;31(1):65–70.
124. Chiang S, Oliva E. Recent developments in uterine mesenchymal neoplasms. Histopathology. 2013;62 (1):124–37.
125. Micci F, Walter CU, Teixeira MR, et al. Cytogenetic and molecular genetic analyses of endometrial stromal sarcoma: nonrandom involvement of chromosome arms 6p and 7p and confirmation of JAZF1/JJAZ1 gene fusion in *t*(7;17). Cancer Genet Cytogenet. 2003;144(2):119–24.
126. Micci F, Gorunova L, Gatius S, et al. MEAF6/PHF1 is a recurrent gene fusion in endometrial stromal sarcoma. Cancer Lett. 2014;347(1):75–8.
127. D'Angelo E, Ali RH, Espinosa I, Lee CH, Huntsman DG, Gilks B, Prat J. Endometrial stromal sarcomas with sex cord differentiation are associated with PHF1 rearrangement. Am J Surg Pathol. 2013;37 (4):514–21.
128. Panagopoulos I, Thorsen J, Gorunova L, et al. Fusion of the ZC3H7B and BCOR genes in endometrial stromal sarcomas carrying an X;22-translocation. Genes Chromosomes Cancer. 2013;52(7):610–8.
129. Dewaele B, Przybyl J, Quattrone A, et al. Identification of a novel, recurrent MBTD1-CXorf67 fusion in low-grade endometrial stromal sarcoma. Int J Cancer. 2014;134(5):1112–22.
130. Antonescu CR, Sung YS, Chen CL, Zhang L, et al. Novel ZC3H7B-BCOR, MEAF6-PHF1, and EPC1-PHF1 fusions in ossifying fibromyxoid tumors--molecular characterization shows genetic overlap with endometrial stromal sarcoma. Genes Chromosomes Cancer. 2014;53(2):183–93.
131. Schoolmeester JK, Sukov WR, Maleszewski JJ, Bedroske PP, Folpe AL, Hodge JC. JAZF1 rearrangement in a mesenchymal tumor of nonendometrial stromal origin: report of an unusual ossifying sarcoma of the heart demonstrating JAZF1/PHF1 fusion. Am J Surg Pathol. 2013;37(6):938–42.
132. Lee CH, Ou W, Mariño-Enriquez A, Zhu M, et al. 14-3-3 Fusion oncogenes in high-grade endometrial stromal sarcoma. Proc Natl Acad Sci U S A. 2012;109:929–34.
133. Lee C-H, Mariño-Enriquez A, Ou W, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas – a histologically high-grade and clinically aggressive tumor. Am J Surg Pathol. 2012;36:641–53.
134. Stewart CJ, Leung YC, Murch A, Peverall J. Evaluation of fluorescence in-situ hybridization in monomorphic endometrial stromal neoplasms and their histological mimics: a review of 49 cases. Histopathology. 2014;65(4):473–82.
135. Sciallis AP, Bedroske PP, Schoolmeester JK, et al. High-grade endometrial stromal sarcomas: a clinicopathologic study of a group of tumors with heterogenous morphologic and genetic features. Am J Surg Pathol. 2014;38(9):1161–72.
136. Lee C-H, Ali RH, Rouzbahman M, Marino-Enriquez A, et al. Cyclin D1 as a diagnostic immunomarker for endometrial stromal sarcoma with YWHAE-FAM22 rearrangement. Am J Surg Pathol. 2012;36:641–53.
137. O'Meara E, Stack D, Lee CH, et al. Characterization of the chromosomal translocation *t*(10;17)(q22;p13) in clear cell sarcoma of kidney. J Pathol. 2012;227 (1):72–80.
138. Oliva E. Cellular mesenchymal tumors of the uterus: a review emphasizing recent observations. Int J Gynecol Pathol. 2014;33(4):374–84.
139. Parra-Herran C, Quick CM, Howitt BE, Dal Cin PD, Quade BJ, Nucci MR. Inflammatory myofibroblastic tumor of the uterus: clinical and pathologic review of 10 cases including a subset with aggressive clinical course. Am J Surg Pathol. 2015;39(2):157–68.

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Erratum to: Molecular Pathology and Cytogenetics of Endometrial Carcinoma, Carcinosarcoma, and Uterine Sarcomas

Jose Palacios and Paola Dal Cin

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Page 3
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Page 8
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Prognostic Factors in Uterine Cancer

Patricia M. Baker and Esther Oliva

Abstract

Pathologic staging determines the management of patients with endometrial adenocarcinoma and uterine sarcomas following the initial surgery, and it is an essential component of the initial assessment. FIGO stage, tumor subtype, grade of differentiation, myometrial invasion, lymphovascular invasion, and other factors that guide treatment decisions covered in the subsequent chapters are extensively discussed.

Keywords

Differentiation • Histologic subtype • Lymphovascular invasion • Myometrial invasion • Stage

Endometrial Carcinoma

Endometrial carcinoma (EC) is the fourth most common malignancy in women and is the most prevalent malignancy in the female reproductive tract [1], with 49,560 new cases and 8190 deaths in the USA in 2013 [2]. Most women are postmenopausal and have low-grade, low-stage disease at diagnosis [3, 4] with an approximately 80% overall 5-year survival rate [5], yet poor outcome in "low-risk" patients assessed by conventional histologic parameters does occur. Thus, although conventional histopathologic evaluation to determine pathologic stage remains the cornerstone of prognosis and therapy [6], the discovery of new molecular pathways may lead to additional predictive biomarkers and potential new therapies. The success of adjuvant therapy has generated much interest and work in finding new markers that are more accurate prognostic indicators. This work parallels the recent knowledge that the molecular biology of tumors is strongly related to aggressiveness, and therefore to patient outcome. The ability to individualize treatment by accurately separating low-risk from

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P.M. Baker
Department of Pathology, Health Science Center, Winnipeg, MB, Canada
e-mail: pmbaker@hsc.mb.ca

E. Oliva (✉)
Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Professor of Pathology, Harvard Medical School, Boston, MA, USA
e-mail: eoliva@partners.org

Table 1 Clinicopathologic prognostic factors in endometrial carcinoma

Confirmed prognostic factors
1. Pathologic stage
2. Histologic grade
3. Histologic type
4. Myometrial invasion
5. Lymphovascular invasion
6. Lymph node metastases
7. Age
Conflicting-possible prognostic factors
1. Serosal involvement
2. Cervical involvement

high-risk patients is important to improve outcome and avoid potential complications and morbidity of unnecessary treatment in the low-risk group, many of whom are elderly. Clinicopathologic factors to be considered in prognosis are listed in Table 1.

FIGO Stage

The International Federation of Gynecology and Obstetrics (FIGO) stage is the single most powerful prognostic parameter in EC. In its earlier form, FIGO (1971) was a clinical based staging system, where imaging was used to determine depth of invasion, fractional curettage to assess cervical involvement, and pelvic examination to exclude spread beyond the uterus. The surgicopathologic FIGO stage replaced the clinically based staging system in 1988 [7]. It was based on histopathologic examination of a hysterectomy specimen as well as assessment of the peritoneal cavity and ascitic fluid, adnexa, and pelvic and para-aortic lymph nodes [7, 8]. The initial clinical staging system frequently underestimated surgical stage as the cervical fraction of the D&C specimen was interpreted as positive for adenocarcinoma even though the tumor was found free floating and not attached to cervical tissue; consequently, the patient was automatically assigned to a stage II [9–13]. Besides downstaging clinical stage II tumors to surgicopathologic stage I tumors, the second biggest change occurred with clinical stage III tumors which frequently became pathologic stage IV tumors [13]. The most recent revision of the FIGO staging occurred in 2008 [14] and included changes in stage I tumors combining stage IA and IB as stage IA. Second, cervical glandular involvement was eliminated from staging criteria. Third, as positive peritoneal cytology was no longer found to have independent prognostic significance, it was also removed. Finally, the pelvic and periaortic lymph nodes were not grouped together because the evidence suggested that the prognosis was worse if para-aortic lymph nodes were affected. This resulted in stage IIIC being divided into IIIC-1 (positive lymph pelvic nodes) and IIIC-2 (positive periaortic lymph nodes with or without positive pelvic lymph nodes) [15, 16]. Using the 2008 surgicopathologic FIGO staging system, EC is divided into four main stages (Table 2): (I) tumor is confined to the uterine corpus, (II) tumor involves the cervix, (III) tumor extents to the true pelvis, and (IV) tumor is present beyond the true pelvis. Stage I disease is further subclassified into two categories based on depth of myometrial invasion, the latter closely related to prognosis in stage I tumors [6, 17–19]. Stage IA tumors are confined to the endometrium or invade less than half of the myometrium and carry an excellent prognosis with greater than 90% overall survival for grade 1 and 2 endometrioid carcinomas (Fig. 1) [15]. Stage IB tumors show invasion equal to or more than half of the myometrium. Stage II tumors are those showing cervical stromal invasion (Fig. 2). Stage III tumors are further subdivided into three categories; IIIA indicates uterine serosal and/or adnexal involvement (Fig. 3), IIIB tumors involve the vagina either by direct extension or metastases and/or parametrial involvement, and IIIC tumors are subdivided into IIIC-1 when there is only involvement of the pelvic lymph nodes and IIIC-2 when there are positive para-aortic lymph nodes with or without positive pelvic lymph nodes (Fig. 4). Finally, stage IV tumors directly extend to bladder and/or bowel mucosa (IVA) or are associated with distant metastases including intra-abdominal and/or inguinal lymph nodes (IVB) [7]. In the revised 2008 FIGO staging system, the number of patients with stage I tumors has increased (up to 80%) while patients with stage

Table 2

Carcinoma of the endometrium
Stage I*: tumor confined to the corpus uteri
IA*: no or less than half myometrial invasion
IB*: invasion equal to or more than half of the myometrium
Stage II*: tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III*: local and/or regional spread of the tumor
IIIA*: tumor invades the serosa of the corpus uteri and/or adnexae#
IIIB*: vaginal and/or parametrial involvement#
IIIC*: metastases to pelvic and/or para-aortic lymph nodes#
IIIC1*: positive pelvic nodes
IIIC2*: positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*: tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*: tumor invasion of bladder and/or bowel mucosa
IVB*: distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes.
*Either G1, G2, or G3
**Endocervical glandular involvement should be considered as Stage I and no longer as Stage II
#Positive cytology has to be reported separately without changing the stage
Leiomyosarcoma and endometrial stromal sarcoma
Stage I: tumor limited to uterus
IA: less than 5 cm
IB: greater than or equal to 5 cm
Stage II: tumor extends to the pelvis
IIA: adnexal involvement
IIB: tumor extends to extrauterine pelvic tissues
Stage III: tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA: one site
IIIB: more than one site
IIIC: metastases to pelvic and/or para-aortic lymph nodes
Stage IV: tumor invades bladder and/or rectum and/or distant metastases
IVA: tumor invades bladder and/or rectum
IVB: distant metastases
Adenosarcoma
Stage I: tumor limited to uterus
IA: tumor limited to endometrium/endocervix (without myometrial invasion)
IB: tumor invades up to less than half of myometrium
IC: tumor invades to more than one half of myometrium
Stage II: tumor extends to the pelvis
IIA: adnexal involvement
IIB: tumor extends to extrauterine pelvic tissues
Stage III: tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA: one site
IIIB: more than one site
IIIC: metastasis to pelvic and/or para-aortic lymph nodes
Stage IV: tumor invades bladder and/or rectum and/or distant metastases
IVA: tumor invades bladder and/or rectum
IVB: distant metastases

IIA tumors will be reclassified as having stage IA or IB, and therefore the number of stage II tumors has decreased, and the remainder will have stage III or IV disease. Importantly, patients with stage IIIA tumors will decrease in frequency as positive cytology is no longer considered to be part of

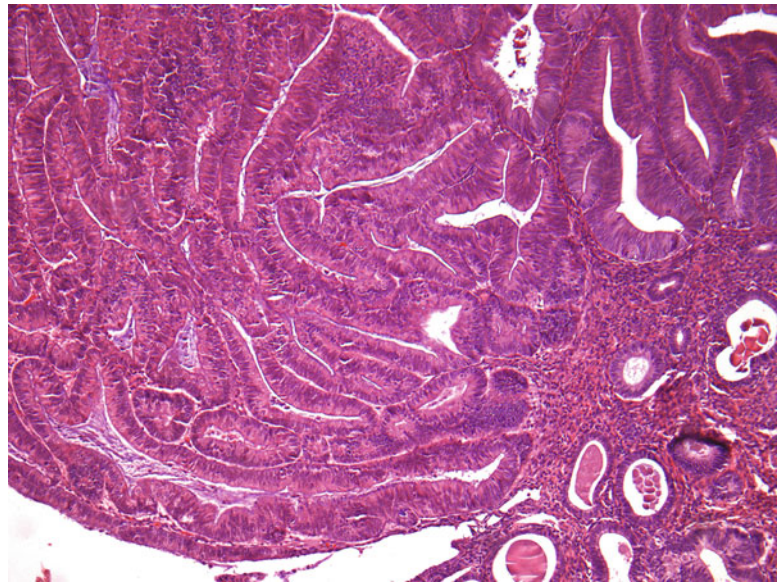

Fig. 1 A well-differentiated endometrioid carcinoma composed of well-formed glands is confined to the endometrium (stage IA)

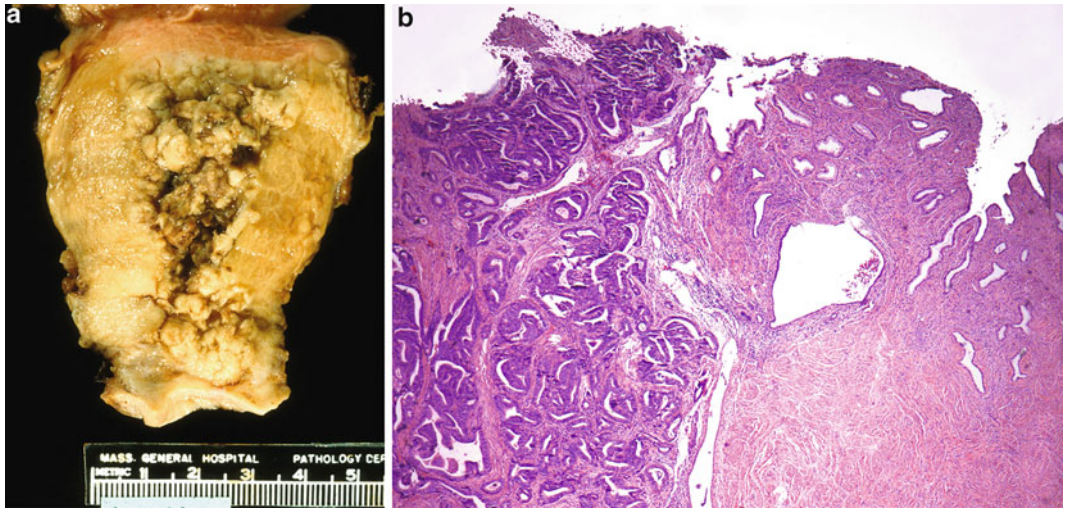

Fig. 2 Secondary involvement by direct extension of the cervix by endometrial carcinoma may be seen grossly (**a**) or only microscopically (**b**). Notice that only cervical stromal involvement counts towards stage II

the staging system and most of these patients will have disease confined to the uterus [13, 19, 20].

Surgico-pathologic staging has proven to be very accurate and has been shown to be the single strongest predictor of survival in multivariate analysis studies [6, 21–25]. The revised 2008 FIGO staging system has shown to produce even more accurate stratification of survival rates in patients with endometrial cancer [19, 20]. Thus, surgically staged patients without extrauterine disease are associated with low recurrence rates, whereas if disease is found outside the uterus, the recurrence rate is close to 50% [26]. Although not perfect, the surgico-pathologic staging system allows for the best approach to tailoring treatment of patients with EC. One group has developed a binary grading system incorporating histology (grade 1 and

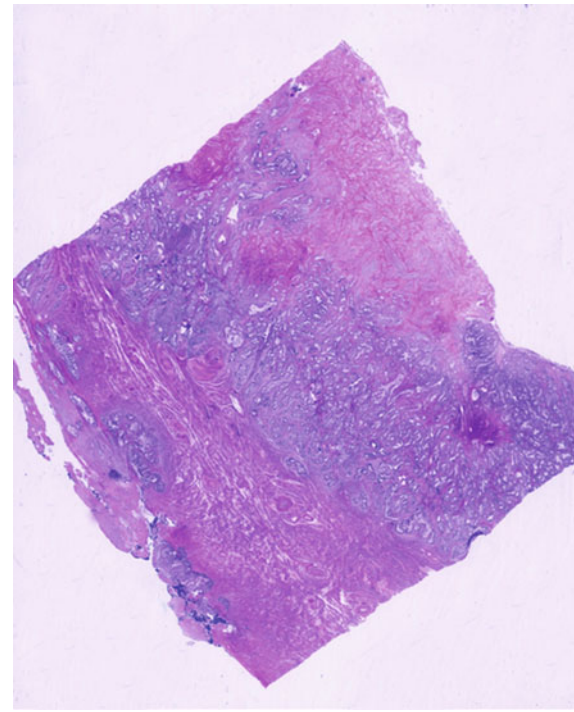

Fig. 3 The endometrial carcinoma invades through the myometrium into the serosa (stage IIIA)

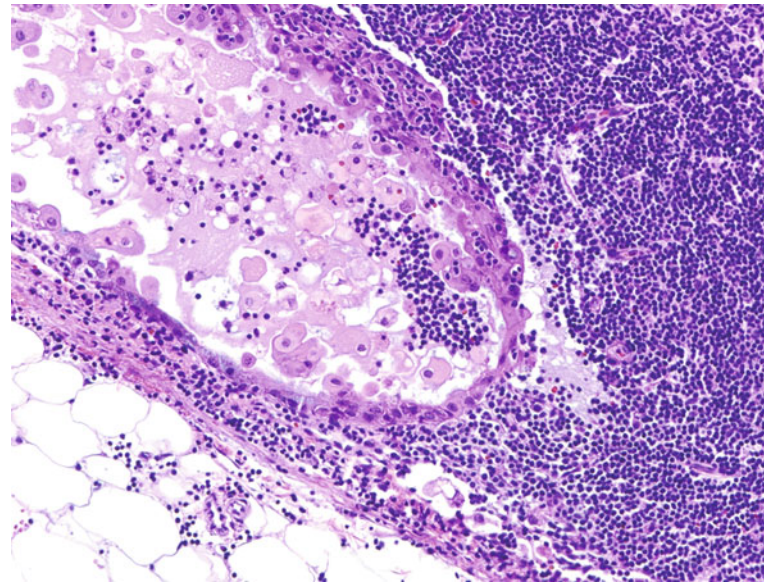

Fig. 4 A neoplastic gland is present in the subcapsular sinus of a lymph node (stage IIIC)

2 versus grade 3 and non endometrioid), myometrial invasion, and lymph node assessment for stage I EC and has suggested that it has an improved predictability of survival compared to the 2008 FIGO [27]. Staging should be assigned at the time of definitive surgery and prior to administration of adjuvant treatment and should not be changed based on disease progression, recurrence, or response to adjuvant treatment preceding surgical treatment.

Even though the overall 5-year survival rate for EC is approximately 75–80%, when stratified by stage, the 5-year survival rate for EC is as follows: 90% for stage I tumors, 75% for stage II tumors, and 45% and 25% for stage III and IV tumors, respectively [13, 21, 28]. As EC patients typically require long term follow-up and the newly revised FIGO staging system has only been in use for the last 7 years, information related to survival is lacking.

Histologic Grade

Histologic grade is an important prognostic parameter in EC, especially for endometrioid carcinomas (EECs). However, in some large studies, histologic grade is not as important prognostic factor as surgico-pathologic stage or myometrial invasion in multivariate analyses, but is closely related to them [6, 21, 29]. EECs are graded in a three-tier system based on the amount of solid growth of the glandular component following the FIGO/ISGP surgico-pathologic grading system. EEC grade 1 shows $\leq$5% of solid areas Fig. 1), grade 2 contains 6–50% of solid areas Fig. 5), and grade 3 EEC displays >50% of a solid glandular component (Fig. 6). The squamous component which may be present as keratinizing or morular differentiation should not be taken into account when grading EEC. The 1988 FIGO stage revision incorporated nuclear grade as part of the grading system and this rule has not been changed in the new revised FIGO staging system. However, the definition used at that time was subjective as stated that "notable cytologic atypia, inappropriate for the architectural grade, should raise the grade of a grade 1 or grade 2 tumor by one" [7]. Some investigators have found the interobserver reproducibility acceptable for architectural grade but poor for nuclear grade [30, 31]. Only when striking nuclear atypia, defined by large, pleomorphic nuclei with coarse chromatin and large and irregular nucleoli equating nuclear grade 3, is present in a grade 1 or grade 2 EEC, should the tumor be upgraded to a grade 2 or 3 EECs, respectively. Upgrading a grade 1 EECs when either grade 2 or 3 nuclei is identified results in reassignment of a sizable number of EECs. This may not always be justified, as patients with architectural grade 1 tumors and grade 2 nuclei have a similar outcome compared with patients with grade 1 tumors by architecture and cytologic features [6]. The distribution of EECs by grade is approximately as follows: 20–35% grade

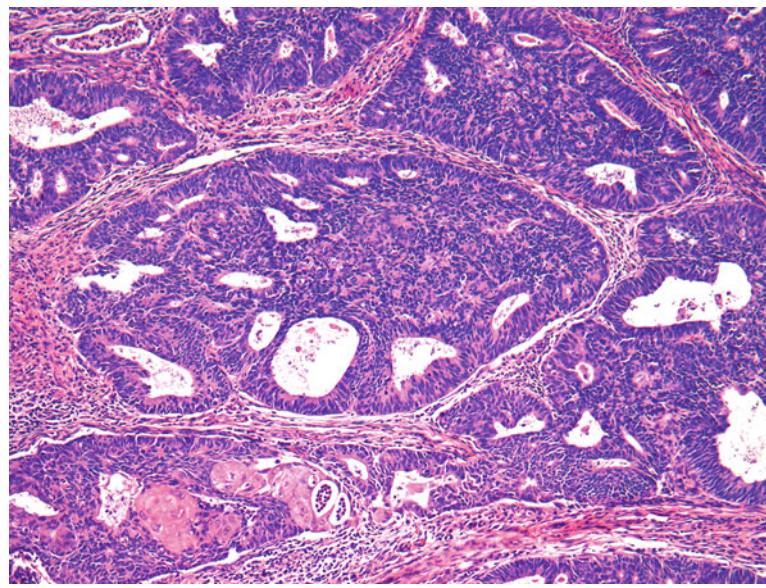

Fig. 5 Moderately differentiated endometrioid carcinoma with solid growth that comprised >5% and <50% of the malignant glandular growth

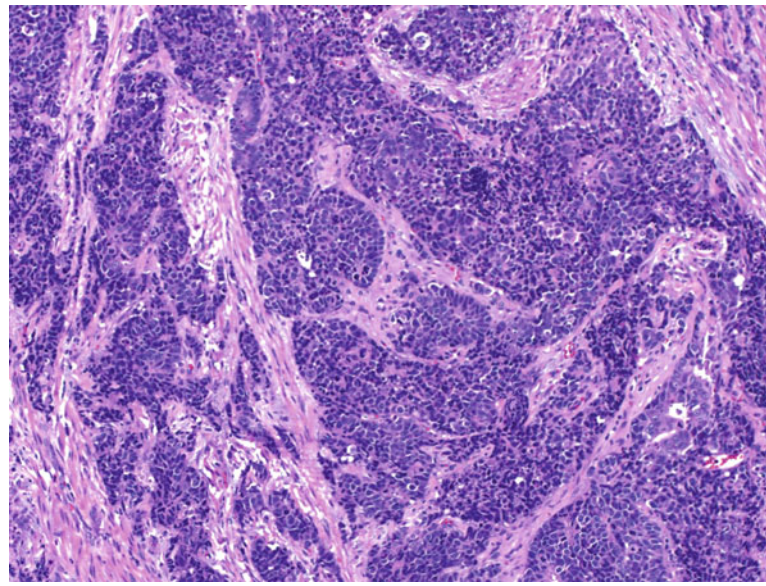

Fig. 6 Poorly differentiated endometrioid carcinoma composed of diffuse solid growth

1, 40–45% grade 2, and 15–30% grade 3 [21, 32, 33]. One caveat when dealing with an EC with "gland" formation and high-grade cytology is the consideration of the glandular variant of serous carcinoma [34]. As mentioned earlier, grade is closely related to myometrial invasion, <10% of grade 1 in contrast to >40% of grade 3 EECs show invasion of the outer half of the myometrium [21, 29]. FIGO grade is also closely related to the risk of lymph node metastases as well as the risk of recurrences [25, 26, 35–37]. Grade 1 and 2 EECs, considered within the low-risk group, are associated with a very low risk (2.4%) of lymph node metastases compared to 10% in patients with grade 3 tumors when myometrial invasion was removed from the analysis [38]. The 5-year survival rate for grade 1 EECs ranges from 85% to 100% while it decreases to 55% for grade 3 tumors [21, 39–41]. In some studies, the survival rate of grade 3 EECs is comparable to serous papillary and clear cell carcinoma (CCC) [42–44] but other studies have shown that patients with grade 3 EECs have better outcome when compared to serous carcinomas especially in early stage disease [45, 46]. Furthermore, in some studies, grade 3 EECs are associated with the highest risk of recurrence among all surgico-pathologic parameters [28]. Two other binary grading systems have been proposed to grade EECs into either low or high grade. The first one uses low-magnification assessment of the amount of solid growth, pattern of invasion, and the presence of necrosis. An EEC is classified as high grade if it has at least two of the following three criteria: (1) >50% solid growth (without distinction of squamous from non-squamous epithelium), (2) a diffusely infiltrative rather than expansive growth pattern, and (3) tumor cell necrosis. This system separates patients into three prognostically and therapeutically different groups. Patients with stage I low-grade tumors with invasion confined to the inner half of the myometrium (stages IA and IB) have 100% survival rates. Patients with low-grade tumors that invade the outer half of the myometrium (stage IC and stages II–IV) and patients with high-grade tumors with invasion confined to the myometrium (stage IB and IC) have 5-year survival rates of 67–76% [47]. This binary grading system permits greater interobserver and intraobserver reproducibility compared to FIGO and nuclear grading. However, overall, no dramatic differences exist between the two systems [33]. A second system divides EECs into high or low grade based on assessment of the following

features: 1] predominantly papillary or solid growth pattern, (2) mitotic index ≥6/10 HPFs, and (3) severe nuclear atypia. The presence of at least two of these three criteria results in a tumor being classified as high grade. This system seems more reproducible than FIGO and at the same time is an independent predictor of patient outcome when survival is adjusted for FIGO stage, patient age, and tumor cell type. However, the FIGO grading system is still superior for prognostication in EECs [48, 49]. The grading system in serous carcinomas, CCCs, and squamous cell carcinomas is based on nuclear features even though most of these tumors form glands. As these tumors typically display high-grade nuclei, they are classified as grade 2 or 3 cancers.

Histologic Type

Cell type is an important prognostic factor in EC [39, 50]. A dualistic model to explain the pathogenesis of EC based on cell type was first described by Bokhman [35]. Type I tumors represent about 80% of ECs, are typically EECs that develop in premenopausal or perimenopausal women, are associated with estrogenic stimulation, and frequently coexist or are preceded by endometrial hyperplasia. Most EECs are confined to the uterus at the time of presentation (Fig. 1), display ER positivity, and have a favorable prognosis [51]. Squamous differentiation is seen in approximately 25% of EECs. In the past, EECs with squamous differentiation were divided into adenoacanthoma and adenosquamous carcinoma depending on cytologic features. Initially, it was thought that adenosquamous carcinomas had a poorer prognosis than adenoacanthomas; however, it has been shown that the degree of differentiation of the squamous component parallels that of the glandular component in the majority of the cases and that the clinical behavior of EECs with squamous foci is similar to that of conventional EECs [50, 52]. There is a subgroup of EECs that despite being well differentiated show a diffuse infiltrative pattern into the myometrium

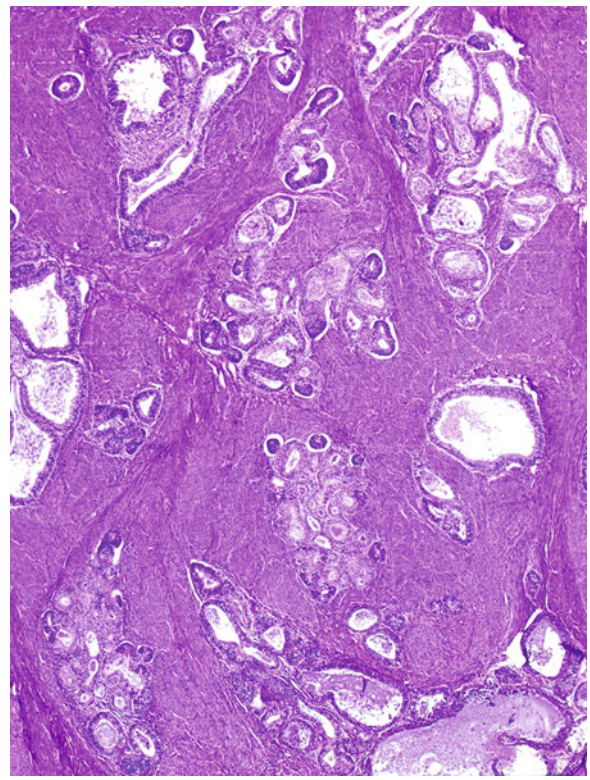

Fig. 7 A well-differentiated endometrioid carcinoma shows diffuse permeative invasion (the so-called "adenoma malignum")

(the so-called "adenoma malignum") (Fig. 7); in some studies, this finding is associated with a worse prognosis compared to more well-differentiated EECs [37, 53–55]. Villoglandular adenocarcinoma, considered a variant of EEC, has been shown by some investigators to behave in a more aggressive manner than conventional EECs when the papillary component infiltrates into the myometrium. Higher rates of lymphovascular invasion, lymph node metastases, and a worse outcome have been found in these types of tumors compared to EECs showing myometrial invasion in the form of glandular or solid patterns [56]. However, these findings have not been corroborated by other investigators who found these tumors to have a similar behavior to that observed in conventional EECs [57]. Other variants of EECs including those with squamous differentiation, secretory changes, or ciliated have a similar outcome to that observed in conventional ECC. Endometrioid carcinomas with an MELF (microcystic, elongated and fragmented glands) pattern of invasion have been associated with a higher frequency of lymphovascular invasion and consequently of lymph node involvement (Fig. 8) [58, 59]. Well-differentiated EECs associated with an undifferentiated component (dedifferentiated carcinoma) (Fig. 9) are aggressive tumors with a poor outcome even when diagnosed at a low stage [60].

Mucinous adenocarcinomas are uncommon (<5%) and are related to EECs [61]. These are defined as tumors with >50% of cells containing mucin (WHO) and have an outcome comparable to conventional EECs [61, 62]. In a recent study in which the Surveillance, Epidemiology, and End Results (SEER) Program data for 1988 to 2009 was reviewed, no differences were found in patient outcome when comparing mucinous adenocarcinomas to EECs although it was stated that patients with mucinous carcinoma had a higher frequency of pelvic but not para-aortic lymph node involvement [63].

Non-endometrioid carcinomas (the so-called "type II") represent about 10% of ECs. This category is largely composed of serous and clear cell carcinomas. These tumors typically occur in postmenopausal women and are unrelated to estrogen exposure, developing from atrophic endometrium. Additionally serous carcinomas develop in endometrial polyps [64, 65] or from the putative precancerous lesion "endometrial intraepithelial carcinoma" [66], a term that should be discouraged as it is misleading. Serous carcinomas are very aggressive, often with myometrial or lymphovascular

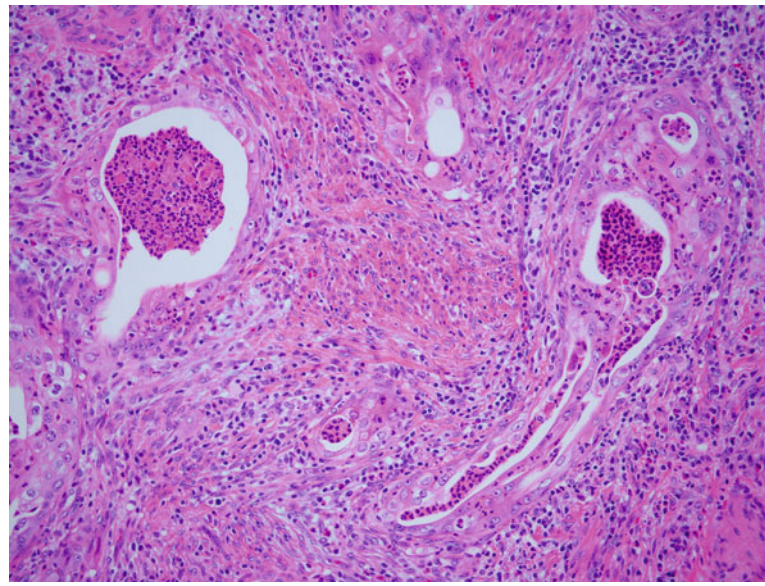

Fig. 8 Elongated focally fragmented neoplastic endometrioid glands associated with acute inflammatory cells and marked stromal response invade the myometrium

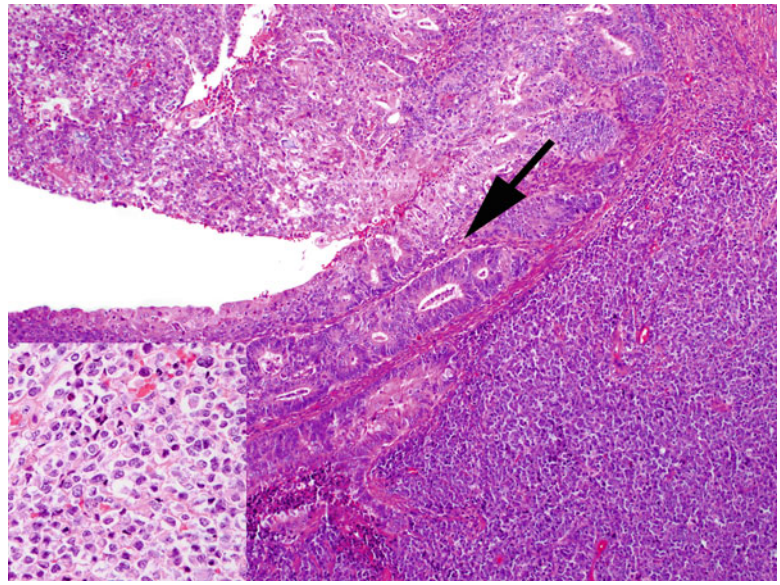

Fig. 9 A well to moderately differentiated endometrioid carcinoma (*arrow*) is juxtaposed to an undifferentiated component (dedifferentiated carcinoma). Notice the non-cohesive nature of the latter component (*insert*)

invasion, and carry a poor prognosis even when confined to endometrial polyps [65, 67–73]. Tumors arising within polyps or measuring $\leq$1 cm in diameter (minimal uterine serous carcinoma) may have a better prognosis when compared to larger tumors [74, 75]. However, even patients with stage I serous carcinomas have an overall survival of 30% ranging from 54 to 72% and from 27 to 59% in stage I and stage II tumors, respectively [65, 68–70, 90]. Some studies have shown that patients with stage I serous carcinoma have a better prognosis [76] especially when they have a comprehensive staging procedure [77] as patients with serous carcinoma confined to the endometrium have a frequency of lymph node involvement as high as 19% [78]. These tumors are responsible for 50% of all relapses that occur in ECs and surgical staging is extremely important as up to 58% of clinically stage I tumors may be upstaged surgically [67, 79]. The binary grading system adopted for serous carcinomas of the ovary [80] which provides a framework for predicting better clinical outcomes [81] does not seem to help in endometrial tumors [82]. These tumors are associated with p53 mutations, are ER negative, and show a high degree of chromosomal instability [83–85]. Some investigators have hypothesized that non-EECs may arise from two different pathways: (1) de novo through p53 mutations, LOH at several loci, or by other still unknown gene alterations; or (2) through dedifferentiation of a preexisting EEC [86]. This, in fact, may explain EC with endometrioid and serous components, and additionally may explain why high-grade EECs behave more like serous and CCCs, as they may have similar molecular alterations but may not have yet switched phenotypes. It is important to recognize and report any foci of serous carcinoma as it is prognostically significant.

Clear cell carcinoma is also considered a type II carcinoma, associated with an aggressive behavior and poor outcome with an overall 5- and 10-year survival rates of 42 and 31%, respectively [69, 87]. In one study, 41.5% patients with CCC had localized disease, 12.2% were associated with regional spread, and 46.3% with distant metastases ($p = 0.2$) with a median progression free survival of 31.4 months [88]. Myometrial invasion occurs in approximately 80% and lymphovascular invasion in about 25% of these tumors [87, 89, 90]. As reported for serous carcinoma, CCC is associated with a high incidence of extrapelvic disease. Several studies have shown a high propensity,

up to 25%, of extrauterine spread in patients with stage I tumors [24, 91–93]. In contrast to peritoneal spread seen in serous carcinoma, the distribution of recurrent disease does not have a distinctive pattern but includes intra-abdominal and retroperitoneal organs as well as distant sites [90]. One study has shown that patients with stage I CCC did better than patients with same stage serous carcinoma [90]. Another study found a very similar prognosis when compared to patients with stage I grade 3 EECs [94]. However, overall, high-grade endometrial cancers, including serous, clear cell and grade 3 EECs treated in an individualized manner are associated with similar clinical outcomes [44].

Squamous cell carcinomas and transitional cell carcinomas are rare tumors and their prognosis may be related to tumor stage. Stage II–IV squamous cell carcinomas carry a poor prognosis [95, 96], while transitional cell carcinomas seem not to have a more aggressive behavior than conventional EECs [97, 98]. Other rare carcinomas, including small cell carcinoma and undifferentiated carcinoma are typically associated with poor outcome [99–102].

Myometrial Invasion

The depth of myometrial invasion often has an inverse relationship to the degree of tumor differentiation and has been shown to be a strong [26, 37, 39, 103, 104] and often independent prognostic risk factor based on multivariate analysis in several studies [6, 13, 21, 32]. In the FIGO (1988) staging system, the presence or absence of myometrial invasion and the depth of the invasion defined stage I tumors. However, tumors that invade the inner half of the myometrium are grouped with tumors confined to the endometrium in the 2008 FIGO classification as grade 1 and grade 2 stage IA and IB tumors have a very similar outcome ranging from 91.3 to 93.4% [15, 18, 19, 105]. However, one group has shown that combining the 1988 FIGO stage IA and IB eliminates the group with the most favorable outcome (stage IA) and the overall survival for stage IB is substantially affected and thus this new system does not improve predictability of outcome [17]. The histologic features of myometrial invasion include irregularly shaped endometrial glands that are unaccompanied by stroma, often appearing "naked" within the myometrial smooth muscle, lying below the level of the endomyometrial junction, which is by nature very irregular. On occasion, the infiltrative nature of the glands is recognized by an adjacent desmoplastic appearing stroma containing scattered inflammatory cells [106]. Failure to recognize the very irregular, undulating nature of the endomyometrial junction may result in the diagnosis of a noninvasive carcinoma as invasive (Fig. 10). In fact, two studies have shown that not infrequently the assessment of myometrial invasion is overestimated (up to 32% of cases) [107, 108]. Besides, the typical infiltrative growth pattern of invasion, a MELF (microcystic, elongated and fragmented glands) [109] as well as a "single-cell/cell clusters" [110] which is often seen in association with MELF pattern of invasion have been considered to have an increased frequency of lymphovascular invasion and lymph node metastases [58, 111, 112] while the infiltrative pattern of invasion was associated with a higher stage, higher frequency of lymphovascular invasion and recurrence in one study [59]. The depth of invasion may be overestimated if carcinoma involving adenomyotic foci is not recognized. Studies have shown that carcinoma involving adenomyosis does not adversely affect prognosis [108, 113–115] even when it involves deep foci of adenomyosis [115]. It is important to keep in mind that EECs may have an "adenomyosis-like" pattern of invasion that should not be confused with adenomyosis [59]. Foci of adenomyosis are felt to represent deep herniation of endometrium into the myometrium with continuity to the surface. The finding of residual benign endometrial glands or stroma and lack of a desmoplastic reaction are helpful in identifying adenomyotic foci involved by carcinoma. Very rarely, carcinoma may arise in adenomyosis in the absence of carcinoma in the endometrium and the prognosis in these cases is the same as carcinoma confined to the endometrium [108].

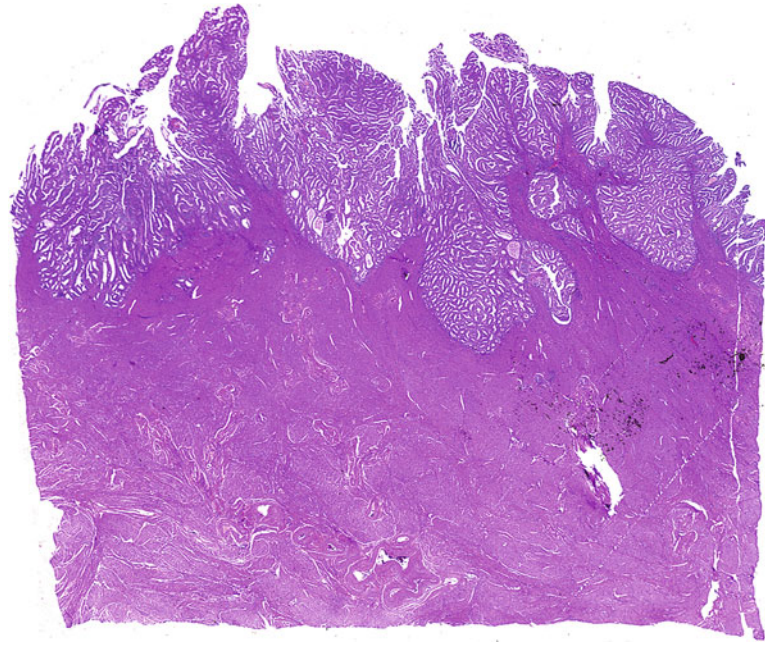

Fig. 10 A well-differentiated endometrioid carcinoma is filling the irregular endomyometrial junction. This phenomenon should not be misinterpreted as myometrial invasion

Other methods to measure the depth of myometrial invasion, besides the FIGO staging system, have been suggested. These methods include division of the myometrium into thirds or measurement of the distance of the invasive tumor from the uterine serosa. One study found the tumor-free distance from the serosa to be a more accurate predictor of survival than depth of invasion [116]. No conclusion or consensus has been reached as to the best method of measuring depth of invasion.

A large study of women with EC showed the overall 5-year survival rate to be 94% when tumor was confined to the endometrium, while it decreased to 59% with tumor involving the outer one-third of the myometrium [117]. The importance of accurately assessing myometrial invasion is underscored by the fact that pelvic and para-aortic lymph node dissection is in part determined by the degree of invasion. Studies have suggested that the use of intraoperative frozen section to determine depth of invasion, particularly in high-grade carcinomas, is more accurate than gross intraoperative assessment alone [118–120]. Low-grade carcinomas may be associated with lymph node involvement particularly when deep myometrial invasion is present. The depth of invasion can often be accurately assessed by gross examination, particularly in low-grade tumors [121], while the depth of invasion in high-grade tumors may be difficult to assess grossly. In fact, assessment of myometrial invasion at the time of frozen section, is part of an algorithm that includes tumor size, endometrioid versus non endometrioid histology, grade of endometrioid carcinoma, depth of myometrial invasion and lymphovascular invasion if noted in order to predict the need of lymph node dissection [122]. Finally, a study involving 80 women with stage I EC determined that the presence of lower uterine segment involvement does not correlate with outcome [123].

Cervical Involvement

Cervical involvement was added to FIGO staging in 1963 based on the results of fractional dilation and curettage. Since then, many authors have commented on the inaccuracy of clinical staging in detecting cervical involvement in EC [10, 124, 125]. A 52% false positive rate for predicting cervical invasion by endocervical curettage was

found in one series [11], and in another, endocervical curettage was found to have a 50% false positive rate and a 13% false negative rate [10]. Overall, cervical involvement was present in 9–32% of ECs when staged by the 1988 FIGO system [126, 127] as a result of contiguous extension (Fig. 2a, b) or due to lymphovascular spread [124, 126]. One study noted that free-floating tumor, the so-called "tumor migrants", were often seen in association with cervical involvement and this relationship was found to be statistically significant in that "tumor migrants" were found to be more often associated with high-grade tumors such as serous carcinoma [126]. Some investigators found a statistically worse outcome for women with cervical stromal invasion compared with those with endocervical glandular involvement [11, 128] while others suggested no significant difference in outcome between women with stage IIA and IIB EC [124, 129]. As several studies have shown that the prognosis of patients with stage IIA tumors is similar to those with stage I tumors, and although pathologists are able to recognize cervical spread by EC, their accuracy in determining the type of involvement is low [130], the latest FIGO staging system decided to eliminate endocervical glandular involvement, thus stage II is now represented by EC with cervical stromal invasion [14]. As a consequence, the number of patients with stage II EC has decreased when compared to the 1988 FIGO staging system [18–20]. Some studies found cervical involvement to be an independent prognostic indicator on multivariate analysis [131] while others have shown that even stromal cervical involvement may not have independent prognostic significance [130, 132] and due to this controversy as well as the lack of controlled prospective trials, optimal management for stage II patients has yet to be determined [133]. Finally, in exceptional cases, an independent, primary endocervical adenocarcinoma may be found in women with EC [134]. In cases where this possibility is considered, additional sections to show continuity between the endocervical and endometrial tumors or immunohistochemical studies to differentiate between the two are usually helpful. Thus, in general, close gross examination and adequate sectioning of the upper endocervix should be performed [135].

Age

Most ECs occur in postmenopausal females who are older than 50 years. Studies have highlighted the higher incidence of obesity in younger women with EC which are typically low-grade [136, 137]. In one study, patients with body mass index (BMI) >50 presented at an average age of 56 years versus 67 years for those with normal BMI [136]. Additionally, a recent study has further emphasized the role of obesity in EC in young women (≤40 years); typically these tumors being low-grade and low-stage EEC. In young nonobese patients, the possibility of a mismatch repair defect, specifically Lynch syndrome, should be ruled out as these tumors may be associated with higher grade EEC, non-endometrioid histology, and higher stage and possibly poorer prognosis [138].

Several studies support age as an independent, non-tumor factor strongly related to prognosis [6, 21, 131, 139–142]. One study found age > 70 years to be an independent predictor of local disease recurrence as well as overall survival. This study also found age to be independent of other poor prognostic factors including tumor type or deep myometrial invasion [131]. This finding was supported by other investigators who found age to be a significant predictor of poor outcome even in patients with CCC and serous carcinoma [89, 143]. Some investigators have suggested that poor outcome in elderly patients is due to an association with high-grade tumors and less-aggressive therapy [144]. It has also been found that poor outcomes in women of advanced age are not due to treatment toxicities [131]. In summary, many studies support the finding that EC is intrinsically more aggressive in older patients and in some studies age seems to be a specific, significant, and independent predictor of outcome [6, 21, 37, 128, 131, 145, 146].

Lymphovascular Invasion

Lymphovascular invasion has been reported to occur in approximately one-quarter of ECs [147–149] with a considerable range of frequencies up to 37% [33]. This variability may be due in part to differences in the criteria used to diagnose lymphovascular invasion as well as to interobserver variation. Mimics of lymphovascular invasion, such as retraction artifact around invasive tumor nests within the myometrium can be diagnostically challenging, and the use of immunohistochemical studies to highlight vascular endothelium have been found to be of help [37, 147]. The use of robotic hysterectomy has been shown to be associated with a increased rate of artifactual lymphovascular "pseudoinvasion" [150–152].

A greater frequency of lymphovascular invasion has been found in high-grade EECs and tumors of serous and clear cell types in some series. For example, lymphovascular invasion has been noted in 42% of poorly differentiated tumors when compared to 2% of well-differentiated tumors [153]. Several studies have looked at the strength of lymphovascular invasion as a predictor of pelvic lymph node metastases and/or recurrent disease as well as whether lymphovascular invasion should be used to determine the need for pelvic lymph node sampling or adjuvant therapy. Lymphovascular invasion has been found to be an independent prognostic factor [6, 8, 25, 29, 32, 33, 37, 128, 147–149, 153–158], and some investigators advocate its inclusion in staging [122, 159, 160]. Furthermore, investigators have shown that lymphovascular invasion significantly increases the risk of pelvic lymph node metastases compared to cancers with no lymphovascular invasion for all FIGO grades and depths of myometrial invasion [149, 161, 162]. Furthermore, the presence of lymphovascular invasion is associated with increased frequency of recurrence even in stage I tumors [163–165].

Perivascular lymphocytic infiltrates and related changes have been noted to be associated with lymphovascular invasion. In one study, lymphovascular invasion and/or perivascular associated infiltrates were not found to be independent prognostic variables, but proved to be the best predictors of pelvic lymph node metastasis in a multivariate analysis [166]. In another study, lymphovascular invasion was found in 12% of cases and perivascular lymphocytic infiltrates in 20%, with the latter being present in 93% of cases with lymphovascular invasion. The authors found this feature to be an independent poor prognostic factor on multivariate analysis [147]. It is noteworthy that not all authors have found perivascular lymphocytic infiltrates to be associated with an unfavorable outcome. It can be hypothesized that this finding may reflect a favorable immune response by the host, at least in some cases [37, 167]. It is worth mentioning that the MELF (microcystic, elongated, and fragmented glands) pattern of EEC is associated with a higher frequency of lymphovascular invasion which can be very subtle as cells may have a banal "histiocyte-like" appearance [58, 109, 111, 112].

Stage IIIA

Stage IIIA previously combined three very diverse prognostic indicators, namely adnexal involvement, serosal invasion, and positive peritoneal cytology. The current FIGO staging system has removed positive peritoneal cytology, and thus, the small number of patients presenting with stage IIIA has been further reduced. Studies show conflicting data regarding the prognostic significance of each [168]. In stage IIIA, poor outcome appears to be related to coexistent risk factors, such as unfavorable histology, deep myometrial invasion, lymphovascular invasion, or other sites of metastatic disease [155].

Positive peritoneal cytology occurs in approximately 15% of ECs [169] and the prognostic significance of peritoneal cytology is controversial, with variable results in the literature. A recent study found the 5-year survival rate to be >90% even in patients with positive peritoneal cytology [170]. This finding is often found

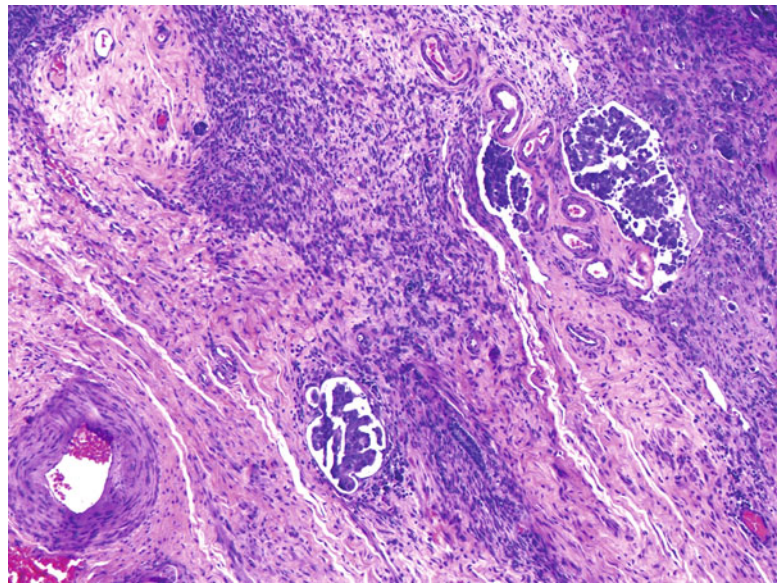

Fig. 11 An endometrial carcinoma shows lymphovascular permeation of the ovary

in conjunction with other adverse prognostic factors. Most studies have not found peritoneal cytology to be an independent prognostic factor as patients with isolated positive peritoneal cytology have an excellent outcome [155, 168–176]. Other studies, some recent, have found positive peritoneal cytology to be an independent prognostic factor in EC both endometrioid and non-endometrioid types [141, 177–181].

Serosal involvement defined as disease extending through the myometrium into the uterine serosa is uncommon, occurring in about 7% of patients [182], with a range of frequencies reported between 3% and 16% [183, 184] (Fig. 3). When present, it is associated with a significant risk of recurrence and a poor outcome (~40%), even if it is the only site of extrauterine disease [39, 182]. Solitary serosal involvement, defined as the only site of extrauterine disease, has an outcome that is significantly better than serosal involvement with disease at other extrauterine sites [182]. However, overall isolated serosal involvement has a worse outcome than either isolated adnexal involvement [185, 186] or isolated positive peritoneal cytology [172, 173].

Adnexal involvement occurs in approximately 7% of patients with EC [32], but solitary involvement, which refers to adnexal metastasis as the only site of extrauterine spread, has been found in 2–3% of patients [185]. The exact mechanism of spread has been debated, with several theories emerging. A close association between adnexal involvement and positive peritoneal washings has been recognized, and for this reason, transtubal spread is felt to be responsible for the majority of cases of ovarian or fallopian tube involvement. Direct extension of tumor through the uterine wall or lymphovascular spread likely accounts for a much smaller number of cases (Fig. 11). The fact that the overall survival for patients with adnexal involvement is ~75% [185] may suggest that the adnexal tumor is a synchronous primary tumor as has been noted over a range of 5–20% of patients [187–189]. Criteria proposed by Ulbright and Roth as well as Clement and Young suggest that metastasis is typically associated with bilateral ovarian involvement, small ovaries, multinodular growth, and lymphovascular invasion as well as deep myometrial invasion, lymphovascular invasion, and poorly differentiated histology in the EEC [188, 190]. While many studies report that patients with adnexal involvement have a relatively poor prognosis [175, 184, 185, 191], the 5-year survival rate is generally more favorable than that expected for stage III disease, if this is

the only site of extrauterine spread [28, 175, 185, 186]. In fact, some investigators found that the incidence of adnexal involvement increased when other known pathologic risk factors were present; a poor outcome in patients with adnexal involvement seemed to be a result of other coexistent prognostic indicators [185]. Adnexal involvement has generally not been found to be an independent prognostic factor on multivariable analysis with the exception of a few studies [184, 192].

The fallopian tube may be the only site of metastases. The finding of free floating tumor within the lumen of the fallopian tube should be ignored. Only when tumor is incorporated within the tubal mucosa, present within lymphovascular spaces or within tubal wall or in the serosa should be considered metastases. However, if only involving the tubal mucosa, especially if the tumor is of serous type, scrutiny of the surrounding tubal epithelium in order to detect serous intraepithelial neoplasia (STIC) is recommended.

Stage IIIB

Vaginal involvement by EC is much more frequently seen as recurrence rather than involvement at the time of initial diagnosis, the latter more often seen as tumor within lymphovascular spaces and it is associated with poor prognosis [193].

Stage IIIC

Lymph node metastases have a strong [26, 28, 29, 32] and often independent [166, 194–196] prognostic significance in patients with EC (Fig. 4). The new revised FIGO has subdivided the IIIC group into IIIC-1 (indicating positive pelvic lymph nodes) and IIIC-2 (indicating positive para-aortic lymph nodes with or without positive pelvic lymph nodes) as positive para-aortic lymph nodes appear to be associated with a worse outcome when compared to only positive pelvic lymph nodes [197, 198]. Standardized guidelines for the anatomical extent of lymph node dissection and the minimum adequate number of lymph nodes to be sampled have not been universally established [199]. Some authors deem that an appropriate pelvic lymph node dissection should consist of at least 10–12 lymph nodes and at least 5 for para-aortic lymph nodes [200–203]. Methods of lymph node assessment have included palpation with biopsy of suspicious nodes, selective sampling of multiple sites, limited sampling of <4 sites or complete, systematic pelvic and para-aortic lymphadenectomy [194, 204–206]. Intraoperative assessment of lymph nodes by palpation is inaccurate as <10% of patients with metastases have grossly enlarged lymph nodes [29]. Larson found 13% of positive lymph nodes to be normal on palpation [205]. Arango found 36% of positive lymph nodes to be missed on palpation [207], while Chuang and Boronow found approximately 50% of metastases to be missed by palpation [32, 194]. The practice of routine, systematic pelvic and para-aortic lymphadenectomy potentially places patients at risk for morbidity, particularly those that are elderly, obese, or have preexisting medical conditions. In one study, low-risk patients (grade 1 histology with or without myometrial invasion or grade 2 or 3 tumors without myometrial invasion excluding serous and clear cell carcinoma) had <5% chance of lymph node metastases while the high-risk group (grade 3 tumors with invasion into the outer one-third of the myometrium) had >10% risk of lymph node metastases. The remaining patients, with a few exceptions due to limited experience, including grade 2 and 3 tumors and/or tumors having inner or mid muscle invasion had a moderate risk of lymph node metastases [29]. In the same study, the relative risk of pelvic and para-aortic node involvement increased to 25% and 17%, respectively, for deep muscle invasion [29]. However, a recent study has shown that almost 25% of patients with clinical stage I EEC have positive lymph nodes [208].

In general, pelvic lymph node metastases have been found to be highly predictive of para-aortic lymph node involvement as approximately up to

60% of patients with positive pelvic lymph nodes also have positive para-aortic lymph nodes at the time of initial surgery [32, 199, 209, 210]. Creasman and Mariani found only 2% of para-aortic lymph nodes to be positive when patients had negative pelvic lymph nodes, while Yokoyama et al. found a slightly higher rate of 8% positivity in para-aortic lymph nodes with negative pelvic nodes [29, 203, 206]. A significant number of stage I patients have been found to have pelvic and para-aortic lymph node metastases [29, 206]. In one study, multivariate analysis found only two independent factors predictive of para-aortic metastases: positive pelvic lymph nodes and lymphovascular space invasion [209]. Some investigators have suggested that surgical evaluation of para-aortic lymph nodes could be limited to those patients with suspicious nodes on palpation or high-risk factors such as positive pelvic lymph nodes, gross adnexal involvement, grade 2 or 3 tumors, or outer one-third myometrial invasion [28]. A range of positivity from 10 to 80% has been found in para-aortic lymph nodes [28, 29, 203, 205, 206, 209, 210]. This variability may in part be due to the incidence of serous or clear cell tumors in the series as well as to the extent of sampling.

The need for routine lymph node dissection in the treatment of stage I EC is controversial. It has been suggested that lymph node dissection (pelvic and para-aortic) could safely be avoided in low-risk patients having EEC, either grade 1 or 2 with <50% myometrial invasion, and tumor <2 cm in maximal dimension [122, 210]. In a recent study of 607 patients, survival for all patients with retroperitoneal lymph node dissection (pelvic and/or para-aortic) was 77% at 3 year and 65% at 5 year; however, it did not find survival to be statistically different for patients with positive para-aortic nodes compared to patients with only positive pelvic lymph nodes. For patients with para-aortic lymph node involvement, the 3- and 5-year survival rates were 70% and 62%, respectively, versus 87% and 69% for patients with only positive pelvic lymph nodes. When patients with IIIC disease were separated into those with positive peritoneal cytology or adnexal involvement, a marked reduction in survival for patients with nodal and extranodal disease compared to those with nodal disease only was shown [210]. A therapeutic benefit of lymphadenectomy was found in patients both in low-risk and high-risk groups [204, 211]. Mariani et al. noted that para-aortic lymphadenectomy may have a therapeutic effect in select patients with positive lymph nodes [203]. Similarly, Lutman found that in patients with stage I and II disease, a lymph node count of 12 or greater was an important positive prognostic variable [201]. Despite the therapeutic benefit found by these two studies, most investigators have found lymphadenectomy to be of prognostic value only. Finally, Girardi et al. noted that approximately 37% of metastatic tumors are <2 cm and have suggested that submission of the entire lymph node for histologic examination with stepwise sectioning improves tumor detection [212], while other investigators have suggested that small metastatic tumor emboli can be better detected by immunohistochemistry, particularly cytokeratin [213, 214]. These approaches are time consuming and costly and are not currently recommended.

The combined use of surgical, imaging and/or pathologic findings to predict the need for lymph node dissection is not always accurate. Sentinel lymph node is gaining popularity at large cancer centers as it is increasingly being accepted as a compromise between a radical lymphadenectomy and no lymph node removal. Unlike cervical carcinoma where only one injection site is required, several injection sites are used in EC due to the difference in the manner of drainage. In EC, the uterine corpus drainage may flow directly into the aortic lymph nodes through the ovarian vein allowing a metastasis to skip. It seems likely based on the present knowledge that sampling of sentinel lymph mode(s) will have a significant impact on clinical management of EC [215, 216].

DNA Ploidy

DNA analysis with either flow cytometry or image cytometry measures the quantity of

nuclear DNA present in cells, and can therefore be used to measure the number of copies of DNA present in tumors [217]. Differences exist between flow and image cytometry with each having advantages and disadvantages. Both methods can be performed on formalin-fixed, paraffin-embedded tissue or on fresh single-cell suspensions. Image cytometry requires a microscopic analysis of Feulgen-stained cells; this technique results in fewer cells being analyzed and a greater ability to separate tumor cells from normal cells. In contrast, flow cytometry can analyze large numbers of cells but does not separate neoplastic from normal cells. This method can also be used to calculate the fraction of cells in the S-phase. While there is an 80% agreement between the two methods, small aneuploid populations detected by image cytometry can be missed by flow cytometry which often measures large numbers of normal cells resulting in diploid DNA patterns. As a general principle, tumors that are diploid are less aggressive than tumors that are non-diploid or aneuploid.

In general, within EC, most EECs are diploid while non-EEC are non-diploid in over 50% of cases [218–221]. Among patients with EEC, Britton et al. found non-diploid DNA patterns in 13% of tumors compared to 55% in patients with non-EECs, with the corresponding 5-year progression-free survival being 91% and 35%, respectively [218]. They also used DNA ploidy to stratify patients with low-grade tumors and found the estimated 5-year survival to be significantly different between diploid (94%) and non-diploid neoplasms (64%). In the same study, patients with endometrioid tumors having diploid patterns versus those with non-diploid patterns had estimated 5-year survivals of 93% and 74%, respectively [218]. Several investigators have found DNA ploidy to be an independent prognostic indicator on multivariate analysis [218, 222–228] while the prognostic significance of ploidy has not been supported by other studies [229–231]. One recent study has suggested the potential utility of DNA ploidy in the prognosis of stage I serous carcinomas [232]. Furthermore, genomic imbalances have been noted to be much more frequent within non-EEC including gains in chromosomes 7 and 8, only noted in 2% of EEC but between 50 and 60% of non-ECC [233]. The balance of data suggests that DNA ploidy is an independent, objective predictor of outcome in patients with EC. Moreover, its use in stratifying patients considered to be low risk based on more traditional prognostic factors may identify patients at risk of recurrence [218].

Estrogen and Progesterone Receptors

The importance of ER and PR in the pathogenesis and treatment of EC has been recognized for many years. In general, the range of positivity for ER varies from 60 to 100% and for PR from 50 to 88%. Approximately 40–80% of tumors contain both receptors (Fig. 12a, b), while tumors having neither represent the minority (10–36%). Endometrioid and mucinous carcinomas are related to estrogen stimulation unopposed by progesterone and usually express ER and PR. It has been shown that in patients with stage I EC, receptor status is a significant independent prognostic factor [229, 234–238]. Although many studies have shown a relationship between ER/PR status and other prognostic factors, this has not been found to be consistent. In serous and clear cell carcinomas, the ER and PR levels are usually negative or much lower than those observed in EEC [223, 239–241]. Recurrence in patients with stage I disease is significantly more common in PR or ER negative tumors [242]. An important consideration is the inherent problem in evaluating ER and PR status, which is due to the lack of a quantitative standard for the measurement of these receptors by immunohistochemical methods [243]. Recent studies have looked at ER isoforms and have found that most EECs express ER-α alone or in combination with ER-β. It has been suggested that the ER-β–ER-α ratio significantly increases in neoplastic compared to normal endometrium. It has also been found that the ER-β–ER-α ratio increases in atypical hyperplasia and adenocarcinoma and decreases in hyperplasia without atypia. The finding that the ER-β–ER-α ratio is very high in invasive ECs has led some authors to

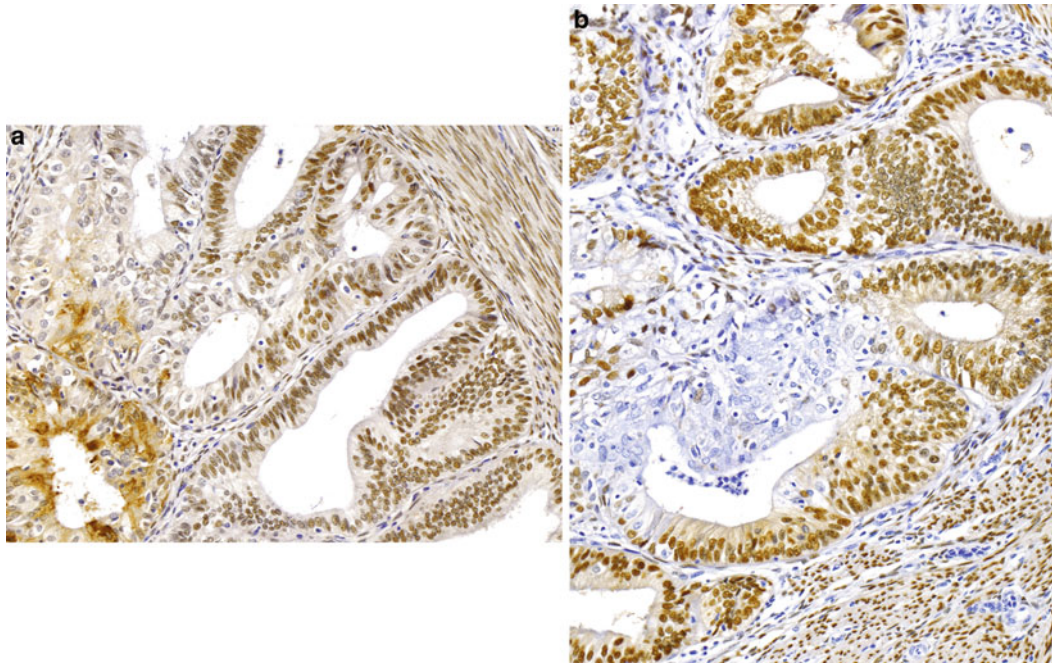

Fig. 12 A well-differentiated endometrioid endometrial carcinoma shows nuclear positivity for ER (**a**) and PR (**b**)

suggest that ER-β may play an important role in the progression of myometrial invasion [243]. Similar results have been found when looking at the A and B PR isoforms, as increasing expression of the B isoform seems to play a role in EC [244].

C-Erb-B2 (HER-2/Neu)

The human epidermal growth factor receptor-2 (HER-2/neu), also known as c-erb-B2, is located on 17q21 and encodes a transmembrane glycoprotein with tyrosine kinase activity, which is partially homologous to the epidermal growth factor receptor. As such, amplification results in large amounts of receptor on the cell surface with activation of signal transduction pathways, cellular proliferation, and/or neoplastic transformation. Recent interest in this marker is due to its potential role in patient treatment. HER-2/neu amplification has been identified in 10–20% of ECs and tissue overexpression in 10–30% of cases. The role of HER-2/neu overexpression as a prognostic indicator in EC is speculative, with conflicting data, some of which show an association with aggressive biologic behavior and poor survival [223, 245–250]. Other studies have shown HER-2/neu expression not to be associated with clinicopathologic factors and in general with prognosis [248, 251–255]. HER-2/neu in EC seems to be more frequently observed in high-stage grade 3 EECs [256] as well as non-endometrioid carcinomas, but in the latter when correlated with clinical features is not associated with stage or outcome [257, 258].

p53

p53 is a tumor suppressor gene that encodes a nuclear transcription factor involved in cell cycle arrest and apoptosis. It is the most commonly mutated tumor suppressor gene in malignancies. It is felt that mutations in p53 provide an unstable background allowing for additional mutations. In particular, in EEC, p53 mutations occur late in tumor development and in a relatively low percentage of tumors (approximately 20%), being more frequently

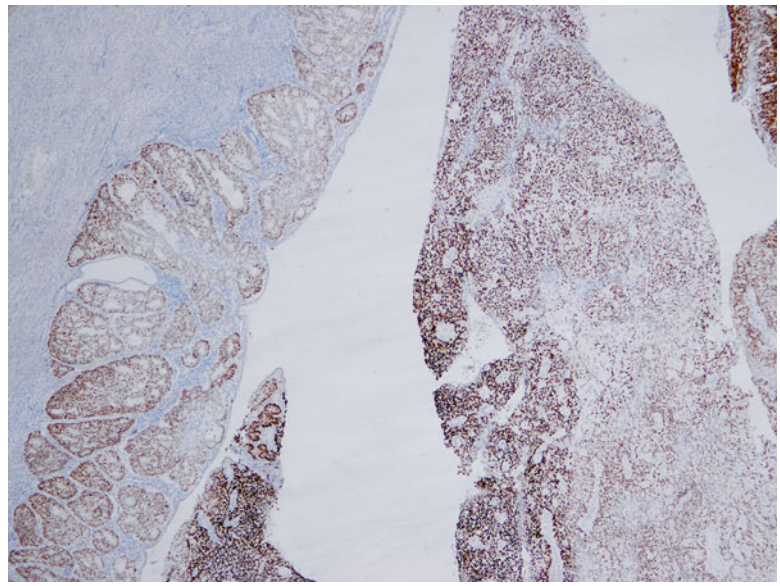

Fig. 13 Moderate to poorly differentiated endometrioid carcinoma shows diffuse moderate to strong p53 positivity

expressed in grade 3 EEC [256, 259] (Fig. 13). In contrast, p53 is an early event in serous carcinoma and is expressed in the vast majority of these tumors (up to 100%) and in endometrial intraepithelial carcinoma, the putative precursor lesion of serous carcinoma [72, 73, 259, 260]. p53 expression is much less frequent in CCC with only approximately 25% of tumors showing strong positivity [241, 261]. p53 has been found to be a strong independent predictor of survival by some investigators [223, 253, 255, 262, 263]; however, other studies have not corroborated this association [22, 73, 264]. In one study, p53 immunostaining was found to be a prognostic indicator independent of patient age and tumor stage; however, when FIGO grade and cell type were included, it lost its predictive value [264]. Overall, while p53 overexpression is of prognostic significance in EC, its clinical importance, especially as a single marker, is unclear in patient management.

Bcl-2

Bcl-2 is a proto-oncogene that inhibits programmed cell death or apoptosis. Bcl-2 is normally expressed in the endometrium in a hormone-dependent manner with higher expression in the proliferative phase. Bcl-2 expression is also detected in endometrial hyperplasia but it diminishes in EC. The relationship between the loss of bcl-2 expression and the aggressiveness of EC is a seemingly contradictory one. The mechanism of downregulation of bcl-2 in advanced EC is largely unknown. Loss of bcl-2 expression has been associated with poor prognosis [265–268]. Patients with grade 1 or 2 EECs overexpressing bcl-2 are more likely to present with extrauterine disease than those not expressing bcl-2 [269].

Pten

The tumor suppressor gene PTEN (phosphatase and tensin homologue) located on chromosome 10q, plays an important role as a negative regulator of the AKT growth survival pathway [270, 271]. PTEN mutations occur almost exclusively in EECs ranging in frequency from 37% to 61%, being only seen in up to 5% of non-endometrioid carcinomas [270, 272, 273]. In contrast to other tumors where PTEN mutations are associated with poor prognosis, it is frequently seen in early-stage EECs and commonly coexists with endometrial hyperplasia,

suggesting that PTEN mutations are an early event in tumorigenesis [270, 273]. PTEN mutations are frequently present in tumors with microsatellite instability and those lacking p53 overexpression [270–272, 274]. Recently, it has been noted that PTEN-positive staining is an indicator of longer survival in patients with advanced EC who received postoperative chemotherapy [275].

Cowden syndrome is an autosomal-dominant disorder characterized by PTEN germ-line mutations in which patients develop multiple hamartomas and, importantly, carcinomas of the thyroid, breast, endometrium, and kidney. This germ-line mutation confers an increased lifetime risk of breast, uterine, and renal cancers of 85%, 28%, and 33%, respectively [276].

K-ras

K-ras encodes a protein (p21) located on the inner plasma cell membranes which has GTPase activity and is involved in cell receptor signal transduction pathways. It has been largely related to tumor growth and differentiation. K-ras mutations occur more frequently in codons 12 and 13 of exon 1 and have been detected in 10–30% of ECs, being quite rare in type II tumors [72]. It has been also noted an increase of k-ras mutation in EC with mucinous differentiation [277]. K-ras has been identified in 4–23% of atypical hyperplasias and is also present in non-atypical hyperplasia [278–280]. K-ras may correlate with tumor progression and represents an early neoplastic event; however, K-ras mutations are not related to other prognostic factors or survival in most studies [278, 279, 281, 282].

Microsatellite Instability

Microsatellites are short repeat DNA sequences that occur throughout the genome and because of their repetitive sequences are prone to mutations during DNA replication. The majority of these mutations are recognized and fixed by the DNA mismatch repair family of genes. When these genes are mutated, the microsatellites show alterations in size, a phenomenon known as microsatellite instability (MI) which occurs in approximately 20% of ECs [72, 86]. Abnormalities in mismatch repair proteins typically occur in combinations of two, either MLH1 (both germ-line mutations and promoter methylation) with PMS2 (Fig. 14) or MSH2 and MSH6. Sporadic MLH1 promoter methylation is far more common than MLH1 mutations and is seen in young obese women with EEC being unassociated with Lynch syndrome. Currently, mismatch repair protein abnormalities are

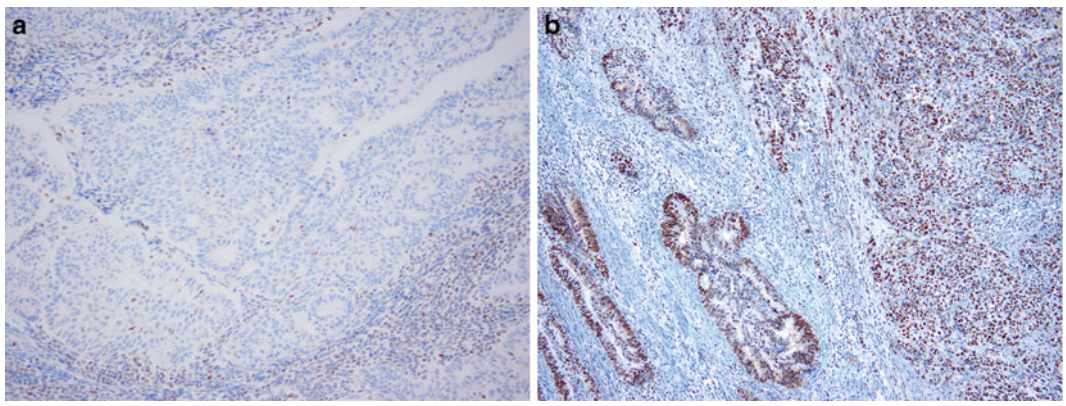

Fig. 14 (**a**) Loss of PMS2 is frequently associated with loss of MLH1 in EEC. (**b**) Preserved MSH2 is typically associated with preserved MSH6

identified by immunohistochemical screening, and an abnormal result should prompt genetic counseling and further testing [138, 283–286].

MI has been detected in 20–30% of sporadic ECs and in 75% of EC associated with hereditary nonpolyposis colon cancer (HNPCC). In women with HNPCC, EC is often the first manifestation of the disease. In this setting, tumors have a predilection for the lower uterine segment and may be associated with abundant tumor infiltrating lymphocytes as seen in colon cancer. Tumors may be endometrioid or non-endometrioid. The latter are rare in young patients, and particularly when seen in women <40 year, should raise the possibility of Lynch syndrome [287, 288]. Tumors show lymphovascular invasion and present with high FIGO stage [289]. It has also been noted that EC associated with mismatch repair abnormalities and Lynch syndrome may show ambiguous morphologic features with overlapping architectural and cytologic features of endometrioid, serous, and/or clear cell carcinoma, and may be difficult to classify [290]. EECs arising in the lower uterine segment can display overlapping histological and immunohistochemical features with endocervical adenocarcinomas [291].

In sporadic ECs, MI has been associated in some studies with a favorable outcome in EECs, even when accounting for other prognostic factors [292]. However, in general, MI does not seem to have any definitive association with grade, stage, depth of invasion, hormonal status, or survival [86, 274, 293–299]. A large systematic review of the literature has shown no significant association between deficiency in MMR and worse overall survival or disease free survival [300].

β-Catenin

β-catenin is involved in cell to cell adhesion forming complexes with e-cadherin and is important in the maintenance of tissue architecture and cell polarity. Mutations in exon 3 of β -catenin have been found in approximately 15–40% of low-grade EECs and in atypical hyperplasia, more frequently when squamous differentiation is present [301–303]. β-catenin mutations are very rare in serous and clear cell carcinomas. In the majority of cases, the presence of β-catenin mutations does not correlate with age, hormonal status, grade, or stage [303]. However, a few series have shown an association with early onset [304], low-tumor grade, and the absence of lymph node metastases [305].

New Molecular Alterations in EC

PIK3CA mutations occur in up to 36% of EC, are more frequent in EECs and are associated with poor prognostic factors [306]. They have also been reported in non-endometrioid carcinomas. PIK3CA mutations coexist with PTEN mutations in up to 25% of EC [307–309]. The presence of frequent mutations in genes involved in the PI3K-AKT pathway in EC has raised the possibility that PI3K inhibitors can be used, specifically PARP inhibitors (poly(ADP-ribose) polymerase (PARP) family of nuclear proteins properties that promote DNA repair) which have been also suggested in the treatment of patients with EC with PTEN mutations [310].

Recent exome sequence analysis performed by the Cancer Genome Atlas Research Network [311] has revealed that EECs are often associated with low copy number alterations or p53 mutations, but frequent mutations in PTEN, b-catenin, PIK3CA, ARID1a (tumor suppressor gene) [312]; KRAS, and novel mutations in the SWI/SNF chromatin remodeling complex gene ARID5B. 4 groups of EC have been identified: Group 1 consisting of EECs with mutations in *POLE* (group of DNA polymerases responsible for DNA synthesis and replication in human cells) showing high mutations rates "ultramutated," associated with good prognosis; Group 2 including EECs with microsatellite instability "hypermutated"; Group 3 composed of EECs with low copy number alterations; and Group 4 "serous-like" EC including serous carcinoma but also EEC, usually grade 3, exhibiting p53 mutations and worse prognosis. These results show that there is a group of EEC,

which is molecularly and prognostically similar to serous carcinoma (group 4) and also suggest a potential prognostic role for *POLE* mutations as they may help in identifying a subset of EECs with high-grade histology but relatively indolent clinical course [313].

Uterine Sarcomas

Prior to 2008, uterine sarcomas were staged following the modified FIGO 1988 criteria for EC, but use of that system was not reflective of survival. The new FIGO/AJCC system is an effort to adopt a single unified staging system. However, the staging system for leiomyosarcomas and endometrial stromal tumors differs from that use for müllerian adenosarcomas and malignant mixed müllerian tumor (carcinosarcoma) for which the 2008 FIGO staging for EC is used [314]

Malignant Smooth Muscle Tumor (Leiomyosarcoma)

Leiomyosarcomas have an overall poor prognosis with estimated 5-year survival rates ranging from 25 to 75% and reported risk of recurrence ranging from 45–73% [315, 316]. Multiple studies have looked at individual prognostic factors and their effects on survival, including age, tumor size, cytologic atypia, mitotic activity, tumor cell necrosis, lymphovascular invasion, type of tumor, margin, and extrauterine extension. Only tumor grade [317, 318], mitotic count [319–323], and tumor stage [317, 324–331] have consistently been reported as significant predictors of survival in leiomyosarcomas. In the largest study of 208 patients with leiomyosarcoma, parameters that were associated with increased overall survival by univariate analysis included age (<51 year), smaller tumor size (<5 cm), low-grade, and low-stage disease at the time of diagnosis. However, when these parameters were entered into a multivariate analysis, only low grade and low stage remained as independent prognostic factors of survival [318]. Although grade is an important prognostic factor in leiomyosarcoma, there is no universally adopted grading system and the vast majority of tumors are high grade. One group has highlighted that low-grade leiomyosarcoma is rare and that various other indolent uterine tumors are often misdiagnosed as low-grade leiomyosarcomas [332]. When comparing the 1988 and 2008 FIGO staging systems, no improvement has been shown in patient risk stratification [333–335], however, the addition of size in the new system has provide more accurate prognostic information in stage I tumors [336, 337]. There are no clinicopathologic factors within stage I leiomyosarcomas that predict outcome in these patients [338]. Several studies have reported that epithelioid and myxoid leiomyosarcomas are associated with a more aggressive behavior compared to leiomyosarcomas of conventional type [339–341]. Because of the rarity of these tumors, criteria predictive of behavior are less well established [342, 343]. ER and PR expression in leiomyosarcomas is diminished when compared to benign smooth muscle tumors. Approximately 30–50% of uterine leiomyosarcomas express ER and PR. One study has also shown androgen receptor expression in these tumors [250]. Several studies have found tumors positive for steroid receptors to be associated with better prognosis than tumors with negative steroid receptors [317, 328, 344]. However, results in the literature are not uniform and some investigators have not found correlation of ER and PR with other prognostic parameters and no influence on disease-free or overall survival [317, 345].

Patients with positive lymph nodes typically also show extrauterine disease. The incidence of lymph node metastases in patients with disease confined to the uterus is 2.5% [322, 346]. Therapeutic lymph node sampling does not seem to have a role in increasing the free survival rate in patients with leiomyosarcoma. Only patients with clinically suspicious lymph nodes should undergo lymph node dissection [347]. Several studies have suggested DNA ploidy, S-phase, p53, bcl-2, and c-kit, among others, as potential prognostic parameters [325, 330, 348–354]. So

far, molecular markers do not appear to play a prognostic role in malignant smooth muscle tumors.

As there are no preoperative means to differentiate between benign and malignant smooth muscle tumors and minimally invasive procedures such as morcellation have gain popularity, an increase of peritoneal dissemination of leiomyosarcoma has occurred [355, 356].

Endometrial Stromal Sarcoma

Low-grade endometrial stromal sarcomas which are the most common endometrial stromal tumors are characterized by late recurrences and indolent behavior in most cases. Historically, endometrial stromal sarcomas were stratified on the bases of mitotic activity into low grade (<10/10HPFs) and high grade (≥ 10/10HPFs) [357, 358]. However, in the largest study to date of endometrial stromal sarcomas, mitotic index and cytologic atypia were evaluated and neither were found to be predictive of recurrence in patients with stage I tumors. In the same study, stage was more important than mitotic activity to predict overall survival and recurrences in stage I patients. However, when all patients were considered as a group, stage and mitotic activity were both independent prognostic factors of survival and time to first relapse [359]. In two recent studies, the prognosis of endometrial stromal sarcomas has been related to mitotic index and tumor cell necrosis [324, 360]. Other parameters including tumor size and grade may have an impact on prognosis [361, 362].

A new subset of endometrial stromal sarcomas characterized by a diffuse or nested growth of small epithelioid cells associated with brisk mitotic activity and necrosis has emerged. This variant of endometrial stromal sarcoma is characterized by a *t*(10,17) and pursues a more aggressive behavior when compared to low-grade endometrial sarcoma [363].

A few studies have noted that DNA content may be a useful adjunct to predict behavior in these tumors [364–366]; however, tumor stage is overall still the most influential prognostic factor. ER and PR are expressed in low-grade endometrial stromal sarcomas but not in high-grade tumors including those with *t*(10,17); these findings may determine if hormonal treatment should be part of the primary treatment [367–370].

Undifferentiated Endometrial Sarcoma

There are no well-established prognostic parameters for these tumors due to the very limited experience. For practical purposes, these are high-grade tumors and some authors consider them as aggressive as leiomyosarcomas [371]. These tumors are more frequently associated with lymphovascular invasion compared to other sarcoma subtypes, a finding that has associated with poor outcome [324]. Thus, lymph node dissection has been advocated by some investigators, but its prognostic significance is controversial. A recent publication has shown that either the old or recent modified FIGO staging system are unable to stratify patients in risk groups with prognostic significance [334]

Low-Grade Müllerian Adenosarcoma

Myometrial invasion, therefore stage, and sarcomatous overgrowth are the only two independent prognostic parameters that determine survival in these tumors. Several studies have found that among patients with myometrial invasion, those with outer half invasion had a poorer outcome [372–377]. Sarcomatous overgrowth in low-grade müllerian adenosarcomas has been strongly related to postoperative recurrence and metastases and fatal outcome [373, 378]. Even though adenosarcomas with heterologous elements were initially thought to be associated with worse prognosis, the presence of this feature was not found to be statistically significant [376]. In the study from the Norwegian group, tumor cell necrosis was strongly associated with prognosis by multivariate analysis [324].

It has been shown that adenosarcomas with sarcomatous overgrowth are typically aneuploid compared to typical adenosarcomas, a feature associated with poor outcome [379].

Malignant Mixed Müllerian Tumor (Carcinosarcoma)

Malignant mixed müllerian tumors are among the most aggressive uterine tumors associated with an overall poor prognosis and a 5-year survival rate ranging from 20 to 35% for all stages despite aggressive treatment [380–382]. Even though initially malignant mixed müllerian tumors were included among sarcomas, more recent data suggests that these tumors behave similarly to high-grade carcinomas. In fact, some authors have reported that malignant mixed müllerian tumors have a worse prognosis when compared to high-grade carcinomas [383, 384]. Stage is the single and strongest prognostic factor in this malignancy [322, 323, 366, 385–392]. In tumors confined to the uterus, survival is related to the degree of myometrial invasion [322, 323, 385, 386, 390, 391, 393]. In some studies, nuclear grade of the carcinoma component [386, 394], patient age [387], and presence of gross residual disease [385, 387, 390] have also been found to have prognostic significance. Other histologic variables such as type and grade of the sarcomatous elements [386, 393] do not seem to have any prognostic significance. In fact in one study, stage I malignant mixed müllerian tumors without heterologous elements had outcomes similar to high-grade EC, supporting that carcinosarcomas have behaviors closely related to carcinomas. In the same study, the presence of heterologous sarcomatous elements was found to be a strong negative prognostic factor in surgical stage I tumors [395]. The prognostic importance of lymphovascular invasion is unclear [322, 385, 387, 393], but it is suggested that it should be documented in the surgical report [393]. Positive peritoneal cytology has been shown to be an indicator of poor outcome in the few studies that have looked at this parameter [396, 397], particularly in stage I tumors, but this finding is no longer included in the new FIGO staging system [396]. Patients with a history of previous radiation seem to be associated with more advance stage and carry a worse prognosis [381]. To date, DNA ploidy, proliferation markers, and ER and PR have not been found to be clinically significant [388, 390, 398]. As carcinosarcomas share similar molecular alterations with EC including p53, K-ras, b-catenin, and PIK3CA mutations, there may be a role for PARP inhibitors in the treatment of some carcinosarcomas as reported in EC with PIK3CA alterations [399]

Conclusions

- Endometrial carcinoma is the fourth most common malignancy in women and it has an overall favorable prognosis.
- The new FIGO surgico-pathologic staging system introduced in 2008 has combined stage IA and B from the prior staging system and it has eliminated stage IIA as well as positive peritoneal cytology from stage IIIA.
- The most important prognostic factor in endometrial carcinoma is stage.
- Tumor grade and depth of invasion are the most important factors in stage I tumors.
- The FIGO grading system applies only to EECs and is based primarily on the degree of glandular differentiation and secondarily modified by discordant nuclear grade.
- Endometrioid carcinomas are typically estrogen related, while serous and clear cell carcinomas are independent of estrogen stimulation.
- Serous and clear cell carcinomas are high-grade aggressive neoplasms regardless of stage.
- Other potential prognostic factors including ER/PR, DNA ploidy, p53, and others have not been shown to have independent prognostic significance on multivariate analysis in EC.
- The new FIGO staging system for leiomyosarcoma and endometrial stromal

sarcoma includes size as the most important parameter for stage I tumors.

- In uterine leiomyosarcoma, tumor stage and tumor grade are the most important predictors of survival. The role of therapeutic lymph node dissection is limited.
- Stage is the most important prognostic factor in low-grade endometrial stromal sarcomas, while undifferentiated endometrial sarcomas are associated with poor prognosis even when low stage.
- Low-grade adenosarcomas and carcinosarcomas are staged based on the 2008 FIGO classification system used for carcinomas.
- In low-grade müllerian adenosarcomas, the most important prognostic factors are depth of myometrial invasion and sarcomatous overgrowth.
- The behavior of malignant mixed müllerian tumors parallels that of the epithelial component, with most metastases being composed of epithelial elements.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. Jan-Feb 2012;62(1):10–29.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. Jan 2013;63(1):11–30.
3. Chan JK, Cheung MK, Huh WK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer. 2006;107 (8):1823–30.
4. Chan JK, Wu H, Cheung MK, Shin JY, Osann K, Kapp DS. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. Gynecol Oncol. Aug 2007;106(2):282–8.
5. Sartori E, Laface B, Gadducci A, et al. Factors influencing survival in endometrial cancer relapsing patients: a Cooperation Task Force (CTF) study. Int J Gynecol Cancer. Jul-Aug 2003;13(4):458–65.
6. Zaino RJ, Kurman RJ, Diana KL, Morrow CP. Pathologic models to predict outcome for women with endometrial adenocarcinoma: the importance of the distinction between surgical stage and clinical stage—a Gynecologic Oncology Group study. Cancer. 1996;77(6):1115–21.
7. Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. Int J Gynaecol Obstet. May 2008;101(2):205–10.
8. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. J Epidemiol Biostat. 2001;6(1):47–86.
9. Chen SS. Extrauterine spread in endometrial carcinoma clinically confined to the uterus. Gynecol Oncol. May 1985;21(1):23–31.
10. Cowles TA, Magrina JF, Masterson BJ, Capen CV. Comparison of clinical and surgical-staging in patients with endometrial carcinoma. Obstet Gynecol. Sep 1985;66(3):413–6.
11. Fanning J, Alvarez PM, Tsukada Y, Piver MS. Prognostic significance of the extent of cervical involvement by endometrial cancer. Gynecol Oncol. Jan 1991;40(1):46–7.
12. Soothill PW, Alcock CJ, MacKenzie IZ. Discrepancy between curettage and hysterectomy histology in patients with stage 1 uterine malignancy. Br J Obstet Gynaecol. Apr 1989;96 (4):478–81.
13. Wolfson AH, Sightler SE, Markoe AM, et al. The prognostic significance of surgical staging for carcinoma of the endometrium. Gynecol Oncol. 1992;45 (2):142–6.
14. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009;105(2):103–4.
15. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet. May 2009;105(2):109.
16. Lewin SN. Revised FIGO staging system for endometrial cancer. Clin Obstet Gynecol. 2011;54 (2):215–8.
17. Abu-Rustum NR, Zhou Q, Iasonos A, et al. The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered? Int J Gynecol Cancer. 2011;21(3):511–6.
18. Cooke EW, Pappas L, Gaffney DK. Does the revised International Federation of Gynecology and Obstetrics staging system for endometrial cancer lead to increased discrimination in patient outcomes? Cancer. 2011;117(18):4231–7.
19. Kato T, Watari H, Endo D, et al. New revised FIGO 2008 staging system for endometrial cancer produces better discrimination in survival compared with the 1988 staging system. J Surg Oncol. Dec 2012;106(8):938–41.
20. Korczynski J, Jesionek-Kupnicka D, Gottwald L, Piekarski J. Comparison of FIGO 1989 and 2009 recommendations on staging of endometrial carcinoma: pathologic analysis and cervical status in 123 consecutive cases. Int J Gynecol Pathol. Jul 2011;30(4):328–34.
21. Abeler VM, Kjorstad KE. Endometrial adenocarcinoma in Norway. A study of a total population. Cancer. 1991;67(12):3093–103.
22. AlKushi A, Lim P, Aquino-Parsons C, Gilks CB. Markers of proliferative activity are predictors of patient outcome for low-grade endometrioid

adenocarcinoma but not papillary serous carcinoma of endometrium. Mod Pathol. Apr 2002;15 (4):365–71.
23. Gal D, Recio FO, Zamurovic D. The new International Federation of Gynecology and Obstetrics surgical staging and survival rates in early endometrial carcinoma. Cancer. 1992;69(1):200–2.
24. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. Semin Surg Oncol. Jan-Feb 1994;10 (1):31–46.
25. Steiner E, Eicher O, Sagemuller J, et al. Multivariate independent prognostic factors in endometrial carcinoma: a clinicopathologic study in 181 patients: 10 years experience at the Department of Obstetrics and Gynecology of the Mainz University. Int J Gynecol Cancer. 2003;13(2):197–203.
26. DiSaia PJ, Creasman WT, Boronow RC, Blessing JA. Risk factors and recurrent patterns in Stage I endometrial cancer. Am J Obstet Gynecol. 1985;151(8):1009–15.
27. Barlin JN, Soslow RA, Lutz M, et al. Redefining stage I endometrial cancer: incorporating histology, a binary grading system, myometrial invasion, and lymph node assessment. Int J Gynecol Cancer. Nov 2013;23(9):1620–8.
28. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. Jan 1991;40(1):55–65.
29. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60 (8 Suppl):2035–41.
30. Mittal KR, Schwartz PE, Barwick KW. Architectural (FIGO) grading, nuclear grading, and other prognostic indicators in stage I endometrial adenocarcinoma with identification of high-risk and low-risk groups. Cancer. 1988;61(3):538–45.
31. Nielsen AL, Thomsen HK, Nyholm HC. Evaluation of the reproducibility of the revised 1988 International Federation of Gynecology and Obstetrics grading system of endometrial cancers with special emphasis on nuclear grading. Cancer. 1991;68 (10):2303–9.
32. Boronow RC, Morrow CP, Creasman WT, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstet Gynecol. Jun 1984;63(6):825–32.
33. Stefansson IM, Salvesen HB, Immervoll H, Akslen LA. Prognostic impact of histological grade and vascular invasion compared with tumour cell proliferation in endometrial carcinoma of endometrioid type. Histopathology. 2004;44(5):472–9.
34. Darvishian F, Hummer AJ, Thaler HT, et al. Serous endometrial cancers that mimic endometrioid adenocarcinomas: a clinicopathologic and immunohistochemical study of a group of problematic cases. Am J Surg Pathol. 2004;28(12):1568–78.
35. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10–7.
36. Grigsby PW, Perez CA, Kuten A, et al. Clinical stage I endometrial cancer: prognostic factors for local control and distant metastasis and implications of the new FIGO surgical staging system. Int J Radiat Oncol Biol Phys. 1992;22(5):905–11.
37. Lee KR, Vacek PM, Belinson JL. Traditional and nontraditional histopathologic predictors of recurrence in uterine endometrioid adenocarcinoma. Gynecol Oncol. 1994;54(1):10–8.
38. Vargas R, Rauh-Hain JA, Clemmer J, et al. Tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node involvement in endometrial cancer: a SEER analysis. Gynecol Oncol. 2014;133(2):216–20.
39. Abeler VM, Kjorstad KE, Berle E. Carcinoma of the endometrium in Norway: a histopathological and prognostic survey of a total population. Int J Gynecol Cancer. 1992;2(1):9–22.
40. Gayar OH, Patel S, Schultz D, Mahan M, Rasool N, Elshaikh MA. The impact of tumor grade on survival end points and patterns of recurrence of 949 patients with early-stage endometrioid carcinoma: a single institution study. Int J Gynecol Cancer. 2014;24 (1):97–101.
41. Konski A, Domenico D, Tyrkus M, et al. Prognostic characteristics of surgical stage I endometrial adenocarcinoma. Int J Radiat Oncol Biol Phys. 1996;35 (5):935–40.
42. Alektiar KM, McKee A, Lin O, et al. Is there a difference in outcome between stage I-II endometrial cancer of papillary serous/clear cell and endometrioid FIGO Grade 3 cancer? Int J Radiat Oncol Biol Phys. 2002;54(1):79–85.
43. Ayeni TA, Bakkum-Gamez JN, Mariani A, et al. Comparative outcomes assessment of uterine grade 3 endometrioid, serous, and clear cell carcinomas. Gynecol Oncol. 2013;129(3):478–85.
44. Soslow RA, Bissonnette JP, Wilton A, et al. Clinicopathologic analysis of 187 high-grade endometrial carcinomas of different histologic subtypes: similar outcomes belie distinctive biologic differences. Am J Surg Pathol. 2007;31(7):979–87.
45. Alkushi A, Kobel M, Kalloger SE, Gilks CB. High-grade endometrial carcinoma: serous and grade 3 endometrioid carcinomas have different immunophenotypes and outcomes. Int J Gynecol Pathol. 2010;29(4):343–50.
46. Park JY, Nam JH, Kim YT, et al. Poor prognosis of uterine serous carcinoma compared with grade 3 endometrioid carcinoma in early stage patients. Virchows Arch. 2013;462(3):289–96.

47. Lax SF, Kurman RJ, Pizer ES, Wu L, Ronnett BM. A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. Am J Surg Pathol. 2000;24(9):1201–8.
48. Alkushi A, Abdul-Rahman ZH, Lim P, et al. Description of a novel system for grading of endometrial carcinoma and comparison with existing grading systems. Am J Surg Pathol. 2005;29 (3):295–304.
49. Guan H, Semaan A, Bandyopadhyay S, et al. Prognosis and reproducibility of new and existing binary grading systems for endometrial carcinoma compared to FIGO grading in hysterectomy specimens. Int J Gynecol Cancer. 2011;21(4):654–60.
50. Zaino RJ, Kurman R, Herbold D, et al. The significance of squamous differentiation in endometrial carcinoma. Data from a Gynecologic Oncology Group study. Cancer. 1991;68(10):2293–302.
51. Prat J. Prognostic parameters of endometrial carcinoma. Hum Pathol. 2004;35(6):649–62.
52. Abeler VM, Kjorstad KE. Endometrial adenocarcinoma with squamous cell differentiation. Cancer. 1992;69(2):488–95.
53. Landry D, Mai KT, Senterman MK, et al. Endometrioid adenocarcinoma of the uterus with a minimal deviation invasive pattern. Histopathology. 2003;42(1):77–82.
54. Longacre TA, Hendrickson MR. Diffusely infiltrative endometrial adenocarcinoma: an adenoma malignum pattern of myoinvasion. Am J Surg Pathol. 1999;23(1):69–78.
55. Mittal KR, Barwick KW. Diffusely infiltrating adenocarcinoma of the endometrium. A subtype with poor prognosis. Am J Surg Pathol. 1988;12 (10):754–8.
56. Ambros RA, Ballouk F, Malfetano JH, Ross JS. Significance of papillary (villoglandular) differentiation in endometrioid carcinoma of the uterus. Am J Surg Pathol. 1994;18(6):569–75.
57. Esteller M, Garcia A, Martinez-Palones JM, Xercavins J, Reventos J. Clinicopathologic features and genetic alterations in endometrioid carcinoma of the uterus with villoglandular differentiation. Am J Clin Pathol. 1999;111(3):336–42.
58. Hertel JD, Huettner PC, Pfeifer JD. Lymphovascular space invasion in microcystic elongated and fragmented (MELF)-pattern well-differentiated endometrioid adenocarcinoma is associated with a higher rate of lymph node metastasis. Int J Gynecol Pathol. 2014;33(2):127–34.
59. Quick CM, May T, Horowitz NS, Nucci MR. - Low-grade, low-stage endometrioid endometrial adenocarcinoma: a clinicopathologic analysis of 324 cases focusing on frequency and pattern of myoinvasion. Int J Gynecol Pathol. 2012;31 (4):337–43.
60. Tafe LJ, Garg K, Chew I, Tornos C, Soslow RA. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently underrecognized neoplasms. Mod Pathol. 2010;23(6):781–9.
61. Jalloul RJ, Elshaikh MA, Ali-Fehmi R, et al. Mucinous adenocarcinoma of the endometrium: case series and review of the literature. Int J Gynecol Cancer. 2012;22(5):812–8.
62. Ross JC, Eifel PJ, Cox RS, Kempson RL, Hendrickson MR. Primary mucinous adenocarcinoma of the endometrium. A clinicopathologic and histochemical study. Am J Surg Pathol. 1983;7 (8):715–29.
63. Rauh-Hain JA, Vargas RJ, Clemmer J, et al. Mucinous adenocarcinoma of the endometrium compared with endometrioid endometrial cancer: A SEER analysis. Am J Clin Oncol. 2016;39(1):43–8.
64. McCluggage WG, Sumathi VP, McManus DT. Uterine serous carcinoma and endometrial intraepithelial carcinoma arising in endometrial polyps: report of 5 cases, including 2 associated with tamoxifen therapy. Hum Pathol. 2003;34 (9):939–43.
65. Semaan A, Mert I, Munkarah AR, et al. Clinical and pathologic characteristics of serous carcinoma confined to the endometrium: a multi-institutional study. Int J Gynecol Pathol. 2013;32(2):181–7.
66. Soslow RA, Pirog E, Isacson C. Endometrial intraepithelial carcinoma with associated peritoneal carcinomatosis. Am J Surg Pathol. 2000;24 (5):726–32.
67. Chambers JT, Merino M, Kohorn EI, Peschel RE, Schwartz PE. Uterine papillary serous carcinoma. Obstet Gynecol. 1987;69(1):109–13.
68. Goff BA, Kato D, Schmidt RA, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecol Oncol. 1994;54(3):264–8.
69. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94(5):642–6.
70. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982;6(2):93–108.
71. Lauchlan SC. Tubal (serous) carcinoma of the endometrium. Arch Pathol Lab Med. 1981;105 (11):615–8.
72. Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. Cancer. 2000;88 (4):814–24.
73. Prat J, Oliva E, Lerma E, Vaquero M, Matias-Guiu X. Uterine papillary serous adenocarcinoma. A 10-case study of p53 and c-erbB-2 expression and DNA content. Cancer. 1994;74(6):1778–83.

74. Rabban JT, Zaloudek CJ. Minimal uterine serous carcinoma: current concepts in diagnosis and prognosis. Pathology. 2007;39(1):125–33.
75. Wheeler DT, Bell KA, Kurman RJ, Sherman ME. Minimal uterine serous carcinoma: diagnosis and clinicopathologic correlation. Am J Surg Pathol. 2000;24(6):797–806.
76. Hui P, Kelly M, O'Malley DM, Tavassoli F, Schwartz PE. Minimal uterine serous carcinoma: a clinicopathological study of 40 cases. Mod Pathol. 2005;18(1):75–82.
77. Giuntoli 2nd RL, Gerardi MA, Yemelyanova AV, et al. Stage I noninvasive and minimally invasive uterine serous carcinoma: comprehensive staging associated with improved survival. Int J Gynecol Cancer. 2012;22(2):273–9.
78. Slomovitz BM, Burke TW, Eifel PJ, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol. 2003;91 (3):463–9.
79. Chan JK, Loizzi V, Youssef M, et al. Significance of comprehensive surgical staging in noninvasive papillary serous carcinoma of the endometrium. Gynecol Oncol. 2003;90(1):181–5.
80. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol. 2004;28(4):496–504.
81. Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system: a Gynecologic Oncology Group Study. Cancer. 2012;118(12):3087–94.
82. Ahmed Q, Hussein Y, Hayek K, et al. Is the two-tier ovarian serous carcinoma grading system potentially useful in stratifying uterine serous carcinoma? A large multi-institutional analysis. Gynecol Oncol. 2014;132(2):372–6.
83. Bartosch C, Manuel Lopes J, Oliva E. Endometrial carcinomas: a review emphasizing overlapping and distinctive morphological and immunohistochemical features. Adv Anat Pathol. 2011;18(6):415–37.
84. Lim D, Oliva E. Nonendometrioid endometrial carcinomas. Semin Diagn Pathol. 2010;27(4):241–60.
85. Matias-Guiu X, Catasus L, Bussaglia E, et al. Molecular pathology of endometrial hyperplasia and carcinoma. Hum Pathol. 2001;32(6):569–77.
86. Catasus L, Machin P, Matias-Guiu X, Prat J. Microsatellite instability in endometrial carcinomas: clinicopathologic correlations in a series of 42 cases. Hum Pathol. 1998;29(10):1160–4.
87. Abeler VM, Kjorstad KE. Clear cell carcinoma of the endometrium: a histopathological and clinical study of 97 cases. Gynecol Oncol. 1991;40 (3):207–17.
88. Rauh-Hain JA, Winograd D, Growdon WB, et al. Prognostic determinants in patients with uterine and ovarian clear carcinoma. Gynecol Oncol. 2012;125 (2):376–80.
89. Abeler VM, Vergote IB, Kjorstad KE, Trope CG. Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern. Cancer. 1996;78 (8):1740–7.
90. Carcangiu ML, Chambers JT. Early pathologic stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinicopathologic features and survival. Int J Gynecol Pathol. 1995;14(1):30–8.
91. Cirisano Jr FD, Robboy SJ, Dodge RK, et al. Epidemiologic and surgicopathologic findings of papillary serous and clear cell endometrial cancers when compared to endometrioid carcinoma. Gynecol Oncol. 1999;74(3):385–94.
92. Olawaiye AB, Boruta 2nd. DM. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol. 2009;113(2):277–83.
93. Thomas M, Mariani A, Wright JD, et al. Surgical management and adjuvant therapy for patients with uterine clear cell carcinoma: a multi-institutional review. Gynecol Oncol. 2008;108(2):293–7.
94. Rauh-Hain JA, Costaaggini I, Olawaiye AB, Growdon WB, Horowitz NS, del Carmen MG. A comparison of outcome in patients with stage 1 clear cell and grade 3 endometrioid adenocarcinoma of the endometrium with and without adjuvant therapy. Eur J Gynaecol Oncol. 2010;31(3):284–7.
95. Bures N, Nelson G, Duan Q, Magliocco A, Demetrick D, Duggan MA. Primary squamous cell carcinoma of the endometrium: clinicopathologic and molecular characteristics. Int J Gynecol Pathol. 2013;32(6):566–75.
96. Goodman A, Zukerberg LR, Rice LW, Fuller AF, Young RH, Scully RE. Squamous cell carcinoma of the endometrium: a report of eight cases and a review of the literature. Gynecol Oncol. 1996;61 (1):54–60.
97. Lininger RA, Ashfaq R, Albores-Saavedra J, Tavassoli FA. Transitional cell carcinoma of the endometrium and endometrial carcinoma with transitional cell differentiation. Cancer. 1997;79 (10):1933–43.
98. Marino-Enriquez A, Gonzalez-Rocha T, Burgos E, et al. Transitional cell carcinoma of the endometrium and endometrial carcinoma with transitional cell differentiation: a clinicopathologic study of 5 cases and review of the literature. Hum Pathol. 2008;39 (11):1606–13.
99. Abeler VM, Kjorstad KE, Nesland JM. Undifferentiated carcinoma of the endometrium. A histopathologic and clinical study of 31 cases. Cancer. 1991;68 (1):98–105.
100. Atienza-Amores M, Guerini-Rocco E, Soslow RA, Park KJ, Weigelt B. Small cell carcinoma of the gynecologic tract: a multifaceted spectrum of lesions. Gynecol Oncol. 2014;134(2):410–8.
101. Huntsman DG, Clement PB, Gilks CB, Scully RE. - Small-cell carcinoma of the endometrium. A clinicopathological study of sixteen cases. Am J Surg Pathol. 1994;18(4):364–75.

102. Silva EG, Deavers MT, Malpica A. Undifferentiated carcinoma of the endometrium: a review. Pathology. 2007;39(1):134–8.
103. Eifel PJ, Ross J, Hendrickson M, Cox RS, Kempson R, Martinez A. Adenocarcinoma of the endometrium. Analysis of 256 cases with disease limited to the uterine corpus: treatment comparisons. Cancer. 1983;52(6):1026–31.
104. Mariani A, Webb MJ, Keeney GL, Lesnick TG, Podratz KC. Surgical stage I endometrial cancer: predictors of distant failure and death. Gynecol Oncol. 2002;87(3):274–80.
105. Page BR, Pappas L, Cooke EW, Gaffney DK. Does the FIGO 2009 endometrial cancer staging system more accurately correlate with clinical outcome in different histologies? Revised staging, endometrial cancer, histology. Int J Gynecol Cancer. 2012;22 (4):593–8.
106. Longacre TA, Chung MH, Jensen DN, Hendrickson MR. Proposed criteria for the diagnosis of well-differentiated endometrial carcinoma. A diagnostic test for myoinvasion. Am J Surg Pathol. 1995;19 (4):371–406.
107. Ali A, Black D, Soslow RA. Difficulties in assessing the depth of myometrial invasion in endometrial carcinoma. Int J Gynecol Pathol. 2007;26 (2):115–23.
108. Jacques SM, Lawrence WD. Endometrial adenocarcinoma with variable-level myometrial involvement limited to adenomyosis: a clinicopathologic study of 23 cases. Gynecol Oncol. 1990;37(3):401–7.
109. Murray SK, Young RH, Scully RE. Unusual epithelial and stromal changes in myoinvasive endometrioid adenocarcinoma: a study of their frequency, associated diagnostic problems, and prognostic significance. Int J Gynecol Pathol. 2003;22 (4):324–33.
110. Euscher E, Fox P, Bassett R, et al. The pattern of myometrial invasion as a predictor of lymph node metastasis or extrauterine disease in low-grade endometrial carcinoma. Am J Surg Pathol. 2013;37 (11):1728–36.
111. Han G, Lim D, Leitao Jr MM, Abu-Rustum NR, Soslow RA. Histological features associated with occult lymph node metastasis in FIGO clinical stage I, grade I endometrioid carcinoma. Histopathology. 2014;64(3):389–98.
112. Pavlakis K, Messini I, Vrekoussis T, et al. MELF invasion in endometrial cancer as a risk factor for lymph node metastasis. Histopathology. 2011;58 (6):966–73.
113. Hall JB, Young RH, Nelson Jr JH. The prognostic significance of adenomyosis in endometrial carcinoma. Gynecol Oncol. 1984;17(1):32–40.
114. Mittal KR, Barwick KW. Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades, and excellent prognosis. Gynecol Oncol. 1993;49 (2):197–201.
115. Hanley KZ, Dustin SM, Stoler MH, Atkins KA. The significance of tumor involved adenomyosis in otherwise low-stage endometrioid adenocarcinoma. Int J Gynecol Pathol. 2010;29(5):445–51.
116. Gemer O, Uriev L, Harkovsky T, et al. The significance of the degree of myometrial invasion in patients with stage IB endometrial cancer. Eur J Gynaecol Oncol. 2004;25(3):336–8.
117. Zaino R. Conventional and novel prognostic factors in endometrial adenocarcinoma: a critical appraisal. Pathol Case Rev. 2000;5:138–52.
118. Shim JU, Rose PG, Reale FR, Soto H, Tak WK, Hunter RE. Accuracy of frozen-section diagnosis at surgery in clinical stage I and II endometrial carcinoma. Am J Obstet Gynecol. 1992;166(5):1335–8.
119. Fanning J, Tsukada Y, Piver MS. Intraoperative frozen section diagnosis of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol. 1990;37(1):47–50.
120. Goff BA, Rice LW. Assessment of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol. 1990;38(1):46–8.
121. Doering DL, Barnhill DR, Weiser EB, Burke TW, Woodward JE, Park RC. Intraoperative evaluation of depth of myometrial invasion in stage I endometrial adenocarcinoma. Obstet Gynecol. 1989;74 (6):930–3.
122. AlHilli MM, Podratz KC, Dowdy SC, et al. Risk-scoring system for the individualized prediction of lymphatic dissemination in patients with endometrioid endometrial cancer. Gynecol Oncol. 2013;131(1):103–8.
123. Gemer O, Uriev L, Harkovsky T, et al. Significance of lower uterine segment involvement in women with stage I endometrial adenocarcinoma. J Reprod Med. 2004;49(9):703–6.
124. Kadar NR, Kohorn EI, LiVolsi VA, Kapp DS. Histologic variants of cervical involvement by endometrial carcinoma. Obstet Gynecol. 1982;59 (1):85–92.
125. Leminen A, Forss M, Lehtovirta P. Endometrial adenocarcinoma with clinical evidence of cervical involvement: accuracy of diagnostic procedures, clinical course, and prognostic factors. Acta Obstet Gynecol Scand. 1995;74(1):61–6.
126. Jordan LB, Al-Nafussi A. Clinicopathological study of the pattern and significance of cervical involvement in cases of endometrial adenocarcinoma. Int J Gynecol Cancer. 2002;12(1):42–8.
127. Weiner J, Bigelow B, Demopoulos RI, Beckman EM, Weiner I. The value of endocervical sampling in the staging of endometrial carcinoma. Diagn Gynecol Obstet. 1980;2(4):265–8.
128. Pitson G, Colgan T, Levin W, et al. Stage II endometrial carcinoma: prognostic factors and risk classification in 170 patients. Int J Radiat Oncol Biol Phys. 2002;53(4):862–7.
129. Eltabbakh GH, Moore AD. Survival of women with surgical stage II endometrial cancer. Gynecol Oncol. 1999;74(1):80–5.

130. Zaino RJ, Abendroth C, Yemelyanova A, et al. Endocervical involvement in endometrial adenocarcinoma is not prognostically significant and the pathologic assessment of the pattern of involvement is not reproducible. Gynecol Oncol. 2013;128(1):83–7.
131. Alektiar KM, Venkatraman E, Abu-Rustum N, Barakat RR. Is endometrial carcinoma intrinsically more aggressive in elderly patients? Cancer. 2003;98 (11):2368–77.
132. Orezzoli JP, Sioletic S, Olawaiye A, Oliva E, del Carmen MG. Stage II endometrioid adenocarcinoma of the endometrium: clinical implications of cervical stromal invasion. Gynecol Oncol. 2009;113 (3):316–23.
133. Menczer J. Management of endometrial carcinoma with cervical involvement. An unsettled issue. Eur J Gynaecol Oncol. 2005;26(3):245–55.
134. Tambouret R, Clement PB, Young RH. Endometrial endometrioid adenocarcinoma with a deceptive pattern of spread to the uterine cervix: a manifestation of stage IIb endometrial carcinoma liable to be misinterpreted as an independent carcinoma or a benign lesion. Am J Surg Pathol. 2003;27 (8):1080–8.
135. McCluggage WG, Hirschowitz L, Wilson GE, Oliva E, Soslow RA, Zaino RJ. Significant variation in the assessment of cervical involvement in endometrial carcinoma: an interobserver variation study. Am J Surg Pathol. 2011;35(2):289–94.
136. Nevadunsky NS, Van Arsdale A, Strickler HD, et al. Obesity and age at diagnosis of endometrial cancer. Obstet Gynecol. 2014;124(2 Pt 1):300–6.
137. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371 (9612):569–78.
138. Garg K, Soslow RA. Endometrial carcinoma in women aged 40 years and younger. Arch Pathol Lab Med. 2014;138(3):335–42.
139. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355 (9213):1404–11.
140. Gayar OH, Robbins JR, Parikh K, et al. Hysterectomy for uterine adenocarcinoma in the elderly: tumor characteristics, and long-term outcome. Gynecol Oncol. 2011;123(1):71–5.
141. Kennedy AW, Webster KD, Nunez C, Bauer LJ. Pelvic washings for cytologic analysis in endometrial adenocarcinoma. J Reprod Med. 1993;38 (8):637–42.
142. Okuma K, Yamashita H, Kawana K, Nakagawa S, Oda K, Nakagawa K. Advanced age is a significant determinant of poor prognosis in patients treated with surgery plus postoperative radiotherapy for endometrial cancer. J Obstet Gynaecol Res. 2010;36(4):757–63.
143. Vance S, Yechieli R, Cogan C, Hanna R, Munkarah A, Elshaikh MA. The prognostic significance of age in surgically staged patients with Type II endometrial carcinoma. Gynecol Oncol. 2012;126 (1):16–9.
144. Mundt AJ, Waggoner S, Yamada D, Rotmensch J, Connell PP. Age as a prognostic factor for recurrence in patients with endometrial carcinoma. Gynecol Oncol. 2000;79(1):79–85.
145. Beckner ME, Mori T, Silverberg SG. Endometrial carcinoma: nontumor factors in prognosis. Int J Gynecol Pathol. 1985;4(2):131–45.
146. Farley JH, Nycum LR, Birrer MJ, Park RC, Taylor RR. Age-specific survival of women with endometrioid adenocarcinoma of the uterus. Gynecol Oncol. 2000;79(1):86–9.
147. Ambros RA, Kurman RJ. Combined assessment of vascular and myometrial invasion as a model to predict prognosis in stage I endometrioid adenocarcinoma of the uterine corpus. Cancer. 1992;69 (6):1424–31.
148. Briet JM, Hollema H, Reesink N, et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. Gynecol Oncol. 2005;96(3):799–804.
149. Cohn DE, Horowitz NS, Mutch DG, Kim SM, Manolitsas T, Fowler JM. Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol. 2002;87(3):243–6.
150. Dewdney SB, Jiao Z, Roma AA, et al. The prognostic significance of lymphovascular space invasion in laparoscopic versus abdominal hysterectomy for endometrioid endometrial cancer. Eur J Gynaecol Oncol. 2014;35(1):7–10.
151. Folkins AK, Nevadunsky NS, Saleemuddin A, et al. Evaluation of vascular space involvement in endometrial adenocarcinomas: laparoscopic vs abdominal hysterectomies. Mod Pathol. 2010;23 (8):1073–9.
152. Krizova A, Clarke BA, Bernardini MQ, et al. Histologic artifacts in abdominal, vaginal, laparoscopic, and robotic hysterectomy specimens: a blinded, retrospective review. Am J Surg Pathol. 2011;35 (1):115–26.
153. Hanson MB, van Nagell JR, Jr., Powell DE, et al. The prognostic significance of lymph-vascular space invasion in stage I endometrial cancer. Cancer 1985;55(8):1753-1757.
154. Gal D, Recio FO, Zamurovic D, Tancer ML. Lymphvascular space involvement – a prognostic indicator in endometrial adenocarcinoma. Gynecol Oncol. 1991;42(2):142–5.
155. Kadar N, Homesley HD, Malfetano JH. Positive peritoneal cytology is an adverse factor in endometrial carcinoma only if there is other evidence of

extrauterine disease. Gynecol Oncol. 1992;46 (2):145–9.
156. Shah C, Johnson EB, Everett E, et al. Does size matter? Tumor size and morphology as predictors of nodal status and recurrence in endometrial cancer. Gynecol Oncol. 2005;99(3):564–70.
157. Sivridis E, Buckley CH, Fox H. The prognostic significance of lymphatic vascular space invasion in endometrial adenocarcinoma. Br J Obstet Gynaecol. 1987;94(10):991–4.
158. Watari H, Todo Y, Takeda M, Ebina Y, Yamamoto R, Sakuragi N. Lymph-vascular space invasion and number of positive para-aortic node groups predict survival in node-positive patients with endometrial cancer. Gynecol Oncol. 2005;96 (3):651–7.
159. Bendifallah S, Canlorbe G, Raimond E, et al. A clue towards improving the European Society of Medical Oncology risk group classification in apparent early stage endometrial cancer? Impact of lymphovascular space invasion. Br J Cancer. 2014;110(11):2640–6.
160. Weinberg LE, Kunos CA, Zanotti KM. Lymphovascular space invasion (LVSI) is an isolated poor prognostic factor for recurrence and survival among women with intermediate- to high-risk early-stage endometrioid endometrial cancer. Int J Gynecol Cancer. 2013;23(8):1438–45.
161. Guntupalli SR, Zighelboim I, Kizer NT, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol. 2012;124(1):31–5.
162. O'Brien DJ, Flannelly G, Mooney EE, Foley M. Lymphovascular space involvement in early stage well-differentiated endometrial cancer is associated with increased mortality. BJOG. 2009;116(7):991–4.
163. Mariani A, Dowdy SC, Keeney GL, Haddock MG, Lesnick TG, Podratz KC. Predictors of vaginal relapse in stage I endometrial cancer. Gynecol Oncol. 2005;97(3):820–7.
164. Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC. Predictors of lymphatic failure in endometrial cancer. Gynecol Oncol. 2002;84(3):437–42.
165. Simpkins F, Papadia A, Kunos C, et al. Patterns of recurrence in stage I endometrioid endometrial adenocarcinoma with lymphovascular space invasion. Int J Gynecol Cancer. 2013;23(1):98–104.
166. Yamazawa K, Seki K, Matsui H, Sekiya S. Significance of perivascular lymphocytic infiltrates in endometrial carcinoma. Cancer. 2001;91(9):1777–84.
167. Deligdisch L. Morphologic correlates of host response in endometrial carcinoma. Am J Reprod Immunol. 1982;2(1):54–7.
168. Wong FC, Pang CP, Tang SK, et al. Treatment results of endometrial carcinoma with positive peritoneal washing, adnexal involvement and serosal involvement. Clin Oncol (R Coll Radiol). 2004;16 (5):350–5.
169. Kashimura M, Sugihara K, Toki N, et al. The significance of peritoneal cytology in uterine cervix and endometrial cancer. Gynecol Oncol. 1997;67 (3):285–90.
170. Kasamatsu T, Onda T, Katsumata N, et al. Prognostic significance of positive peritoneal cytology in endometrial carcinoma confined to the uterus. Br J Cancer. 2003;88(2):245–50.
171. Grimshaw RN, Tupper WC, Fraser RC, Tompkins MG, Jeffrey JF. Prognostic value of peritoneal cytology in endometrial carcinoma. Gynecol Oncol. 1990;36(1):97–100.
172. Lurain JR. The significance of positive peritoneal cytology in endometrial cancer. Gynecol Oncol. 1992;46(2):143–4.
173. Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC. Assessment of prognostic factors in stage IIIA endometrial cancer. Gynecol Oncol. 2002;86 (1):38–44.
174. Mlyncek M, Uharcek P. Peritoneal cytology in endometrial cancer. Neoplasma. 2005;52(2):103–8.
175. Takeshima N, Nishida H, Tabata T, Hirai Y, Hasumi K. Positive peritoneal cytology in endometrial cancer: enhancement of other prognostic indicators. Gynecol Oncol. 2001;82(3):470–3.
176. Tebeu PM, Popowski Y, Verkooijen HM, et al. Positive peritoneal cytology in early-stage endometrial cancer does not influence prognosis. Br J Cancer. 2004;91(4):720–4.
177. Ayhan A, Taskiran C, Celik C, Aksu T, Yuce K. Surgical stage III endometrial cancer: analysis of treatment outcomes, prognostic factors and failure patterns. Eur J Gynaecol Oncol. 2002;23(6):553–6.
178. Han KH, Park NH, Kim HS, Chung HH, Kim JW, Song YS. Peritoneal cytology: A risk factor of recurrence for non-endometrioid endometrial cancer. Gynecol Oncol. 2014;134(2):293–6.
179. Milgrom SA, Kollmeier MA, Abu-Rustum NR, et al. Positive peritoneal cytology is highly predictive of prognosis and relapse patterns in stage III (FIGO 2009) endometrial cancer. Gynecol Oncol. 2013;130(1):49–53.
180. Santala M, Talvensaari-Mattila A, Kauppila A. Peritoneal cytology and preoperative serum CA 125 level are important prognostic indicators of overall survival in advanced endometrial cancer. Anticancer Res. 2003;23(3C):3097–103.
181. Turner DA, Gershenson DM, Atkinson N, Sneige N, Wharton AT. The prognostic significance of peritoneal cytology for stage I endometrial cancer. Obstet Gynecol. 1989;74(5):775–80.
182. Ashman JB, Connell PP, Yamada D, Rotmensch J, Waggoner SE, Mundt AJ. Outcome of endometrial carcinoma patients with involvement of the uterine serosa. Gynecol Oncol. 2001;82(2):338–43.
183. Grigsby PW, Perez CA, Kuske RR, Kao MS, Galakatos AE. Results of therapy, analysis of

failures, and prognostic factors for clinical and pathologic stage III adenocarcinoma of the endometrium. Gynecol Oncol. 1987;27(1):44–57.
184. Schorge JO, Molpus KL, Goodman A, Nikrui N, Fuller Jr AF. The effect of postsurgical therapy on stage III endometrial carcinoma. Gynecol Oncol. 1996;63(1):34–9.
185. Connell PP, Rotmensch J, Waggoner S, Mundt AJ. The significance of adnexal involvement in endometrial carcinoma. Gynecol Oncol. 1999;74 (1):74–9.
186. Greven KM, Lanciano RM, Corn B, Case D, Randall ME. Pathologic stage III endometrial carcinoma. Prognostic factors and patterns of recurrence. Cancer. 1993;71(11):3697–702.
187. Irving JA, Catasus L, Gallardo A, et al. Synchronous endometrioid carcinomas of the uterine corpus and ovary: alterations in the beta-catenin (CTNNB1) pathway are associated with independent primary tumors and favorable prognosis. Hum Pathol. 2005;36(6):605–19.
188. Ulbright TM, Roth LM. Metastatic and independent cancers of the endometrium and ovary: a clinicopathologic study of 34 cases. Hum Pathol. 1985;16 (1):28–34.
189. Zaino R, Whitney C, Brady MF, DeGeest K, Burger RA, Buller RE. Simultaneously detected endometrial and ovarian carcinomas—a prospective clinicopathologic study of 74 cases: a gynecologic oncology group study. Gynecol Oncol. 2001;83 (2):355–62.
190. Clement PB, Young RH. Endometrioid carcinoma of the uterine corpus: a review of its pathology with emphasis on recent advances and problematic aspects. Adv Anat Pathol. 2002;9(3):145–84.
191. Sutton GP. The significance of positive peritoneal cytology in endometrial cancer. Oncology (Williston Park). 1990;4(6):21–6. discussion 30-22
192. Takeshima N, Hirai Y, Yano K, Tanaka N, Yamauchi K, Hasumi K. Ovarian metastasis in endometrial carcinoma. Gynecol Oncol. 1998;70 (2):183–7.
193. Nicklin JL, Petersen RW. Stage 3B adenocarcinoma of the endometrium: a clinicopathologic study. Gynecol Oncol. 2000;78(2):203–7.
194. Chuang L, Burke TW, Tornos C, et al. Staging laparotomy for endometrial carcinoma: assessment of retroperitoneal lymph nodes. Gynecol Oncol. 1995;58(2):189–93.
195. Lampe B, Kurzl R, Hantschmann P. Prognostic factors that predict pelvic lymph node metastasis from endometrial carcinoma. Cancer. 1994;74 (9):2502–8.
196. Ohkouchi T, Sakuragi N, Watari H, et al. Prognostic significance of Bcl-2, p53 overexpression, and lymph node metastasis in surgically staged endometrial carcinoma. Am J Obstet Gynecol. 2002;187 (2):353–9.
197. Chang SJ, Kim WY, Yoon JH, Yoo SC, Chang KH, Ryu HS. Para-aortic lymphadenectomy improves survival in patients with intermediate to high-risk endometrial carcinoma. Acta Obstet Gynecol Scand. 2008;87(12):1361–9.
198. Kim HS, Kim HY, Park CY, et al. Lymphadenectomy increases the prognostic value of the revised 2009 FIGO staging system for endometrial cancer: a multi-center study. Eur J Surg Oncol. 2012;38(3):230–7.
199. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol. 2008;109(1):11–8.
200. Abu-Rustum NR, Iasonos A, Zhou Q, et al. Is there a therapeutic impact to regional lymphadenectomy in the surgical treatment of endometrial carcinoma? Am J Obstet Gynecol. 2008;198(4):457 e451–5; discussion 457 e455–56.
201. Lutman CV, Havrilesky LJ, Cragun JM, et al. Pelvic lymph node count is an important prognostic variable for FIGO stage I and II endometrial carcinoma with high-risk histology. Gynecol Oncol. 2006;102 (1):92–7.
202. Mariani A, Dowdy SC, Cliby WA, et al. Efficacy of systematic lymphadenectomy and adjuvant radiotherapy in node-positive endometrial cancer patients. Gynecol Oncol. May 2006;101(2):200–8.
203. Mariani A, Webb MJ, Galli L, Podratz KC. Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer. Gynecol Oncol. 2000;76(3):348–56.
204. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol. 1995;56(1):29–33.
205. Larson DM, Johnson KK. Pelvic and para-aortic lymphadenectomy for surgical staging of high-risk endometrioid adenocarcinoma of the endometrium. Gynecol Oncol. 1993;51(3):345–8.
206. Yokoyama Y, Maruyama H, Sato S, Saito Y. Indispensability of pelvic and paraaortic lymphadenectomy in endometrial cancers. Gynecol Oncol. 1997;64(3):411–7.
207. Arango HA, Hoffman MS, Roberts WS, DeCesare SL, Fiorica JV, Drake J. Accuracy of lymph node palpation to determine need for lymphadenectomy in gynecologic malignancies. Obstet Gynecol. 2000;95 (4):553–6.
208. Nugent EK, Bishop EA, Mathews CA, et al. Do uterine risk factors or lymph node metastasis more significantly affect recurrence in patients with endometrioid adenocarcinoma? Gynecol Oncol. 2012;125(1):94–8.
209. Mariani A, Keeney GL, Aletti G, Webb MJ, Haddock MG, Podratz KC. Endometrial carcinoma: paraaortic dissemination. Gynecol Oncol. 2004;92 (3):833–8.

210. McMeekin DS, Lashbrook D, Gold M, Johnson G, Walker JL, Mannel R. Analysis of FIGO Stage IIIc endometrial cancer patients. Gynecol Oncol. 2001;81(2):273–8.
211. Mohan DS, Samuels MA, Selim MA, et al. Long-term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. Gynecol Oncol. 1998;70(2):165–71.
212. Girardi F, Petru E, Heydarfadai M, Haas J, Winter R. Pelvic lymphadenectomy in the surgical treatment of endometrial cancer. Gynecol Oncol. 1993;49 (2):177–80.
213. Gonzalez Bosquet J, Keeney GL, Mariani A, Webb MJ, Cliby WA. Cytokeratin staining of resected lymph nodes may improve the sensitivity of surgical staging for endometrial cancer. Gynecol Oncol. 2003;91(3):518–25.
214. Yabushita H, Shimazu M, Yamada H, et al. Occult lymph node metastases detected by cytokeratin immunohistochemistry predict recurrence in node-negative endometrial cancer. Gynecol Oncol. 2001;80(2):139–44.
215. Abu-Rustum NR. Update on sentinel node mapping in uterine cancer: 10-year experience at Memorial Sloan-Kettering Cancer Center. J Obstet Gynaecol Res. 2014;40(2):327–34.
216. Touboul C, Bentivegna E, Uzan C, et al. Sentinel lymph node in endometrial cancer: a review. Curr Oncol Rep. 2013;15(6):559–65.
217. Evans MP, Podratz KC. Endometrial neoplasia: prognostic significance of ploidy status. Clin Obstet Gynecol. 1996;39(3):696–706.
218. Britton LC, Wilson TO, Gaffey TA, Lieber MM, Wieand HS, Podratz KC. Flow cytometric DNA analysis of stage I endometrial carcinoma. Gynecol Oncol. 1989;34(3):317–22.
219. Pradhan M, Abeler VM, Danielsen HE, Trope CG, Risberg BA. Image cytometry DNA ploidy correlates with histological subtypes in endometrial carcinomas. Mod Pathol. 2006;19(9):1227–35.
220. Susini T, Amunni G, Molino C, et al. Ten-year results of a prospective study on the prognostic role of ploidy in endometrial carcinoma: dNA aneuploidy identifies high-risk cases among the so-called "low-risk" patients with well and moderately differentiated tumors. Cancer. 2007;109 (5):882–90.
221. Terada K, Mattson D, Goo D, Shimizu D. DNA aneuploidy is associated with increased mortality for stage I endometrial cancer. Gynecol Oncol. 2004;95(3):483–7.
222. Genest DR, Sheets E, Lage JM. Flow-cytometric analysis of nuclear DNA content in endometrial adenocarcinoma. Atypical mitoses are associated with DNA aneuploidy. Am J Clin Pathol. 1994;102 (3):341–8.
223. Kudela M, Pilka R, Lubusky M, Hejtmanek P, Dzubak P, Brychtova S. Prognostic importance of selected molecular immunohistochemical markers and DNA ploidy in endometrial cancer. Eur J Gynaecol Oncol. 2012;33(2):159–63.
224. Lukes AS, Kohler MF, Pieper CF, et al. Multivariable analysis of DNA ploidy, p53, and HER-2/neu as prognostic factors in endometrial cancer. Cancer. 1994;73(9):2380–5.
225. Lundgren C, Auer G, Frankendal B, Moberger B, Nilsson B, Nordstrom B. Nuclear DNA content, proliferative activity, and p53 expression related to clinical and histopathologic features in endometrial carcinoma. Int J Gynecol Cancer. 2002;12 (1):110–8.
226. Mangili G, De Marzi P, Vigano R, et al. Identification of high risk patients with endometrial carcinoma. Prognostic assessment of endometrial cancer. Eur J Gynaecol Oncol. 2002;23(3):216–20.
227. Mauland KK, Wik E, Salvesen HB. Clinical value of DNA content assessment in endometrial cancer. Cytometry B Clin Cytom. 2014;86(3):154–63.
228. Santala M, Talvensaari-Mattila A. DNA ploidy is an independent prognostic indicator of overall survival in stage I endometrial endometrioid carcinoma. Anticancer Res. 2003;23(6D):5191–6.
229. Geisinger KR, Homesley HD, Morgan TM, Kute TE, Marshall RB. Endometrial adenocarcinoma. A multiparameter clinicopathologic analysis including the DNA profile and the sex steroid hormone receptors. Cancer. 1986;58(7):1518–25.
230. Pfisterer J, Kommoss F, Sauerbrei W, et al. Prognostic value of DNA ploidy and S-phase fraction in stage I endometrial carcinoma. Gynecol Oncol. 1995;58(2):149–56.
231. Sorbe B, Risberg B, Frankendal B. DNA ploidy, morphometry, and nuclear grade as prognostic factors in endometrial carcinoma. Gynecol Oncol. 1990;38(1):22–7.
232. Pradhan M, Davidson B, Abeler VM, et al. DNA ploidy may be a prognostic marker in stage I and II serous adenocarcinoma of the endometrium. Virchows Arch. 2012;461(3):291–8.
233. Kildal W, Micci F, Risberg B, et al. Genomic imbalances in endometrial adenocarcinomas—comparison of DNA ploidy, karyotyping and comparative genomic hybridization. Mol Oncol. 2012;6 (1):98–107.
234. Chambers JT, MacLusky N, Eisenfield A, Kohorn EI, Lawrence R, Schwartz PE. Estrogen and progestin receptor levels as prognosticators for survival in endometrial cancer. Gynecol Oncol. 1988;31 (1):65–81.
235. Creasman WT. Prognostic significance of hormone receptors in endometrial cancer. Cancer. 1993;71 (4 Suppl):1467–70.
236. Hanekamp EE, Gielen SC, Smid-Koopman E, et al. Consequences of loss of progesterone receptor expression in development of invasive endometrial cancer. Clin Cancer Res. 2003;9(11):4190–9.
237. Kadar N, Malfetano JH, Homesley HD. Steroid receptor concentrations in endometrial carcinoma:

effect on survival in surgically staged patients. Gynecol Oncol. 1993;50(3):281–6.
238. Morris PC, Anderson JR, Anderson B, Buller RE. Steroid hormone receptor content and lymph node status in endometrial cancer. Gynecol Oncol. 1995;56(3):406–11.
239. Arai T, Watanabe J, Kawaguchi M, et al. Clear cell adenocarcinoma of the endometrium is a biologically distinct entity from endometrioid adenocarcinoma. Int J Gynecol Cancer. 2006;16(1):391–5.
240. Carcangiu ML, Chambers JT, Voynick IM, Pirro M, Schwartz PE. Immunohistochemical evaluation of estrogen and progesterone receptor content in 183 patients with endometrial carcinoma. Part I: Clinical and histologic correlations. Am J Clin Pathol. 1990;94(3):247–54.
241. Lax SF, Pizer ES, Ronnett BM, Kurman RJ. Clear cell carcinoma of the endometrium is characterized by a distinctive profile of p53, Ki-67, estrogen, and progesterone receptor expression. Hum Pathol. 1998;29(6):551–8.
242. Ehrlich CE, Young PC, Stehman FB, Sutton GP, Alford WM. Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium. Am J Obstet Gynecol. 1988;158(4):796–807.
243. Hu K, Zhong G, He F. Expression of estrogen receptors ERalpha and ERbeta in endometrial hyperplasia and adenocarcinoma. Int J Gynecol Cancer. 2005;15(3):537–41.
244. De Vivo I, Huggins GS, Hankinson SE, et al. A functional polymorphism in the promoter of the progesterone receptor gene associated with endometrial cancer risk. Proc Natl Acad Sci U S A. 2002;99 (19):12263–8.
245. Kalogiannidis I, Petousis S, Bobos M, et al. HER-2/neu is an independent prognostic factor in type I endometrial adenocarcinoma. Arch Gynecol Obstet. 2014;290(6):1231–7.
246. Berchuck A, Rodriguez G, Kinney RB, et al. Overexpression of HER-2/neu in endometrial cancer is associated with advanced stage disease. Am J Obstet Gynecol. 1991;164(1 Pt 1):15–21.
247. Hetzel DJ, Wilson TO, Keeney GL, Roche PC, Cha SS, Podratz KC. HER-2/neu expression: a major prognostic factor in endometrial cancer. Gynecol Oncol. 1992;47(2):179–85.
248. Peiro G, Mayr D, Hillemanns P, Lohrs U, Diebold J. Analysis of HER-2/neu amplification in endometrial carcinoma by chromogenic in situ hybridization. Correlation with fluorescence in situ hybridization, HER-2/neu, p53 and Ki-67 protein expression, and outcome. Mod Pathol. 2004;17 (3):227–87.
249. Saffari B, Jones LA. el-Naggar A, Felix JC, George J, Press MF. Amplification and overexpression of HER-2/neu (c-erbB2) in endometrial cancers: correlation with overall survival. Cancer Res. 1995;55(23):5693–8.
250. Santin AD. HER2/neu overexpression: has the Achilles' heel of uterine serous papillary carcinoma been exposed? Gynecol Oncol. 2003;88(3):263–5.
251. Coronado PJ, Vidart JA, Lopez-asenjo JA, et al. P53 overexpression predicts endometrial carcinoma recurrence better than HER-2/neu overexpression. Eur J Obstet Gynecol Reprod Biol. 2001;98 (1):103–8.
252. Heffner HM, Freedman AN, Asirwatham JE, Lele SB. Prognostic significance of p53, PCNA, and c-erbB-2 in endometrial enocarcinoma. Eur J Gynaecol Oncol. 1999;20(1):8–12.
253. Pisani AL, Barbuto DA, Chen D, Ramos L, Lagasse LD, Karlan BY. HER-2/neu, p53, and DNA analyses as prognosticators for survival in endometrial carcinoma. Obstet Gynecol. 1995;85(5 Pt 1):729–34.
254. Riben MW, Malfetano JH, Nazeer T, Muraca PJ, Ambros RA, Ross JS. Identification of HER-2/neu oncogene amplification by fluorescence in situ hybridization in stage I endometrial carcinoma. Mod Pathol. 1997;10(8):823–31.
255. Williams Jr JA, Wang ZR, Parrish RS, Hazlett LJ, Smith ST, Young SR. Fluorescence in situ hybridization analysis of HER-2/neu, c-myc, and p53 in endometrial cancer. Exp Mol Pathol. 1999;67(3):135–43.
256. Alvarez T, Miller E, Duska L, Oliva E. Molecular profile of grade 3 endometrioid endometrial carcinoma: is it a type I or type II endometrial carcinoma? Am J Surg Pathol. 2012;36(5):753–61.
257. Khalifa MA, Mannel RS, Haraway SD, Walker J, Min KW. Expression of EGFR, HER-2/neu, P53, and PCNA in endometrioid, serous papillary, and clear cell endometrial adenocarcinomas. Gynecol Oncol. 1994;53(1):84–92.
258. Rolitsky CD, Theil KS, McGaughy VR, Copeland LJ, Niemann TH. HER-2/neu amplification and overexpression in endometrial carcinoma. Int J Gynecol Pathol. 1999;18(2):138–43.
259. Tashiro H, Isacson C, Levine R, Kurman RJ, Cho KR, Hedrick L. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. Am J Pathol. 1997;150 (1):177–85.
260. Yamazawa K, Shimada H, Hirai M, et al. Serum p53 antibody as a diagnostic marker of high-risk endometrial cancer. Am J Obstet Gynecol. 2007;197 (5):505 e501–7.
261. An HJ, Logani S, Isacson C, Ellenson LH. Molecular characterization of uterine clear cell carcinoma. Mod Pathol. 2004;17(5):530–7.
262. Gadducci A, Tana R, Cosio S, Fanucchi A, Genazzani AR. Molecular target therapies in endometrial cancer: from the basic research to the clinic. Gynecol Endocrinol. 2008;24(5):239–49.
263. Lee EJ, Kim TJ, Kim DS, et al. p53 alteration independently predicts poor outcomes in patients with endometrial cancer: a clinicopathologic study of

131 cases and literature review. Gynecol Oncol. 2010;116(3):533–8.
264. Alkushi A, Lim P, Coldman A, Huntsman D, Miller D, Gilks CB. Interpretation of p53 immunoreactivity in endometrial carcinoma: establishing a clinically relevant cut-off level. Int J Gynecol Pathol. 2004;23(2):129–37.
265. Geisler JP, Geisler HE, Wiemann MC, Zhou Z, Miller GA, Crabtree W. Lack of bcl-2 persistence: an independent prognostic indicator of poor prognosis in endometrial carcinoma. Gynecol Oncol. 1998;71(2):305–7.
266. Taskin M, Lallas TA, Barber HR, Shevchuk MM. bcl-2 and p53 in endometrial adenocarcinoma. Mod Pathol. 1997;10(7):728–34.
267. Yamauchi N, Sakamoto A, Uozaki H, Iihara K, Machinami R. Immunohistochemical analysis of endometrial adenocarcinoma for bcl-2 and p53 in relation to expression of sex steroid receptor and proliferative activity. Int J Gynecol Pathol. 1996;15 (3):202–8.
268. Zheng W, Cao P, Zheng M, Kramer EE, Godwin TA. p53 overexpression and bcl-2 persistence in endometrial carcinoma: comparison of papillary serous and endometrioid subtypes. Gynecol Oncol. 1996;61(2):167–74.
269. Mariani A, Sebo TJ, Cliby WA, et al. Role of bcl-2 in endometrioid corpus cancer: an experimental study. Anticancer Res. 2006;26(2A):823–7.
270. Risinger JI, Hayes K, Maxwell GL, et al. PTEN mutation in endometrial cancers is associated with favorable clinical and pathologic characteristics. Clin Cancer Res. 1998;4(12):3005–10.
271. Tashiro H, Blazes MS, Wu R, et al. Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. Cancer Res. 1997;57(18):3935–40.
272. Bussaglia E, del Rio E, Matias-Guiu X, Prat J. PTEN mutations in endometrial carcinomas: a molecular and clinicopathologic analysis of 38 cases. Hum Pathol. 2000;31(3):312–7.
273. Levine RL, Cargile CB, Blazes MS, van Rees B, Kurman RJ, Ellenson LH. PTEN mutations and microsatellite instability in complex atypical hyperplasia, a precursor lesion to uterine endometrioid carcinoma. Cancer Res. 1998;58(15):3254–8.
274. Bilbao C, Rodriguez G, Ramirez R, et al. The relationship between microsatellite instability and PTEN gene mutations in endometrial cancer. Int J Cancer. 2006;119(3):563–70.
275. Terakawa N, Kanamori Y, Yoshida S. Loss of PTEN expression followed by Akt phosphorylation is a poor prognostic factor for patients with endometrial cancer. Endocr Relat Cancer. 2003;10(2):203–8.
276. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400–7.
277. Xiong J, He M, Jackson C, et al. Endometrial carcinomas with significant mucinous differentiation associated with higher frequency of k-ras mutations: a morphologic and molecular correlation study. Int J Gynecol Cancer. 2013;23(7):1231–6.
278. Duggan BD, Felix JC, Muderspach LI, Tsao JL, Shibata DK. Early mutational activation of the c-Ki-ras oncogene in endometrial carcinoma. Cancer Res. 1994;54(6):1604–7.
279. Lagarda H, Catasus L, Arguelles R, Matias-Guiu X, Prat J. K-ras mutations in endometrial carcinomas with microsatellite instability. J Pathol. 2001;193 (2):193–9.
280. Mutter GL, Wada H, Faquin WC, Enomoto T. K-ras mutations appear in the premalignant phase of both microsatellite stable and unstable endometrial carcinogenesis. Mol Pathol. 1999;52(5):257–62.
281. Caduff RF, Johnston CM, Frank TS. Mutations of the Ki-ras oncogene in carcinoma of the endometrium. Am J Pathol. 1995;146(1):182–8.
282. Doll A, Abal M, Rigau M, et al. Novel molecular profiles of endometrial cancer-new light through old windows. J Steroid Biochem Mol Biol. 2008;108 (3-5):221–9.
283. Buttin BM, Powell MA, Mutch DG, et al. Increased risk for hereditary nonpolyposis colorectal cancer-associated synchronous and metachronous malignancies in patients with microsatellite instability-positive endometrial carcinoma lacking MLH1 promoter methylation. Clin Cancer Res. 2004;10(2):481–90.
284. Hagen CE, Lefferts J, Hornick JL, Srivastava A. "Null pattern" of immunoreactivity in a Lynch syndrome-associated colon cancer due to germline MSH2 mutation and somatic MLH1 hypermethylation. Am J Surg Pathol. 2011;35 (12):1902–5.
285. Kwon JS, Scott JL, Gilks CB, Daniels MS, Sun CC, Lu KH. Testing women with endometrial cancer to detect Lynch syndrome. J Clin Oncol. 2011;29 (16):2247–52.
286. Whelan AJ, Babb S, Mutch DG, et al. MSI in endometrial carcinoma: absence of MLH1 promoter methylation is associated with increased familial risk for cancers. Int J Cancer. 2002;99(5):697–704.
287. Broaddus RR, Lynch HT, Chen LM, et al. Pathologic features of endometrial carcinoma associated with HNPCC: a comparison with sporadic endometrial carcinoma. Cancer. 2006;106(1):87–94.
288. Carcangiu ML, Radice P, Casalini P, Bertario L, Merola M, Sala P. Lynch syndrome-related endometrial carcinomas show a high frequency of nonendometrioid types and of high FIGO grade endometrioid types. Int J Surg Pathol. 2010;18 (1):21–6.
289. Parc YR, Halling KC, Burgart LJ, et al. Microsatellite instability and hMLH1/hMSH2 expression in young endometrial carcinoma patients: associations

with family history and histopathology. Int J Cancer. 2000;86(1):60–6.
290. Soslow RA. Endometrial carcinomas with ambiguous features. Semin Diagn Pathol. 2010;27 (4):261–73.
291. Westin SN, Lacour RA, Urbauer DL, et al. Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome. J Clin Oncol. 2008;26(36):5965–71.
292. Maxwell GL, Risinger JI, Alvarez AA, Barrett JC, Berchuck A. Favorable survival associated with microsatellite instability in endometrioid endometrial cancers. Obstet Gynecol. 2001;97(3):417–22.
293. Caduff RF, Johnston CM, Svoboda-Newman SM, Poy EL, Merajver SD, Frank TS. Clinical and pathological significance of microsatellite instability in sporadic endometrial carcinoma. Am J Pathol. 1996;148(5):1671–8.
294. Fiumicino S, Ercoli A, Ferrandina G, et al. Microsatellite instability is an independent indicator of recurrence in sporadic stage I-II endometrial adenocarcinoma. J Clin Oncol. 2001;19(4):1008–14.
295. Kobayashi K, Sagae S, Kudo R, Saito H, Koi S, Nakamura Y. Microsatellite instability in endometrial carcinomas: frequent replication errors in tumors of early onset and/or of poorly differentiated type. Genes Chromosomes Cancer. 1995;14 (2):128–32.
296. MacDonald ND, Salvesen HB, Ryan A, Iversen OE, Akslen LA, Jacobs IJ. Frequency and prognostic impact of microsatellite instability in a large population-based study of endometrial carcinomas. Cancer Res. 2000;60(6):1750–2.
297. Orbo A, Eklo K, Kopp M. A semiautomated test for microsatellite instability and its significance for the prognosis of sporadic endometrial cancer in northern Norway. Int J Gynecol Pathol. 2002;21 (1):27–33.
298. Tibiletti MG, Furlan D, Taborelli M, et al. Microsatellite instability in endometrial cancer: relation to histological subtypes. Gynecol Oncol. 1999;73 (2):247–52.
299. Wong YF, Ip TY, Chung TK, et al. Clinical and pathologic significance of microsatellite instability in endometrial cancer. Int J Gynecol Cancer. 1999;9 (5):406–10.
300. Diaz-Padilla I, Romero N, Amir E, et al. Mismatch repair status and clinical outcome in endometrial cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2013;88(1):154–67.
301. Fukuchi T, Sakamoto M, Tsuda H, Maruyama K, Nozawa S, Hirohashi S. Beta-catenin mutation in carcinoma of the uterine endometrium. Cancer Res. 1998;58(16):3526–8.
302. Machin P, Catasus L, Pons C, Munoz J, Matias-Guiu X, Prat J. CTNNB1 mutations and beta-catenin expression in endometrial carcinomas. Hum Pathol. 2002;33(2):206–12.
303. Moreno-Bueno G, Hardisson D, Sanchez C, et al. Abnormalities of the APC/beta-catenin pathway in endometrial cancer. Oncogene. 2002;21 (52):7981–90.
304. Ikeda T, Yoshinaga K, Semba S, Kondo E, Ohmori H, Horii A. Mutational analysis of the CTNNB1 (beta-catenin) gene in human endometrial cancer: frequent mutations at codon 34 that cause nuclear accumulation. Oncol Rep. 2000;7(2):323–6.
305. Saegusa M, Hashimura M, Yoshida T, Okayasu I. beta-Catenin mutations and aberrant nuclear expression during endometrial tumorigenesis. Br J Cancer. 2001;84(2):209–17.
306. Catasus L, Gallardo A, Cuatrecasas M, Prat J. PIK3CA mutations in the kinase domain (exon 20) of uterine endometrial adenocarcinomas are associated with adverse prognostic parameters. Mod Pathol. 2008;21(2):131–9.
307. Ellis PE, Ghaem-Maghami S. Molecular characteristics and risk factors in endometrial cancer: what are the treatment and preventative strategies? Int J Gynecol Cancer. 2010;20 (7):1207–16.
308. Oda K, Stokoe D, Taketani Y, McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. Cancer Res. 2005;65(23):10669–73.
309. Velasco A, Bussaglia E, Pallares J, et al. PIK3CA gene mutations in endometrial carcinoma: correlation with PTEN and K-RAS alterations. Hum Pathol. 2006;37(11):1465–72.
310. Matias-Guiu X, Davidson B. Prognostic biomarkers in endometrial and ovarian carcinoma. Virchows Arch. 2014;464(3):315–31.
311. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73.
312. Mao TL, Shih IM. The roles of ARID1A in gynecologic cancer. J Gynecol Oncol. 2013;24(4):376–81.
313. Meng B, Hoang LN, McIntyre JB, et al. POLE exonuclease domain mutation predicts long progression-free survival in grade 3 endometrioid carcinoma of the endometrium. Gynecol Oncol. 2014;134 (1):15–9.
314. Meeting Report: The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas. Gynecol Oncol. 2009;115(3):325–8.
315. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. 2008;112(4):820–30.
316. Leitao MM, Brennan MF, Hensley M, et al. Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. Gynecol Oncol. 2002;87(3):287–94.
317. Bodner K, Bodner-Adler B, Kimberger O, Czerwenka K, Leodolter S, Mayerhofer

K. Evaluating prognostic parameters in women with uterine leiomyosarcoma. A clinicopathologic study. J Reprod Med. 2003;48(2):95–100.
318. Giuntoli 2nd RL, Metzinger DS, DiMarco CS, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol. 2003;89(3):460–9.
319. Dinh TA, Oliva EA, Fuller Jr AF, Lee H, Goodman A. The treatment of uterine leiomyosarcoma. Results from a 10-year experience (1990-1999) at the Massachusetts General Hospital. Gynecol Oncol. 2004;92(2):648–52.
320. Jones MW, Norris HJ. Clinicopathologic study of 28 uterine leiomyosarcomas with metastasis. Int J Gynecol Pathol. 1995;14(3):243–9.
321. Larson B, Silfversward C, Nilsson B, Pettersson F. Prognostic factors in uterine leiomyosarcoma. A clinical and histopathological study of 143 cases. The Radiumhemmet series 1936-1981. Acta Oncol. 1990;29(2):185–91.
322. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993;71(4 Suppl):1702–9.
323. Pautier P, Genestie C, Rey A, et al. Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of a grading score validated for soft tissue sarcoma. Cancer. 2000;88 (6):1425–31.
324. Abeler VM, Royne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology. 2009;54(3):355–64.
325. D'Angelo E, Espinosa I, Ali R, et al. Uterine leiomyosarcomas: tumor size, mitotic index, and biomarkers Ki67, and Bcl-2 identify two groups with different prognosis. Gynecol Oncol. 2011;121 (2):328–33.
326. Evans HL, Chawla SP, Simpson C, Finn KP. Smooth muscle neoplasms of the uterus other than ordinary leiomyoma. A study of 46 cases, with emphasis on diagnostic criteria and prognostic factors. Cancer. 1988;62(10):2239–47.
327. Hsieh CH, Lin H, Huang CC, Huang EY, Chang SY, ChangChien CC. Leiomyosarcoma of the uterus: a clinicopathologic study of 21 cases. Acta Obstet Gynecol Scand. 2003;82(1):74–81.
328. Leitao MM, Soslow RA, Nonaka D, et al. Tissue microarray immunohistochemical expression of estrogen, progesterone, and androgen receptors in uterine leiomyomata and leiomyosarcoma. Cancer. 2004;101(6):1455–62.
329. Mayerhofer K, Obermair A, Windbichler G, et al. Leiomyosarcoma of the uterus: a clinicopathologic multicenter study of 71 cases. Gynecol Oncol. 1999;74(2):196–201.
330. Nordal RR, Kristensen GB, Kaern J, Stenwig AE, Pettersen EO, Trope CG. The prognostic significance of stage, tumor size, cellular atypia and DNA ploidy in uterine leiomyosarcoma. Acta Oncol. 1995;34(6):797–802.
331. Pelmus M, Penault-Llorca F, Guillou L, et al. Prognostic factors in early-stage leiomyosarcoma of the uterus. Int J Gynecol Cancer. 2009;19(3):385–90.
332. Veras E, Zivanovic O, Jacks L, Chiappetta D, Hensley M, Soslow R. "Low-grade leiomyosarcoma" and late-recurring smooth muscle tumors of the uterus: a heterogenous collection of frequently misdiagnosed tumors associated with an overall favorable prognosis relative to conventional uterine leiomyosarcomas. Am J Surg Pathol. 2011;35(11):1626–37.
333. Lim D, Wang WL, Lee CH, Dodge T, Gilks B, Oliva E. Old versus new FIGO staging systems in predicting overall survival in patients with uterine leiomyosarcoma: a study of 86 cases. Gynecol Oncol. 2013;128(2):322–6.
334. Malouf GG, Lhomme C, Duvillard P, Morice P, Haie-Meder C, Pautier P. Prognostic factors and outcome of undifferentiated endometrial sarcoma treated by multimodal therapy. Int J Gynaecol Obstet. 2013;122(1):57–61.
335. Raut CP, Nucci MR, Wang Q, et al. Predictive value of FIGO and AJCC staging systems in patients with uterine leiomyosarcoma. Eur J Cancer. 2009;45 (16):2818–24.
336. Garg G, Shah JP, Liu JR, et al. Validation of tumor size as staging variable in the revised International Federation of Gynecology and Obstetrics stage I leiomyosarcoma: a population-based study. Int J Gynecol Cancer. 2010;20(7):1201–6.
337. Giuntoli 2nd RL, Lessard-Anderson CR, Gerardi MA, et al. Comparison of current staging systems and a novel staging system for uterine leiomyosarcoma. Int J Gynecol Cancer. 2013;23(5):869–76.
338. Wang WL, Soslow R, Hensley M, et al. Histopathologic prognostic factors in stage I leiomyosarcoma of the uterus: a detailed analysis of 27 cases. Am J Surg Pathol. 2011;35(4):522–9.
339. King ME, Dickersin GR, Scully RE. Myxoid leiomyosarcoma of the uterus. A report of six cases. Am J Surg Pathol. 1982;6(7):589–98.
340. Kurman RJ, Norris HJ. Mesenchymal tumors of the uterus. VI. Epithelioid smooth muscle tumors including leiomyoblastoma and clear-cell leiomyoma: a clinical and pathologic analysis of 26 cases. Cancer. 1976;37(4):1853–65.
341. Prayson RA, Goldblum JR, Hart WR. Epithelioid smooth-muscle tumors of the uterus: a clinicopathologic study of 18 patients. Am J Surg Pathol. 1997;21 (4):383–91.
342. Burch DM, Tavassoli FA. Myxoid leiomyosarcoma of the uterus. Histopathology. 2011;59(6):1144–55.

343. Toledo G, Oliva E. Smooth muscle tumors of the uterus: a practical approach. Arch Pathol Lab Med. 2008;132(4):595–605.
344. Raspollini MR, Amunni G, Villanucci A, et al. Estrogen and progesterone receptors expression in uterine malignant smooth muscle tumors: correlation with clinical outcome. J Chemother. 2003;15 (6):596–602.
345. Bodner K, Bodner-Adler B, Kimberger O, Czerwenka K, Leodolter S, Mayerhofer K. Estrogen and progesterone receptor expression in patients with uterine leiomyosarcoma and correlation with different clinicopathological parameters. Anticancer Res. 2003;23(1B):729–32.
346. Goff BA, Rice LW, Fleischhacker D, et al. Uterine leiomyosarcoma and endometrial stromal sarcoma: lymph node metastases and sites of recurrence. Gynecol Oncol. 1993;50(1):105–9.
347. Leitao MM, Sonoda Y, Brennan MF, Barakat RR, Chi DS. Incidence of lymph node and ovarian metastases in leiomyosarcoma of the uterus. Gynecol Oncol. 2003;91(1):209–12.
348. Lennart K, Lennart B, Ulf S, Bernard T. Flow cytometric analysis of uterine sarcomas. Gynecol Oncol. 1994;55(3 Pt 1):339–42.
349. Liu FS, Kohler MF, Marks JR, Bast Jr RC, Boyd J, Berchuck A. Mutation and overexpression of the p53 tumor suppressor gene frequently occurs in uterine and ovarian sarcomas. Obstet Gynecol. 1994;83 (1):118–24.
350. Raspollini MR, Paglierani M, Taddei GL, Villanucci A, Amunni G, Taddei A. The protooncogene c-KIT is expressed in leiomyosarcomas of the uterus. Gynecol Oncol. 2004;93(3):718.
351. Raspollini MR, Pinzani P, Simi L, et al. Uterine leiomyosarcomas express KIT protein but lack mutation(s) in exon 9 of c-KIT. Gynecol Oncol. 2005;98 (2):334–5.
352. Rushing RS, Shajahan S, Chendil D, et al. Uterine sarcomas express KIT protein but lack mutation(s) in exon 11 or 17 of c-KIT. Gynecol Oncol. 2003;91 (1):9–14.
353. Wang L, Felix JC, Lee JL, et al. The proto-oncogene c-kit is expressed in leiomyosarcomas of the uterus. Gynecol Oncol. 2003;90(2):402–6.
354. Winter 3rd WE, Seidman JD, Krivak TC, et al. Clinicopathological analysis of c-kit expression in carcinosarcomas and leiomyosarcomas of the uterine corpus. Gynecol Oncol. 2003;91(1):3–8.
355. Einstein MH, Barakat RR, Chi DS, et al. Management of uterine malignancy found incidentally after supracervical hysterectomy or uterine morcellation for presumed benign disease. Int J Gynecol Cancer. 2008;18(5):1065–70.
356. George S, Barysauskas C, Serrano C, et al. Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma. Cancer. 2014;120 (20):3154–8.
357. Larson B, Silfversward C, Nilsson B, Pettersson F. Endometrial stromal sarcoma of the uterus. A clinical and histopathological study. The Radiumhemmet series 1936-1981. Eur J Obstet Gynecol Reprod Biol. 1990;35(2-3):239–49.
358. Norris HJ, Taylor HB. Mesenchymal tumors of the uterus. I. A clinical and pathological study of 53 endometrial stromal tumors. Cancer. 1966;19 (6):755–66.
359. Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. Am J Surg Pathol. 1990;14(5):415–38.
360. Feng W, Malpica A, Robboy SJ, et al. Prognostic value of the diagnostic criteria distinguishing endometrial stromal sarcoma, low grade from undifferentiated endometrial sarcoma, 2 entities within the invasive endometrial stromal neoplasia family. Int J Gynecol Pathol. 2013;32(3):299–306.
361. Chew I, Oliva E. Endometrial stromal sarcomas: a review of potential prognostic factors. Adv Anat Pathol. 2010;17(2):113–21.
362. De Fusco PA, Gaffey TA, Malkasian Jr GD, Long HJ, Cha SS. Endometrial stromal sarcoma: review of Mayo Clinic experience, 1945-1980. Gynecol Oncol. 1989;35(1):8–14.
363. Lee CH, Ali RH, Rouzbahman M, et al. Cyclin D1 as a diagnostic immunomarker for endometrial stromal sarcoma with YWHAE-FAM22 rearrangement. Am J Surg Pathol. 2012;36(10):1562–70.
364. August CZ, Bauer KD, Lurain J, Murad T. Neoplasms of endometrial stroma: histopathologic and flow cytometric analysis with clinical correlation. Hum Pathol. 1989;20(3):232–7.
365. el-Naggar AK, Abdul-Karim FW, Silva EG, McLemore D, Garnsey L. Uterine stromal neoplasms: a clinicopathologic and DNA flow cytometric correlation. Hum Pathol. 1991;22 (9):897–903.
366. Nola M, Babic D, Ilic J, et al. Prognostic parameters for survival of patients with malignant mesenchymal tumors of the uterus. Cancer. 1996;78(12):2543–50.
367. Balleine RL, Earls PJ, Webster LR, et al. Expression of progesterone receptor A and B isoforms in low-grade endometrial stromal sarcoma. Int J Gynecol Pathol. 2004;23(2):138–44.
368. Leunen M, Breugelmans M, De Sutter P, Bourgain C, Amy JJ. Low-grade endometrial stromal sarcoma treated with the aromatase inhibitor letrozole. Gynecol Oncol. 2004;95(3):769–71.
369. Maluf FC, Sabbatini P, Schwartz L, Xia J, Aghajanian C. Endometrial stromal sarcoma: objective response to letrozole. Gynecol Oncol. 2001;82 (2):384–8.
370. Spano JP, Soria JC, Kambouchner M, et al. Long-term survival of patients given hormonal therapy for

metastatic endometrial stromal sarcoma. Med Oncol. 2003;20(1):87–93.
371. Gadducci A, Sartori E, Landoni F, et al. Endometrial stromal sarcoma: analysis of treatment failures and survival. Gynecol Oncol. 1996;63(2):247–53.
372. Arend R, Bagaria M, Lewin SN, et al. Long-term outcome and natural history of uterine adenosarcomas. Gynecol Oncol. 2010;119(2):305–8.
373. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum Pathol. 1990;21 (4):363–81.
374. Bernard B, Clarke BA, Malowany JI, et al. Uterine adenosarcomas: a dual-institution update on staging, prognosis and survival. Gynecol Oncol. 2013;131 (3):634–9.
375. Clement PB, Scully RE. Mullerian adenofibroma of the uterus with invasion of myometrium and pelvic veins. Int J Gynecol Pathol. 1990;9(4):363–71.
376. Kaku T, Silverberg SG, Major FJ, Miller A, Fetter B, Brady MF. Adenosarcoma of the uterus: a Gynecologic Oncology Group clinicopathologic study of 31 cases. Int J Gynecol Pathol. 1992;11(2):75–88.
377. Zaloudek CJ, Norris HJ. Adenofibroma and adenosarcoma of the uterus: a clinicopathologic study of 35 cases. Cancer. 1981;48(2):354–66.
378. Krivak TC, Seidman JD, McBroom JW, MacKoul PJ, Aye LM, Rose GS. Uterine adenosarcoma with sarcomatous overgrowth versus uterine carcinosarcoma: comparison of treatment and survival. Gynecol Oncol. 2001;83(1):89–94.
379. Blom R, Guerrieri C. Adenosarcoma of the uterus: a clinicopathologic, DNA flow cytometric, p53 and mdm-2 analysis of 11 cases. Int J Gynecol Cancer. 1999;9(1):37–43.
380. Chuang JT, Van Velden DJ, Graham JB. Carcinosarcoma and mixed mesodermal tumor of the uterine corpus. Review of 49 cases. Obstet Gynecol. 1970;35(5):769–80.
381. Dinh TV, Slavin RE, Bhagavan BS, Hannigan EV, Tiamson EM, Yandell RB. Mixed mullerian tumors of the uterus: a clinicopathologic study. Obstet Gynecol. 1989;74(3 Pt 1):388–92.
382. DiSaia PJ, Castro JR, Rutledge FN. Mixed mesodermal sarcoma of the uterus. Am J Roentgenol Radium Therapy, Nucl Med. 1973;117(3):632–6.
383. Amant F, Cadron I, Fuso L, et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. Gynecol Oncol. 2005;98(2):274–80.
384. Vaidya AP, Horowitz NS, Oliva E, Halpern EF, Duska LR. Uterine malignant mixed mullerian tumors should not be included in studies of endometrial carcinoma. Gynecol Oncol. 2006;103 (2):684–7.
385. Arrastia CD, Fruchter RG, Clark M, et al. Uterine carcinosarcomas: incidence and trends in management and survival. Gynecol Oncol. 1997;65 (1):158–63.
386. Gerszten K, Faul C, Kounelis S, Huang Q, Kelley J, Jones MW. The impact of adjuvant radiotherapy on carcinosarcoma of the uterus. Gynecol Oncol. 1998;68(1):8–13.
387. Inthasorn P, Carter J, Valmadre S, Beale P, Russell P, Dalrymple C. Analysis of clinicopathologic factors in malignant mixed Mullerian tumors of the uterine corpus. Int J Gynecol Cancer. 2002;12 (4):348–53.
388. Iwasa Y, Haga H, Konishi I, et al. Prognostic factors in uterine carcinosarcoma: a clinicopathologic study of 25 patients. Cancer. 1998;82(3):512–9.
389. Larson B, Silfversward C, Nilsson B, Pettersson F. Mixed mullerian tumours of the uterus—prognostic factors: a clinical and histopathologic study of 147 cases. Radiother Oncol. 1990;17(2):123–32.
390. Nordal RR, Kristensen GB, Stenwig AE, Nesland JM, Pettersen EO, Trope CG. An evaluation of prognostic factors in uterine carcinosarcoma. Gynecol Oncol. 1997;67(3):316–21.
391. Sartori E, Bazzurini L, Gadducci A, et al. Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. Gynecol Oncol. 1997;67 (1):70–5.
392. Yamada SD, Burger RA, Brewster WR, Anton D, Kohler MF, Monk BJ. Pathologic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus. Cancer. 2000;88 (12):2782–6.
393. Silverberg SG, Major FJ, Blessing JA, et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. Int J Gynecol Pathol. 1990;9(1):1–19.
394. Barwick KW, LiVolsi VA. Malignant mixed mullerian tumors of the uterus. A clinicopathologic assessment of 34 cases. Am J Surg Pathol. 1979;3 (2):125–35.
395. Ferguson SE, Tornos C, Hummer A, Barakat RR, Soslow RA. Prognostic features of surgical stage I uterine carcinosarcoma. Am J Surg Pathol. 2007;31 (11):1653–61.
396. Kanbour AI, Buchsbaum HJ, Hall A. Peritoneal cytology in malignant mixed mullerian tumors of the uterus. Gynecol Oncol. 1989;33(1):91–5.
397. Lotocki R, Rosenshein NB, Grumbine F, Dillon M, Parmley T, Woodruff JD. Mixed Mullerian tumors of the uterus: clinical and pathologic correlations. Int J Gynaecol Obstet. 1982;20(3):237–43.
398. Blom R, Guerrieri C, Stal O, Malmstrom H, Sullivan S, Simonsen E. Malignant mixed Mullerian tumors of the uterus: a clinicopathologic, DNA flow cytometric, p53, and mdm-2 analysis of 44 cases. Gynecol Oncol. 1998;68(1):18–24.
399. Growdon WB, Roussel BN, Scialabba VL, et al. Tissue-specific signatures of activating PIK3CA and RAS mutations in carcinosarcomas of gynecologic origin. Gynecol Oncol. 2011;121(1):212–7.

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Erratum to: Prognostic Factors in Uterine Cancer

Patricia M. Baker and Esther Oliva

Erratum to:
Chapter "Prognostic Factors in Uterine Cancer" in:
P. M. Baker, E. Oliva, Current Clinical Oncology,
DOI 10.1007/7631_2015_4

All the bracketed citation numbers have been corrected throughout the chapter.
All instances of grade numbers presented in roman numerals were changed to arabic numerals.

Page 2
Section '**FIGO Stage**', 1st paragraph:
Lines 35-36: 'lymph nodes' was inserted after 'para-aortic'
Line 37: 'CIII-1" was revised to 'IIIC-1'.
Line 38: 'CIII-2' was revised to 'IIIC-2".
Line 63: 'the e' was revised to 'there'.

Page 3: Table 2 was replaced with a revised table.

Page 5
2nd paragraph, 9th line: '5 years' has been revised to '7 years'.

Page 6
Section '**Histologic Grade'**, 1st paragraph:
Line 18: 'EC' was revise to 'EEC'.

Page 10, 2nd paragraph,
6th line: 'clear cell carcinomas' was replaced with 'CCC'.
12th line: 'in about 25% of clear cell carcinomas' was replace with 'in about 25% of these tumors'.

The updated online version of this chapter can be found at
https://doi.org/10.1007/7631_2015_4

Page 11, 1st paragraph
6th line: 'stage I clear cell carcinoma' was replaced with 'stage I tumors'.

12th line: 'CCC' was inserted after 'stage I'.
Section '**Myometrial Invasion**', 1st paragraph, line 49: 'adenomyotic foci, rather than true myometrial invasion, is not recognized.' has been replaced with 'adenomyotic foci is not recognized.'

59th line: 'Residual benign endometrial glands' was replaced with 'The finding of residual benign endometrial glands'.

Page 13
27th line: 'IIA tumors is similar to stage I tumors,' was replaced with 'IIA tumors is similar to those with stage I tumors,'.

Section '**Age**', 1st paragraph,
4th line: 'women with endometrial carcinoma' was replaced with 'women with EC.

Lines 17-19: 'and may associated with higher stage and possibly poorer prognosis' was replaced with 'and higher stage and possibly poorer prognosis'.

Page 14
Section '**Lymphovascular Invasion'**, 2nd paragraph, 9th line: 'lymph node metastasis' was replaced with 'lymph node metastases'

Page 15:
'(stage IIIA)' was deleted from caption for figure 11.

3rd paragraph, lines 23-24: 'ovarian involvement, small ovaries, a multinodular pattern of growth,' was replaced with 'ovarian involvement, small ovaries, multinodular growth,"

Page 16
1st paragraph, 1st line: 'in the EEC [188, 190]' was inserted after 'and poorly differentiated histology'.
Section '**Stage IIIC**', 1st paragraph, line 49: 'moderate risk of lymph node metastasis [34].' was replaced with 'moderate risk of lymph node metastases [29].

Page 18
Section '**DNA Ploidy**, 2nd paragraph:
Line 13: 'patients with favorable endometrioid tumors' was replaced with 'patients with endometrioid tumors'.

Lines 17-18: 'Several investigators have found DNA ploidy and to be independent' was replaced with 'Several investigators have found DNA ploidy to be an independent'.

Page 19
Section title 'c-erb-B2 (HER-2/neu)' was revised to 'C-Erb-B2 (Her-2/Neu)'

Page 20: Figure 14 was moved to page 21. 'in EEC' was added to end of caption (a). The words 'depression of' was deleted from caption (b).

Page 21
Section '**Pten**', lines 1-2: 'PTEN (phosphatase and tensin homologue detected from chromosome 10)' was revised to 'PTEN (phosphatase and tensin homologue) located on chromosome 10q'.

Page 22
Figure 14 was moved to page 21.

2nd paragraph, lines 23-25: 'overlapping features, both histologic and immunohistochemical that overlap with endocervical adenocarcinomas [298].' was revised to 'overlapping histological and immunohistochemical features with endocervical adenocarcinomas [291].'

Page 24
Section '**Low-Grade Endometrial Stromal**' was renamed to '**Endometrial Stromal Sarcoma**'.

Section **'Undifferentiated Endometrial Sarcoma':** The 2nd sentence 'Note that most of the high-grade endometrial stromal sarcomas referred to in the literature have been diagnosed largely by mitotic activity, a feature that is now known not to be significant.' has been deleted.

Section '**Malignant Mixed Müllerian Tumor (Carcinosarcoma)**', 2nd paragraph, lines 25-27: 'although some recent studies suggest that malignant mixed müllerian tumors exhibit decreased ER and PR [217].' has been deleted.

Page 25
Section '**Conclusions**':
2nd bulleted item: 'has eliminated stage IIA as well positive peritoneal cytology from stage IIIA' was revised to 'has eliminated stage IIA as well as positive peritoneal cytology from stage IIIA'.

4th bulleted item: 'most important factors in tumor stage.' has been revised to 'most important factors in stage I tumors'.

Page 26
11th bulleted item: 'are associated with poor prognosis even when stage I.' was revised to 'are associated with poor prognosis even when low stage.'

Pages 26-40: The list of references was renumbered.

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Primary Hormonal Therapy of Endometrial Cancer

Linda R. Duska

Abstract

This chapter discusses the treatment of endometrioid adenocarcinoma of the endometrium in premenopausal women with hormonal therapy for the purpose of preserving the corpus and future fertility. In addition, postmenopausal women who are not candidates for surgery may benefit from similar approaches.

Keywords

Endometrial cancer • Premenopausal • Fertility preservation • Hormonal treatment

Introduction

Endometrial cancer is the most common of the gynecologic malignancies. In 2014, 52,630 cases of endometrial cancer and 8,590 deaths from the disease are estimated in the USA [1]. Most endometrial cancers occur in women who are postmenopausal, and therefore completed their childbearing. However, a small percentage of endometrial carcinomas occur in women who perhaps have not yet begun or not completed their families.

L.R. Duska (✉)
Professor of Obstetrics and Gynecology, Department of Gynecology Oncology, University of Virginia Medical Centre, PO Box 800712, Charlottesville, VA 22908, USA
e-mail: lrd5d@hscmail.mcc.virginia.edu

The standard of care for endometrial cancer is surgery. The primary surgery consists of total hysterectomy with the removal of both tubes and ovaries. In the USA, this is often associated with staging surgery, including removal of the pelvic and para-aortic lymph nodes [2]. The surgery may be performed via laparotomy or more commonly via a minimally invasive approach. Obviously, this surgical treatment will make future childbearing for the patient impossible. With surgical staging and adjuvant therapy where appropriate, the 5-year survival for endometrioid endometrial cancer confined to the corpus is 95 %. For those women who have non-myoinvasive grade 1 disease, the disease free 5-year survival following surgical therapy is 99.2 % [3].

This chapter discusses alternative treatment of endometrioid adenocarcinoma of the endometrium

with hormonal therapy for the purpose of preserving the uterus and therefore future fertility. Mainly retrospective data will be discussed, although recent prospective studies also exist and will be presented. It should be stressed, however, that the treatment of endometrial cancer with less than hysterectomy at the current time represents a therapy that is outside of the "standard of care," and therefore should be undertaken with caution with a well-informed patient and an experienced physician.

This discussion will also apply to older women with endometrial cancer who are not surgical candidates for medical reasons. Limited data are now available in this population, though hormonal treatment has a higher rate of success in the premenopausal population. However, many of these older women for whom fertility is not an issue may be better served by primary radiation therapy if they cannot undergo surgery.

Epidemiology

Endometrial cancer most often affects postmenopausal women, with over 70 % of cases occurring in the postmenopause and a mean age of diagnosis of 62 years [4]. Endometrial cancer is most frequently diagnosed in women ages 55–64 years, with the majority of cases diagnosed in women ages 45–74 [4]. However, retrospective reports suggest that between 2 and 14 % of women presenting with endometrial cancer will be less than 40 years old [5–14]. This premenopausal group has both similar and different epidemiologic characteristics than the postmenopausal age group that need to be considered. Moreover, because of their young age, the diagnosis of endometrial cancer is not always entertained in these patients when they present with menstrual irregularities.

Fortunately, premenopausal women with endometrial cancer have a higher rate of low-grade tumors as well as a higher rate of low-stage disease when compared to older patients, resulting in a favorable disease-specific survival rate [15]. One of the largest single institution studies of women under the age of 45 years with endometrial cancer was reported from Yale [16]. A total of 251 patients were identified, 75 % of whom had stage I disease. The majority of patients had grade 1 disease (53 %) with only 5 % having high-grade tumors. Eighty-seven percent of patients had endometrioid histology.

One of the epidemiologic risk factors shared by women of all ages with endometrial cancer is obesity. With the rise in obesity in the USA and the world, the number of endometrial cancer cases is also expected to increase [17]. As a woman's weight increases, so to does her risk for endometrial cancer [18]. Obese women are two to three times more likely to get endometrial cancer than their lean counterparts [19, 20], and women who are 50 pounds overweight are ten times more likely to develop endometrial cancer [21].

Several large retrospective studies have considered obesity rates specifically in younger women with endometrial cancer (defined in most series as a BMI >30). The largest studies that have data regarding BMI in this younger age group are shown in Table 1. If all studies, including those that measure obesity by body weight alone, are included, obesity rates in younger women range from as low as 29 % to as high as 73 % [14]. Interestingly, the obesity rates in young women seem to be higher than those of older women within the same population. For example, in the series from Gallup et al., an obesity rate of 43.8 % in women <40 years

Table 1 Obesity data for women with endometrial cancer ages 40 [47] and under

	Duska [14]	Gitsch[a] [11]	Soliman [13]	Walsh[a] [22]	Park[b] [23]	Wang [24]	Totals
#	92	17	79	102	48	37	375
BMI ≥30	44	6	48	46	23	11	178
Obese (%)	48	35	62	48	48	32	48

[a]Included women up to age 45 years
[b]Data is for BMI ≥25

with endometrial cancer contrasted with 18 % in a group of patients treated at the same institution who were over 40 years of age [8]. Reported obesity rates in young endometrial cancer patients are lower in the series reported from Asian countries.

All young women with endometrial cancer are not obese; in fact, many of them will present with normal weight. In the series from Massachusetts General Hospital (MGH), 52 % of women <40 years with endometrial cancer were of normal weight (BMI < 30), and 43 % had a BMI of 25 or less [14]. In that study, there was a trend toward higher stage disease and high-risk histology in the normal weight women, though the differences did not reach statistical significance. Schmeler et al. presented a series of women <50 years and of normal weight seen at the MD Anderson Cancer Center [22]. They suggested that hormonal factors, and in particular polycystic ovarian syndrome (PCOS), might be a risk factor for developing endometrial cancer in these women with normal weight. Retrospective data suggests that normal weight younger women are not at higher risk for poor survival, though the numbers are too small in all studies to reach any conclusion.

Obviously, women <40 do not present with postmenopausal bleeding or staining. However, the majority of young women with endometrial cancer will present with some type of menstrual irregularity. In the series from MGH, 29 of 91 (32 %) women presented with menorrhagia or increasing menorrhagia and 39 of 91 (43 %) presented with irregular menses or menometrorrhagia [14]. Similarly, 26 of 32 (81 %) women in the Crissman series and 77 % of the patients in the Yale series presented with irregular vaginal bleeding [7, 16]. Other studies have also reported high rates of irregular bleeding as the presenting complaint [6, 9, 12]. Persistent irregular bleeding, therefore, merits endometrial sampling even in those women age <40 to rule out an underlying endometrial neoplasm.

Infertility is also a hallmark of women <40 with endometrial cancer, in contrast to their postmenopausal counterparts, who are often characterized as "fertile." In the MGH series, 11 patients (12 %) were diagnosed with endometrial cancer incidentally during infertility evaluation [14]. In Gallup's study, 44 % of women <40 years with endometrial cancer were classified as "infertile," though information is not provided to suggest that infertility was the presenting symptom prompting evaluation [8]. Schmeler's study reported a 17 % risk of infertility in women under age 50 with endometrial cancer [22]. A large study from Korea reported an infertility rate of 38.3 %, which was higher than that of their general population (10–15 %) [23]. It is likely that in many of these cases, the infertility is a result of anovulation, associated with high levels of circulating unopposed estrogen. In a study from Taiwan, for example, 13 % of patients met the criteria for polycystic ovarian syndrome [24]. Unfortunately, all data is retrospective and often limits obtaining hormonal information about patients unless it is specifically documented in the patient's chart.

Genetic disorders, particularly hereditary nonpolyposis colon cancer or Lynch syndrome, are associated with endometrial cancer, usually at a young age. In fact, endometrial cancer is the most common cancer of Lynch syndrome in women and may be the presenting cancer in some patients [25]. A detailed family history is instrumental in making this diagnosis, and all young women presenting with endometrial cancer should have a careful family history taken.

Finally, endometrial cancer in a young woman may result from an estrogen-producing ovarian tumor, such as a granulosa cell tumor. Clinically, a very young woman may present with an ovarian mass, irregular bleeding, and/or infertility. Treatment of the ovarian tumor must include dilatation and curettage (D&C) to rule out an underlying endometrial neoplasia.

Complex Atypical Hyperplasia in Women Under 40 Years

The issue of complex atypical hyperplasia (CAH) needs to be addressed, particularly in the setting of a discussion of treating young women with grade 1 endometrial cancer with hormones rather than definitive surgery. While CAH is a

precancerous lesion, it cannot reliably be stated that there will be no cancer on the hysterectomy specimen when a preoperative diagnosis of CAH is made. The possibility of an underlying grade 1 (or higher) endometrioid adenocarcinoma must be considered when treating CAH with hormones for the purpose of preserving fertility.

Kurman et al. established retrospectively that a preoperative diagnosis of CAH resulted in a postoperative diagnosis of grade 1 adenocarcinoma on the hysterectomy specimen in 29 % of cases [26]. This study has since been repeated prospectively by the Gynecology Oncology Group (GOG) [27, 28]. The GOG study entered women with a preoperative "community" diagnosis of CAH, all of whom underwent hysterectomy within 12 weeks of diagnosis. All preoperative specimens were reviewed by a panel of "expert" pathologists, as were the final hysterectomy specimens. The rate of carcinoma in the final hysterectomy was 43 %, much higher than in Kurman's retrospective study. In addition, the community diagnosis of CAH was supported by the expert panel in only 38 % of cases. In 29 % of cases, the expert panel felt that the lesion merited a diagnosis of carcinoma. Finally, there was complete agreement of the experts in only 40 % of cases.

From the data presented above, it is clear that CAH on an endometrial biopsy needs to be treated as if an endometrial cancer might be present in the uterus. Care should be taken to exclude carcinoma as a possibility, either via D&C as the "gold standard," slide review by an expert pathologist, or both when considering treatment with hormones and conservation of the uterus.

Staging

Endometrial cancer has been surgically staged since 1988, with the publication of the results of the surgical staging study GOG 33 [29]. This study demonstrated the importance of lymph node status as well as depth of myometrial invasion as markers of prognosis and recommendations for adjuvant therapy. After that publication, for years the GOG defined surgical staging of endometrial cancer as including: exploratory laparotomy, pelvic washings, total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and sampling of pelvic and para-aortic lymph nodes. Over the past decades, however, the GOG and others have published data to suggest that minimally invasive surgery is an appropriate method for surgical staging [30]. In addition, updates to International Federation of Gynecology and Obstetrics (FIGO staging) have removed pelvic washings as part of the staging criteria [2].

The criteria defined by GOG 33 also helped clinicians to predict which patients might have positive retroperitoneal lymph nodes based on the grade of disease and depth of myometrial invasion, and by extension which women would benefit from retroperitoneal node dissection [29]. In GOG 33, women with grade 1 tumors and no myometrial invasion had a 0 % rate of positive pelvic or para-aortic retroperitoneal lymph nodes. In fact, the rate of lymph node metastases for noninvasive carcinoma of any grade was less than 3 %. However, deeply invasive grade 1 tumors had an 11 % rate of positive pelvic lymph nodes and a 6 % rate of positive para-aortic lymph nodes, indicating the need for adjuvant therapy after surgery and a poorer prognosis. Therefore, a patient with a grade 1 carcinoma that is (clinically) noninvasive has a theoretical risk of positive retroperitoneal nodes of 0 %, making her an ideal candidate for hormonal therapy.

When a clinician is considering managing a patient with hormonal treatment, however, surgical staging is not possible. The determination of clinical staging, then, must be made with the best available data, the limitations of which will be discussed below, with surgical staging considered to be the "gold standard." Since it is generally accepted that only patients with noninvasive endometrial cancer (and grade 1 or at most grade 2 endometrioid histology) should be managed with hormones, the clinician needs to use all possible modalities to assure that the patient has "clinical" non myoinvasive grade 1 disease. For the purposes of the remainder of this discussion, it will be assumed that all histology is endometrioid since hormonal management of

any other histology of endometrial cancer is not appropriate.

Grade

Preoperative tumor grade is not always predictive of tumor grade on the final hysterectomy specimen. Cowles et al. demonstrated that preoperative grade 1 tumors were upgraded at the time of hysterectomy in 11 % of cases [31], while a larger study by Daniel et al. reported an overall upgrading of 15–20 % [32]. In combination, the two studies did demonstrate that we do best predicting postoperative grade correctly when the preoperative grade is 1. Eltabbakh et al. reviewed 182 patients at their institution who underwent surgical staging for preoperative grade 1 tumors [33]. In 30 % of cases, the grade was changed on the hysterectomy specimen. In 22 % and 6 % of cases, the postoperative grade was 2 and 3, respectively. Obviously, then, there is a not insignificant risk that a young woman presenting with a grade 1 tumor will have a higher grade histology discovered if she undergoes hysterectomy, and therefore increased risk of disease outside of the uterus. Since D&C is considered the "gold standard" for preoperative diagnosis, hormonal management of a young patient should always be preceded by a D&C rather than an endometrial biopsy only.

Myometrial Invasion

There is no 100 % reliable method to determine the depth of muscle invasion short of removing the uterus and examining the myometrium microscopically. Most clinicians will use a combination of MRI, ultrasound, and/or CT scanning to make the diagnosis of clinical stage I non-myoinvasive disease. None of these modalities are completely reliable, and all are more accurate when diagnosing deep rather than superficial myometrial invasion.

CT scan is useful for identifying large volume extrauterine disease, but fails to detect microscopic lymph node metastases. Accuracy of CT scan in predicting myometrial invasion ranges from 61 to 76 %, increasing to 83 % with deep invasion [34–36]. Zerbe et al. reviewed their experience with preoperative CT scans in predicting the extent of myometrial invasion [37]. All patients had a CT scan performed within 10 days of surgery and the results were classified as $>$ or $<$50 % invasion. In this study, CT scan failed to identify 17 of 44 patients (39 %) who had myometrial invasion. While this study did not look specifically at grade 1 tumors, it suggests that CT is not useful in determining myometrial invasion. Other authors have confirmed this finding [38].

MRI can be useful for evaluating myometrial invasion as well as pelvic nodes and adnexal masses. Many studies about the MRI accuracy in myometrial invasion detection have been published, and the accuracies showed a wide range of variation (66–95 %) with limited number of patients included [39–47]. The accuracy of T2-weighted images in the determination of myometrial invasion by endometrial carcinoma varies between 68 and 82 % [42, 43, 48]. The use of a dynamic study after administration of intravenous contrast increases the accuracy of myometrial invasion to 85–91 %, respectively [43, 49, 50].

In the paper from Sanjuan et al. [51], 72 consecutive patients with endometrial cancer underwent preoperative MRI, and MRI results were compared to final histopathologic findings. Sensitivity, specificity and accuracy of MRI for the detection of myometrial invasion $\geq$50 % were 71 %, 86 %, and 58 %, respectively. This study used both T2 and dynamic images, and only 10 patients in this series had noninvasive endometrial cancer.

Suh et al. reported a retrospective review of 301 patients, all of whom underwent preoperative MRI and had stage I disease on MRI [47]. On final pathology, 17 patients had higher stage disease. Of the remaining 284, 124 had no invasion on preoperative MRI, but only 61 of these women had no myoinvasion on final pathology of the uterus. The negative predictive value of absence of myometrial invasion was 49.2 %. MRI showed an accuracy of 59.2 %, a sensitivity of 68.8 %, a specificity of 74.4 %, and an 86.9 %

positive predictive value for myometrial invasion. Another study showed a similarly low negative predictive value for myoinvasion of 42.2 % [41]. Even when dynamic study was applied, the value improved up to 60 %. Despite the low negative predictive value for myoinvasion, MRI can correctly differentiate whether or not there is deep myometrial invasion [52–55].

Of note, there may also be significant consequences to a false positive MRI result. For example, Ohio State reported a case of a 29-year-old G0 with grade 1 endometrial cancer who wanted to preserve fertility [56]. As part of the evaluation, an MRI suggested myometrial invasion and for this reason a TAHBSO was performed. The final pathology revealed only decidualized endometrium consistent with progesterone use. This case represents a case of a false positive MRI with resulting loss of fertility.

It must also be noted that for both CT and MRI, the postmenopausal woman presents a special diagnostic challenge because of the lack of junctional zone between the endo- and myometrium. It is likely that accuracy will be higher in premenopausal women. Tumor grade, however, did not seem to be a factor in predicting myometrial invasion in one meta-analysis [57].

Despite the above noted limitations, MRI is the most frequently recommended modality for assessing myometrial invasion in the premenopausal woman wishing to preserve her uterus. Contrast-enhanced MRI improves accuracy [50, 53]. Transvaginal ultrasound can also be utilized to exclude ovarian lesions. Like CT, MRI will not be able to accurately diagnose microscopically positive retroperitoneal lymph nodes.

Data Supporting Hormonal Therapy

Retrospective

The majority of historical data supporting hormonal therapy of endometrial cancer is retrospective and, therefore, subject to reporting bias. Most older series are small, with numbers of patients reported ranging from 1 to 15. Recent studies include both complex atypical hyperplasia (CAH) and grade 1 endometrial cancer and have more patients, but the numbers are still low, with 19 CAH and 25 endometrial cancer in one study [58], and 37 patients with only endometrial cancer in another [24].

Ramirez et al. published a literature review of retrospective patients treated with progesterone [59]. They identified 27 studies describing 81 patients treated with hormones for endometrial cancer. Overall, the response to progestin therapy was 76 %, with a median time of response of 12 weeks. Documentation regarding pregnancy was available for 20 patients, all of whom were able to conceive at least once following treatment. Gottlieb et al. performed a similar and more comprehensive literature review and identified 101 women with a mean age of 29 years treated with hormones for endometrial cancer, with a 71 % initial response rate, minimal time to response of 3.6 months, and 56 live births [60]. Most recently, two meta-analyses of oncologic and fertility outcomes with both atypical hyperplasia and grade 1 adenocarcinoma have been reported: both revealed an overall approximate 80 % response to treatment [61, 62].

Historical Retrospective Studies of Interest

One of the earliest and largest retrospective studies was that of Bokhman et al., in 1985 [63]. It preceded surgical staging, and all patients at that time were clinically staged. Nineteen patients ranging in age from 19 to 37 (mean 28.7) years with endometrial cancer were treated with progesterone, 11 patients with grade 1 tumors, and 8 with grade 2 tumors, all with clinical stage I disease. Seventeen patients had primary infertility and 14 were obese. All patients were treated with 500 mg daily of IM oxyprogesterone caproate. All patients who did not demonstrate response after 3 months underwent hysterectomy. In total, 15 of the 19 patients were cured with hormonal therapy. Data regarding live births following treatment was not reported.

The next consecutive larger series was reported by Randall and Kurman in 1997 [64].

While this study is often quoted, it consisted of a retrospective review of cases sent to Johns Hopkins Hospital for pathology consultation rather than as a report of women treated at a single institution. Fourteen women were treated with hormones for grade 1 adenocarcinoma. Most of the patients were described as treated with "high-dose progestins," though the treatments were not standardized as they were in the previous report. In this study, no woman had tumor progression defined as an increase in grade on subsequent sampling. Two women were found to have coexisting ovarian carcinomas following hormonal therapy and underwent surgery; in both cases, a stage IA grade 1 endometrioid adenocarcinoma was confirmed histologically. Three women had five full-term deliveries. One patient experienced recurrence of her cancer after initial response to therapy. She had another complete regression after reinstitution of progesterone therapy, and ultimately had a full-term delivery.

In 2001, the group from MGH presented a retrospective review of 12 patients who underwent hormone therapy of endometrial cancer [14]. The patients ranged in age from 24 to 40 years and 8 presented with infertility. All patients had grade 1 tumors. Two patients eventually underwent hysterectomy for persistent disease, and one of these developed a synchronous ovarian primary tumor. Four women achieved pregnancy with five viable infants delivered.

Gottlieb et al. in 2003 reported 13 patients with ages ranging from 23 to 40 (mean 31) years [60]. In six patients, the diagnosis was made during infertility evaluation. Eleven patients had a grade 1 tumor and two had a grade 2 tumor. All patients received treatment for at least 3 months and all responded to therapy with regression of their disease documented by endometrial biopsy. Progestin therapy was not standardized; eight patients were treated with megestrol acetate 160 mg daily. Five patients developed local recurrence. Three patients delivered nine viable infants and two further patients were pregnant at the time of the report.

Larger Retrospective Studies from Combined Centers

More recently, several groups have reported larger series of women with both CAH and endometrial cancer treated with progesterone therapy. The Korean group searched eight tertiary cancer centers to collect 148 women less than or equal to 40 years old who were treated with progestin for stage IA grade 1 endometrioid adenocarcinoma of the endometrium [65]. In this series, 115 patients (78 %) showed a complete response to progestin, with a mean duration of treatment of 8 months (range, 2–31 months). All patients were treated with either oral medroxyprogesterone acetate or megestrol acetate continuously. Body mass index greater than or equal to 25 kg/m^2 was the only significant factor associated with a failure to achieve CR. Thirty-five patients (30.4 %) experienced disease recurrence. The use of medroxyprogesterone acetate was associated with a higher risk of recurrence than the use of megestrol acetate. The possible superiority of megestrol acetate was also confirmed by a meta-analysis from France [62]. The same Korean group also reported a retrospective cohort study of 48 women age 40 and under who were treated conservatively, with similar results [66].

The group from Toronto reported a series of 44 women, 19 with CAH and 25 with grade 1 endometrial cancer [58]. Twenty-four patients achieved a complete response (CR) to progesterone treatment, with a median time to CR of 5.7 months. Ninety-two percent of patients had responded within 12 months. Older age at diagnosis was associated with a lower likelihood of complete response, as was higher BMI. Thirteen patients (54 %) who achieved a CR experienced disease recurrence.

The group from Taiwan reported 37 patients with grade 1 endometrial cancer treated between 1991 and 2010. In this study, the mean follow-up was lengthy (78 months). Complete response lasting more than 6 months was achieved in 81 % of patients, and like the study from Toronto, responders were significantly younger

than nonresponders. Older women were also more likely to experience disease recurrence.

Finally, one small but provocative study tried to identify predictors for response to or failure of progesterone therapy [67]. The study made the following four important observations: (1) there was a negative correlation between extent of pretreatment architectural abnormality and disease resolution; (2) for patients without significant architectural abnormality, resolution was associated with BMI, with a BMI < 35 associated with the highest resolution rate; (3) the first follow-up biopsy was the strongest predictor of disease resolution; and (4) patients whose first follow-up biopsy reveals stromal decidualization without response of the endometrial glands have a very low disease resolution rate. These factors, if validated in future studies, may assist clinicians in counseling patients regarding the success of therapy both before initiating treatment as well as after the first interval assessment biopsy.

Prospective Studies

There is limited prospective data regarding nonsurgical hormonal treatment of endometrial cancer. In 2001, Wang et al. reported a prospective study of hormonal treatment of endometrial cancer [68]. In this very small study, women with clinical stage I grade 1 endometrioid adenocarcinoma were prospectively entered into an IRB-approved trial of hormonal therapy. Nine patients were accrued to the trial over an 8-year period. Despite the prospective nature of the study, all patients did not receive the same therapy, though the majority were treated with megestrol acetate and tamoxifen. Eight of the nine patients achieved complete remission, though one of them did not initially respond to therapy and had to be treated with GnRH agonist and increased dose of megestrol acetate. Two patients had a total of three term pregnancies. However, four of the eight responders developed recurrent disease.

Niwa et al. presented a very small prospective study of 12 women <40 years with grade 1 endometrial cancer [69]. Ultrasound and MRI were both used to assess myometrial invasion and ovarian involvement. All patients were treated with medroxyprogesterone acetate continuously and all 12 underwent complete remission of disease. Of ten patients attempting pregnancy, five had six full-term deliveries. Eight patients had recurrence of disease, and one of these patients had metastatic disease to the ovary at the time of surgery.

Ushijima et al. published a prospective multicenter study of hormonal treatment of endometrial cancer and complex atypical hyperplasia in 2007 [70]. All women were treated with 600 mg of medroxyprogesterone acetate orally for 26 weeks followed by cyclic estrogen and progesterone therapy for 6 months. For those who desired conception, fertility treatment was started immediately. Response was assessed histologically at 8 weeks and 16 weeks, and at 26 weeks hysteroscopy and curettage were performed. A total of 45 patients were enrolled and eligible. Ages were 22–39 years (mean 31.7 years) and BMI was 16–32.7 (mean 22.8). Twenty-eight women had endometrial cancer: of these, 6 withdrew from the study and underwent hysterectomy. There were 12 complete responders (CR) for a 55 % CR rate. Seventeen patients had atypical hyperplasia, and 14 of these (82 %) had a CR at 26 weeks. During the surveillance period there was neoplastic recurrence in 47 % of the 30 patients, including 8 (57 %) of 14 with endometrial cancer and 6 (38 %) of 16 with atypical hyperplasia.

A prospective study from China was published in 2013 [71]. Women were eligible for entry if they had either grade 1 endometrial cancer or AH and were 40 years old or less, and if their tumor expressed the progesterone receptor (PR). Twenty-six eligible patients were enrolled in the study, 12 with AH and 14 with endometrial cancer. They were treated with oral megestrol acetate 160 mg daily for at least 12 weeks 18 patients achieved CR at 12 weeks (9 endometrial cancer, 9 AH) and another 3 patients achieved CR by 24 weeks (total 81 % CR rate).

There are currently two ongoing prospective trials for young women with CAH or endometrial cancer who want to preserve fertility listed in

clinicaltrials.gov (accessed February 2015) [72, 73].

Risks of Hormonal Therapy

Recurrence of Disease

Recurrence of endometrial neoplasia is a significant concern, particularly if progesterone treatment is stopped. The prospective study from Japan, for example, demonstrated a recurrence rate of 47 % between 7 and 36 months following treatment, prompting the authors to recommend close surveillance following treatment. Similarly, there was a 50 % disease recurrence rate of endometrial cancer reported in the series from Wang et al. [24]. Other studies have documented similar rates of disease recurrence [65, 71]. In some cases disease may recur even when treatment is continued. In these cases, the recurrence may be secondary to the downregulation of the progesterone receptor that occurs with prolonged progesterone treatment.

There remains the option of retreating once disease recurs if a patient desires to retain fertility. The largest retreatment series was reported from Korea in 2013 [74]. Forty-five patients developed recurrent endometrial neoplasia following complete response: recurrence was AH in 13 patients and grade 1 endometrial cancer in 20 patients. After retreatment with oral progesterone, 28 patients (85 %) had a second complete response in an average of 51 months (range 24–160 months).

Progression of Disease

Certainly, there is concern for progression of disease during the delay that occurs during hormonal therapy. It is conceivable that if the cancer being treated is not responsive to hormones and/or more definitive surgical therapy is delayed for 3 months, the stage of disease at the time of ultimate surgery could be higher. Kim et al. reported 3 of 21 initial responders to progesterone who experienced recurrent disease; one of these patients had evidence of metastatic disease at the time of her surgery. The authors raised the possibility of progesterone therapy delaying definitive surgical therapy, possibly resulting in the development of metastatic disease [75]. This patient was also the only one in the series with grade 2 disease, prompting the authors to suggest that only patients with grade 1 disease be considered for hormonal management.

There are several other case reports of patients whose disease has progressed following conservative therapy, in some cases resulting in cancer related mortality. In the case reported by Ferrandina et al., a 30-year-old woman was treated successfully for her grade 1 clinical stage IA endometrial cancer as documented by hysteroscopy and D&C [76]. Three months following resolution of her disease, she became pregnant and had a cesarean section at 36 weeks. Eight months later, she developed irregular bleeding and underwent definitive surgical therapy. She was diagnosed with stage IV poorly differentiated endometrial cancer and died of her disease.

Rubatt et al. reported a 40-year-old obese woman who underwent hormonal therapy for CAH [77]. The patient experienced complete regression and was compliant with follow-up. Two years following initial treatment she was diagnosed with a grade 2 endometrial cancer. At the time of surgery, she was found to have a stage IIIC grade 2 endometrial cancer with significant lymphovascular invasion within the myometrium and one positive pelvic lymph node. Kaku et al. reported 12 women with endometrial cancer who underwent hormonal therapy; 2 of 9 responders later developed relapse, and 1 of these had stage IIIC disease, with a positive obturator lymph node [78]. Kothari et al. reported a case of a 24-year-old woman treated with progestin who at the time of surgery was noted to have stage IV disease [79]. These reports and others point to the potential risk of converting a curable surgical problem into a life threatening illness by foregoing surgery in favor of fertility preservation.

It should be noted that there are a large number of small case reports, usually reporting

between 1 and 4 cases, of women with endometrial cancer who were treated with hormones and achieved pregnancy [80–89]. Most of them had grade 1 tumors that were extensively "clinically" staged with D&C, plus or minus hysteroscopy, CT and/or MRI, and laparoscopy. Many of these women were diagnosed during infertility evaluation and many required artificial reproductive technology (ART) to achieve pregnancy. One must consider when reading these reports the phenomenon of recall bias.

Any patient who chooses hormonal therapy over definitive surgical therapy should be counseled that surgical therapy is almost always curative for stage IA grade 1 cancers and that hormonal therapy as an alternative poses a theoretical risk of progression of disease to a stage that may expose the patient to the need for adjuvant therapy and the not insignificant risk of recurrent disease.

Risk of Metastases to the Ovary and/or Synchronous Ovarian Primary Tumors

There is a risk, though small, of endometrial cancer embolizing through the fallopian tube and metastasizing to the ovary. In the GOG staging study of clinical stage I endometrial cancer, this risk was 5 % [29]. Gross ovarian metastases can be ruled out via pelvic examination and/or pelvic ultrasound, but micrometastases cannot be demonstrated without histologic examination of the ovaries.

Recent literature has raised significant concerns regarding the risk of synchronous ovarian primary tumors in young women with endometrial cancer. The issue was raised by Walsh et al. in the context of considering preserving ovarian function in young women with endometrial cancer, removing the uterus but leaving the ovaries intact [90]. The authors reviewed 102 patients age 45 and younger that underwent hysterectomy for endometrial cancer. Twenty-six women in this series (25 %) had a coexisting ovarian malignancy, which were felt to be a synchronous ovarian primary in 23 cases. All ovarian tumors were epithelial, and all but one were endometrioid carcinomas. Eighteen of the 26 cases (69 %) occurred in women with grade 1 endometrial cancer. Twenty-six patients in this series underwent hormonal treatment for endometrial cancer prior to ultimate surgical management. Four of them (15 %) had ovarian involvement with cancer diagnosed at the time of their surgery and one had an ovarian tumor that was felt to be a synchronous ovarian primary. A population based study from Geneva reported more synchronous ovarian malignancies in young patients (14 % vs. 2 %): in this large series, 5 % of patients 40 years old or less had a synchronous ovarian cancer, compared to 23 % of women 41–45 years old [91]. In the Yale study, patients under age 45 whose surgery included removal of the ovaries had a significantly longer disease free survival but not overall survival and ovarian preservation had no significant influence on disease free survival in patients with grade 1 disease [16].

In contrast to these reports is the SEER report from Wright et al. that considered the safety of ovarian preservation in women with endometrial cancer [92]. In this series, SEER data from 1988 to 2004 for women less than or equal to 45 years of age was analyzed. A total of 402 women had ovarian preservation. In a multivariate analysis, ovarian preservation had no effect on either cancer specific or overall survival. The details of the ovarian cancers was not provided due to the nature of the study; the finding may be related to the low grade and early stage of most ovarian cancers diagnosed in this setting.

Two cases reported from Memorial Sloan Kettering illustrate this point [93]. The patients reported were 29 and 23 years old and strongly desired fertility preservation. When hormonal therapy failed, both women chose to undergo hysterectomy with ovarian preservation for the purposes of ovarian stimulation and surrogacy. Unfortunately, both women subsequently developed ovarian cancer: in both cases the tumors were histologically endometrioid and early stage.

Other authors have also reported a risk of synchronous ovarian primary cancer in patients with an endometrial cancer [7, 11, 12, 14, 94, 95]. Obviously, when considering hormonal

therapy, ovarian involvement needs to be carefully ruled out. Pelvic ultrasound may be the most useful modality to evaluate the ovaries for any abnormality and CA-125 can be used preoperatively as well [71]. It has also suggested the use of laparoscopy preoperatively to rule out ovarian involvement [96], though this is not a standard recommendation.

Risk of Tumor Recurrence During Pregnancy

Unfortunately, endometrial cancer recurrence has been documented during pregnancy. In one study, a lesion was interpreted to have been present during pregnancy, despite documentation of resolution of disease after treatment with hormones, and was diagnosed shortly after delivery [97]. Intuitively, one would think that high levels of progesterone achieved during pregnancy should be protective against recurrence of endometrial cancer, but this is not always the case.

Method of Treatment

There is no standardized agreed upon method for treating women with endometrial cancer with hormones. Most gynecologic oncologists choose megestrol acetate as a first choice, but doses and schedules are not standardized. Doses as low as 40 mg daily and as high as 160 mg four times daily have been reported. Medroxyprogesterone acetate, depo-medroxyprogesterone acetate, and combinations of tamoxifen and progesterone have also been suggested. While some authors suggest using cyclic therapy to induce a monthly withdrawal bleed, most advocate continuous treatment which ultimately results in an atrophic endometrium. Since progesterone is poorly tolerated by many women, with breast tenderness and weight gain being frequent complaints, it is probably best to use the lowest dose that will also be successful in reversing the neoplastic endometrium, though this lowest dose probably varies from woman to woman and likely its success is dependent on patient's BMI and tumor.

Several authors have suggested the use of a progesterone intrauterine device (IUD) as a means of treating the cancer with high doses of progesterone without the systemic side effects. In the study from Montz et al., women with clinical stage IA grade 1 endometrial cancer underwent hysteroscopy and curettage followed by placement of a progesterone IUD and resampling every 3 months [98]. Seven of 11 patients demonstrated complete response at 6 months and 6 of 8 at 12 months.

Dhar et al. performed a similar study using a levonorgestrel containing IUD [99]. Four women with grade 1 adenocarcinoma that expressed PR were treated with IUD; only one patient had a complete response within 6 months. However, this study did not exclude myometrial invasion prior to the treatment with IUD. In both studies, the majority of patients were postmenopausal and underwent hormonal treatment because it was felt that they were poor surgical candidates; thus, it is impossible to know whether a similar treatment regimen in premenopausal women would have similar outcome. Moreover, two women were reported to possibly have developed adenocarcinoma in the uterine isthmus while using a levonorgestrel IUD, suggesting that either the uterine cavity does not receive a uniform dose of progesterone, or that the cancer is not uniformly receptive to hormonal treatment [100]. In any case, the treatment results from systemic (by mouth) progestin or intrauterine progestin appear to be the same [101].

Once the treatment itself is chosen, appropriate follow-up of the patient is also not standardized. How frequently should the endometrium be resampled following treatment? How long should the treating clinician wait for complete response? Once complete response has been established, how should the patient then be followed to rule out recurrence? The appropriate treatment and follow-up course has not been established. It is clear, however, that responses may not be seen at the first 3-month resampling, and that the recurrence risk is high. It seems reasonable to suggest that patients be resampled

3 months after beginning hormonal therapy. If an incomplete response is documented, a further 3-month trial of treatment, perhaps with increased dose or different medication, may be appropriate. Once complete remission is established, pregnancy (if desired) should be aggressively pursued, with ART if required. If pregnancy is not desired, a "maintenance" hormonal treatment must be utilized to prevent recurrence. This maintenance therapy might consist of the birth control pill, monthly withdrawal bleeds with progesterone, or continuous progesterone therapy, either by mouth, intramuscular, or intrauterine.

Many women with endometrial cancer treated with progesterone will require ART to achieve pregnancy. In the study from Korea, 44 of 70 women used ART to achieve pregnancy; with a higher pregnancy rate (86 % vs. 50 %) and live birth rate (71 % vs. 42 %) than those patients who attempted natural pregnancy [23]. Since ART generates very high serum estradiol levels (which thereby put the patient at risk for recurrence if pregnancy is not achieved), many community in vitro fertility (IVF) programs may feel uncomfortable managing these patients. Moreover, many of these women are in the older range of reproductive age and therefore have lower success rates for IVF, perhaps requiring multiple attempts at ovulation induction to achieve pregnancy. These risks must be considered in the overall counseling of these patients when they are contemplating hormonal management for preservation of fertility.

Mechanisms of Hormone Receptor Action in Endometrial Cancer

The presence of PR in endometrial cancer does not guarantee response to progesterone. The simple notion of a generic progesterone receptor has been replaced over the last 10 years with a better understanding of the complexity of the PR and the mechanism of action of hormones on endometrial cancer. Nevertheless, currently there is no method to predict which cancers will regress with hormonal therapy and which will persist. Moreover, tumors may respond to progesterone therapy only partially, with persistence of disease in some areas of the uterus and response in others. While we have a general clinical sense that many CAH and endometrial cancers will respond to progesterone, the understanding of this response at the molecular level is rudimentary at best.

Most endometrioid adenocarcinomas express PR [102]. The lower grade tumors express PR more frequently, with a decrease in PR expression with increasing tumor grade [103–105]. However, there is a variable response to progesterone treatment within a single tumor and tumors can have both PR-positive and PR-negative areas [106–109]. Therefore, the presence of PR by immunohistochemistry does not reliably predict response to progesterone therapy. Furthermore, we now have more information regarding the complexity of the PR and the interactions between its two isoforms, PRA and PRB. Either the two isoforms have divergent responses or the ratio of the isoforms might be important [110–113]. There are also several cofactors and corepressors that can influence PR-mediated action [114–119]. The study of Arnett-Mansfield et al. illustrates the difficulty of utilizing immunohistochemistry and the presence or absence of receptor to predict response [120]. The authors studied PR isoforms in archived endometrial cancer tissue. Ninety-six percent of tumors expressed PR. Only 30 % of tumors expressed PRA alone, 42 % expressed both isoforms, and 28 % expressed PRB alone. PRB-only tumors had low levels of PR and those tumors that expressed both isoforms tended to express predominantly PRA. Based on their data, the authors hypothesized that loss of PRB resulted in the development of endometrial cancer. The finding of different expression of the isoforms has been supported by other groups (67, 70) [110, 113]. Other authors have suggested that it is the ratio of the isoforms that is most important (78) [121]. Thus, it is most likely that the ratio of PRA to PRB determines both the development of endometrial cancer and the ultimate response or lack thereof to progesterone treatment.

GOG211 was the first nontherapeutic preoperative trial in women with endometrial cancer

[122]. In this study, mainly postmenopausal women were registered, resulting in a lower treatment response than would be expected from a younger (premenopausal) population. After diagnosis of endometrial cancer by endometrial biopsy, patients were enrolled to receive Depo-medroxyprogesterone acetate 21–24 days prior to planned surgery. The biopsy and hysterectomy specimens were evaluated for estrogen and progesterone receptor expression, as well as other markers for proliferation and apoptosis. Fifty-nine women received treatment with progestin per protocol and had available slides. Only one complete histologic response was seen, and 37 tumors (87 %) had a partial response. PR and PRB were both significantly downregulated following treatment with progesterone. This downregulation of PR and PRB following treatment may contribute to later resistance to progesterone therapy.

As the presence of PR alone does not predict response to progesterone therapy, molecular markers of progesterone response that are measurable in paraffin-fixed tissue will be needed in the future to predict response of an individual tumor to progesterone therapy. Moreover, since different areas of each tumor may respond to treatment differently, careful monitoring of response will always be necessary.

Treatment of the Postmenopausal Woman with Progestin

Certain postmenopausal women will not be candidates for surgery for their endometrial cancer, most often due to medical comorbidities such as morbid obesity, diabetes, heart disease, etc. For those women with grade 1 non-invasive disease, progestin therapy may be a therapeutic option. There is very little data addressing the response rates of older women to progestin, but it has been documented that response rates for both CAH and endometrial cancer are lower in the post menopause than in the premenopause [95]. Further study is needed in this area.

Future Directions

As women in the USA continue to delay childbearing and as obesity rates rise, the numbers of women with endometrial cancer who wish to preserve their fertility will continue to increase. Counseling of these women regarding uterine preservation is limited by the lack of data and lack of standardized management schemas. Prospective trials are underway, seeking to establish a standard drug, dose, and schedule for progesterone therapy, and its appropriate monitoring. In order to establish a new standard of care in this setting, we require a better understanding at the molecular and genetic level of the mechanism of the different progesterone formulations on endometrial cancer at the level of the PR isoforms. It may be that a specific novel progesterone directed at one or the other PR isoforms will be the best treatment in the future, or perhaps directed therapy to each particular tumor depending upon that tumor's expression pattern of PR isoforms.

For the present time, any young woman with endometrial cancer wishing to be treated with progesterone in order to preserve fertility should be managed with the guidance of a gynecologic oncologist wherever possible and should be informed of all of the risks of less than standard of care treatment, including the not insignificant risk of progression of disease and potential development of ovarian synchronous primary tumors or ovarian metastases. Only women with grade 1 endometrioid adenocarcinomas and disease that is clinically felt to be confined to the endometrium with the best available radiologic modality should be considered for therapy. While the MGH study failed to identify any clinical or immunohistologic factors other than grade that are predictive of stage IA disease and thus predictive of successful hormonal therapy, other small studies have suggested histologic architectural complexity and high BMI to be predictive of treatment failure. It is however premature to use this data in counseling women against an attempt at conservative fertility sparing therapy if otherwise appropriate.

Patients who wish to proceed with progesterone therapy rather than surgery should be counseled that this therapy is not the standard of care treatment for endometrial cancer. Treating with less than the standard of care could potentially result in a young woman dying of a surgically curable disease.

Conclusions

To pursue primary hormonal therapy of endometrial cancer, the following steps are required:

- Confirm that the tumor is endometrioid and grade 1 by pathologic review. If diagnosis was made by endometrial biopsy, perform D&C to ensure complete sampling of the endometrial cavity.
- Obtain a careful medical history and perform physical examination with particular attention to family history. A family history that suggests Lynch syndrome should result in genetic counseling and possible testing as patient is at increased risk for colon and ovarian cancer. Attention should also be paid to medical history that might complicate future pregnancies (obesity, diabetes, hypertension). Microsatellite instability testing may be performed on endometrial biopsy samples to assist in screening for genetic syndromes.
- MRI and/or ultrasound should be performed to rule out adnexal metastases and evaluate for myometrial invasion.

If the tumor is well sampled and grade 1 with no evidence of extrauterine disease or myometrial invasion, the patient should undergo:

- Informed counseling, preferably with a gynecologic oncologist.
- Treatment with progesterone, either continuous or cyclic, or via intrauterine device.
- Resampling in 3 months to assess response.
- If resolution of disease: patient should be encouraged to achieve pregnancy quickly. Many of these patients will require ART.
- If incomplete resolution of disease: patient may be continued on treatment for another 3 months and rebiopsied. The clinician may also consider another medication regimen or a higher dose of the same formulation and resample in 3 months.
- Once childbearing is complete or if treatment fails, the patient should be counseled for definitive surgical therapy consisting of TAH–BSO with lymphadenectomy as appropriate. Certain patients may be candidates for ovarian preservation but this should be done with caution and appropriate counseling.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Can J Clin. 2014;64(1):9–29.
2. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009;105(2):103–4.
3. Lajer H, Elnegaard S, Christensen RD, Ortoft G, Schledermann DE, Mogensen O. Survival after stage IA endometrial cancer; can follow-up be altered? A prospective nationwide Danish survey. Acta Obstet Gynecol Scand. 2012;91(8):976–82.
4. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/ , based on November 2013 SEER data submission, posted to the SEER web site, April 2014. 1975-2011
5. Peterson EP. Endometrial carcinoma in young women. A clinical profile. Obstet Gynecol. 1968;31 (5):702–7.
6. Kempson RL, Pokorny GE. Adenocarcinoma of the endometrium in women aged forty and younger. Cancer. 1968;21(4):650–62.
7. Crissman JD, Azoury RS, Barnes AE, Schellhas HF. Endometrial carcinoma in women 40 years of age or younger. Obstet Gynecol. 1981;57 (6):699–704.
8. Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol. 1984;64(3):417–20.
9. Farhi DC, Nosanchuk J, Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. Obstet Gynecol. 1986;68(6):741–5.
10. Jeffery JD, Taylor R, Robertson DI, Stuart GC. Endometrial carcinoma occurring in patients under the age of 45 years. Am J Obstet Gynecol. 1987;156(2):366–70.
11. Gitsch G, Hanzal E, Jensen D, Hacker NF. Endometrial cancer in premenopausal women

45 years and younger. Obstet Gynecol. 1995;85 (4):504–8.
12. Evans-Metcalf ER, Brooks SE, Reale FR, Baker SP. Profile of women 45 years of age and younger with endometrial cancer. Obstet Gynecol. 1998;91 (3):349–54.
13. Soliman PT, Oh JC, Schmeler KM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol. 2005;105(3):575–80.
14. Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. Gynecol Oncol. 2001;83(2):388–93.
15. Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109(3):655–62.
16. Richter CE, Qian B, Martel M, et al. Ovarian preservation and staging in reproductive-age endometrial cancer patients. Gynecol Oncol. 2009;114 (1):99–104.
17. Polednak AP. Trends in incidence rates for obesity-associated cancers in the US. Cancer Detect Prev. 2003;27(6):415–21.
18. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335 (7630):1134.
19. Havrilesky LJ, Maxwell GL, Myers ER. Cost-effectiveness analysis of annual screening strategies for endometrial cancer. Am J Obstet Gynecol. 2009;200(6):640, e641–e648.
20. Kwon JS, Lu KH. Cost-effectiveness analysis of endometrial cancer prevention strategies for obese women. Obstet Gynecol. 2008;112(1):56–63.
21. Rose PG. Endometrial carcinoma. N Engl J Med. 1996;335(9):640–9.
22. Schmeler KM, Soliman PT, Sun CC, Slomovitz BM, Gershenson DM, Lu KH. Endometrial cancer in young, normal-weight women. Gynecol Oncol. 2005;99(2):388–92.
23. Park JY, Seong SJ, Kim TJ, et al. Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. Obstet Gynecol. 2013;121(1):136–42.
24. Wang CJ, Chao A, Yang LY, et al. Fertility-preserving treatment in young women with endometrial adenocarcinoma: a long-term cohort study. Int J Gynecol Cancer. 2014;24(4):718–28.
25. Lu KH, Dinh M, Kohlmann W, et al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol. 2005;105(3):569–74.
26. Kurman RJ, Norris HJ. Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma. Cancer. 1982;49(12):2547–59.
27. Zaino RJ, Kauderer J, Trimble CL, et al. Reproducibility of the diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106(4):804–11.
28. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106(4):812–9.
29. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer. 1987;60 (8 Suppl):2035–41.
30. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group study LAP2. J Clin Oncol. 2009;27(32):5331–6.
31. Cowles TA, Magrina JF, Masterson BJ, Capen CV. Comparison of clinical and surgical-staging in patients with endometrial carcinoma. Obstet Gynecol. 1985;66(3):413–6.
32. Daniel AG, Peters 3rd WA. Accuracy of office and operating room curettage in the grading of endometrial carcinoma. Obstet Gynecol. 1988;71 (4):612–4.
33. Eltabbakh GH, Shamonki J, Mount SL. Surgical stage, final grade, and survival of women with endometrial carcinoma whose preoperative endometrial biopsy shows well-differentiated tumors. Gynecol Oncol. 2005;99(2):309–12.
34. DelMaschio A, Vanzulli A, Sironi S, et al. Estimating the depth of myometrial involvement by endometrial carcinoma: efficacy of transvaginal sonography vs MR imaging. AJR Am J Roentgenol. 1993;160(3):533–8.
35. Gordon AN, Fleischer AC, Dudley BS, et al. Preoperative assessment of myometrial invasion of endometrial adenocarcinoma by sonography (US) and magnetic resonance imaging (MRI). Gynecol Oncol. 1989;34(2):175–9.
36. Kim SH, Kim HD, Song YS, Kang SB, Lee HP. Detection of deep myometrial invasion in endometrial carcinoma: comparison of transvaginal ultrasound, CT, and MRI. J Comput Assist Tomogr. 1995;19(5):766–72.
37. Zerbe MJ, Bristow R, Grumbine FC, Montz FJ. Inability of preoperative computed tomography scans to accurately predict the extent of myometrial invasion and extracorporal spread in endometrial cancer. Gynecol Oncol. 2000;78(1):67–70.
38. Hardesty LA, Sumkin JH, Hakim C, Johns C, Nath M. The ability of helical CT to preoperatively stage endometrial carcinoma. AJR Am J Roentgenol. 2001;176(3):603–6.
39. Frei KA, Kinkel K. Staging endometrial cancer: role of magnetic resonance imaging. J Magn Res Imag JMRI. 2001;13(6):850–5.
40. Chung HH, Kang SB, Cho JY, et al. Accuracy of MR imaging for the prediction of myometrial invasion of endometrial carcinoma. Gynecol Oncol. 2007;104 (3):654–9.

41. Nakao Y, Yokoyama M, Hara K, et al. MR imaging in endometrial carcinoma as a diagnostic tool for the absence of myometrial invasion. Gynecol Oncol. 2006;102(2):343–7.
42. Yamashita Y, Harada M, Sawada T, Takahashi M, Miyazaki K, Okamura H. Normal uterus and FIGO stage I endometrial carcinoma: dynamic gadolinium-enhanced MR imaging. Radiology. 1993;186 (2):495–501.
43. Sironi S, Colombo E, Villa G, et al. Myometrial invasion by endometrial carcinoma: assessment with plain and gadolinium-enhanced MR imaging. Radiology. 1992;185(1):207–12.
44. Scoutt LM, McCarthy SM, Flynn SD, et al. Clinical stage I endometrial carcinoma: pitfalls in preoperative assessment with MR imaging. Work in progress. Radiology. 1995;194(2):567–72.
45. Lee EJ, Byun JY, Kim BS, Koong SE, Shinn KS. Staging of early endometrial carcinoma: assessment with T2-weighted and gadolinium-enhanced T1-weighted MR imaging. Radiographics. 1999;19 (4):937–45. discussion 946–937.
46. Minderhoud-Bassie W, Treurniet FE, Koops W, Chadha-Ajwani S, Hage JC, Huikeshoven FJ. Magnetic resonance imaging (MRI) in endometrial carcinoma; preoperative estimation of depth of myometrial invasion. Acta Obstet Gynecol Scand. 1995;74(10):827–31.
47. Suh DS, Kim JK, Kim KR, et al. Reliability of magnetic resonance imaging in assessing myometrial invasion absence in endometrial carcinoma. Acta Obstet Gynecol Scand. 2009;88(9):990–3.
48. Hricak H, Stern JL, Fisher MR, Shapeero LG, Winkler ML, Lacey CG. Endometrial carcinoma staging by MR imaging. Radiology. 1987;162 (2):297–305.
49. Ito K, Matsumoto T, Nakada T, Nakanishi T, Fujita N, Yamashita H. Assessing myometrial invasion by endometrial carcinoma with dynamic MRI. J Comput Assist Tomogr. 1994;18(1):77–86.
50. Kinkel K, Kaji Y, Yu KK, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology. 1999;212(3):711–8.
51. Sanjuan A, Escaramis G, Ayuso JR, et al. Role of magnetic resonance imaging and cause of pitfalls in detecting myometrial invasion and cervical involvement in endometrial cancer. Arch Gynecol Obstet. 2008;278(6):535–9.
52. Joja I, Asakawa M, Asakawa T, et al. Endometrial carcinoma: dynamic MRI with turbo-FLASH technique. J Comput Assist Tomogr. 1996;20(6):878–87.
53. Saez F, Urresola A, Larena JA, et al. Endometrial carcinoma: assessment of myometrial invasion with plain and gadolinium-enhanced MR imaging. J Magn Res Imag JMRI. 2000;12(3):460–6.
54. Savci G, Ozyaman T, Tutar M, Bilgin T, Erol O, Tuncel E. Assessment of depth of myometrial invasion by endometrial carcinoma: comparison of T2-weighted SE and contrast-enhanced dynamic GRE MR imaging. Eur Radiol. 1998;8(2):218–23.
55. Seki H, Kimura M, Sakai K. Myometrial invasion of endometrial carcinoma: assessment with dynamic MR and contrast-enhanced T1-weighted images. Clin Radiol. 1997;52(1):18–23.
56. Ben-Shachar I, Vitellas KM, Cohn DE. The role of MRI in the conservative management of endometrial cancer. Gynecol Oncol. 2004;93(1):233–7.
57. Frei KA, Kinkel K, Bonel HM, Lu Y, Zaloudek C, Hricak H. Prediction of deep myometrial invasion in patients with endometrial cancer: clinical utility of contrast-enhanced MR imaging-a meta-analysis and Bayesian analysis. Radiology. 2000;216(2):444–9.
58. Simpson AN, Feigenberg T, Clarke BA, et al. Fertility sparing treatment of complex atypical hyperplasia and low grade endometrial cancer using oral progestin. Gynecol Oncol. 2014;133(2):229–33.
59. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95(1):133–8.
60. Gotlieb WH, Beiner ME, Shalmon B, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol. 2003;102(4):718–25.
61. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol. 2012;125(2):477–82.
62. Koskas M, Uzan J, Luton D, Rouzier R, Darai E. Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril. 2014;101(3):785–94.
63. Bokhman JV, Chepick OF, Volkova AT, Vishnevsky AS. Can primary endometrial carcinoma stage I be cured without surgery and radiation therapy? Gynecol Oncol. 1985;20(2):139–55.
64. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstet Gynecol. 1997;90(3):434–40.
65. Park JY, Kim DY, Kim JH, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer. 2013;49 (4):868–74.
66. Park JY, Kim DY, Kim TJ, et al. Hormonal therapy for women with stage IA endometrial cancer of all grades. Obstet Gynecol. 2013;122(1):7–14.
67. Penner KR, Dorigo O, Aoyama C, et al. Predictors of resolution of complex atypical hyperplasia or grade 1 endometrial adenocarcinoma in premenopausal women treated with progestin therapy. Gynecol Oncol. 2012;124(3):542–8.

68. Wang CB, Wang CJ, Huang HJ, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer. 2002;94 (8):2192–8.
69. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG. 2005;112(3):317–20.
70. Ushijima K, Yahata H, Yoshikawa H, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol. 2007;25(19):2798–803.
71. Shan BE, Ren YL, Sun JM, et al. A prospective study of fertility-sparing treatment with megestrol acetate following hysteroscopic curettage for well-differentiated endometrioid carcinoma and atypical hyperplasia in young women. Arch Gynecol Obstet. 2013;288(5):1115–23.
72. NCT00788671. Levonorgestrel Intrauterine Device (IUD) to Treat Complex Atypical Hyperplasia (CAH) and Grade 1 Endometrioid Endometrial Carcinoma (G1EEC). (Sponsor: MD Anderson PI: Shannon Westin, MD).
73. NCT01594879. Treatment With Medroxyprogesterone Acetate Plus LNG-IUS in Young Women With Early Stage Endometrial Cancer.Sponsor: Korean Gynecologic Oncology Group PI: Seok Ju Soeng, MD.
74. Park JY, Lee SH, Seong SJ, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. Gynecol Oncol. 2013;129(1):7–11.
75. Kim YB, Holschneider CH, Ghosh K, Nieberg RK, Montz FJ. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. Cancer. 1997;79(2):320–7.
76. Ferrandina G, Zannoni GF, Gallotta V, Foti E, Mancuso S, Scambia G. Progression of conservatively treated endometrial carcinoma after full term pregnancy: a case report. Gynecol Oncol. 2005;99 (1):215–7.
77. Rubatt JM, Slomovitz BM, Burke TW, Broaddus RR. Development of metastatic endometrial endometrioid adenocarcinoma while on progestin therapy for endometrial hyperplasia. Gynecol Oncol. 2005;99(2):472–6.
78. Kaku T, Yoshikawa H, Tsuda H, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett. 2001;167(1):39–48.
79. Kothari R, Seamon L, Cohn D, Fowler J, O'Malley DM. Stage IV endometrial cancer after failed conservative management: a case report. Gynecol Oncol. 2008;111(3):579–82.
80. Ogawa S, Koike T, Shibahara H, et al. Assisted reproductive technologies in conjunction with conservatively treated endometrial adenocarcinoma. A case report. Gynecol Obstet Investig. 2001;51 (3):214–6.
81. Jobo T, Imai M, Kawaguchi M, Kenmochi M, Kuramoto H. Successful conservative treatment of endometrial carcinoma permitting subsequent pregnancy: report of two cases. Eur J Gynaecol Oncol. 2000;21(2):119–22.
82. Sardi J, Anchezar Henry JP, Paniceres G, Gomez Rueda N, Vighi S. Primary hormonal treatment for early endometrial carcinoma. Eur J Gynaecol Oncol. 1998;19(6):565–8.
83. Shibahara H, Shigeta M, Toji H, et al. Successful pregnancy in an infertile patient with conservatively treated endometrial adenocarcinoma after transfer of embryos obtained by intracytoplasmic sperm injection. Hum Reprod. 1999;14(7):1908–11.
84. Kung FT, Chen WJ, Chou HH, Ko SF, Chang SY. Conservative management of early endometrial adenocarcinoma with repeat curettage and hormone therapy under assistance of hysteroscopy and laparoscopy. Hum Reprod. 1997;12(8):1649–53.
85. Mazzon I, Corrado G, Morricone D, Scambia G. Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection. Int J Gynecol Cancer. 2005;15 (5):974–8.
86. Yarali H, Bozdag G, Aksu T, Ayhan A. A successful pregnancy after intracytoplasmic sperm injection and embryo transfer in a patient with endometrial cancer who was treated conservatively. Fertil Steril. 2004;81(1):214–6.
87. Nakao Y, Nomiyama M, Kojima K, Matsumoto Y, Yamasaki F, Iwasaka T. Successful pregnancies in 2 infertile patients with endometrial adenocarcinoma. Gynecol Obstet Investig. 2004;58 (2):68–71.
88. Pinto AB, Gopal M, Herzog TJ, Pfeifer JD, Williams DB. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. Fertil Steril. 2001;76(4):826–9.
89. Kimmig R, Strowitzki T, Muller-Hocker J, Kurzl R, Korell M, Hepp H. Conservative treatment of endometrial cancer permitting subsequent triplet pregnancy. Gynecol Oncol. 1995;58(2):255–7.
90. Walsh C, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol. 2005;106(4):693–9.
91. Navarria I, Usel M, Rapiti E, et al. Young patients with endometrial cancer: how many could be eligible for fertility-sparing treatment? Gynecol Oncol. 2009;114(3):448–51.

92. Wright JD, Buck AM, Shah M, Burke WM, Schiff PB, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol. 2009;27(8):1214–9.
93. Zivanovic O, Carter J, Kauff ND, Barakat RR. A review of the challenges faced in the conservative treatment of young women with endometrial carcinoma and risk of ovarian cancer. Gynecol Oncol. 2009;115(3):504–9.
94. Shamshirsaz AA, Withiam-Leitch M, Odunsi K, Baker T, Frederick PJ, Lele S. Young patients with endometrial carcinoma selected for conservative treatment: a need for vigilance for synchronous ovarian carcinomas, case report and literature review. Gynecol Oncol. 2007;104(3):757–60.
95. Zaino R, Whitney C, Brady MF, DeGeest K, Burger RA, Buller RE. Simultaneously detected endometrial and ovarian carcinomas—a prospective clinicopathologic study of 74 cases: a Gynecologic Oncology Group study. Gynecol Oncol. 2001;83 (2):355–62.
96. Morice P, Fourchotte V, Sideris L, Gariel C, Duvillard P, Castaigne D. A need for laparoscopic evaluation of patients with endometrial carcinoma selected for conservative treatment. Gynecol Oncol. 2005;96(1):245–8.
97. Mitsushita J, Toki T, Kato K, Fujii S, Konishi I. Endometrial carcinoma remaining after term pregnancy following conservative treatment with medroxyprogesterone acetate. Gynecol Oncol. 2000;79(1):129–32.
98. Montz FJ, Bristow RE, Bovicelli A, Tomacruz R, Kurman RJ. Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol. 2002;186(4):651–7.
99. Dhar KK, NeedhiRajan T, Koslowski M, Woolas RP. Is levonorgestrel intrauterine system effective for treatment of early endometrial cancer? Report of four cases and review of the literature. Gynecol Oncol. 2005;97(3):924–7.
100. Jones K, Georgiou M, Hyatt D, Spencer T, Thomas H. Endometrial adenocarcinoma following the insertion of a Mirena IUCD. Gynecol Oncol. 2002;87 (2):216–8.
101. Hubbs JL, Saig RM, Abaid LN, Bae-Jump VL, Gehrig PA. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol. 2013;121(6):1172–80.
102. Jeon YT, Park IA, Kim YB, et al. Steroid receptor expressions in endometrial cancer: clinical significance and epidemiological implication. Cancer Lett. 2006;239(2):198–204.
103. Ehrlich CE, Young PC, Cleary RE. Cytoplasmic progesterone and estradiol receptors in normal, hyperplastic, and carcinomatous endometria: therapeutic implications. Am J Obstet Gynecol. 1981;141 (5):539–46.
104. Ehrlich CE, Young PC, Stehman FB, Sutton GP, Alford WM. Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium. Am J Obstet Gynecol. 1988;158 (4):796–807.
105. Creasman WT, Soper JT, McCarty Jr KS, McCarty Sr KS, Hinshaw W, Clarke-Pearson DL. Influence of cytoplasmic steroid receptor content on prognosis of early stage endometrial carcinoma. Am J Obstet Gynecol. 1985;151(7):922–32.
106. Benraad TJ, Friberg LG, Koenders AJ, Kullander S. Do estrogen and progesterone receptors (E2R and PR) in metastasizing endometrial cancers predict the response to gestagen therapy? Acta Obstet Gynecol Scand. 1980;59(2):155–9.
107. Creasman WT, McCarty Sr KS, Barton TK, McCarty Jr KS. Clinical correlates of estrogen- and progesterone-binding proteins in human endometrial adenocarcinoma. Obstet Gynecol. 1980;55(3):363–70.
108. Martin PM, Rolland PH, Gammerre M, Serment H, Toga M. Estradiol and progesterone receptors in normal and neoplastic endometrium: correlations between receptors, histopathological examinations and clinical responses under progestin therapy. Inter J Can. 1979;23(3):321–9.
109. Kauppila A, Kujansuu E, Vihko R. Cytosol estrogen and progestin receptors in endometrial carcinoma of patients treated with surgery, radiotherapy, and progestin. Clinical correlates. Cancer. 1982;50 (10):2157–62.
110. Smid-Koopman E, Kuhne LC, Hanekamp EE, et al. Progesterone-induced inhibition of growth and differential regulation of gene expression in PRA- and/or PRB-expressing endometrial cancer cell lines. J Soc Gynecol Investig. 2005;12 (4):285–92.
111. Hanekamp EE, Gielen SC, Smid-Koopman E, et al. Consequences of loss of progesterone receptor expression in development of invasive endometrial cancer. Clin Cancer Res. 2003;9(11):4190–9.
112. Smid-Koopman E, Blok LJ, Kuhne LC, et al. Distinct functional differences of human progesterone receptors A and B on gene expression and growth regulation in two endometrial carcinoma cell lines. J Soc Gynecol Investig. 2003;10 (1):49–57.
113. Miyamoto T, Watanabe J, Hata H, et al. Significance of progesterone receptor-A and -B expressions in endometrial adenocarcinoma. J Steroid Biochem Mol Biol. 2004;92(3):111–8.
114. Conneely OM. Perspective: female steroid hormone action. Endocrinology. 2001;142(6):2194–9.
115. Conneely OM, Lydon JP. Progesterone receptors in reproduction: functional impact of the A and B isoforms. Steroids. 2000;65(10–11):571–7.
116. Conneely OM, Mulac-Jericevic B, Lydon JP, De Mayo FJ. Reproductive functions of the progesterone receptor isoforms: lessons from

knock-out mice. Mol Cell Endocrinol. 2001;179 (1–2):97–103.
117. Rowan BG, O'Malley BW. Progesterone receptor coactivators. Steroids. 2000;65(10–11):545–9.
118. Spitz IM, Coelingh Bennink HJ. Progesterone receptor modulators at the start of a new millennium. Steroids. 2000;65(10–11):837–8.
119. Bouchard P. Progesterone and the progesterone receptor. J Reprod Med. 1999;44(2 Suppl):153–7.
120. Arnett-Mansfield RL, deFazio A, Wain GV, et al. Relative expression of progesterone receptors A and B in endometrioid cancers of the endometrium. Cancer Res. 2001;61(11):4576–82.
121. Dai D, Kumar NS, Wolf DM, Leslie KK. Molecular tools to reestablish progestin control of endometrial cancer cell proliferation. Am J Obstet Gynecol. 2001;184(5):790–7.
122. Zaino RJ, Brady WE, Todd W, et al. Histologic effects of medroxyprogesterone acetate on endometrioid endometrial adenocarcinoma: a Gynecologic Oncology Group study. Int J Gynecol Pathol. 2014;33(6):543–53.

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Early-Stage Endometrial Cancer: Surgery

Yukio Sonoda and George Monemvasitis

Abstract

Endometrial cancer typically presents at an early stage, and surgery alone can be curative in many of these cases. Traditionally, surgery for early-stage disease has been carried out using an open approach; however, the use of minimally invasive surgery has rapidly grown in the field of gynecologic oncology. Multiple studies have demonstrated its feasibility, and oncologic outcomes continue to be validated.

Keywords

Endometrial cancer • Surgery • Laparoscopy

Introduction

Endometrial cancer remains the most common gynecologic malignancy in the USA, and it ranks as the fourth most common cancer among American women. There will be an estimated 54,870 newly diagnosed cancers of the uterine corpus and 10,170 deaths from this disease in 2015 [1]. Fortunately, the vast majority of endometrial cancers are detected at early stages; approximately 75 % of these cancers are limited to the uterus at time of discovery. This is in large part due to the early warning sign of abnormal uterine bleeding present during the early stages of the disease.

Y. Sonoda (✉) and G. Monemvasitis
Gynecology Service, Department of Surgery, Memorial Sloan Ketering Cancer Center, New York, NY, USA
e-mail: sonoday@mskcc.org

Endometrial cancer has traditionally been classified into two types [2], although some have proposed an integrated classification system incorporating molecular and clinicopathologic features [3]. Type I cancers are more common and are associated with increased levels of circulating estrogen. These tumors usually begin as endometrial hyperplasia and progress to cancer. They tend to occur at a younger age and are less aggressive (typically grade 1 and 2 endometrioid adenocarcinomas). Type II cancers are of higher grade, more aggressive, and tend to arise in a background of atrophic endometrium. Histologically, they encompass serous, clear cell, and grade 3 endometrioid adenocarcinomas. They occur in older patients and do not have an estrogen-related precursor.

Fortunately, early-stage type I endometrial cancers comprise the vast majority of cases

and can be cured. The surgical treatment of early-stage type I cancers is the focus of this chapter.

Surgical Therapy

With the change of the staging system for this disease from a clinical to a surgical evaluation, primary treatment for women with endometrial cancer begins with surgery. Prior to undergoing a major surgical procedure, and given that this disease is associated with surgical risk factors such as obesity, hypertension, and diabetes, all patients should undergo a thorough history and physical examination. Physical examination should include areas of potential tumor spread: enlarged supraclavicular and inguinal lymph nodes, signs of intra-abdominal disease or ascites, and close inspection of the cervix and vagina. Chest radiography has traditionally been obtained to rule out any pulmonary spread. Other imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scan, are usually obtained when findings on history and physical examination warrant further investigation. Serum CA-125 has been shown to be elevated in patients with advanced disease, and this may provide additional information if intra-abdominal spread is suspected [4].

The standard surgical approach to the patient with endometrial cancer clinically confined to the uterus entails an exploration of the peritoneal cavity, biopsies of any suspicious lesions, total hysterectomy, bilateral salpingo-oophorectomy (BSO), and selected pelvic and para-aortic lymph node sampling.

After entering the peritoneal cavity, a thorough exploration is performed. Any suspicious lesions should be biopsied. Although no longer required for surgical staging, obtaining peritoneal washings is still recommended; washings are acquired by instilling approximately 100 cm^3 of saline into the pelvis and aspirating for cytological analysis. An extrafascial hysterectomy with BSO can then be performed.

Once the primary specimen has been removed, the pelvic ± para-aortic lymph nodes should be sampled. This is an area that remains controversial in the management of endometrial cancer. The basis for lymph node sampling arose from Gynecologic Oncology Group (GOG) protocol 33 [5]. This study demonstrated that the incidence of pelvic and para-aortic lymph node metastasis was higher for patients with high-grade and deeply invasive tumors. Low-grade tumors with no or only superficial myometrial invasion were associated with a very low incidence of lymph node spread.

Intraoperative Management

In the absence of obvious extrauterine spread, some have advocated using a combination of preoperative tumor grade, intraoperative assessment of myometrial invasion, and clinical evaluation of the lymph nodes to determine if lymph node assessment should be undertaken. Mariani et al. [6] prospectively examined 281 patients undergoing lymphadenectomy at the time of surgery for endometrial cancer. They found that 22 % of patients with high-risk disease had lymph node metastases. They also identified a low-risk group consisting of patients with low-grade disease (grade 1 or 2, endometrioid histology), with $\leq$50 % myometrial invasion and tumor size $\leq$2 cm, who probably do not benefit from lymphadenectomy. Using the "Mayo Criteria" at time of frozen section to omit lymphadenectomy does rely on several pathologic uncertainties (assessing tumor grade and depth of myometrial invasion) that may vary from institution to institution. Tumor grade cannot be accurately determined using office biopsy or curettage. In a retrospective study by Obermair et al. [7], the preoperative histologic grade of the curettage specimen was compared with that of the final specimen. Only 78 % of well-differentiated tumors diagnosed on curettage maintained the same histologic grade on final analysis. Similar results of the inaccuracy of preoperative grade assessment have been demonstrated by other authors [8–10].

Accurately assessing depth of myometrial invasion by either intraoperative visual inspection or frozen-section analysis can be difficult. Intraoperative visual examination can correctly predict the degree of myometrial invasion in 87 % of grade 1 tumors, 65 % of grade 2 tumors, and 31 % of grade 3 tumors [11]. The use of frozen-section analysis to assess myometrial invasion has been advocated by some [12]. In a recent study of 153 patients with grade 1 or 2 endometrioid endometrial cancer, Frumovitz et al. [13] compared preoperative grade and intraoperative myometrial invasion with final pathology. Forty-nine patients (32 %) had a discrepancy between preoperative and final histology. Thirty-seven patients (27 %) had their lesions upgraded or were found to have disease of histology other than endometrioid adenocarcinoma. Twenty-six percent of Pipelle biopsies and 23 % of curettage specimens were upgraded on final pathology. The authors concluded that a clinically significant number of patients will be found to have more advanced disease than can be predicted using preoperative and intraoperative prognostic factors, and these should not be relied upon for staging. Palpation of the retroperitoneal nodes can be inaccurate even in experienced hands. In one study of 126 women, assessment by palpation alone would have missed 36 % of positive nodes [14]. Others have also demonstrated this inaccuracy [15]. Additionally, over one-third of lymph nodes may have only microscopic metastasis [16].

Routine Staging

Since intraoperative assessment of pathologic risk factors for extrauterine spread is not perfect, many have advocated the routine use of surgical staging for all patients. In a large population-based study of more than 10,000 patients, Trimble et al. [17] demonstrated the impact of lymph node sampling on survival in women with International Federation of Gynecology and Obstetrics (FIGO) stage I and II endometrial adenocarcinoma. Five-year relative survival was not significantly improved in stage I patients who underwent lymph node sampling. When stage I patients were stratified by histologic grade, lymph node sampling was associated with an increased survival in patients with grade 3, but not grade 1 or 2, tumors. This may have been due to the identification of women with more advanced disease. The American College of Obstetricians and Gynecologists recently published its clinical management guidelines for endometrial cancer and recommended systemic surgical staging for most women with endometrial cancer. Exceptions to this approach were made after consultation with a gynecologic oncologist [18].

Lymph Node Evaluation

The extent of lymph node sampling required for accurate staging is debatable. Improved outcomes have been associated with an increased number of nodes removed. Kilgore et al. [19] reviewed their experience on 649 patients with adenocarcinoma of the endometrium. Patients were categorized into one of three groups: multiple-site pelvic node sampling, limited pelvic node sampling, and no sampling. Patients in whom multiple-site sampling, which was defined as having at least four sites sampled, was performed had a significantly better survival than patients who had no sampling. Patients with limited or less than four sites sampled did not have a significantly better survival compared with patients who did not undergo sampling. Cragun et al. [20] recently published a single-institution series on selective lymphadenectomy in apparent early-stage endometrial cancer. An improvement in overall and progression-free survival was seen in patients with poorly differentiated tumors and more than 11 nodes removed. This survival advantage was not seen in patients with grade 1 or 2 tumors. These retrospective data suggest a therapeutic value to performing a lymphadenectomy, and some have advocated the routine use of lymphadenectomy in the management of these patients. Complete lymphadenectomy can provide excellent local control (Table 1) [21–26].

Table 1 Recurrences in moderate and high-risk patients treated with lymphadenectomy without whole-pelvic radiation

Author	Number of patients	Mean number of pelvic nodes	Mean follow-up (months)	Postoperative brachytherapy	Number of local recurrences	Number of distant recurrences
Fanning et al. [21]	22	28	34	Yes	0	1
Orr et al. [22]	115	24	39	Yes	0	7
Larson et al. [23]	105	N/A	43	No	4	4
Mohan et al. [24]	63	33	96	Yes	0	5 (1 site unknown)
Seago et al. [25]	23	N/A	26	Yes	0	2
Berclaz et al. [26]	19	18	54	Yes	1	0

One potential explanation for the therapeutic benefits of lymphadenectomy may be the removal of any subclinically involved nodes. Girardi et al. [16] reported on their experience with systematic pelvic lymphadenectomy in the treatment of endometrial cancer. A mean of 37 pelvic nodes were removed, and 27 (36 %) of 76 patients were upstaged based on lymph node metastases. Thirty-seven percent of lymph node metastases were $\leq$2 mm in diameter. Additionally, Yabushita et al. [27] demonstrated that up to 38 % of patients with stage I endometrial cancers were found to have metastatic disease detectable by immunostain only. Removal of this otherwise undetectable disease can be performed with low morbidity [22, 28] and may explain the potential therapeutic benefit to lymphadenectomy in early-stage endometrial cancer.

Alternatively, inadequate evaluation of the lymph nodes may lead to missed metastasis and undertreatment of more advanced disease [29]. Inadequate nodal evaluation may account for the difference in survival observed in cases that are at higher risk for spread. In a retrospective study of 467 patients with FIGO stage I and II endometrial cancers, a pelvic lymph node count of $\geq$12 nodes was associated with an improved survival only in cases with high-risk histology. The authors suggested that this observation was a result of improved staging in patients with higher node counts who were at higher risk for spread [30].

Despite these data supporting the use of routine lymphadenectomy, there has been no randomized trial showing a benefit in early-stage endometrial cancer. There have been two randomized trials demonstrating a lack of benefit for routine surgical staging. Panici et al. [31] reported on 514 women with clinical stage I endometrial cancer who were randomized to either systemic lymphadenectomy or no lymphadenectomy. No improvement in disease-free or overall survival was found between the two groups. Similarly, a large multicenter European trial randomized 1408 women with clinical stage I endometrial cancer to surgery with or without routine pelvic lymphadenectomy. The design of this trial was flawed, but similar to the Italian study, the performance of routine pelvic lymphadenectomy did not impact disease-free or overall survival [32].

Since the identification of nodal metastases has profound effects on postoperative management and adjuvant therapy, novel techniques have been studied to obtain this valuable information. A more targeted approach to lymph node evaluation may eventually do away with the need to perform lymph node sampling to any degree. Sentinel lymph node mapping for endometrial cancer was first reported in 1996 [33], and over time, feasibility studies have begun to appear in the literature [34–37]. Sentinel lymph node mapping has become a topic of debate in the management of endometrial cancer; however, it may provide diagnostic accuracy while minimizing the morbidity associated with complete lymphadenectomy [38]. Although there have not been any large randomized studies to support the use of sentinel lymph node mapping

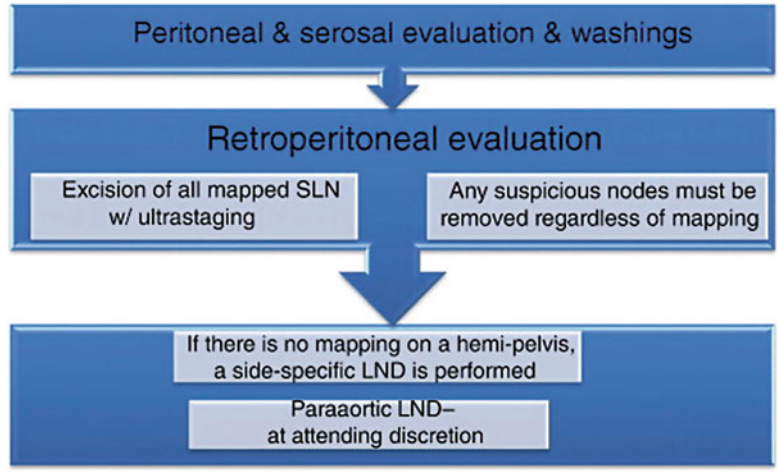

Fig. 1 Sentinel lymph node mapping algorithm for the staging of endometrial cancer

for apparent early-stage endometrial cancer, there are data that seem to support this novel technique.

The Senti-Endo study was conducted to assess the detection rate and diagnostic accuracy of sentinel lymph node mapping for early-stage endometrial cancer. Sentinel lymph node mapping was performed using a cervical dual injection technique with technetium patent blue dye. Completion pelvic lymphadenectomy was performed in all patients. The authors reported that 111 of the 125 eligible patients had at least one sentinel node detected. Seventeen percent (19 of 111 patients) were found to have a positive pelvic node and 5 % (5 of 111 patients) had a positive aortic node. The reported negative predictive value for each hemipelvis was 100 %, and the sensitivity was also 100 %. When evaluating the patients, the negative predictive value was 97 %, and the sensitivity was 84 %. The authors concluded that sentinel lymph node biopsy could be a trade-off between systematic lymphadenectomy and no dissection in patients with low- and intermediate-risk endometrial cancer [39].

Barlin et al. [40] published on the use of a sentinel lymph node mapping algorithm for endometrial cancer staging. The specific algorithm consists of (1) peritoneal and serosal evaluation and washings; (2) retroperitoneal evaluation including excision of all mapped sentinel nodes and suspicious nodes regardless of mapping; and (3) if there is no mapping on a hemipelvis, a site-specific pelvic common iliac and internal iliac lymph node dissection is performed. Para-aortic lymph node dissection is performed at the surgeon's discretion (Fig. 1). Over a 6-year period, 498 patients underwent sentinel lymph node mapping with a cervical injection of blue dye. Eighty-one percent of the patients had at least one lymph node removed, and the sentinel lymph node correctly identified 40 of 47 patients with nodal metastases. The false-negative rate was 15 %; however, when applying the described algorithm to these patients, the false-negative rate was decreased to 2 %. The authors concluded that satisfactory sentinel lymph node mapping for endometrial cancer requires the use of a sentinel lymph node mapping algorithm in which side-specific lymphadenectomy is performed when a sentinel lymph node is not identified. The use of this algorithm does not appear to compromise the detection rate of lymph node metastases. In a retrospective study of 507 patients, Leitao et al. [41] demonstrated that the incorporation of the described sentinel lymph node mapping algorithm resulted in a decreased nodal count while maintaining the same detection rate of lymph node metastases.

Different techniques have been described for sentinel lymph node mapping in endometrial cancer. There have been three injection sites described for sentinel lymph node mapping in

endometrial cancer. A cervical, a subserosal/myometrial, and a hysteroscopic endometrial injection have all been described. A cervical injection appears to be the easiest and most convenient technique; however, some have questioned its accuracy. Abu-Rustum et al. [42] compared the sentinel lymph node detection of a subserosal and cervical injection with a cervical-alone injection, and found comparable rates. Newer techniques of sentinel lymph node mapping, such as the use of near infrared imaging with indocyanine green, appear to yield higher rates of detection and bilateral mapping compared with blue dye alone or in combination with technetium [43].

Surgery is the mainstay treatment of this disease. Yet, surgeons specifically trained for the surgical management of this disease, gynecologic oncologists, are only involved in the care of 40 % of women with this disease [44]. Thus, a significant portion of patients diagnosed with endometrial cancer will not have appropriate surgery, as gynecologic oncologists are 2.5 times more likely to perform complete surgical staging compared with general obstetrician/gynecologists [44]. Such figures have led the Society of Gynecologic Oncology (SGO) to issue statements advising that patients with a primary diagnosis of endometrial cancer or recurrent disease be referred to a gynecologic oncologist to assist in determining the most appropriate surgical approach as well as extent of surgery and the potential benefits of adjuvant therapy [45].

Laparoscopic Surgery and Endometrial Cancer

Minimally invasive surgery has been incorporated into the management of gynecologic malignancies. Vaginal hysterectomy has been used in the management of endometrial cancers in certain situations [46]. However, the vaginal route does not allow for the evaluation of the peritoneal cavity or the retroperitoneal lymph nodes. With the development of improved instruments and surgeon skill, laparoscopic surgeons began to perform more complicated procedures, including sampling of the retroperitoneal lymph nodes.

Childers et al. [47] first reported on the combined use of laparoscopy with vaginal hysterectomy for the treatment of early-stage endometrial cancer. This group later reported on a series of 59 patients with clinical stage I endometrial cancer who were staged by this new procedure. Their technique included an inspection of the peritoneal cavity, intraperitoneal washings, and a laparoscopically assisted vaginal hysterectomy (LVAH). Patients with preoperative grade 2 or 3 tumors or grade 1 tumors with > 50 % myometrial invasion underwent laparoscopic pelvic and para-aortic lymphadenectomy. Six patients had intraperitoneal disease. Two patients could not undergo laparoscopic lymphadenectomy secondary to obesity, and two patients required conversion to laparotomy for intraoperative complications.

Advances in minimally invasive surgical techniques have allowed the use of laparoscopy in endometrial cancer surgery. Many studies have described the use of a combined laparoscopic and vaginal approach to perform all of the procedures involved in endometrial cancer staging, including a complete assessment of peritoneal surfaces and retroperitoneum [48–51]. Total laparoscopic hysterectomy (TLH) has also been well described as a technique that eliminates the need for vaginal surgery during the procedure [52].

Despite many early reports of the potential benefits of laparoscopy, it was only recently that the GOG LAP 2 trial established this as a standard approach to the management of early-stage endometrial cancer. In their initial report, Walker et al. [53] reported the initial findings of 2616 patients who were enrolled in this large randomized multi-institutional study. Patients were randomly assigned to laparoscopy or open surgery including hysterectomy salpingo-oophorectomy, pelvic cytology, and pelvic and para-aortic lymphadenectomy. In the trial, 1682 patients were assigned to laparoscopic surgery, and 1248 (74.2 %) had their surgery completed without conversion to laparotomy. Laparoscopy

resulted in fewer moderate-to-severe postoperative adverse events compared with open surgery. Hospitalization was also shorter. Although there was a larger number of patients in the laparoscopic arm who did not have an adequate number of pelvic and para-aortic nodes removed (8 % in the laparoscopic arm vs. 4 % in the laparotomy arm, $p < 0.0001$), there was no difference in the detection of advanced-stage disease. The authors concluded that laparoscopic surgical staging was feasible and safe, with fewer complications and shorter hospital stay. The oncologic outcomes were recently reported. With a median follow-up of 59 months, the 3-year recurrence rates were comparable among the two arms (11.4 % with laparoscopy and 10.2 % with laparotomy). The estimated 5-year overall survival was 89.8 % in both arms [54]. These results and the improved quality of life demonstrated with laparoscopy [55] help support the acceptance of laparoscopy in the management of early-stage endometrial cancer.

A robotic platform for performing minimally invasive surgery has made a significant impact on the management of patients with early-stage endometrial cancer. Robotically assisted surgery has allowed surgeons to overcome many of the technical difficulties associated with traditional laparoscopy, such as lack of depth perception, two-dimensional optics, and limited range of motion. The learning curve for robotic hysterectomy and lymphadenectomy is faster compared with that of laparoscopic hysterectomy and lymphadenectomy, with comparable adequacy of surgical staging between the two techniques. Several surveys of the SGO demonstrated an increasing trend in the use of laparoscopy for the management of endometrial cancer over an 8-year period. In 2004, 10 % of respondents identified endometrial cancer surgery as the most commonly performed laparoscopic procedure compared with 70 % of respondents in 2012. Much of this may be related to the increase in use of robotic surgery, which increased from 29 % in 2007 to 97 % in 2012 among respondents [56–58].

Gaia et al. [59] performed a systematic review of eight studies with 1591 patients who underwent surgical staging for endometrial cancer (robotic, 589; laparoscopic, 396; and laparotomy, 606). The pooled mean number of aortic and pelvic lymph nodes was similar when comparing the robotic approach to laparotomy and the robotic approach to laparoscopy. Estimated blood loss was less with robotic hysterectomy compared with laparoscopy and laparotomy. Robotic and laparoscopic surgery were associated with a shorter length of stay but longer operative time compared with laparotomy. The authors concluded that perioperative outcomes were similar for the robotic and laparoscopic approach. The robotic approach had the lowest blood loss.

This may also be accomplished with decreased pain requirements. In a retrospective study of 475 patients with endometrial cancer who underwent robotic or laparoscopic surgery, the robotic approach was associated with a significantly lower total dose of fentanyl used [60]. In a time of cost containment in medicine, robotic surgery may also be attractive. Leitao et al. conducted a cost analysis of three surgical approaches (laparoscopy, robotic, and laparotomy) of patients with endometrial cancer over a 2-year period. Although laparoscopic surgery was associated with the lowest cost compared with the robotic and open approaches, the non-amortized cost was comparable between laparoscopy and the robotic platform after the initial learning period. The authors saw a shift from laparotomy to robotic surgery during their study period, leading them to conclude that there is cost neutralization with the robot when it helps to decrease laparotomy rates [61].

Surgery for Stage II Disease

Extrafascial hysterectomy is usually employed in the surgical management of endometrial cancer. However, when there is known or suspected cervical involvement, radical hysterectomy can be used to effectively control local disease. In a retrospective series of 202 patients with cervical involvement from endometrial cancer, Boente et al. [62] defined five treatment groups: radical

hysterectomy ± radiation, TAH/BSO, radiation therapy alone, radiation therapy followed by TAH/BSO, and TAH/BSO followed by radiation therapy. Despite having more frequent adverse prognostic factors, patients treated with radical hysterectomy had an 86 % 5-year actuarial survival rate. This was in contrast to 5-year survival rates of 38 % and 19 % in the radiation group followed by TAH/BSO and TAH/BSO ± radiotherapy groups, respectively. Although formal statistical comparisons were not made, the authors supported the use of radical hysterectomy in patients with stage II endometrial cancer.

Improved outcomes with radical hysterectomy were described by Mariani et al. [63] in a review of 82 patients with cervical involvement. Although this study included both stage II and III patients, a subgroup analysis of only patients with stage II disease treated with radical hysterectomy demonstrated superior results. Both disease-related and recurrence-free survival rates were 100 % in patients treated with radical hysterectomy compared with 80 % and 73 %, respectively, in patients treated with simple hysterectomy. Thus, treatment of patients that have known cervical extension using radical hysterectomy appears to be a reasonable approach.

Surgery in the Morbidly Obese Patient

Obesity is a major risk factor for the development of endometrial cancer, and many patients will present with a high body mass index (BMI) (also described as Quetelet Index [QI]). Patients classified as morbidly obese can be technically challenging to surgically manage. This subclassification of patients may comprise over one-quarter of patients with endometrial cancer [64]. These patients require longer operating times and experience greater blood loss when compared with patients with BMIs $< 30\ kg/m^2$. However, hospital stay and perioperative complications do not appear to be increased.

Consideration may be given to performing a panniculectomy in these patients. In a retrospective series of patients undergoing panniculectomy for endometrial neoplasms, the procedure was associated with a higher para-aortic node count compared with that of matched controls [65]. The procedure was not associated with an increase in perioperative morbidity. Although pelvic node count was not higher, the authors suggested that panniculectomy may enhance operative exposure and facilitate the staging procedure.

While technically challenging, obesity may not be an absolute contraindication to performing a laparoscopic staging procedure. Scribner et al. [66] reported on their experience of laparoscopic pelvic and para-aortic lymphadenectomy in obese patients. In 55 patients, laparoscopic staging was completed in 82 % of those with a QI < 35 compared with only 44 % of those with a QI ≥ 35 ($p = 0.004$). Despite this difference, these authors and others concluded that obesity is not an absolute contraindication to laparoscopic staging [67, 68]. Robotic surgery may expand the role of minimally invasive surgery in this patient population. In a study of obese and morbidly obese patients with endometrial cancer, Gerhig et al. [69] demonstrated that the use of robotic surgery in this population was associated with shorter operative times, reduced blood loss, and a shorter hospital stay compared with traditional laparoscopy. Similarly, Seamon et al. [70] concluded that robotic hysterectomy and lymphadenectomy for endometrial cancer could be performed in heavier patients compared to laparoscopy, with shorter operating room times and hospital stay, decreased transfusion rates, and fewer conversions to laparotomy.

Conclusions

- Early-stage endometrial cancer is surgically treated, yielding valuable information for diagnostic and therapeutic purposes.
- The potential variability between preoperative and final histologic grade, depth of invasion, and other prognostic factors mandates that surgical staging be performed in the majority of patients with early-stage cancer.
- A sentinel lymph node mapping algorithm appears to be a promising approach for staging patients.

- Advances in minimally invasive techniques, skills, and instrumentation offer many potential benefits to patients undergoing surgical management. Some anatomic barriers, however, such as large fibroid uteri, are contraindications to laparoscopic surgery in the presence of endometrial cancer.
- The equivalency of outcome with the abdominal approach, when applying such laparoscopic procedures, has been demonstrated by the Gynecologic Oncology Group. The laparoscopic approach is associated with improved patient satisfaction, decreased morbidity, and comparable survival, and should be considered the main treatment option in patients with early-stage endometrial cancer.
- The introduction of a robotic platform has expanded the role of minimally invasive surgery and may be particularly helpful in the obese patient population.

References

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
2. Kurman RJ, Zaino RJ, Norris HJ. Endometrial carcinoma. In: Kurman RJ, editor. Blaustein's pathology of the female genital tract. 4th ed. New York, NY: Springer; 1994. p. 439–86.
3. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol. 2014;15(7):e268–78.
4. Sood AK, Buller RE, Burger RA, Dawson JD, Sorosky JI, Berman M. Value of preoperative CA 125 level in the management of uterine cancer and prediction of clinical outcome. Obstet Gynecol. 1997;90(3):441–7.
5. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. Cancer. 1987;60 (8 Suppl):2035–41.
6. Mariani A, Dowdy SC, Keeney GL, Long HJ, Lesnick TG, Podratz KC. High-risk endometrial cancer subgroups: candidates for target-based adjuvant therapy. Gynecol Oncol. 2004;95:120–6.
7. Obermair A, Geramou M, Gucer F, et al. Endometrial cancer: accuracy of the finding of a well differentiated tumor at dilatation and curettage compared to the findings at subsequent hysterectomy. Int J Gynecol Cancer. 1999;9(5):383–6.
8. Daniel AG, Peters 3rd WA. Accuracy of office and operating room curettage in the grading of endometrial carcinoma. Obstet Gynecol. 1988;71(4):612–4.
9. Ben-Shachar I, Pavelka J, Cohn DE, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. Obstet Gynecol. 2005;105 (3):487–93.
10. Larson DM, Johnson KK, Broste SK, Krawisz BR, Kresl JJ. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. Obstet Gynecol. 1995;86 (1):38–42.
11. Goff BA, Rice LW. Assessment of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol. 1990;38(1):46–8.
12. Fanning J, Tsukada Y, Piver MS. Intraoperative frozen section diagnosis of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol. 1990;37(1):47–50.
13. Frumovitz M, Singh DK, Meyer L, et al. Predictors of final histology in patients with endometrial cancer. Gynecol Oncol. 2004;95(3):463–8.
14. Arango HA, Hoffman MS, Roberts WS, DeCesare SL, Fiorica JV, Drake J. Accuracy of lymph node palpation to determine need for lymphadenectomy in gynecologic malignancies. Obstet Gynecol. 2000;95 (4):553–6.
15. Eltabbakh GH. Intraoperative clinical evaluation of lymph nodes in women with gynecologic cancer. Am J Obstet Gynecol. 2001;184(6):1177–81.
16. Girardi F, Petru E, Heydarfadai M, Haas J, Winter R. Pelvic lymphadenectomy in the surgical treatment of endometrial cancer. Gynecol Oncol. 1993;49 (2):177–80.
17. Trimble EL, Kosary C, Park RC. Lymph node sampling and survival in endometrial cancer. Gynecol Oncol. 1998;71(3):340–3.
18. ACOG. Practice bulletin #149. Endometrial cancer. Obstet Gynecol. 2015;125:1006–26.
19. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol. 1995;56(1):29–33.
20. Cragun JM, Havrilesky LJ, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol. 2005;23(16):3668–75.
21. Fanning J, Nanavati PJ, Hilgers RD. Surgical staging and high dose rate brachytherapy for endometrial cancer: limiting external radiotherapy to node-positive tumors. Obstet Gynecol. 1996;87(6):1041–4.
22. Orr Jr JW, Holimon JL, Orr PF. Stage I corpus cancer: is teletherapy necessary? Am J Obstet Gynecol. 1997;176(4):777–88.
23. Larson DM, Broste SK, Krawisz BR. Surgery without radiotherapy for primary treatment of endometrial cancer. Obstet Gynecol. 1998;91(3):355–9.
24. Mohan DS, Samuels MA, Selim MA, et al. Long-term outcomes of therapeutic pelvic lymphadenectomy for

stage I endometrial adenocarcinoma. Gynecol Oncol. 1998;70(2):165–71.
25. Seago DP, Raman A, Lele S. Potential benefit of lymphadenectomy for the treatment of node-negative locally advanced uterine cancers. Gynecol Oncol. 2001;83(2):282–5.
26. Berclaz G, Hanggi W, Kratzer-Berger A, Altermatt HJ, Greiner RH, Dreher E. Lymphadenectomy in high risk endometrial carcinoma stage I and II: no more morbidity and no need for external pelvic radiation. Int J Gynecol Cancer. 1999;9(4):322–8.
27. Yabushita H, Shimazu M, Yamada H, et al. Occult lymph node metastases detected by cytokeratin immunohistochemistry predict recurrence in node-negative endometrial cancer. Gynecol Oncol. 2001;80(2):139–44.
28. Fanning S, Firestein S. Prospective evaluation of the morbidity of complete lymphadenectomy in endometrial cancer. Int J Gynecol Cancer. 1998;8:270–3.
29. Benedetti-Panici P, Maneschi F, Cutillo G, et al. Anatomical and pathological study of retroperitoneal nodes in endometrial cancer. Int J Gynecol Cancer. 1998;8:322–7.
30. Lutman CV, Havrilesky LJ, Cragun JM, et al. Pelvic lymph node count is an important prognostic variable for FIGO stage I and II endometrial carcinoma with high-risk histology. Gynecol Oncol. 2006;102 (1):92–7.
31. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, Angioli R, Tateo S, Mangili G, Katsaros D, Garozzo G, Campagnutta E, Donadello N, Greggi S, Melpignano M, Raspagliesi F, Ragni N, Cormio G, Grassi R, Franchi M, Giannarelli D, Fossati R, Torri V, Amoroso M, Crocè C, Mangioni C. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100(23):1707–16.
32. ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373 (9658):125–36. Erratum in: Lancet. 2009; 373(9677): 1764.
33. Burke TW, Levenback C, Tornos C, Morris M, Wharton JT, Gershenson DM. Intraabdominal lymphatic mapping to direct selective pelvic and paraaortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. Gynecol Oncol. 1996;62(2):169–73.
34. Holub Z, Kliment L, Lukac J, Voracek J. - Laparoscopically-assisted intraoperative lymphatic mapping in endometrial cancer: preliminary results. Eur J Gynaecol Oncol. 2001;22(2):118–21.
35. Pelosi E, Arena V, Baudino B, et al. Pre-operative lymphatic mapping and intra-operative sentinel lymph node detection in early stage endometrial cancer. Nucl Med Commun. 2003;24(9):971–5.
36. Niikura H, Okamura C, Utsunomiya H, et al. Sentinel lymph node detection in patients with endometrial cancer. Gynecol Oncol. 2004;92(2):669–74.
37. Raspagliesi F, Ditto A, Kusamura S, et al. Hysteroscopic injection of tracers in sentinel node detection of endometrial cancer: a feasibility study. Am J Obstet Gynecol. 2004;191(2):435–9.
38. Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, Soslow RA, Dao F, Sonoda Y, Levine DA, Brown CL, Chi DS, Barakat RR, Gemignani ML. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol. 2009;113(2):163–9.
39. Ballester M, Dubernard G, Lécuru F, Heitz D, Mathevet P, Marret H, Querleu D, Golfier F, Leblanc E, Rouzier R, Daraï E. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol. 2011;12 (5):469–76.
40. Barlin JN, Khoury-Collado F, Kim CH, Leitao Jr MM, Chi DS, Sonoda Y, Alektiar K, DeLair DF, Barakat RR, Abu-Rustum NR. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol. 2012;125(3):531–5.
41. Leitao Jr MM, Khoury-Collado F, Gardner G, Sonoda Y, Brown CL, Alektiar KM, Hensley ML, Soslow RA, Barakat RR, Abu-Rustum NR. Impact of incorporating an algorithm that utilizes sentinel lymph node mapping during minimally invasive procedures on the detection of stage IIIC endometrial cancer. Gynecol Oncol. 2013;129(1):38–41.
42. Abu-Rustum NR, Khoury-Collado F, Gemignani ML. Techniques of sentinel lymph node identification for early-stage cervical and uterine cancer. Gynecol Oncol. 2008;111(2 Suppl):S44–50.
43. Jewell EL, Huang JJ, Abu-Rustum NR, Gardner GJ, Brown CL, Sonoda Y, Barakat RR, Levine DA, Leitao Jr MM. Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies. Gynecol Oncol. 2014;133 (2):274–7.
44. Partridge EE, Jessup JM, Donaldson ES, et al. 1996 Patient care evaluation study (PCE) of cancer of the corpus uteri. National cancer database (NCDB), American college of surgery. Gynecol Oncol. 1999;72(3):445.
45. Society of Gynecologic Oncologists. Referral guidelines in gynecologic oncology. Gynecol Oncol. 2000;78:S1–13.
46. Chan JK, Lin YG, Monk BJ, Tewari K, Bloss JD, Berman ML. Vaginal hysterectomy as primary treatment of endometrial cancer in medically compromised women. Obstet Gynecol. 2001;97:707–11.
47. Childers JM, Brzechffa PR, Hatch KD, Surwit EA. Laparoscopically assisted surgical staging (LASS) of endometrial cancer. Gynecol Oncol. 1993;51(1):33–8.

48. Eltabbakh GH, Shamonki MI, Moody JM, Garafano LL. Laparoscopy as the primary modality for the treatment of women with endometrial carcinoma. Cancer. 2001;91(2):378–87.
49. Homesley HD, Boike G, Spiegel GW. Feasibility of laparoscopic management of presumed stage I endometrial carcinoma and assessment of accuracy of myoinvasion estimates by frozen section: a gynecologic oncology group study. Int J Gynecol Cancer. 2004;14(2):341–7.
50. Magriña JF, Mutone NF, Weaver AL, Magtibay PM, Fowler RS, Cornella JL. Laparoscopic lymphadenectomy and vaginal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy for endometrial cancer: morbidity and survival. Am J Obstet Gynecol. 1999;181(2):376–81.
51. Gil-Moreno A, Diaz-Feijoo B, Morchon S, Xercavins J. Analysis of survival after laparoscopic-assisted vaginal hysterectomy compared with the conventional abdominal approach for early-stage endometrial carcinoma: A review of the literature. J Minim Invasive Gynecol. 2006;13(1):26–35.
52. Obermair A, Manolitsas TP, Leung Y, Hammond IG, McCartney AJ. Total laparoscopic hysterectomy for endometrial cancer: patterns of recurrence and survival. Gynecol Oncol. 2004;92(3):789–93.
53. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol. 2009;27:5331–6.
54. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 study. J Clin Oncol. 2012;30:695–700.
55. Kornblith AB, Huang HQ, Walker JL, Spirtos NM, Rotmensch J, Cella D. Quality of life of patients with endometrial cancer undergoing laparoscopic International Federation of Gynecology and Obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. J Clin Oncol. 2009;27:5337–42.
56. Gemignani ML, Curtin JP, Zelmanovich J, Patel DA, Venkatraman E, Barakat RR. Laparoscopic-assisted vaginal hysterectomy for endometrial cancer: clinical outcomes and hospital charges. Gynecol Oncol. 1999;73(1):5–11.
57. Frumovitz M, Ramirez PT, Greer M, Gregurich MA, Wolf J, Bodurka DC, Levenback C. Laparoscopic training and practice in gynecologic oncology among Society of Gynecologic Oncologists members and fellows-in-training. Gynecol Oncol. 2004;94 (3):746–53.
58. Mabrouk M, Frumovitz M, Greer M, Sharma S, Schmeler KM, Soliman PT, Ramirez PT. Trends in laparoscopic and robotic surgery among gynecologic oncologists: A survey update. Gynecol Oncol. 2009;112(3):501–5.
59. Conrad LB, Ramirez PT, Burke W, Naumann RW, Ring KL, Munsell MF, Frumovitz M. Role of minimally invasive surgery in gynecologic oncology: An updated survey of members of the society of gynecologic oncology. Int J Gynecol Cancer. 2015;25 (6):1121–7.
60. Gaia G, Holloway RW, Santoro L, Ahmad S, Di Silverio E, Spinillo A. Robotic-assisted hysterectomy for endometrial cancer compared with traditional laparoscopic and laparotomy approaches: a systematic review. Obstet Gynecol. 2010;116(6):1422–31.
61. Leitao Jr MM, Bartashnik A, Wagner I, et al. Cost-effectiveness analysis of robotically assisted laparoscopy for newly diagnosed uterine cancers. Obstet Gynecol. 2014;123:1031–7.
62. Boente MP, Yordan Jr EL, McIntosh DG, et al. Prognostic factors and long-term survival in endometrial adenocarcinoma with cervical involvement. Gynecol Oncol. 1993;51(3):316–22.
63. Mariani A, Webb MJ, Keeney GL, Calori G, Podratz KC. Role of wide/radical hysterectomy and pelvic lymph node dissection in endometrial cancer with cervical involvement. Gynecol Oncol. 2001;83 (1):72–80.
64. Everett E, Tamimi H, Greer B, et al. The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol. 2003;90(1):150–7.
65. Wright JD, Powell MA, Herzog TJ, et al. Panniculectomy: improving lymph node yield in morbidly obese patients with endometrial neoplasms. Gynecol Oncol. 2004;94(2):436–41.
66. Scribner Jr DR, Walker JL, Johnson GA, McMeekin DS, Gold MA, Mannel RS. Laparoscopic pelvic and paraaortic lymph node dissection in the obese. Gynecol Oncol. 2002;84(3):426–30.
67. Obermair A, Manolitsas TP, Leung Y, Hammond IG, McCartney AJ. Total laparoscopic hysterectomy versus total abdominal hysterectomy for obese women with endometrial cancer. Int J Gynecol Cancer. 2005;15(2):319–24.
68. Kohler C, Klemm P, Schau A, et al. Introduction of transperitoneal lymphadenectomy in a gynecologic center: analysis of 650 laparoscopic pelvic and paraaortic transperitoneal lymphadenectomies. Gynecol Oncol. 2004;95(1):52–61.
69. Gehrig PA, Cantrell LA, Shafer A, Abaid LN, Mendivil A, Boggess JF. What is the optimal minimally invasive surgical procedure for endometrial cancer staging in the obese and morbidly obese woman? Gynecol Oncol. 2008;111:41–5.
70. Seamon LG, Bryant SA, Rheaume PS, Kimball KJ, Huh WK, Fowler JM, Phillips GS, Cohn DE. Comprehensive surgical staging for endometrial cancer in obese patients. Obstet Gynecol. 2009;114:16–21.

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Early-Stage Endometrial Cancer: Radiation—Less May Be More

Onyinye Balogun, Stella Lymberis, and Peter B. Schiff

Abstract

Due to its documented efficacy in improving locoregional control and reducing rates of vaginal vault recurrence, radiation therapy has been used as an adjunct to surgical intervention for the last 5 decades. Several randomized studies have established the role of adjuvant radiotherapy in decreasing local recurrence among patients at intermediate to high risk of local failure. External beam radiotherapy achieves local control at the cost of some morbidity but does not influence overall survival. Intracavitary brachytherapy has emerged as an alternative to external beam radiotherapy due to its overall lower morbidity. Trials are ongoing to determine the potential added benefit of chemotherapy to radiation therapy as well as to explore lower brachytherapy doses in early stage disease. For management of high risk, more advanced stage disease and carcinosarcoma, please see Chaps. 10, 11, and 13, respectively.

Keywords

Endometrial cancer • Brachytherapy • External beam radiotherapy

Introduction

In the USA, endometrial cancer (EC) is the most common gynecologic malignancy and the fifth most common malignancy overall [1]. Seventy percent of patients have localized disease, heralded by the clinical presentation of abnormal vaginal bleeding in 75–90 % of women [2, 3]. Radiotherapy (RT) has been used as an adjunct to surgical intervention for the last 5 decades, following seminal reports of improved locoregional control and reduced rates of vaginal recurrence. The type and extent of RT used is based on the estimated risk of locoregional recurrence and it ranges from a brief course of vaginal intracavitary brachytherapy (VBT), whole pelvic external beam radiotherapy (WP EBRT), or a combination of both. The role of adjuvant RT in the treatment of

O. Balogun, S. Lymberis, and P.B. Schiff (✉)
Department of Radiation Oncology, Laura and Isaac Perlmutter Cancer Center, NYU School of Medicine, NYU Langone Medical Center, New York, NY, USA
e-mail: peter.schiff@nyumc.org

patients in low- or intermediate-risk groups has been established through multiple randomized controlled trials that demonstrate similar gains in local control though they do not reveal improvement in overall survival. However, issues such as when to select WP EBRT rather than VBT or when to combine both modalities are still being debated.

Definition of Low, Intermediate, High-Intermediate and High Risk

Women with Stage I EC are considered to be at low risk of recurrence if surgicopathologic staging reveals a grade 1–2 tumor, with <50 % myometrial invasion or a grade 3 tumor with no myometrial invasion (stage IA per 2009 FIGO staging system[1]) [4]. Additionally, the tumor has to be confined to the uterine fundus with no evidence of lymphovascular involvement (LVSI) or lymph node involvement. Women are considered to be at intermediate risk for disease recurrence if diagnosed with a grade 1–2 EC with invasion >50 % of the myometrial thickness (stage IB per 2009 FIGO Staging system) or with disease extension to the cervix (stage II per 2009 FIGO staging system). Additionally, no evidence of distant metastases is required to be included in the intermediate-risk subset. High risk patients include women with Stage III disease or those with serous or clear cell uterine carcinoma at any stage.

Of note, two different definitions for high-intermediate risk emerged from randomized trials. The Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial identified three risk factors: age ≥60 years, grade 3 disease, and deep myometrial invasion [5]. Patients with two or more of these risk factors were considered at high-intermediate risk of recurrence. The randomized trial conducted by the Gynecologic Oncology Group, GOG-99, also identified a high-intermediate risk subgroup [6]. In this trial, patients with grade 2 or 3 disease, lymphovascular invasion, and outer third myometrial invasion were classified as high-intermediate risk. Also, women who were 50 or older with two of the aforementioned risk factors or at least 70 years old with any one of the risk factors were considered high-intermediate risk.

Conservative Management

The locoregional relapse rate found in the control arm of prospective studies evaluating adjuvant therapy for early-stage EC ranges from 14 % in trials without surgical staging [5] to 7 % in those requiring surgical staging [6]. Two-thirds of the recurrences involve the vagina and specifically the vaginal vault. However, distant relapse rates are similar, regardless of the extent of lymph node dissection, with 7 % in the absence of surgical staging and 8 % following surgical staging. While the salvage rate of isolated vaginal recurrence in previously unirradiated patients ranges from 40 to 81 %, the salvage rate after a pelvic or distant relapse is dismal [5, 7–10].

Pelvic lymph node metastases are found in clinical Stage I grades 1, 2, and 3 EC in 2.8 %, 8.7 %, and 18.3 % of women, respectively. The risk of aortic lymph node involvement is reported to be 1.6 %, 4.9 %, and 11.1 %, respectively [11]. Some authors recommend routine lymph node sampling in patients with clinical low- or intermediate-risk early-stage disease due to reports of significant rates of both histologic and stage upgrades [11–13]. Mariani et al. reported on 328 patients with clinical low-risk EC (endometrioid histology, stages IA–IB, and grades 1–2). One hundred and eighty-seven patients were assessed for pelvic

[1] The staging in this chapter reflects the 1988 FIGO staging system unless otherwise noted. However, it is important to know that the following changes were made in the 2009 FIGO staging system: (1) Stage IC was eliminated. Stage IA now represents <50 % myometrial invasion and Stage IB represents ≥50 % myometrial invasion. (2) The designations, Stage IIA and IIB were eliminated. Stage II now represents cervical stromal invasion. (3) Peritoneal washings are no longer factored into disease staging. Stage IIIC disease now consists of Stage IIIC1 (pelvic lymph node involvement) and IIIC2 (para-aortic lymph node involvement).

node involvement by either sampling or full dissection, with nine patients diagnosed with positive nodes (5 %), all of them with tumors >2 cm in diameter. Twenty-three women out of 308 were assessed for peritoneal cytology and 23 had positive cytology (7 %). Altogether, 10 % of patients were upgraded to Stage III disease following surgical staging [13].

A complete surgical staging results in significant upstaging of clinical stage II patients as well. Creasman et al. analyzed 148 patients with clinical stage II accrued to Gynecologic Oncology Group (GOG) clinical trials that underwent surgical staging. Only 66 (45 %) patients were found to have pathologic involvement of the cervix. However, 31 of 66 (46 %) were found to have extrauterine disease with lymph node or adnexal involvement; therefore, the patients were upstaged to Stage III [11].

Straughn et al. reported on 617 women treated with surgery alone for early-stage EC (14). All women underwent complete surgical Staging including peritoneal cytology, bilateral pelvic lymphadenectomy, and para-aortic lymphadenectomy. No recurrences were reported in women with Stage IA, grades 1–2 tumors. In the 296 patients with Stage IB, grades 1–2 EC, 11 recurrences were recorded. Five of them were in patients with adenosquamous carcinomas. In the six patients with endometrioid EC, four had vaginal recurrence, one had distant metastases, and one was diagnosed with both vaginal and distant relapses. Other surgical series have reported vaginal failure rates of 1–3 % and recurrence rates of 4–7 % (15–17). Kilgore et al. found that patients undergoing multiple-site pelvic node sampling had significantly better survival than patients without node sampling ($p = 0.0002$). Sampling conveyed a survival advantage even in patients categorized as low risk defined as carrier of EC confined to the corpus ($p = 0.026$) and the effect persisted even in the absence of adjuvant radiation (17).

Adjuvant Radiotherapy

The value of adjuvant RT after surgical treatment of early-stage EC was initially evaluated in several retrospective series and in two population-based analyses from the National Cancer Institute of Surveillance, Epidemiology, and End Results (SEER) database and the American College of Surgeons National Cancer Database [14, 15]. While most series suggested an improvement in locoregional control, a survival benefit was not evident. Such retrospective analyses are obviously greatly limited by selection biases (preferential assignment of patients with high-risk features to adjuvant radiation), inconsistent surgical staging (lymph node sampling versus formal dissection, with or without peritoneal washing), and the use of a variety of radiation regimens and modalities.

Adjuvant Pelvic External Beam Radiotherapy

Four large prospective randomized trials have shed light on the effect of adjuvant pelvic external beam radiation. The multicenter prospective clinical trial—Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) I evaluated the benefit of adjuvant radiation in Stage I EC (4). A total of 715 patients were accrued and randomized to postoperative 46 Gy of pelvic EBRT in 23 fractions or no further treatment. Eligible patients included those with Stage IB, grade 2–3 disease or IC grade 1–2 disease. Patients with Stage IB grade 1 or IC grade 3 disease were excluded as their recurrence risk was considered too low or too high, respectively. Patients underwent TAH-BSO without lymph node sampling or dissection. Following a median follow-up of 52 months, 714 patients were evaluated. The 5-year actuarial locoregional recurrence rates were 4 % in the treatment arm and 14 % in the control arm ($p < 0.001$). Actuarial 5-year overall survival rates were not statistically different being 81 % in the treatment arm and 85 % in the control arm ($p = 0.31$). Endometrial cancer specific death rates were 9 % in the radiation arm and 6 % in the control arm ($p = 0.37$). Twenty-five percent of the patients in the radiation arm experienced late treatment-related complications of which two-thirds were grade 1. Eight patients

experienced grade 3–4 complications, seven of them in the treatment arm. Multivariate analysis showed that for locoregional recurrence, RT and age <60 years were statistically significant favorable prognostic factors. With long-term follow-up, the locoregional control continued to be better with pelvic EBRT. The 15-year locoregional recurrence rates were 5.8 % for pelvic EBRT compared to 15.5 % for the control arm ($p < 0.001$) [16]. Overall survival remained similar at 52 % for pelvic EBRT versus 60 % for the control arm.

In GOG 99, a randomized trial comparing adjuvant pelvic EBRT (50.4 Gy in 28 fractions) to no additional therapy, 392 women underwent surgical staging with TAH-BSO, peritoneal cytology, and bilateral pelvic and para-aortic lymphadenectomy [6]. While the study was aimed at patients with intermediate risk of recurrence, two-thirds of the patients accrued were actually at low-risk (58.9 % stage IB, >70 % grades 1–2, 75 % with endometrioid histology, and most patients with myometrial invasion < inner two-thirds) with only a 6 % recurrence rate in the control arm. The relative hazard reduction following pelvic EBRT was similar in the intermediate-risk group and the low-risk group (58 % and 54 %, respectively), but the absolute difference was more pronounced in the higher risk group (recurrence rate reduced from 27 to 13 % in the higher risk group versus 6 to 2 % in the low risk group). No survival difference was detected. It is worth noting that grade 3–4 gastrointestinal complications were more common in the pelvic EBRT arm in this study than other studies utilizing similar radiation regimens, 8 % in the GOG 99 versus 3 % in the PORTEC trial [5], arguably due to the extensive node dissection. In addition, the Norwegian trial assessed the role of pelvic EBRT, after initial intracavitary brachytherapy [17]. Aalders et al. reported on 540 patients with surgical stage IB-IC EC that underwent TAH-BSO. Postoperatively, all patients were treated with vaginal brachytherapy (VBT), delivering 60 Gy to the surface of the vaginal mucosa. Subsequently, patients were randomized to no further treatment or to an additional 40 Gy to the pelvis by EBRT. A significant reduction in locoregional recurrence was observed, 1.9 % in the BT plus EBRT arm compared with 6.9 % in BT only arm ($p < 0.01$). No improvement was documented in survival (5-year survival 89 % vs. 91 % and 9-year survival 87 % vs. 90 %, respectively). An unplanned subset analysis demonstrated that EBRT conferred a clear benefit in the IC Grade 3 subgroup of patients, resulting in a reduction in both local recurrence (4.5 % vs. 19.6 %) and cancer-specific death (18.2 % vs. 27.5 %).

Finally, the MRC ASTEC—EN5 trial randomized 906 patients to observation or adjuvant pelvic EBRT with doses ranging from 40 to 46 Gy [18]. Eligible patients had Stage IA-IB grade 3, Stage IC grades 1–3, Stage IIA, papillary serous or clear cell disease. Half of the patients (52 %) received VBT. Thirty percent of patients underwent lymph node dissection. Five year overall survival was 84 % for both arms and there was no difference in disease-specific survival. There was a statistically significant though small difference in isolated vaginal or pelvic recurrence (6.1 % in the observation group and 3.2 % in the pelvic EBRT group, $p = 0.02$).

These four randomized trials consistently demonstrate improvement in local control with EBRT among women at intermediate or high risk of recurrence. However, the degree of absolute benefit varies among these studies.

Adjuvant Chemoradiotherapy

A few randomized phase III trials have attempted to define the benefit of combining chemotherapy with adjuvant RT in early stage endometrial cancer. The NSGO EC-9501/EORTC-55991 randomized 383 patients with stages I–IIIC EC to receive either pelvic EBRT (≥44 Gy) or radiation therapy administered before or after chemotherapy [19]. All patients underwent TAH-BSO with optional lymphadenectomy. The majority of the cohort (91 %) had Stage I disease. The most common chemotherapy regimen (83 % of patients) consisted of 4 cycles of doxorubicin/epirubicin and cisplatin every 4 weeks. Other regimens included paclitaxel,

carboplatin, and epirubicin or doxorubicin every 3 weeks or paclitaxel and carboplatin every 3 weeks. While 95 % of the patients received ≥44 Gy, only 73 % of patients randomized to the chemoradiation therapy arm received 4 chemotherapy cycles as planned. Vaginal brachytherapy was optional and 157 patients (42 %) received it. At 5 years, chemoradiation therapy improved progression-free survival (85 % vs. 76 %, $p = 0.04$) and cause-specific survival (90 % vs. 82 %, $p = 0.02$). Overall survival was not different (79 % vs. 85 %). Of note, subset analysis revealed that patients with serous and clear cell carcinoma (140 patients) did not derive cause-specific, progression-free, or overall survival benefit.

The Gynecologic Oncology Group (GOG) 249 trial also compared vaginal cuff brachytherapy (VBT) followed by paclitaxel and carboplatin chemotherapy to whole pelvic radiation therapy (WPRT) in women with high-intermediate-risk, early stage endometrial cancer who had undergone hysterectomy [20]. Eligible patients had Stage I endometrioid disease that met GOG 99 based high-intermediate risk criteria (grade 2 or 3 disease, lymphovascular invasion, and outer third myometrial invasion), Stage II disease, or Stage I–II serous (S) or clear cell (CC) tumors. Patients were assigned to either WPRT using standard four-field or IMRT techniques or VBT using HDR or LDR followed by paclitaxel 175 mg/m2 (3 h) + carboplatin AUC 6 every 21 days for a total of 3 cycles. Additional VBT was optional for patients with S/CC tumors or stage II disease randomized to the WPRT arm. An early report of this randomized phase III trial was presented at the 2014 Society of Gynecologic Oncology meeting. Among 601 patients accrued, 74 % had Stage I disease and 71 % had endometrioid type cancer. Treatment was generally well tolerated with 91 % of WPRT patients and 87 % of VBT patients completing therapy. Acute toxicity was more common on the VBT arm. With a median follow-up of 2 years, recurrence-free survival was 82 % and 84 % in the WPRT arm and the VBT arm, respectively (HR 0.97). Recurrence sites for the WPRT vs. VBT arms were 5 vs. 3 (vaginal), 2 vs. 19 (pelvic), and 32 vs. 34 (distant). Two-year overall survival was 93 % in the WPRT group and 92 % in the VBT group (HR 1.28). At this time, VBT followed by chemotherapy does not improve recurrence-free survival compared to WPRT. Long-term follow-up is needed to determine the relative contribution of chemotherapy as well as to determine the late effects of WPRT and VBT with chemotherapy.

The ongoing PORTEC-3 trial also aims to elucidate the benefit of chemoradiation therapy over radiation therapy alone in endometrial cancer patients. All patients will receive pelvic EBRT (48.6 Gy in 1.8 Gy fractions) and brachytherapy boost will also be given to those patients with evidence of cervical invasion. Unlike NSGO EC-9501/EORTC-55991, a standardized chemotherapy regimen of 2 cycles of cisplatin concurrent with EBRT followed by 4 adjuvant cycles of carboplatin/paclitaxel will be employed for those patients randomized to the concurrent and adjuvant chemotherapy arm. Eligible patients include those with Stage (1) IB Grade 3 and LVSI, (2) IC or IIA Grade 3, (3) IIB, (4) IIIA or IIIC, or (5) Stages IB-III and serous or clear cell histology. The primary endpoints are 5 year overall survival and failure-free survival. Toxicity and quality of life will also be investigated.

NRG Oncology/RTOG 0921 trial also investigated adjuvant chemoradiotherapy in high-risk endometrial cancer patients [21]. In this prospective Phase II study, women with one or more of the following risk factors: grade 3 with >50 % myometrial invasion, grade 2 or 3 with any cervical stromal invasion or known extrauterine extension limited to the pelvis, were treated with postoperative pelvic intensity-modulated radiotherapy (IMRT) with concurrent cisplatin and bevacizumab followed by carboplatin and paclitaxel for 4 cycles [21]. A total of 30 patients received treatment on study. Sixty percent had endometrioid histology while 40 % had papillary serous or clear cell adenocarcinoma. Six patients (20 %) had Stage II adenocarcinoma while the majority 19 patients (63.6 %) had FIGO Stage III disease. With a 2-year overall survival rate of 96.7 % and a

disease-free survival rate of 79.1 %, this approach seems promising for patients with high-risk endometrial carcinoma.

Adjuvant Brachytherapy

Although pelvic EBRT prevents local recurrence, this treatment increases the risk of adverse side effects, particularly gastrointestinal complications. Several single-institution studies have explored the use of intracavitary BT to prevent the more common vaginal failure while minimizing the risk of treatment-related toxicity (28–30). In a prospective series, Eltabbakh et al. reported on 303 low-risk patients (Stages IA-IB, Grades 1–2) treated with postoperative VBT (30 Gy to 0.5 cm depth using low-dose rate brachytherapy) [22]. With a follow-up of 8.1 years, no vaginal recurrences had occurred and the 10-year disease-free survival was 97.8 %. All of the six patients with distant relapse died of disease (1.8 %).

Similarly, Alektiar et al. reported on 382 Stage IB-IIB patients treated with postoperative high-dose rate (HDR) BT [23]. The median dose was 21 Gy (range 6–21 Gy) delivered in three fractions. Comprehensive surgical staging with lymph node sampling and peritoneal washing was performed in only 20 % of the patients. The indications for surgical staging were based on depth of myometrial invasion and tumor grade. With a median follow-up of 48 months, the 5-year local control rate was 95 % with a minimal incidence of grade 3–4 complications (1 %). The 5-year disease-specific survival rate was 97 %. Pearcey et al. reviewed 13 publications on HDR BT in low- to intermediate-risk EC [24]. The vaginal control rates ranged from 98 to 100 % corresponding to a reduction in relative risk of recurrence of 80–85 %.

PORTEC-2, a multicenter randomized phase III trial, compared EBRT alone versus VBT alone in patients with one of the following combinations of postoperative FIGO stage and age: (1) stage IC, grade 1 or 2 and age $\geq$60; (2) stage IB, grade 3 and age 60 or over; (3) stage IIA, any age, grade 1 or 2; (4) stage IIA, any age, grade 3 with $<$50 % myometrial invasion [25]. The prescribed EBRT dose was 46 Gy in 2-Gy daily fractions while VBT was delivered to the upper half of the vagina using either HDR (21 Gy in 3 weekly fractions) or LDR (30 Gy in one session). Ultimately, there was no difference in 5-year vaginal recurrence rates (1.6 % after EBRT vs. 1.8 % after VBT), 5-year locoregional recurrence (2.1 % after EBRT vs. 5.1 % after VBT) or 5-year overall survival (79.6 % after EBRT vs. 84.8 % after VBT). There was a higher rate of pelvic recurrence after VBT (0.5 % vs. 3.8 %, $p = 0.02$) and most patients with pelvic recurrence had simultaneous distant disease. Although patients treated with pelvic EBRT had a lower rate of pelvic recurrence, the absolute rate of pelvic recurrence was low in the VBT arm likely due to the fact that most of the patients enrolled on the trial (79 %) on central pathology review had grade 1 disease. In addition, very few patients were included with deeply invasive ($>$50 %) grade 2 disease and none with minimally invasive grade 3 disease. As a result, this study does not provide evidence for using vaginal cuff brachytherapy in place of pelvic radiation for patients with deeply invasive grade 2 and minimally invasive grade 3 disease.

The results of the ongoing PORTEC-4 trial will shed light on whether the dose of VBT can be reduced. The inclusion criteria are similar to those for patients enrolled in the PORTEC-2 trial. Eligible patients will be randomized to observation or one of two vaginal brachytherapy regimens (7 Gy $\times$ 3 or 5 Gy $\times$ 3 prescribed to 5 mm depth).

Sequelae of Radiotherapy

External Beam Radiotherapy to the Pelvis

Acutely, pelvic irradiation may cause self-limiting diarrhea, cystitis, and abdominal bloating. In the PORTEC 1 trial, 63 % of patients received medication or implemented dietary changes due to treatment-related symptoms [5]. However, only seven patients (2 %)

experienced acute complications that led to early termination of radiation therapy after doses ranging from 10 to 44 Gy. One of these was a grade 4 complication in a patient who had Crohn's disease and died of this illness 1 month later. Late toxicities are mostly related to small bowel adhesions and/or obstruction (a result of combined treatment with surgery and RT), proctitis, and cystitis. The overall rate of late complications reported in the PORTEC 1 trial was 25 % in the irradiated group as compared to 6 % in the control group ($p < 0.0001$) [5]. While the majority of complications were Grade 1 (68 %), seven patients (2 %) experienced grade 3 toxicity, all GI related and requiring surgical intervention [26].

Unfortunately, bowel and urinary symptoms may persist over a decade after treatment is completed. At 15 years, patients who received EBRT on the PORTEC 1 trial reported higher rates of urinary incontinence, diarrhea and fecal leakage. In addition, urinary and bowel symptoms significantly limited these patients' daily activities. Of note, there was no difference in sexual functioning, vaginal symptoms, or body image between the groups [16].

Additional complications of external beam radiotherapy to the pelvis include hematologic toxicity as well as pelvic insufficiency fractures. In a cohort of cervical and endometrial cancer patients treated at Memorial Sloan Kettering [27], the risk of pelvic insufficiency fractures (PIF) after postoperative pelvic radiotherapy was 5 % at 5 years. The most frequent site of fracture was the sacro-iliac joint (68 %), followed by pubic bone (18.5 %). Treatment in this study was observation in 6/11 (55 %), bisphosphonate in 4 (36 %), and surgery (L5 vertebroplasty) in 1 (9 %). At the time of last follow-up, 10 of 11 patients (91 %) were asymptomatic.

The risk of developing a second radiation-related malignancy has long been of concern especially among younger patients. However, a recent meta-analysis of the PORTEC-1, PORTEC-2, and Total Mesorectal Excision trials did not reveal an increased probability of developing a second cancer among patients who received radiation therapy compared to those who were on the control arms and did not receive radiation therapy [28]. The 10-year rate of second cancer was 15.8 % for those treated without RT, 15.4 % for those treated with EBRT and 14.9 % for those who received VBT. As expected, there was an increased risk of developing a second cancer compared to the general populace.

Vaginal Brachytherapy

Vaginal brachytherapy enables the delivery of high doses of RT to the vagina while sparing nearby normal structures such as the bowel and bladder. This feature of VBT translates into a low rate (0–1 %) of Grade 3 or higher long-term sequelae [23, 29–31]. Yet vaginal stenosis is a long-term side effect of vaginal HDR with reported frequencies as high as 15 % [32].

As expected in the PORTEC-2 trial, Grade 1–2 GI side effects were higher after treatment among patients who received EBRT (53.8 % vs. 12.6 %) but by 24 months, this difference was no longer statistically significant. Late grade 3 GI side effects requiring surgery developed in 4 patients on the EBRT arm (2 %) compared to one patient (<1 %) on the VBT arm. There were no treatment-related deaths. On the other hand, Grade 1–2 vaginal mucosal atrophy was increased among women who received VBT. This difference was detectable within 6 months after ending treatment (12.8 % vs. 25.2 %) and persisted after 3 years of follow-up (17.2 % vs. 35.2 %). Grade 3 atrophy was present in one patient who received EBRT (<1 %) and four (2 %) who received VBT.

Quality of life assessment revealed that women who received VBT on the PORTEC-2 trial reported less diarrhea (12.8 % vs. 5.6 %) and fecal leakage (8.7 % vs. 1.7 %) 2 years after treatment [33]. As a result, EBRT patients experienced greater limitation in their daily activities due to bowel symptoms and worse social functioning. There was higher urinary urgency among those who received EBRT (34.3 % vs. 28.3 % at 2 years). Interestingly, sexual

symptoms were not significantly different between the two groups.

Despite low rates of severe complications with VBT, a radiation oncologist should carefully select dose per fraction, prescription point, length of vagina irradiated, and the diameter of the vaginal cylinder utilized since these factors can all affect the risk of side effects.

High Dose Rate Brachytherapy

Brachytherapy, traditionally delivered by low-dose rate (LDR) techniques, is increasingly being replaced worldwide by high-dose rate (HDR) techniques. HDR offers several advantages over LDR BT, especially in the treatment of EC, including minimization of radiation exposure of the professional staff, elimination of hospitalization, anesthesia and bed immobilization that can lead to thromboembolism, and minimization of patient discomfort. A report by Orton et al. suggested a radiobiologic advantage to HDR owing to the slow repair of late-responding normal tissue [34]. The two intracavitary radiation techniques were compared in three retrospective studies [35–37]. In a large review, Fayed et al. reported on 1179 patients with stages I–III ECs treated with postoperative brachytherapy [36]. Approximately 1004 patients were treated with LDR, 695 diagnosed with stage I disease (69.2 %). One hundred and seventy-five patients were treated with HDR, 74 with stage I (42.3 %), 47 with stage II (26.8 %), and 54 with stage III tumors (30.9 %). The median follow-up was 50 months in the LDR group and 28 months in the HDR group. Overall survival for all stages at 5 years was 70 % in the LDR group and 68 % in the HDR group ($p = 0.44$). Subgroup analysis revealed statistically significant differences only in the stage II patients subset. The actuarial overall survival at 5 years for patients with stage II EC was 53 % in the LDR group and 74 % in the HDR group ($p = 0.026$) and the actuarial 5-year disease-free survival of stage II patients was 50 % for the LDR group and 75 % for the HDR group ($p = 0.009$). Actuarial 5-year local control for stage II patients was 65 % in the LDR group and 90 % in the HDR group ($p = 0.016$), with the rate of grade 3–4 complications being comparable in both LDR and HDR.

Compelled by the lack of standardized treatment recommendations, a panel of the ABS members with clinical experience in HDR endometrial BT performed a literature review, supplemented their clinical experience with biomathematical modeling, and formulated recommendations for HDR-BT for EC [38]. They included intravaginal BT typically delivered about 4–6 weeks postoperatively or a week after completion of EBRT and administered in three fractions every 1–2 weeks. In 2005, an American Brachytherapy Society (ABS) survey regarding practice patterns of postoperative irradiation of EC reported that HDR had become an increasingly popular method with 69 % of respondents employing HDR [39]. The most common fractionation was 5 Gy × 3 prescribed to 5 mm depth when used in conjunction with EBRT (43.3 %) or 7 Gy × 3 prescribed to 5 mm depth without EBRT (42.1 %). An update reporting practice patterns in 2014 revealed that 98 % of respondents delivered HDR while only 2 % utilized LDR [40]. The most common prescription continued to be 7 Gy × 3 fractions (64 %). If combined with EBRT, the most common prescriptions were 5.0–5.5 Gy × 3 fractions (55 %) to 0.5 cm depth and 6 Gy × 3 fractions (39 %) to the surface. In addition, 47 % delivered 2 fractions per week while 36 % delivered 1 per week and 17 % delivered 3 or more per week.

Selection of High-Dose Rate Applicators

Cylinders

Selection of HDR applicators largely depends on patient anatomy. Postoperatively, the vagina displays a cylindrical shape and can be adequately treated by a vaginal cylinder. Since

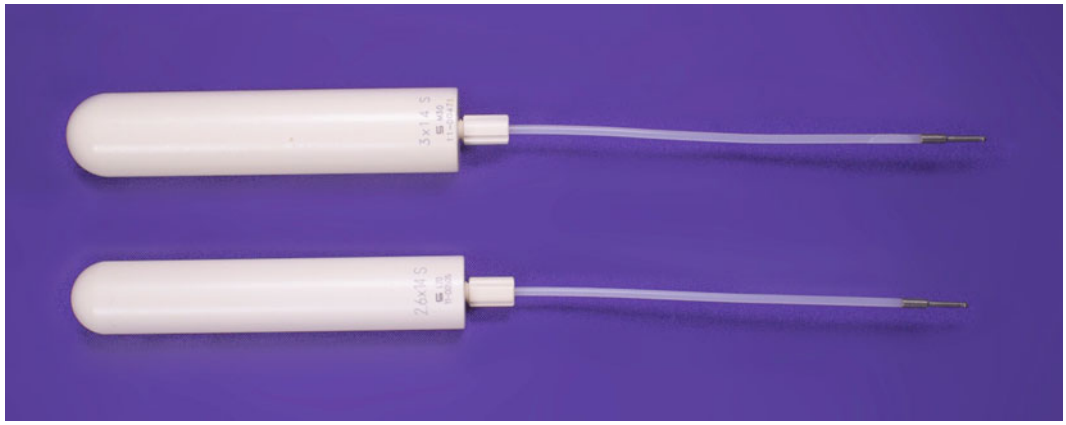

Fig. 1 Stump vaginal cylinders of various diameters used in brachytherapy. Pictured are 3.0 and 2.6 cm diameter cylinders

Fig. 2 Multichannel applicator for intravaginal brachytherapy, Capri^{TM} multichannel applicator

cylinders are available in various lengths, they can treat not only the vaginal cuff but also the entire vaginal canal, including the introitus, if necessary. Furthermore, due to the range of diameters (1.5–4.0 cm, Fig. 1), vaginal cylinders can accommodate a narrow as well as a wide vaginal canal. The disadvantage of the use of vaginal cylinders is delivery of higher doses to the bladder and rectum for a given vaginal dose.

Other varieties of vaginal cylinders exist including shielded models that selectively decrease the absorbed dose to adjacent normal structures. ABS deems the choice of applicators to be a personal and institutional preference as long as the desired segment of vagina is adequately covered with radiation [38].

Multi-channel Applicator Brachytherapy

The vagina or vaginal cuff is usually treated with a rigid intracavitary single-channel (SC) cylinder, which produces a radial homogeneous dose. However, there are other variations to this construct such as a multichannel (MC) vaginal applicator (Fig. 2). Modulation of dwell times at various positions along the channels can decrease the dose delivered to the bladder and rectum while covering the vaginal apex [41, 42]. A recent dosimetric study compared MC with SC applicators and demonstrated similar tumor coverage, however, there was a statistically significant dose reduction to the bladder and rectum in favor of the MC applicator at 5 mm prescription depth [43]. Despite

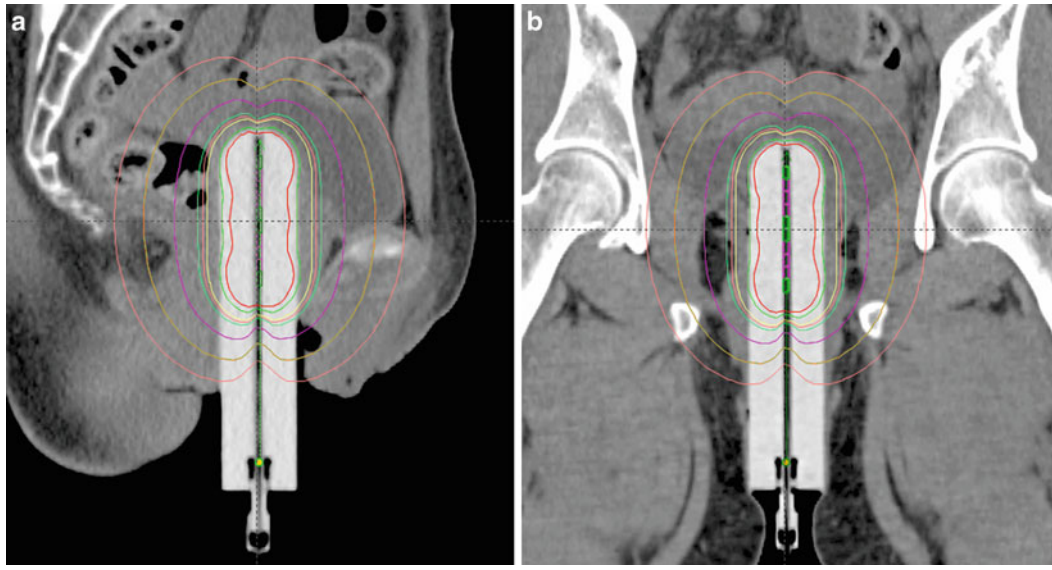

Fig. 3 Sagittal (**a**) and coronal (**b**) slices of the isodose distribution of vaginal cylinder brachytherapy treatment using Ir-192 HDR treating upper vaginal canal 700 cGy (100 % isodose shown in *yellow*) prescribed to 0.5 cm vaginal depth for 3 weekly fractions

demonstration of superior dosimetry with the use of MC applicators with respect to tumor coverage and decreased dose to the bladder and rectum, SC applicators are more commonly used due to decreased cost, ease of use, and availability [41, 43, 44].

The first clinical implementation of the newly FDA approved Capri^{TM} multichannel applicator (Fig. 2) in five patients demonstrated reduced rectal dose and suggested usefulness for covering vaginal disease [45].

Brachytherapy Treatment Principles

Upon insertion of the vaginal cylinder, it is imperative for the vaginal mucosa to be in contact with the applicator surface to achieve the desired dose distribution (Fig. 3). The ABS recommends the use of the largest diameter cylinder that can comfortably fit in the vagina. To minimize dose exposure to bladder and bowel, simulation and treatment should be performed with a full bladder. The applicator should be positioned in the midline of the patient and secured with an external immobilizing device to minimize movement between planning and treatment.

External Beam Radiotherapy to the Pelvis Whole Pelvic RT (WPRT)

With no evidence of gross residual disease after hysterectomy, the majority of patients are treated with adjuvant EBRT to the pelvis to encompass areas at risk: pelvic lymph node stations (lower common iliac, external, and internal) and proximal two-thirds of the vagina.

3D-Conformal Radiation Therapy (3D-CRT)

A conventional four-field pelvic box technique (Fig. 4) is employed along with the use of high-energy linear accelerators to deliver the designated therapy. The use of multiple fields and higher energy photons allows normal tissue sparing and reduction in radiation-related complications [46]. Conventional techniques for WPRT involve four static photon fields. These techniques expose

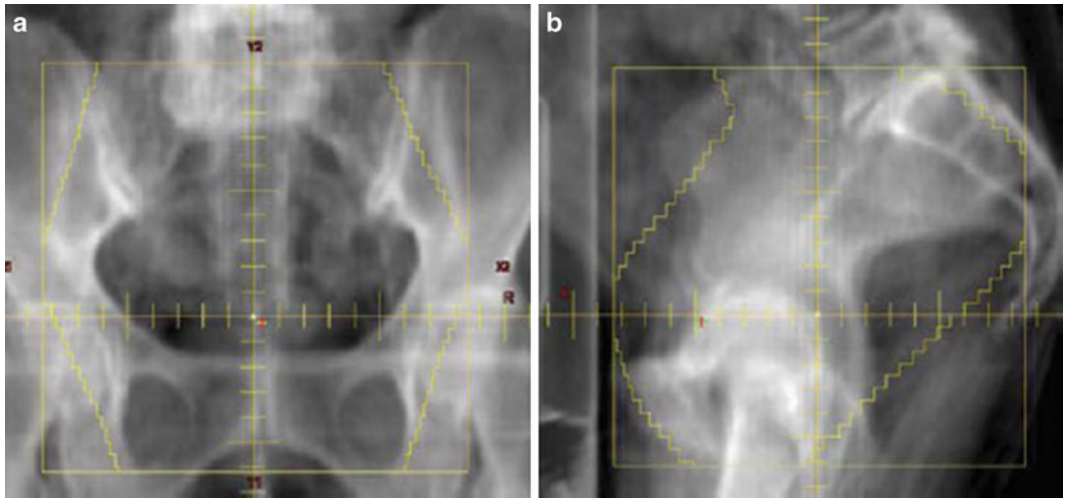

Fig. 4 Images of anterior–posterior (**a**) and lateral radiation portals (**b**) of a patient treated with external beam radiotherapy for endometrial cancer

most of the contents of the true pelvis, including the small bowel, to the prescribed dose. Even with modest doses of radiation (45–50 Gy), the risk of long-term severe complication rates associated with pelvic radiation following hysterectomy range between 2 and 5 %, with reduced toxicity using modern radiotherapeutic techniques [5, 46–48]. All fields are treated daily with a minimum dose of 1.8 Gy to the target. When EBRT is used alone, a total dose of 50.4 is typically used, but when used in combination with intravaginal BT, it is lowered to 45 Gy.

Intensity Modulated Radiation Therapy (IMRT)

Pelvic EBRT was usually delivered using two or four-field plans with uniform intensity across the field. Over time, intensity modulated radiation therapy (IMRT) gained popularity due to its ability to deliver highly conformal therapy with non-uniform beam intensities and decrease irradiation of normal organs. However, with the use of IMRT, it became increasingly important to accurately delineate the clinical target volume (CTV). The Radiation Therapy Oncology Group published guidelines for defining the CTV in postoperative endometrial cancer patients [49]. According to this publication, the CTV should include the common, external, and internal iliac LN regions by contouring the common, external, and internal iliac vessels then adding a 7 mm margin. In patients with cervical stromal invasion, the CTV should also include presacral lymph nodes. The upper 3 cm of vagina and parametrial soft tissue are also part of the CTV. The RTOG guidelines suggest that the vaginal/parametrial CTV be outlined on CT scans obtained with a full and empty bladder. These two vaginal/parametrial CTVs should then be merged to form an internal target volume (ITV) that accounts for daily variation in the location of the vaginal cuff due to differences in bladder filling. However, rather than obtain 2 CT scans, many radiation oncologists use daily image-guided RT to account for the variation in bladder filling.

The superior border of the CTV should begin 7 mm below the L4-L5 interspace and the inferior border should extend 3 cm below the upper extent of the vagina or 1 cm above the inferior extent of the obturator foramen, whichever is lower. The rectum, bladder, bone, muscle, bowel, and the vertebral bodies should not be included in the CTV. A 1.0–1.5 cm expansion to the planning target volume is considered acceptable.

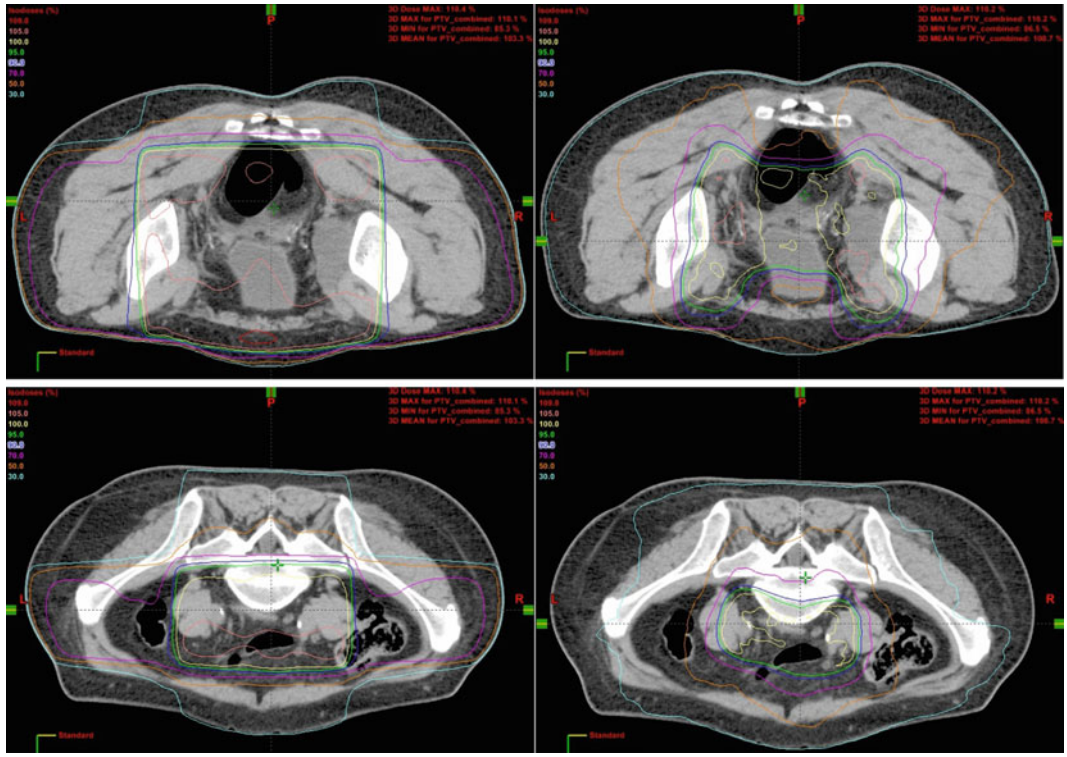

Fig. 5 Axial CT images with isodose distributions for conventional four-field (*left*) and IMRT (*right*) plans. The 50 % (*orange*), 70 % (*pink*), and 100 % (*yellow*) isodose lines are shown. Courtesy of NYU Department of Radiation Oncology [53]

Shih KK et al. reported on a single institution series of 46 patients with high-risk endometrial cancer (22 % stage I/II and 78 % stage III) treated with postoperative IMRT with or without chemotherapy [50]. Simulation and treatment was in the supine position. Lymphatic contouring was performed according to the RTOG consensus guidelines. Contrast was used to better visualize the vaginal cuff contour, which is expanded initially by 2 cm to generate the "vaginal cuff CTV," and then an additional 1 cm expansion is applied to create the "vaginal cuff PTV." The 2 cm expansion to create the vaginal cuff CTV was based on data showing that the position of the vagina could shift by as much as 2 cm simply with variations in bladder filling [51]. With median follow-up of 52 months, DFS and OS rates were >88 % and toxicity was minimal.

Several studies have reported that compared to conventional 3D conformal radiation therapy, IMRT reduces the volume of normal tissues irradiated (Fig. 5). A comparison of four-field box and seven-field IMRT plans in ten patients at the University of Pittsburgh demonstrated a 52 % reduction in the volume of small bowel receiving >30 Gy [52]. In addition, there was a 66 % and 36 % reduction in the volume of rectum and bladder receiving >30 Gy, respectively. Similarly, in a report from Roeske et al. [53], ten patients (five with Stages IC-IIB endometrial cancer, five with Stages IB-IIB cervical cancer) underwent a planning CT scan and two different plans were created. The nine-field IMRT plan halved the average volume of small bowel irradiated (17.4 % vs. 33.8 %). In addition, IMRT reduced the average volume of rectum and bladder receiving 45 Gy by 23 %.

A Phase II trial, RTOG 0418, explored the feasibility of pelvic IMRT in endometrial cancer patients across multiple institutions and assessed

the short-term bowel adverse events [54]. Eligible patients had undergone surgical staging and had Stage IB grade 3, Stage IC grade 1–3, Stage IIA, IIB, or IIIC disease. Forty-four percent of the patients had Stage IC, grade 1–3 disease and 45 % had Stage IIA or IIB disease. The prescribed dose was 50.4 Gy to the vaginal and nodal PTVs. Fifty-eight patients from 25 institutions were enrolled with 43 patients available for analysis. Each participating institution was pre-approved to deliver IMRT and the first case had to be submitted for review. Forty-two of forty-three (98 %) patients had acceptable IMRT plans. Twelve patients (28 %) developed grade $\geq$2 bowel adverse events within 90 days after treatment initiation compared with an approximated rate of 40 % rate of such events in a historical cohort treated with 3D-CRT static field whole pelvic RT ($p = 0.12$). Sample size for this study did not provide sufficient power to detect a 12 % difference in grade $\geq$2 bowel adverse events, however, there was a clinical reduction in acute bowel toxicities. Only 3 patients (7 %) experienced a grade 3 short-term gastrointestinal adverse event and 7.2 % developed late grade 2+ GI toxicity.

An ongoing randomized trial, RTOG 1203 (TIME-C), aims to determine the effect of normal tissue sparing on acute and chronic toxicity in women who require pelvic EBRT. Patients with FIGO 2009 Stage IB grade 3, Stage II any grade and Stage IIIC1 disease have been randomized to receive IMRT or four-field pelvic radiation therapy with or without weekly cisplatin chemotherapy. The prescribed dose is 45 or 50.4 Gy. This head-to-head comparison of IMRT and four-field pelvic radiation therapy will reveal the extent to which IMRT impacts bowel, bladder, and hematologic toxicity.

Guidelines

The American Society for Radiation Oncology evidence-based guidelines for the role of postoperative radiation therapy for endometrial cancer was published in 2014 in Practical Radiation Oncology [55]. These guidelines were subsequently reviewed by an ASCO Endorsement Panel and published in the Journal of Clinical Oncology in July 2015 with ASCO largely endorsing the recommendations with several qualifying statements on the role of chemotherapy [56].

A summary of their recommendations is as follows:

1. Surveillance without adjuvant radiation therapy is a reasonable option for women without residual disease in the hysterectomy specimen and for women with grade 1 or 2 cancer and <50 % myometrial invasion, especially when no other high-risk features are present.
2. Vaginal brachytherapy is as effective as pelvic radiation therapy at preventing vaginal recurrence and is preferred for women with grade 1 or 2 cancer and $\geq$50 % myometrial invasion or grade 3 cancer and <50 % myometrial invasion.
3. To prevent pelvic recurrence, patients with grade 3 cancer and $\geq$50 % myometrial invasion or cervical stroma invasion may benefit from pelvic radiation.
4. In women with high-risk early-stage disease and advanced disease, the ASCO Endorsement Panel added qualifying statements to the ASTRO recommendations to provide stronger statements in favor of chemotherapy (with or without radiation therapy) listed in the Table 1 using bold lettering.

Conclusions

- Current treatment of early-stage endometrial cancer with radiation is based on surgicopathologic risk factors such as stage, grade, age, tumor size and location, and the presence of lymphovascular space involvement.
- Vaginal brachytherapy is often used for stage IA tumors in the presence of adverse factors such as high grade, age >60 years, lower uterine segment involvement, or

Table 1 ASTRO recommendations for the Role of Postoperative Radiation therapy for Endometrial Cancer are listed in table below, with qualifying statements added by the ASCO panel listed in **bold** [55, 56]

Which patients with endometrioid endometrial cancer require no additional therapy after hysterectomy? • Following total abdominal hysterectomy with or without node dissection, no radiation therapy is a reasonable option for patients without residual disease in the hysterectomy specimen, despite positive biopsy (**despite a positive prehysterectomy biopsy of any grade**). • Following total abdominal hysterectomy with or without node dissection, no radiation therapy is a reasonable option for patients with grade 1 or 2 cancers with either no invasion or <50 % myometrial invasion.
Which patients with endometrioid endometrial cancer should receive vaginal cuff irradiation? • Vaginal cuff brachytherapy is as effective as pelvic radiation at preventing vaginal recurrence for patients with: (1) grade 1 or 2 tumors with 50 % myometrial invasion or (2) grade 3 tumors with <50 % myometrial invasion. • Vaginal cuff brachytherapy is preferred to pelvic radiation in patients with the above risk factors, particularly in patients who have had comprehensive nodal assessment.
Which women should receive postoperative external beam radiation? • Patients with grade 3 cancer with ≥50 % myometrial invasion or cervical stroma invasion of any grade may benefit from pelvic radiation to reduce the risk of pelvic recurrence. • Patients with grade 1 or 2 tumors with ≥50 % myometrial invasion may also benefit from pelvic radiation to reduce pelvic recurrence if other risk factors are present, such as age >60 years and/or LVSI. **Vaginal brachytherapy may be a better option for patients with these features, especially if surgical staging was adequate, and nodes were negative**. • The best available evidence at this time suggests that reasonable options for adjuvant treatment of patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum include external beam radiation therapy, as well as adjuvant chemotherapy. **The best evidence for this population supports the use of chemotherapy, but consideration of external beam radiation therapy is reasonable.** • Chemotherapy without external beam radiation may be considered for some patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum based on pathologic risk factors for pelvic recurrence. • Radiation therapy without chemotherapy may be considered for some patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum based on pathologic risk factors for pelvic recurrence. **Patients receiving chemotherapy seem to have improved survival compared with radiation therapy alone** [19].
When should brachytherapy be used in addition to external beam radiation? • Prospective data are lacking to validate the use of vaginal brachytherapy after pelvic radiation, and most retrospective studies show no evidence of a benefit, albeit with small patient numbers. Use of vaginal brachytherapy in patients also undergoing pelvic external beam radiation is not generally warranted, unless risk factors for vaginal recurrence are present.
How should radiation therapy and chemotherapy be integrated in the management of stage I to III endometrioid endometrial cancer? • The best available evidence suggests that concurrent chemoradiation followed by adjuvant chemotherapy is indicated for patients with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum. **Evidence regarding concurrent chemoradiation is limited at this time, and this recommendation is based on expert opinion; we anticipate level-one evidence from upcoming prospective randomized clinical trials (GOG 0258 and PORTEC-3). Chemotherapy may also be considered in certain patients with high-risk early-stage endometrial cancer, and clinical trials addressing this question are under way**. • Alternative sequencing strategies with external beam radiation and chemotherapy are also acceptable. **Prospective trials have examined sequential radiation therapy and chemotherapy. Evidence supporting sandwich-type therapy is currently limited.**

presence of lymphovascular space involvement.

- Whole pelvic radiation therapy is usually omitted in these IA patients because its morbidity outweighs any possible benefit with relatively low risk of recurrence.
- In stage IB patients, vaginal brachytherapy is the suggested treatment, with whole pelvic radiation therapy being considered in patients with adverse factors.
- Whole pelvic radiation therapy with or without vaginal brachytherapy is recommended in most patients with stages IC (with grade 3 and/or other adverse factors) to IIB since this treatment results in a significant reduction of recurrence rates.

- Future clinical trials need to address the relative benefit of these treatments in combination with chemotherapy in subsets of patients using clearly defined modern prognostication parameters and surgical staging.

References

1. Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst. 2015;107(6):djv048.
2. Kimura T, et al. Abnormal uterine bleeding and prognosis of endometrial cancer. Int J Gynaecol Obstet. 2004;85(2):145–50.
3. Seebacher V, et al. The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. BMC Cancer. 2009;9:460.
4. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet. 2009;105 (2):109.
5. Creutzberg CL, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355(9213):1404–11.
6. Keys HM, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(3):744–51.
7. Huh WK, et al. Salvage of isolated vaginal recurrences in women with surgical stage I endometrial cancer: a multiinstitutional experience. Int J Gynecol Cancer. 2007;17(4):886–9.
8. Jereczek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy. Int J Radiat Oncol Biol Phys. 2000;48(2):405–13.
9. Nag S, et al. Interstitial brachytherapy for salvage treatment of vaginal recurrences in previously unirradiated endometrial cancer patients. Int J Radiat Oncol Biol Phys. 2002;54(4):1153–9.
10. Petignat P, et al. Salvage treatment with high-dose-rate brachytherapy for isolated vaginal endometrial cancer recurrence. Gynecol Oncol. 2006;101 (3):445–9.
11. Creasman WT, et al. Significance of true surgical pathologic staging: a Gynecologic Oncology Group Study. Am J Obstet Gynecol. 1999;181(1):31–4.
12. Ben-Shachar I, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. Obstet Gynecol. 2005;105(3):487–93.
13. Mariani A, et al. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol. 2000;182(6):1506–19.
14. Lee CM, et al. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. JAMA. 2006;295(4):389–97.
15. Straughn Jr JM, et al. The use of adjuvant radiation therapy in patients with intermediate-risk Stages IC and II uterine corpus cancer: a patient care evaluation study from the American College of Surgeons National Cancer Data Base. Gynecol Oncol. 2005;99 (3):530–5.
16. Nout RA, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol. 2011;29(13):1692–700.
17. Aalders J, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980;56(4):419–27.
18. ASTEC/EN.5 Study Group, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet. 2009;373 (9658):137–46.
19. Hogberg T, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer. 2010;46 (13):2422–31.
20. McMeekin DS, Filiaci VL, Aghajanian C. A randomized Phase III trial of pelvic radiation therapy (WPRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): a Gyencologic Oncology Group trial. In Society of Gynecologic Oncology Annual Meeting. 2014. Tampa, FL.
21. Viswanathan AN, et al. NRG Oncology/RTOG 0921: A phase 2 study of postoperative intensity-modulated radiotherapy with concurrent cisplatin and bevacizumab followed by carboplatin and paclitaxel for patients with endometrial cancer. Cancer. 2015;121(13):2156–63.
22. Eltabbakh GH, et al. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. Int J Radiat Oncol Biol Phys. 1997;38 (2):373–80.
23. Alektiar KM, et al. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys. 2005;62(1):111–7.

24. Pearcey RG, Petereit DG. Post-operative high dose rate brachytherapy in patients with low to intermediate risk endometrial cancer. Radiother Oncol. 2000;56 (1):17–22.
25. Nout RA, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010;375(9717):816–23.
26. Creutzberg CL, et al. The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys. 2001;51(5):1246–55.
27. Shih KK, et al. Pelvic insufficiency fractures in patients with cervical and endometrial cancer treated with postoperative pelvic radiation. Gynecol Oncol. 2013;128(3):540–3.
28. Wiltink LM, et al. No increased risk of second cancer after radiotherapy in patients treated for rectal or endometrial cancer in the randomized TME, PORTEC-1, and PORTEC-2 trials. J Clin Oncol. 2015;33(15):1640–6.
29. Alektiar KM, et al. Intravaginal high-dose-rate brachytherapy for Stage IB (FIGO Grade 1, 2) endometrial cancer. Int J Radiat Oncol Biol Phys. 2002;53 (3):707–13.
30. Horowitz NS, et al. Adjuvant high dose rate vaginal brachytherapy as treatment of stage I and II endometrial carcinoma. Obstet Gynecol. 2002;99(2):235–40.
31. Petereit DG, et al. Outpatient vaginal cuff brachytherapy for endometrial cancer. Int J Gynecol Cancer. 1999;9(6):456–62.
32. Sorbe BG, Smeds AC. Postoperative vaginal irradiation with high dose rate afterloading technique in endometrial carcinoma stage I. Int J Radiat Oncol Biol Phys. 1990;18(2):305–14.
33. Nout RA, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol. 2009;27(21):3547–56.
34. Orton CG. High-dose-rate brachytherapy may be radiobiologically superior to low-dose rate due to slow repair of late-responding normal tissue cells. Int J Radiat Oncol Biol Phys. 2001;49(1):183–9.
35. Bekerus M, et al. Comparison of HDR and LDR results in endometrium cancer. Sonderb Strahlenther Onkol. 1988;82:222–7.
36. Fayed A, et al. Comparison of high-dose-rate and low-dose-rate brachytherapy in the treatment of endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2007;67 (2):480–4.
37. Rauthe G, Vahrson H, Giers G. Five-year results and complications in endometrium cancer: HDR afterloading vs. conventional radium therapy. Sonderb Strahlenther Onkol. 1988;82:240–5.
38. Nag S, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. Int J Radiat Oncol Biol Phys. 2000;48(3):779–90.
39. Small Jr W, Erickson B, Kwakwa F. American Brachytherapy Society survey regarding practice patterns of postoperative irradiation for endometrial cancer: current status of vaginal brachytherapy. Int J Radiat Oncol Biol Phys. 2005;63(5):1502–7.
40. Harkenrider MM. Preliminary Results of the American Brachytherapy Society Survey of Practice Patterns for Vaginal Brachytherapy for Postoperative Endometrial Cancer in ASTRO. 2014. San Francisco, CA.
41. Demanes DJ, et al. The use and advantages of a multichannel vaginal cylinder in high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys. 1999;44(1):211–9.
42. Maruyama Y, Ezzell G, Porter AT. Afterloading high dose rate intracavitary vaginal cylinder. Int J Radiat Oncol Biol Phys. 1994;30(2):473–6.
43. Park SJ, et al. Dosimetric comparison of 3-dimensional planning techniques using an intravaginal multichannel balloon applicator for high-dose-rate gynecologic brachytherapy. Int J Radiat Oncol Biol Phys. 2013;87(4):840–6.
44. Tanderup K, Lindegaard JC. Multi-channel intracavitary vaginal brachytherapy using three-dimensional optimization of source geometry. Radiother Oncol. 2004;70(1):81–5.
45. Gloi AM. First clinical implementation of the Capri applicator. J Appl Clin Med Phys. 2014;15(1):4581.
46. Corn BW, et al. Impact of improved irradiation technique, age, and lymph node sampling on the severe complication rate of surgically staged endometrial cancer patients: a multivariate analysis. J Clin Oncol. 1994;12(3):510–5.
47. Algan O, et al. Improved outcome in patients treated with postoperative radiation therapy for pathologic stage I/II endometrial cancer. Int J Radiat Oncol Biol Phys. 1996;35(5):925–33.
48. Carey MS, et al. Good outcome associated with a standardized treatment protocol using selective postoperative radiation in patients with clinical stage I adenocarcinoma of the endometrium. Gynecol Oncol. 1995;57(2):138–44.
49. Small Jr W, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71(2):428–34.
50. Shih KK, et al. Postoperative pelvic intensity-modulated radiotherapy in high risk endometrial cancer. Gynecol Oncol. 2013;128(3):535–9.
51. Jhingran A, et al. Vaginal motion and bladder and rectal volumes during pelvic intensity-modulated radiation therapy after hysterectomy. Int J Radiat Oncol Biol Phys. 2012;82(1):256–62.
52. Heron DE, et al. Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms. Gynecol Oncol. 2003;91(1):39–45.
53. Roeske JC, et al. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2000;48 (5):1613–21.

54. Jhingran A, et al. A phase II study of intensity modulated radiation therapy to the pelvis for postoperative patients with endometrial carcinoma: radiation therapy oncology group trial 0418. Int J Radiat Oncol Biol Phys. 2012;84(1):e23–8.
55. Klopp A, et al. The role of postoperative radiation therapy for endometrial cancer: executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol. 2014;4(3):137–44.
56. Meyer LA, et al. Postoperative radiation therapy for endometrial cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. J Clin Oncol. 2015;33(26):2908–13.

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Therapeutic Modalities in Early-Stage Uterine Papillary Serous Carcinomas, Carcinosarcomas, Clear-Cell and Mixed Histology Carcinomas: Treatment of Choice Is Combined Chemotherapy and Radiation

Laura M. Divine and Matthew A. Powell

Abstract

The entities covered in this chapter are uterine serous carcinoma (USC), carcinosarcoma, and clear-cell carcinoma together with tumors of mixed histology. Overall, these represent 3–10 % of all endometrial cancers but they are responsible for a significant percentage of endometrial cancer mortality. Recent strides in chemotherapy for some of these cancers offer hope that their addition, either alone or as a part of combined modality treatment including radiation, will lead to improvements in survival.

Keywords

Uterine serous • Carcinosarcoma • Clear cell • Chemotherapy • Chemoradiation

Introduction

Endometrial cancer is the most common gynecologic malignancy being responsible for more than 10,000 deaths in 2015 in the USA [1]. The high-risk histologic subtypes of endometrial cancer, carcinosarcoma, uterine serous carcinoma (USC), and clear-cell carcinoma individually represent 3–10 % of all cancers of the uterine corpus. Although rare, these subtypes have a high risk of local and distant recurrence even when diagnosed at an early stage. Hamilton and colleagues compared 4180 cases of high-risk endometrial carcinoma subtypes. USC and clear cell carcinoma accounted for 10 and 3 % of all endometrial carcinomas, respectively; however, they accounted for 39 and 8 % of all cancer deaths [2]. Treatment schemes for early stage (FIGO I and II), high-risk histologic subtypes of endometrial cancer are variable and include radiotherapy, chemotherapy, or a combination of both. This chapter focuses on therapy for FIGO stage I and II uterine carcinosarcomas, USC, clear-cell and mixed histology carcinomas. Given the low frequency of these malignancies, current treatment recommendations are based largely on multiple retrospective series. There is clearly an ongoing need for randomized controlled

L.M. Divine and M.A. Powell (✉)
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO, USA
e-mail: mpowell@wustl.edu

therapeutic trials for early stage, high-risk histology carcinomas of the uterine corpus.

Uterine Serous Carcinoma

Epidemiology and Natural History

Papillary serous carcinoma was first described as a distinct pathologic entity by two different groups in 1982 [3, 4]. It represents approximately 5–10 % of all endometrial cancers [2, 5–7]. Histologically, it resembles serous carcinoma of the ovary and fallopian tube and behaves like them as it commonly spreads to peritoneal surfaces. In one of the original reports, the relapse rate among stage I tumors was 50 % [4]. Table 1 summarizes the most common clinical findings. The median age at diagnosis is 67 years [5, 7, 8], older than the median age (63 years) of endometrioid endometrial cancer [2, 9]. USC appears to occur more frequently in African American women compared to other ethnicities; in a study by Cirisano et al., the rate of USC was significantly more common in African American compared to Caucasian subjects (34 % vs. 15 %, $P < 0.001$) [7]. Postmenopausal bleeding is the most common presenting symptom, occurring in up to 80 % of patients [5, 10]. Preoperative endometrial sampling demonstrates a serous component in 50–89 % of cases [5, 10–12]. Abnormal cervical cytology (AGUS or worse) is present in approximately 50 % of patients [10, 13]. One study examining all stages of USC found that 13 of 16 (81 %) patients had an elevated serum CA-125 level prior to therapy and that 57 % experienced a reduction or normalization of CA-125 following therapy; however, in another study of 51 patients, only 17 % of patients had an elevated preoperative CA-125 [14, 15]. CA-125 elevation appears to be associated with more advanced stage at diagnosis, positive pelvic node involvement, positive peritoneal washings, and the presence of lymphovascular invasion [16]. A diagnosis of USC should be suspected if >10 % of the preoperative endometrial biopsy specimen contains papillary architecture associated with high-grade cytology. It has been shown that even when 10 % of a mixed tumor contains USC, there is a trend toward decreased overall survival when compared to grade 3 endometrioid adenocarcinomas [17]. While obesity is traditionally considered a risk factor for endometrioid carcinomas, recent studies suggest that obesity is a risk factor for the development of all endometrial carcinomas, including USC [18].

Table 1 Uterine serous carcinoma: Clinical features

Median age at diagnosis = 67 years
More common in African American women
Postmenopausal bleeding common (80 %)
Extrauterine disease at time of presentation (40–70 %)
CA-125 frequently elevated
Endometrial sampling establishes the diagnosis in 50–89 %
AGUS or worse cervical cytology in 50 %

AGUS abnormal glands of undetermined significance

A number of retrospective studies have also suggested an association between USC and breast cancer [19–21]. The evidence is conflicting in regard to the role of tamoxifen in the development of USC [19, 20, 22–28]. Similarly, BRCA1 and BRCA2 mutations have not proved to be strong risk factors for USC, though there is an observed association between USC and breast cancer which may be due to other, yet to be described, cancer predisposing genes [29–34].

As stated previously, USC is a biologically aggressive form of endometrial cancer. It has a different spectrum of genetic alterations than endometrioid-type cancers that contribute to its tumorigenesis. Mutations in p53 and e-cadherin are more common in USC, whereas PTEN inactivation, K-ras mutations, and micro-satellite instability are more common in endometrioid endometrial cancers [35]. HER2/neu overexpression has been reported in 26–62 % of USC and associated with cancer cell proliferation, poor survival, and resistance to therapy [36, 37]. HER2/neu represents a potential target for therapies against USC using antibodies targeting the HER2/neu receptor, such as trastuzumab or pertuzumab. Therapy combining trastuzumab and/or pertuzumab with anti-mTOR, AKT, and/or PIK3CA active agents

may have synergistic activity as HER2/neu is located upstream to the PIK3CA/AKT/mTOR pathway representing possible treatments for USC [38]. It also is unclear whether the expression of HER2/neu or tumoral alterations in the PIK3CA/AKT/mTOR pathway affect recurrence and prognosis in women with early stage USC. The Cancer Genome Atlas Research Network (TCGA) published its findings from the genomic characterization of 373 endometrial carcinomas, which included 66 cases of USC. By unsupervised hierarchical clustering, they found that endometrial carcinomas could be grouped into four distinct clusters. USC (along with a subset of the FIGO grade 3 endometrioid carcinomas) formed a separate cluster which was characterized by a high frequency of TP53 mutations (90 %), fewer PTEN mutations (11 %), and MSI (6 %). This cluster also included other gene amplifications, which included ERBB2, MYC, CCNE1, FGFR3, and SOX17. Tumors in this "serous-like" cluster had a worse progression-free survival than tumors in the endometrioid cluster groups ($P = 0.003$) [39].

Approximately 40–60 % of women with USC will have disease spread outside of the uterus at time of presentation, with extrauterine disease common even in clinical stage I and II [40, 41]. All patients with a suspicion of USC should therefore undergo a surgical staging procedure similar to that employed for early-stage ovarian cancer including TAH, BSO, pelvic and para-aortic lymph node dissection, infracolic omentectomy or omental biopsy, pelvic washings, and diaphragmatic cytology. The additional staging procedures are prognostic but their effect of survival remains unknown. Sentinel lymph node biopsy remains investigational for this high-risk population. Goff et al. reviewed 50 cases of USC and found extrauterine disease in 72 % of them [11]. A large retrospective, single-institution analysis found that among patients without myometrial invasion, 37 % had stage III or IV disease [40]. Chan et al. reported on 12 surgically staged patients (including omentectomy) with USC limited to the endometrium and 50 % were found to have disease outside the uterus (3 of 6 had omental disease). In that series, 1 of 6 (16.7 %) patients with stage IA disease had a distant recurrence [42]. Kato et al. found that when patients had an omentectomy or omental biopsy as part of their initial staging laparotomy, seven of eight (88 %) were positive for malignancy [5]. A similar trend was observed by Cirisano in clinical stage II tumors with 64 % of patients being upstaged at laparotomy [7]. Several series have documented a high frequency of retroperitoneal lymph node involvement ranging from 13 to 33 % [11, 43]. In a prospective randomized controlled trial (ASTEC study), pelvic lymphadenectomy in women with endometrial cancer was not associated with improved survival, but only 4 % of cases had USC and subset analysis was not performed [44]. A study of 84 patients with clinical stage I USC found an overall survival (OS) advantage benefiting women who underwent comprehensive surgical staging compared with those treated only with hysterectomy and bilateral salpingo-oophorectomy (16.4 vs. 2.76 years) [45]. Not surprisingly, one retrospective study identified a 2-year and 5-year overall survival advantage in patients who had complete surgical staging ($N = 21$) versus patients who did not ($N = 17$). The 5-year OS was 95 % in the surgically staged group compared to 45 % in the unstaged group [46].

The contribution of pathologic variables such as lymphovascular space invasion (LVSI), myometrial invasion, and admixture of endometrioid features to overall survival in USC is controversial but are important determinants of the risk of nodal disease. One study of 47 patients found that myometrial invasion, LVSI, or presence of an endometrioid component did not contribute to overall survival [47]. The 5-year overall survival of stage I patients in this series was only 44 %, suggesting that many of these patients were understaged. Goff et al. found that histologic grade and presence of mixed histologic subtypes were not predictive of extrauterine disease [11]. Tumors with LVSI, were more likely to have extrauterine disease (85 %); conversely, even in the absence of LVSI, extrauterine disease was common

(58 %). Kato et al. did not demonstrate an association between myometrial invasion and overall survival, but Slomovitz et al. found that among patients with all stages, LVSI and depth of myometrial invasion were pathologic features that were predictive of overall survival in USC [5, 40]. Another study found that age >60, advanced stage, LVSI, and >50 % myometrial invasion were prognostic factors associated with decreased overall survival [7]. The clinical utility of these pathologic variables has proved to be limited and most patients will need some form of adjuvant therapy [48].

The 5-year overall survival of USC limited to the uterus varies from 34 to 81 % depending on completeness of surgical staging as well as substage [5, 12, 40, 47, 49–51]. In a large, single institution study, the 5-year OS was 81.5 % for patients with stage IA, 58.6 % for stage IB, and 34.3 % for patients with stage IC tumors [40]. In contrast, stage I and II (occult) endometrial adenocarcinomas had 5-year survivals in the 90 % range [52].

One of the contributors to poor overall survival in USC is the high frequency of recurrence in patients with early-stage disease. Recurrence rates in USC limited to the uterus can be as high as 20–50 % [4, 5, 7, 12, 50, 53]. Thus, successful therapy for USC should address both local and distant failures.

Treatment

The aggressive intrinsic biology of USC as well as its high relapse rate in patients with disease clinically (and pathologically) confined to the uterus has led many investigators to suggest the addition of some form of adjuvant therapy regardless of stage. Given the pattern of local as well as distant relapse in stage I and II USC, it appears that combined modality therapy with radiation and chemotherapy would be efficacious. Radiation therapy theoretically would provide local control while chemotherapy would provide distant control. USC has been excluded from most prospective, randomized therapeutic trials of early-stage endometrial cancer because of its uniformly poor prognosis. Therefore, currently, there is a paucity of published randomized-controlled trials demonstrating the efficacy of radiotherapy, chemotherapy, or a combined approach in USC. Additionally, much of the published literature has focused on small numbers of early-stage (I and II) USC and many of these series did not require stringent surgical staging. Therefore, perceived treatment benefits may actually reflect more advanced disease. Despite these limitations, available data reflect a therapeutic benefit to adjuvant treatment in early-stage USC.

Radiotherapy

The role of radiotherapy in controlling local disease and improving overall survival is controversial. The type of treatment modality (whole abdominal radiotherapy, whole pelvic radiation, brachytherapy, or some combination thereof) that is best suited for USC has evolved. For early-stage patients who have had complete surgical staging (TAH, BSO, retroperitoneal lymph node dissection, washings, and omentectomy/omental biopsy), radiotherapy is employed to control local recurrence. Table 2 illustrates a review of studies employing various irradiation treatment types, recurrence rates, and sites of failure.

Given the propensity for USC to recur in the peritoneal cavity, treatment focused largely on whole abdominal radiotherapy incorporating a pelvic boost (WAPI) [49, 51, 54–56]. Kwon et al. reported on 23 women with stage I USC (only one was surgically staged) treated with WAPI, no patients received chemotherapy [54]. Five-year survival was 78.3 % but all recurrences were within the irradiated field. An additional retrospective report by Lim et al. described 43 women with clinical stage I USC treated with adjuvant WAPI, of the 10 patients who recurred, 7 were within the irradiated field [49].

Huh and colleagues reviewed 60 patients with surgical stage I USC (omentectomy was not required) from multiple institutions [57]. Of the

Table 2 Stage I and II USC radiation treatment failures

Reference	Modality	Recurrence rate (%)	Failures
Grice et al. [10]	WPRT/WART	25	Local and distant
Turner et al. [46]	HDR/LDR + WART or WPRT +/− chemotherapy	0	N/A
Bristow et al. [12]	BT/WPRT	16.7	Local
Sood et al. [50]	WPRT/BT	29	Local and distant
Huh et al. [57]	WPRT/BT/WART	16.7	Distant
Hamilton et al. [58]	WPRT/WART	15.4	Local and distant
Sutton et al. [56]	WAPI	42	Local and distant
Thomas et al. [59]	WPRT/WART/BT/Chemotherapy	22	Local and distant

Local recurrences are defined as vaginal and pelvic. Distant failures are either abdominal or extra-abdominal
WPRT whole pelvic radiotherapy, *WART* whole abdominal radiotherapy, *BT* brachytherapy, *WAPI* whole abdominal radiotherapy incorporating a pelvic boost, *N/A* not applicable

40 patients who were observed postoperatively, 7 (17.5 %) had recurrences, 4 locally and 3 distally. Six of the seven patients with recurrence died of their disease. Twelve patients received adjuvant radiation: WAPI in 3, whole pelvic RT (WPRT) and brachytherapy in 5, and brachytherapy alone in 4. Two of 12 patients in the radiotherapy group (16.7 %) had recurrences, and both patients died of their disease. The risk of recurrence and OS were equivalent between those that received either no adjuvant therapy or radiation therapy alone.

The GOG completed a prospective study of adjuvant radiotherapy in women with early-stage USC [56]. Twenty-one women were treated with WAPI consisting of 3000 cGy in fractions of 150 cGy/day to the abdomen and a pelvic boost of 1980 cGy at 180 cGy/day. Eight of 19 evaluable patients died of recurrent disease, 5 of whom had recurrence within the irradiated field.

Given the tendency for USC to recur peritoneally, Fakiris et al. performed a study to evaluate the potential role of adjuvant treatment with intraperitoneal radioactive phosphorus (32P) [60]. Seventeen of the 21 patients were stage I-IIB, and all had undergone comprehensive surgical staging. There were two intraperitoneal and two vaginal recurrences. Vaginal brachytherapy was then added to the regimen and no further vaginal recurrences were noted. Thus, pelvic recurrences appear to be well controlled with the addition of adjuvant pelvic radiation, but distant recurrences are problematic as almost all patients who experience distant recurrences will die of their disease [51, 57, 58, 61]. Interestingly, overall, WART has not been able to control abdominal recurrences [51, 58], moreover, in one study [49], 2 of 58 patients receiving WART for USC died of toxicity potentially related to treatment.

For patients with Stage IA disease (no myometrial invasion), risk of recurrence is lower compared to women with myometrial invasion, 9 % versus 29 %, respectively; therefore, vaginal brachytherapy (VBT) without additional adjuvant treatment has proven successful [53, 62]. In special circumstances, such as no residual disease on surgical specimen at time of complete staging, observation may even be reasonable [61, 63, 64]; however, given the possibility of a lethal recurrence, observation alone should be considered only after careful consideration of risks and benefits to the patient. Given the inconsistent responses achieved with radiation most authors have concluded that other adjuvant approaches, namely chemotherapy, perhaps in combination with radiotherapy, should be evaluated in patients with disease beyond the endometrium.

Chemotherapy and Combined Modality Therapy

The most commonly used adjuvant therapy in early stage USC is carboplatin and paclitaxel, based primarily on retrospective studies and

extrapolating from randomized controlled trials (RCT) in advanced or recurrent endometrial cancer. There are only a few retrospective series that have examined the role of chemotherapy as a single adjuvant treatment modality for stage I and II USC. Table 3 provides a summary of treatment failures in several retrospective adjuvant chemotherapy studies. Sood et al. reported on one patient who received chemotherapy in a population of patients who underwent complete surgical staging. The patient received single agent therapy (doxorubicin, paclitaxel, or cisplatin), recurred distally in the bone, and ultimately died of disease [50]. In the aforementioned study, using platinum-based combination chemotherapy with cyclophosphamide, doxorubicin, or paclitaxel, Huh et al. reported more encouraging results [57]. Of seven patients who received platinum-based chemotherapy as adjuvant treatment, none experienced recurrence over a mean follow-up of 32 months. In a multi-institutional review of surgically staged patients with stage I USC, 21 patients received adjuvant combination chemotherapy with carboplatin (AUC 6) and paclitaxel (135–175 mg/m^2). In this group, there was one vaginal recurrence (salvaged) with a median follow-up of 41 months. Six patients were treated with single agent platinum, and in this group two recurred (33 %) [65]. This study highlights the potential value of adding a taxane to the treatment regimen. Paclitaxel at a dose of 200 mg/m^2 given every 3 weeks has demonstrated activity in advanced or recurrent USC with a reported objective response rate of 77 %, but with significant hematologic toxicity [66]. Another retrospective series showed the potential efficacy of platinum-based combination chemotherapy with paclitaxel. Of six stage I USC patients treated adjuvantly with a platinum/paclitaxel combination, there were no recurrences. One stage II USC patient treated with platinum/doxorubicin failed at multiple sites including vagina and abdomen [58].

Gynecologic Oncology Group (GOG) 209 was a RCT in which women with advanced/recurrent endometrial cancer treated with intravenous (IV) carboplatin/paclitaxel experienced noninferior survival outcomes and significantly less toxicity than women treated with IV paclitaxel, Adriamycin, and cisplatin [67]. Thus, carboplatin/paclitaxel with or without the addition of radiation has become a new standard in the treatment of advanced or recurrent endometrial cancer. Table 4 summarizes early studies of combined modality therapy and treatment failures in USC. In a large study of surgically staged, early-stage USC, Kelly et al. found a statistically significant improvement in disease-free survival (DFS) and OS in patients who received platinum-based

Table 3 Stage I and II USC chemotherapy treatment failures

Reference	Modality	Recurrence rate (%)	Failures
Huh et al. [57]	Platinum combined	0	N/A
Dietrich et al. [65]	Carboplatin/paclitaxel	4.8	Local
Hamilton et al. [58]	Platinum combined	14	Local and distant

Platinum combined refers to cisplatin- or carboplatin-based chemotherapy combined with another cytotoxic agent

Table 4 Stage I and II USC: Combined modality treatment failures

Reference	Modality	Recurrence rate (%)	Failures
Rosenberg et al. [68]	WPRT/platinum combination	0	N/A
Sood et al. [50]	WPRT/single agent	60	Distant
Low et al. [127]	WPRT/BT/platinum combination	7.7	Distant
Kelly et al.[a] [61]	WPRT/WART/BT/platinum combination	4.5	Local
Fakiris et al. [126]	Intraperitoneal ^{32}P/BT	17.6	Local and distant

WPRT whole pelvic radiotherapy, *BT* brachytherapy, *WART* whole abdominal radiotherapy, *Platinum combination* platinum-based regimen with another cytotoxic agent, *Single agent* Adriamycin (doxorubicin), paclitaxel, or cisplatin
[a]Excludes patients with IA disease who did not receive adjuvant treatment

chemotherapy. Seventy-four patients with surgical stage I USC received adjuvant therapy with a variety of adjuvant chemotherapy and radiation protocols. In a multivariate analysis controlled for substage, only chemotherapy with or without vaginal brachytherapy was associated with a significant decrease in recurrences ($P < 0.003$). When broken down by substage, patients with IA disease who did not have any residual tumor in the hysterectomy specimen ($N = 7$) and did not receive adjuvant therapy, none of them experienced recurrences. Among patients with stage IA tumor with residual disease in the uterus at the time of hysterectomy who did not receive adjuvant therapy, 6 of 14 (43 %) had recurrences. The same trend was maintained for patients with stage IB and IC tumors. When combined, 1 out of 22 (4.5 %) patients with stage IB and IC tumors that received adjuvant chemotherapy had recurrences while 14 of 18 (77 %) had recurrences in the no adjuvant chemotherapy group. Interestingly, 5 of 12 (42 %) patients who received brachytherapy alone as treatment had recurrences, but no patient who received radiation (brachytherapy or pelvic) with chemotherapy had vaginal recurrences [61]. Only four of 34 stage I patients experienced a recurrence (11.7 %) after a median follow-up of 58 months, and two isolated pelvic recurrences were salvaged.

In a large retrospective series of stage I patients who had undergone comprehensive staging, patients were treated with carboplatin/paclitaxel with or without addition of radiotherapy. Patients who had received chemotherapy experienced a recurrence rate of 9.2 % compared with 24 % among those patients treated only with radiation and 30 % among those observed ($P = 0.016$). This study also demonstrated a statistically significant improvement in 5-year progression free survival among those patients treated with adjuvant platinum/taxane-based chemotherapy (81.5 %) compared with those observed (64.7 %) or treated with radiation alone (64.1 %; $P = 0.013$) [2].

Furthermore, Fields et al. conducted a Phase II study of patients with USC treated with IV carboplatin/paclitaxel chemotherapy and "sandwiched" whole pelvic radiotherapy demonstrated 3-year OS rates of 75 % for women with early stage disease [69]. The largest dataset supporting the adjuvant use of chemotherapy in stage I serous carcinomas comes from the Uterine Papillary Serous Carcinoma Consortium study [48]. Following surgery, of the 142 women with stage I serous cancer, 23 % received no further treatment, 14 % received adjuvant RT alone, and 63 % were treated adjuvant chemotherapy. Of those receiving chemotherapy (primarily carboplatin and paclitaxel administered for at least three cycles), 37 % also received RT. Those who received adjuvant chemotherapy experienced a statistically significant reduction in the recurrence rate, 11 % versus 30 % in those who received surgery alone and 25 % for patients who underwent surgery followed by RT. Chemotherapy also resulted in a statistically significant improvement in 5-year progression-free survival: 82 % versus 64 % and 65 % in the surgery and surgery with RT groups, respectively. As with most retrospective studies, there is the potential that these results are reflective of selection bias of treatments and particularly, in who did or did not receive chemotherapy.

The largest report on outcomes for women with stage II serous carcinoma also comes from the Uterine Papillary Serous Carcinoma Consortium which included 20 women with stage IIA disease and 35 women with stage IIB disease [70]. Of these, 10 (18 %) were observed following surgery, 19 (34.5 %) were treated with chemotherapy (18 received carboplatin plus paclitaxel), and 26 (47.3 %) underwent RT (though it is unclear if pelvic and/or VBT was administered). Those treated with chemotherapy (19 women) received a range of 3–6 cycles (median = 5). Of the 38 total patients treated with RT (with or without chemotherapy), 34 % received BT, 50 % received WPRT plus BT, and 16 % were treated with whole-abdominal RT alone or in combination with pelvic RT or BT. Patients who received adjuvant chemotherapy, regardless of RT, had a 10 % recurrence rate compared to 50 % in patients not treated with chemotherapy, which was statistically significant. Those who received chemotherapy

experienced a statistically significant improvement in PFS at 5 years (86 % vs. 41 %, respectively) and an improvement in overall survival (OS, 88 % vs. 64 %), although it was not statistically significant.

One of only a few prospective studies, Hogberg et al. [63] reported results of the NSGO trial of radiation alone versus adjuvant chemotherapy before or after radiation in 382 patients with stage I, II, IIIA (positive peritoneal cytology only), or IIIC disease who had high-risk factors for recurrence (one or more of deep myometrial invasion, non-diploid DNA, or serous, clear cell, grade 3, anaplastic histology). Chemotherapy was not standardized and included doxorubicin and platinum (AP); paclitaxel, doxorubicin, and platinum (TAP); paclitaxel and platinum (TP); or paclitaxel, cisplatin, and epirubicin. The study suggested an improvement in progression-free survival with chemotherapy (7 % improvement at 5 years, $P = 0.03$), but survival data were too early to draw any conclusion. Specifically, there did not appear to be any benefit of adjuvant chemotherapy in serous/clear cell carcinomas, though the number of patients was relatively small and the CIs were wide. Hogberg et al. [71] subsequently reported more mature results, and combined the results with a similar study carried out by the Mario Negri Institute (MaNGO) trials group in Italy (ILIADE-III). The two studies included 540 patients with endometrial cancer (FIGO stages I–III) with no residual tumor and randomly allocated patients to adjuvant radiotherapy with or without sequential chemotherapy [71]. In the combined analysis, there was a significant reduction in risk of relapse in the chemotherapy arm (hazard ratio [HR] 0.63, CI 0.44–0.89; $P = 0.009$). Neither trial alone showed any significant difference in overall survival.

Although platinum- and taxane-based chemotherapy is commonly used in patients with USC, there is no prospective data. PORTEC 3 (a randomized, phase III trial comparing concurrent chemoradiation and adjuvant chemotherapy with pelvic radiation alone in high risk and advance stage endometrial carcinoma) and GOG 249 (a phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by carboplatin/paclitaxel in patients with high risk early stage endometrial carcinoma) will hopefully provide important answers in treatment of USC.

Summary

Uterine serous carcinoma is a rare histologic subtype of endometrial cancer, representing approximately 5–10 % of all endometrial cancers but a disproportionate number of deaths due to disease. It is an aggressive tumor with a unique spectrum of genetic alterations contributing to its tumorigenesis [35]. Many retrospective studies have demonstrated a high frequency of extrapelvic disease even in clinical stage I tumors and that tumor spread tends to mimic that of serous ovarian cancer rather than endometrioid endometrial adenocarcinoma. If 10 % or more of the preoperative biopsy specimen contains USC, an extended surgical staging procedure should be performed [17]. Extended surgical staging includes hysterectomy, bilateral salpingo-oophorectomy (BSO) pelvic and paraaortic lymph node dissection, infracolic omentectomy or omental biopsy, and peritoneal cytology and should be performed in all patients with clinical stage I or II tumors.

Multiple adjuvant treatment modalities for early-stage USC have been employed (Tables 2, 3, and 4). Taken together, radiation alone affords some degree of local control while still leaving patients at risk for distant failure. Chemotherapy as a single treatment modality is likely best given as a platinum agent combined with a taxane. Single agent chemotherapy alone is associated with a high rate of distant failures [35]. Combined modality therapy with chemotherapy and radiation appears to offer the lowest recurrence rates with acceptable morbidity. Vaginal recurrences can be significantly reduced with brachytherapy alone [60, 61], with lower morbidity than WPRT or WART. In patients with residual disease in the hysterectomy specimen, it is currently our recommendation to treat all early-stage USC patients with chemoradiation [38, 61]. While paclitaxel/

carboplatin appears to be the optimal chemotherapy, the ideal radiation techniques are still under investigation in studies such as PORTEC 3 and GOG 249.

Clear Cell Carcinoma and Tumors of Mixed Histology

Epidemiology and Natural History

Clear cell carcinoma represents <5 % of all endometrial cancers in the United States. It was first described by Scully and Barlow who identified these tumors to originate from müllerian epithelium [72]. Microscopically, they show tubulocystic, papillary, and/or solid patterns [73]. The clear histologic appearance of the tumor cells is due to their high glycogen content. Other histologic hallmarks are eosinophilic and hobnail cells. All tumors are graded as poorly differentiated (grade 3) by FIGO convention, and unlike clear cell carcinoma of the cervix, in the corpus it does not appear to be associated with maternal exposure to diethylstilbestrol. These cancers have a very similar clinical course to that seen in USC with regard to pattern of spread, lack of apparent precursor lesions, and poor prognosis when compared to endometrioid cancers. Thus, clinical outcomes in clear cell cancers have often been reported in combined series with USC.

Tumors of mixed histology are more common than pure serous or clear cell carcinomas. Craighead et al. reported that 11 % of their patients had tumors of mixed histology including some combination of endometrioid, clear cell, and serous carcinoma [74]. Most reports define mixed histology as the coexistence of two or more cell types each of which constitutes at least 10 % of the tumor. Cirisano et al. found that tumors with mixed histology (at least 25 % of serous or clear cell carcinoma) behave similarly to USC [75]. The amount of unusual histology needed in a mixed carcinoma to confer a poor prognosis is unclear. Some investigators believe that any amount of poor-prognosis histology (serous or clear cell carcinoma) is sufficient, whereas others think that a small focus of high-risk histology does not affect prognosis. It has been demonstrated that if 10 % of the tumor is composed of serous carcinoma, the prognosis is worse than that of poorly differentiated endometrioid adenocarcinoma [17].

Clear cell carcinoma is most commonly seen in thin, postmenopausal patients, is not likely related to estrogen exposure, and is more common in African American women [62, 75, 76]. As with other high-risk types of endometrial cancer, there is a high risk of extrauterine spread. A complete staging procedure is therefore indicated. Cirisano et al. showed that nearly 40 % of patients with clear cell carcinoma clinically confined to the uterus had extrauterine spread and a small number had extrauterine disease even in the absence of myometrial invasion [75]. As with USC, survival is highly variable and depends on the extent of surgical staging with most series not requiring retroperitoneal nodal sampling or omentectomy. Abeler et al. reported the Norwegian Radium Hospital experience with 97 patients diagnosed with clear cell carcinoma and unclear surgical staging [77]. They found a 42 % 5-year survival for all stages of clear cell carcinoma compared to 27 % for USC. The 5-year OS rate was 90 % for patients without myometrial invasion, 59 % for patients with disease limited to the corpus, and 27 % for patients with stage II disease. In this series, myometrial invasion and LVSI were poor prognostic factors [77]. Carcangiu et al. reviewed 29 patients with surgical stage I and II clear cell carcinoma. Eleven of 29 patients had retroperitoneal nodal sampling. The 5-year survival for patients with stage I clear cell carcinoma was 73 % and 59 % for those with stage II tumors [78]. Creasman et al. reviewed the FIGO annual data and reported a 5-year survival rate of 81 % for surgical stage I clear cell carcinoma compared to 72 % for USC and 76 % for grade 3 endometrioid cancers [79]. Large studies of clear cell carcinoma patients in which all have been "comprehensively" staged, including lymph nodes and omentectomy, have not been reported.

Treatment

Given the rarity of these tumors, there are no prospective trials involving only early-stage clear cell carcinoma or mixed tumors. Most trials completed by the National Cancer Institute sponsored Gynecologic Oncology Group (GOG) have only included patients at the point of relapse with measurable disease for salvage chemotherapy. GOG 99, a large prospective randomized trial of intermediate risk (stage I and II) endometrial cancer patients, specifically excluded high-risk histologic subtypes [52]. Our recommendations for therapy must, therefore, be extrapolated from retrospective trials involving heterogeneous cohorts of patients (USC, grade 3 endometrioid, and mixed histology). The initial therapy is surgery with a comprehensive staging procedure including hysterectomy BSO, pelvic and paraaortic lymph node resection, omentectomy, and possibly multiple peritoneal biopsies, and diaphragm cytology. Patients with no residual disease at the time of hysterectomy (high-risk tumor only on dilation and curettage or endometrial biopsy) and possibly other stage IA patients can be observed. All other patients should be considered for adjuvant therapy.

As clear cell carcinoma appears to behave clinically like USC and other aggressive histologic variants of endometrial cancer, we recommend consideration of adjuvant cytotoxic chemotherapy for these patients based on available retrospective data for USC. Unfortunately, clear cell carcinomas are less responsive to conventional cytotoxic chemotherapy than other high-risk histologic subtypes of endometrial cancer. McMeekin et al. reported the GOG experience of 1203 patients with measurable recurrent or advanced endometrial cancer treated with a variety of different regimens (doxorubicin, cisplatin, paclitaxel, or combinations). The overall response rate was 42 % for the entire cohort, being 44 % for endometrioid carcinoma, 44 % for USC, and 32 % for clear cell carcinoma [80]. The decreased response for the clear cell carcinoma tumors was statistically significant. Thus the most appropriate chemotherapeutic regimen is not known and toxicity should be taken into account when selecting adjuvant therapies. Therefore, there may be a role for novel biologic agents in treating this malignancy. Although there is limited data available for patients with clear-cell carcinomas and mixed histology, it is likely that they will benefit from some form of pelvic radiotherapy to decrease the risk of local recurrence. As with USC, chemoradiation is likely to have the lowest failure rates in early-stage clear-cell carcinomas and mixed-histology tumors. Our current recommendation is to use vaginal brachytherapy or intensity-modulated radiation therapy (IMRT) to the pelvis in combination with carboplatin and paclitaxel. This regimen is not based on evidence of superior efficacy to other regimens, but on the manageable toxicity of this regimen.

Carcinosarcoma

Epidemiology and Natural History

Uterine carcinosarcomas represent $\leq$5 % of all endometrial cancers. Like USCs, they are biologically aggressive neoplasms with high rate of extrauterine disease, high recurrence rates (about 50 % across multiple series), and poor disease-free and overall survival rates. Whether carcinosarcomas should be classified as epithelial or mesenchymal tumors has been debated. In most of the clinical literature to date, carcinosarcomas have been included with uterine sarcomas, likely because their prognosis is dismal; however, there is mounting molecular evidence that these tumors are clonal [81–85] and epithelial in origin. The malignant epithelial component has been shown to be capable of inducing a mesenchymal component when injected into nude mice whereas the mesenchymal component could not [83]. Furthermore, patterns of metastases indicate the prominent role of the epithelial component as well. Silverberg et al. found a carcinoma component in 30/34 (88 %) lymph node metastases [86]. Autopsy data, however, have shown no

difference in metastatic spread between uterine carcinosarcomas and leiomyosarcomas [87]. Clinically, carcinosarcoma behaves like a combination of aggressive adenocarcinoma and sarcoma with a propensity for both lymphatic and hematogenous spread and uniformly poorer outcome when compared to other high-risk histologic subtypes of endometrial cancer. Amant et al. compared outcomes among three groups of high risk, early-stage endometrial cancer patients including grade 3 endometrioid adenocarcinomas, carcinosarcomas, USC, and clear-cell carcinomas. Although only 45 % of the patients had lymphadenectomy at the time of staging laparotomy, carcinosarcomas were more likely to spread to pelvic and para-aortic lymph nodes. Long-term survival was 86 % for grade 3 endometrioid adenocarcinomas and 44 % for carcinosarcomas. After a median follow-up of 24 months, 58 % of patients with carcinosarcoma had died of their disease compared to 43 % with USC and clear cell and 28 % with grade 3 endometrioid adenocarcinomas [88].

Uterine carcinosarcomas occur more commonly in older (postmenopausal) patients [89] and a review of SEER data found a higher frequency of carcinosarcomas in African American versus Caucasian women (4.3 vs. 1.7/100,000, $P < 0.001$) [90]. Like most histologic variants of endometrial cancer, carcinosarcomas commonly present with vaginal bleeding or pelvic pain [91]. A summary of common clinical findings is presented in Table 5. Grossly, they often grow as fleshy, polypoid masses filling or prolapsing out of the endometrial cavity. There may be an association between long-term tamoxifen use and development of carcinosarcomas [92]. Complete surgical staging is paramount in these patients. In one study, 32 % of patients with clinical stage I disease (thought to be confined to the uterine corpus) were upstaged based on omental involvement (three of nine patients) or positive lymph nodes [91]. The importance of evaluation of extrauterine disease is highlighted in a landmark clinicopathologic study of 203 early-stage (clinical stage I and II) carcinosarcomas [86]. In this study, 40 patients were identified with metastatic disease. The majority of the tumors (25 out of 40) had >50 % myometrial invasion, but 10 % (4 patients) had no myometrial invasion. Notably, the recurrence rate at 31 months for carcinosarcomas without myometrial invasion was 25 %.

Multiple attempts have been made to identify pathologic variables associated with outcome and the results have been controversial. Because prognosis is poor even in early-stage disease, it is difficult to identify pathologic variables that will be statistically associated with outcome. In a study of 301 stage I and II (clinical) carcinosarcomas, adnexal spread, lymph node metastases, heterologous type of mesenchymal component, and grade of sarcomatous component were all associated with decreased progression-free survival (PFS) [93]. The overall recurrence rate in this study was 53 % and 21 % of tumors recurred in the pelvis. In other longitudinal studies of carcinosarcoma, no significant associations have been found between carcinoma grade, sarcoma component, mitotic count, LVSI, sarcoma histologic subtype, or tumor size and overall survival [91, 94]. It has been argued that prognosis is worse when the epithelial component is a serous carcinoma [95, 96], but this has not been definitively proven. Results from TCGA evaluating mutations, DNA aberrations, and proteomic features should help elucidate the molecular characterization of carcinosarcomas.

Table 5 Carcinosarcomas: clinical features

Median age at diagnosis = 62–67 years
More common in African American women
May be associated with long-term tamoxifen use
Postmenopausal bleeding most common
Grossly bulky polypoid masses

Treatment

As outlined above, uterine carcinosarcoma carries a particularly poor prognosis even when diagnosed at an early stage. Ideally, treatment should address the high rate of both local (pelvic)

and distant recurrences. Because carcinosarcomas are rare, the majority of clinical studies are retrospective. The few prospective, randomized trials include other types of uterine sarcomas or include all stages of carcinosarcomas. Therapeutic trials directed specifically to early-stage carcinosarcoma are rare. Current clinical management of these tumors is therefore evolving and more randomized clinical trials are needed.

Initial evaluation of uterine carcinosarcomas is similar to that for other forms of endometrial cancer. A preoperative chest X-ray should be obtained to rule out pulmonary metastases. Abdominal-pelvic CT scan is warranted if surgical resection does not seem clinically/technically feasible to evaluate disease extent and determine protocol eligibility. Complete surgical resection is advisable including total hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and pelvic/para-aortic lymph node dissection and is the primary management of carcinosarcoma limited to the abdomen for both staging and initial treatment [97]. The value of routine omentectomy in carcinosarcomas has not been established, but in the presence of grossly positive lymph nodes, removal/biopsy of the omentum may convey prognostic value. While still investigational, initial data suggest that progression-free survival in women who have undergone sentinel lymph node biopsy is similar to women who underwent routine lymphadenectomy at time of staging [98]. Adjuvant treatment with radiation, chemotherapy, or combination of both is advisable even in early-stage disease. Results from a growing body of evidence suggest that chemotherapy, without adjuvant RT, is treatment of choice for stages IB to IV [99].

Observation for Stage IA

There are low quality data to inform the benefit of adjuvant treatment in patients with disease invading less than half of the endometrium (Stage IA); therefore, observation rather than adjuvant treatment is preferred in some cases because women with stage IA carcinosarcoma have a better prognosis compared with those with IB or later stage disease [100]. In addition, it is unclear adjuvant treatment improves prognosis in these patients [101–103], though some advocate for chemotherapy using a treatment algorithm similar to one used for USC [104].

Adjuvant Radiation

There is only one prospective, randomized controlled trial of adjuvant radiation focused solely on uterine carcinosarcomas (GOG 150). This trial randomized patients with all stages of optimally debulked uterine carcinosarcoma to adjuvant whole abdominal radiotherapy (WAR) or cisplatin 20 mg/m^2 plus ifosfamide 1.5 g/m^2 with mesna for three cycles. Preliminary results suggest improved results for patients receiving chemotherapy [99]. There are multiple retrospective studies analyzing the role of adjuvant radiotherapy in early-stage carcinosarcoma. Although overall survival benefit was identified in a small number of studies, the majority did not require strict surgical staging. Despite these limitations, local control appears to be improved with the addition of WPRT +/− vaginal brachytherapy. A recent study out of Mayo Clinic and Harvard looked at vaginal brachytherapy for early-stage carcinosarcoma of the uterus. This retrospective study included 33 patients from 2 institutions with stage I ($n = 15$) and II ($n = 18$) carcinosarcoma. Eighty-two percent of the patients underwent pelvic LND and 55 % received chemotherapy as well. Two-year vaginal cuff control 94 %, pelvic control 87 %, locoregional control 81 %, DFS 66 %, OS 79 %. Authors concluded that risk of pelvic recurrence was comparable to women treated with pelvic radiation but no lymph node dissection; therefore, pelvic radiation should be considered based on clinical context [105]. Table 6 summarizes recurrence rates in early-stage carcinosarcomas treated with adjuvant radiation.

Gerszten et al. reviewed their experience with 44 early-stage (FIGO stage I and II) uterine carcinosarcomas. Twenty patients received

Table 6 Uterine carcinosarcoma: single modality therapy

Reference	*N*	Modality	Recurrence
Gerszten et al. [106]	20	WPRT +/− brachytherapy	0 %[a]
	24	Surgery	22 % (local and distant)
Knocke et al. [107]	33	WPRT +/− brachytherapy	Local = 4.8 % stage I, 25 % stage II
			Distant = 18.3 % stage I, 33.3 % stage II
Chi et al. [108]	28	WPRT (10 neoadjuvant)	21 % pelvic, 43 % distant[b]
	10	Surgery	50 % pelvic, 40 % distant
Le [109]	12	WPRT	58 %[b]
	16	Surgery	44 %
Omura et al. [102]	93	Adriamycin	38 %[b]
		Surgery	51 %
Sutton et al. [110]	65	Cisplatin/ifosfamide	Overall = 35 %; pelvic = 15.4 %, distant/multiple site = 20 %
Resnik et al. [111]	23	Cisplatin, doxorubicin, etoposide	22 %
Odunsi et al. [112]	8	CYVADIC	38 %
Brown et al. [105]		Brachytherapy +/− chemotherapy	22 %

WPRT whole pelvic radiotherapy, *CYVADIC* cyclophosphamide, vincristine, doxorubicin (Adriamycin), dacarbazine
[a]Significant difference in overall survival favoring radiation therapy
[b]No difference observed in overall survival versus surgery

WPRT with or without vaginal brachytherapy and 24 were managed with surgery alone. Over the whole cohort of all stages ($N = 60$), 73 % had lymph nodes removed as part of the surgical staging. The investigators noted a decrease in local failures (22 % in surgery group and 0 % in RT group) as well as a decrease in combined local and distant failures (32 % and 4 %, respectively). Median survival in the surgically managed group was 12 months compared to 77 months in patients who received adjuvant RT ($P = 0.07$ for all stages). Survival was also improved in patients with stage I and II tumors ($P = 0.02$). In this study, local failure was predictive of distant recurrence and death even when adjusted for clinical stage [106]. Molpus et al. retrospectively examined outcomes in 43 early-stage uterine carcinosarcoma and found a significant survival advantage in patients who were treated with surgery and adjuvant radiation compared to surgery alone. As it has proven typical for this aggressive disease, 29 % of patients with clinical stage I were upstaged at the time of laparotomy and the 5-year OS was only 38 % when the disease was confined to the uterus [113], suggesting that surgical staging was incomplete. Interestingly, a benefit was seen in patients who received RT suggesting that improved local control may decrease distant failure rate. Yamada et al. reviewed 62 patients with clinical stage I uterine carcinosarcoma. Ninety percent of the patients had pelvic lymphadenectomy and 42 % para-aortic lymph node sampling. Of 28 patients who were considered stage I or II, only 11 received adjuvant WPRT. The authors identified an overall survival benefit in these patients, but were unable to show a decrease in pelvic recurrences across all stages. Of note, in this study, occult extrauterine disease was identified in 61 % of 62 patients. The overall recurrence rate was 50 % and 43 % of patients had distal recurrences [96]. Local and distant control was also achieved in a retrospective analysis by Knocke et al. There were 33 patients with early stage tumors (out of 63 reviewed), but only 41 % had some form of lymph node sampling. WPRT +/− vaginal brachytherapy was employed in all patients and local control rates were 95.2 % for patients with stage I and 75 % for patients with stage II tumors. Distant control rates were equally impressive at 81.7 % for stage I and 66.7 % for stage II tumors. Only 3.2 % of patients receiving radiotherapy had grade 3 toxicity [107].

Although these studies demonstrated survival advantage and decreased local and (potentially) distal failures using adjuvant WPRT +/− vaginal brachytherapy, several studies question the therapeutic benefit of adjuvant RT in early-stage uterine carcinosarcomas. Chi et al. reviewed 38 patients with stage I and II carcinosarcomas. Surgical staging was incomplete with only 45 % of patients having some form of lymph node sampling. Out of ten patients managed by surgery alone, 50 % had a pelvic recurrence, 40 % had a distant recurrence, with a 60 % 5-year OS. Out of 28 patients treated with WPRT (10 had RT as neoadjuvant treatment), 21 % had a pelvic recurrence, 43 % a distant recurrence, with a 59 % 5-year OS. Although the overall survival and rate of distant failures were unchanged, pelvic recurrences were reduced by 50 % in the second group [108]. In a review of 32 carcinosarcoma patients (19 stage I and II) with complete surgical staging, Le et al. found similar recurrence rates among those treated with surgery alone or surgery plus adjuvant irradiation; 44 % (7 of 16) in the surgery only group and 58 % (7 of 12) in the surgery plus adjuvant radiation group recurred. Overall survival was equally dismal in both groups with 27 % of patients surviving among those treated with RT versus 33 % of patients who had surgery alone [109]. In another study that examined clinical stage I–III uterine carcinosarcomas, patients who were treated with adjuvant or neoadjuvant (only 35 of 300 patients had surgery followed by RT), WPRT was associated with fewer pelvic recurrences than surgery alone (28 % vs. 48 %, $P < 0.0002$). Pelvic radiotherapy appeared to lengthen the time to distant relapse from 7 to 17 months, but the overall rate of distant failure was similar between surgery and surgery plus radiation groups (54 % vs. 57 %, respectively) [114]. Sartori et al. also found that adjuvant radiation conferred a decrease in the local failure rate but no improvement in overall recurrence rates. Of 66 clinical stage I and II uterine carcinosarcomas, the overall recurrence rates were 38.2 % (stage I) and 63.6 % (stage II). As a combined group, 40 % of early-stage carcinosarcomas failed locally, 40 % failed distally, and 20 % failed at multiple sites. When all stages were included, WPRT reduced pelvic recurrence rates from 21 to 10.7 % in patients who received adjuvant RT [115]. Finally, in one of the only randomized trials conducted in early-stage uterine sarcomas, pelvic radiotherapy appeared to reduce the rate of vaginal recurrences, but was not found to improve distant failure rates even in the doxorubicin (Adriamycin) arm of this trial [102] (to be discussed further in the "Chemotherapy" section of this chapter).

Although the majority of these studies feature admixtures of different surgical stages with a wide variety of therapeutic RT (some neoadjuvant, some adjuvant), it appears that pelvic radiotherapy offers a decrease in local relapse rates. The effect on overall survival varies among studies and will only be adequately addressed in prospective trials. Distant failures are common in patients treated with surgery or a combination of surgery plus irradiation, therefore chemotherapy should be included as part of the adjuvant regimen.

Chemotherapy

As mentioned above, the high-distant failure rate (from 19 to 50 %) across multiple studies in early-stage uterine carcinosarcoma suggests that adding chemotherapy could improve survival. Interestingly, as understanding of the molecular basis of carcinosarcomas has improved, the chemotherapeutic regimens have changed. Initial therapeutic trials assumed that carcinosarcomas behaved clinically like sarcomas and were treated with the same agents. Over time, the epithelial component has been shown to drive tumorigenesis and clinical behavior of this malignancy and therapeutic strategies have shifted accordingly. Although the majority of chemotherapeutic trials include advanced stage patients with measurable disease, it can be extrapolated that agents with activity in advanced or recurrent uterine carcinosarcoma may have activity in early-stage disease as well. A summary of recurrence rates in

patients treated with adjuvant chemotherapy is found in Table 6.

Omura et al. performed a phase III trial of adjuvant Adriamycin (60 mg/m^2) versus observation in patients with clinical stage I and II sarcomas. Lymphadenectomy was not required for surgical staging, but all patients were required to have no residual disease after primary surgery. Pelvic radiotherapy was allowed at the discretion of the treating physician. Of 156 evaluable patients, 93 had a diagnosis of carcinosarcoma. The recurrence rate was 38 % in the adjuvant doxorubicin group and 51 % in patients without further treatment (not statistically different). For clinical stage I tumors, the median survival was 67.2 months. The addition of adjuvant Adriamycin did not prolong OS or PFS, and no difference was seen when a subgroup analysis was performed in patients who received adjuvant pelvic radiotherapy as well. For patients with carcinosarcomas in the doxorubicin arm, 75 % of the recurrences occurred in the pelvis and vagina compared to 33 % in the no chemotherapy arm. Distant metastases (lung and abdomen) were reduced from 66 % in the no treatment group to 25 % in patients treated with doxorubicin. Although no overall statistical differences were seen between treatment and no treatment arms of this trial, there appears to be a trend to reduce distant failure in patients with carcinosarcoma with adjuvant treatment [102].

Other agents have been evaluated as adjuvant therapy in the advanced/recurrent setting. Sutton et al. performed a phase II trial of ifosfamide and mesna in patients with advanced/recurrent uterine carcinosarcoma and found an objective response rate (OR) of 32.2 % with an 18 % complete response (CR) rate. There was one death attributed to therapy among 29 evaluable patients [116]. Sutton et al. also then examined the role of combination chemotherapy with ifosfamide plus or minus cisplatin in a large phase III trial of patients with advanced or recurrent uterine carcinosarcomas. Treatment consisted of 1.5 g/m^2/day ifosfamide for 5 days (a reduced dose was given to patients with a history of radiation therapy) with or without 20 mg/m^2 cisplatin × 5 days. The overall response rate in the combination arm was 54 % compared to 36 % in the ifosfamide alone arm. There was no change in OS with the addition of cisplatin, but a slight prolongation of PFS was observed. The combination regimen was toxic with six treatment-related deaths seen with full (1.5 g/m^2) doses of ifosfamide [117]. Given the improved OR with combination cisplatin and ifosfamide, Sutton et al. examined the same combination regimen in a phase II trial of 65 evaluable patients with clinical stage I and II uterine carcinosarcomas. Lymphadenectomy was not required as part of the surgical staging, and all patients were scheduled to receive three cycles of adjuvant combination chemotherapy. The primary outcome measures were disease-free survival (DFS) and OS. The dosing was similar to the phase III trial [117]. The majority of patients (89 %) completed three cycles. Grade 3 or 4 thrombocytopenia was seen in 63 % of evaluable patients, and 26 % had grade 3 or 4 neutropenia. The 2-year PFS was 69 % while the 2-year and 5-year OS were 82 % and 62 %, respectively. Of the patients that had recurrences (35 % of whole cohort), half of them were in the pelvis [110]. Note that there was no adjuvant radiation allowed in this trial.

Resnik et al. studied combination chemotherapy with cisplatin doxorubicin, and etoposide in 42 patients with uterine carcinosarcoma. In this phase II trial, 23 patients had stage I or II disease. Almost all (22 of 23) patients had complete surgical staging with lymph node sampling with or without omentectomy. Preoperative or postoperative radiotherapy was allowed. Out of the 23 patients with early-stage tumors, 5 had recurrences (22 %). Of note, USC was identified as the carcinoma component in 3/5 (60 %) of the patients with recurrences. In this study, patients with early stage disease had a 92 % 2-year survival rate and an 83 % PFS. Only 22 % of patients experienced grade 3 complications [111]. Other phase II trials in advanced/recurrent carcinosarcoma have not been successful [118, 119].

In GOG 161, Homesley et al. found that adding paclitaxel to ifosfamide improved OS and PFS when compared to ifosfamide alone. In this study, 179 patients with advanced/recurrent

uterine carcinosarcoma were randomized to receive ifosfamide alone at a dose of 2 g/m^2 or ifosfamide at 1.6 g/m^2 plus paclitaxel at 135 mg/m^2 every 21 days for a maximum of eight cycles. The combination arm had significantly better overall response and a 29 % decrease in the adjusted hazard of death or progression ($P = 0.03$), although alopecia and neuropathy were more commonly seen [120]. One retrospective study in patients with advanced/recurrent carcinosarcoma found four of five evaluable patients (80 %) to have a complete response to combination therapy with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) [121]. A phase II trial of paclitaxel and carboplatin in patients with advanced (stage III or IV) disease showed a complete response rate of 13 % (46 patients) and partial response in 41 % with acceptable toxicity[122]. This has led to GOG 261, a randomized phase III trial of paclitaxel plus carboplatin versus ifosfamide plus paclitaxel in chemotherapy-naïve patients with newly diagnosed stage I–IV, persistent or recurrent carcinosarcoma or the uterus, fallopian tube, peritoneum or ovary.

Recurrence remains a significant problem in patients with early-stage uterine carcinosarcoma treated with chemotherapy alone (or in combination with radiotherapy), and more effective treatments are required to reduce the rates of local and distant failures.

Multimodality Therapy

It is evident that recurrence rates are high in uterine carcinosarcomas treated with adjuvant single-modality therapy (either chemotherapy or radiation). This has prompted several investigators to explore combination therapy with radiation and chemotherapy to address local and distant recurrences. Currently, there are no prospective trials open for multimodality therapy in uterine carcinosarcomas, thus, treatment benefit must be extrapolated from small numbers of patients evaluated retrospectively. Table 7 summarizes DFS and OS in patients with uterine carcinosarcoma treated with multimodality therapy.

Kohorn et al. found that four of five (80 %) patients treated with radiation, surgery, and adjuvant chemotherapy (doxorubicin/cyclophosphamide or doxorubicin/ cisplatin) were disease free after a follow-up of 36–60 months [123]. Manolitsas et al. examined outcome in 38 clinical stage I or II (lymphadenectomy not required) patients with uterine carcinosarcoma that received primary surgery followed by pelvic radiation and combination chemotherapy with four to six cycles of cisplatin (75 mg/m^2) and epirubicin (75 mg/m^2). Nine of 38 patients (24 %) were upstaged at the time of surgery. Chemoradiation was administered in a sequential or "sandwich" fashion with two cycles of chemotherapy given prior to pelvic radiotherapy, followed by completion of the chemotherapy. Patients were treated with WPRT unless a complete lymphadenectomy was performed and lymph nodes were documented to be negative. Those patients received vaginal brachytherapy only. Eleven patients (29 %) received no chemotherapy. Only one patient experienced grade 3 toxicity. Impressively, survival for patients who completed multimodality therapy was 95 % (20 of 21 patients) and DFS was 90 % with a median follow-up of 55 months. In contrast, OS among patients who did not receive the recommended treatment protocol was 47 %. There was one death (and one recurrence)

Table 7 Uterine carcinosarcoma: multimodality therapy

Reference	*N*	Modalities	DFS (%)	OS (%)
Kohorn et al. [123]	5	Surgery/RT/Chemotherapy[a]	80	
Manolitsas et al. [124]	21	Surgery/WPRT/cisplatin, epirubicin	90	95
Menczer et al. [125]	10	Surgery/cisplatin, Ifosfamide/WPRT	70	75[b]

RT radiation therapy, *WPRT* whole pelvic radiotherapy
[a]Chemotherapy consisted of doxorubicin/cyclophosphamide or doxorubicin/cisplatin
[b]OS for patients treated with WPRT alone = 50 % and 22 % for chemotherapy alone

among the 21 patients who received combination therapy. This patient experienced local and distant failure and was originally staged as IA (disease confined to a polyp) [124]. A recent study has reviewed all stages of uterine carcinosarcoma treated with chemotherapy alone, WPRT alone, or combined modality (chemotherapy followed by radiation). Out of 49 patients, 25 had clinical stage I tumors. Radiation was delivered as WPRT with HDR brachytherapy. Patients were treated with cisplatin and ifosfamide combination therapy as a single modality and in combination with radiation. Patients who received sequential therapy were administered a higher dose of cisplatin (80 mg/m^2 vs. 60 mg/m^2) and a lower dose of ifosfamide (1.2 g/m^2/day vs. 1.5 g/m^2/day). Ten patients received combined modality therapy with a 75 % 5-year OS compared to that of WPRT alone (50.5 %) and chemotherapy alone (22.2 %). Although sites of failure were not explicitly addressed in this study, multi-site failure (both pelvic and distant) appeared to be most common [125].

Summary

Uterine carcinosarcoma is a particularly aggressive neoplasm with high rates of treatment failure even when disease is confined to the uterus [86]. Molecular evidence points toward a clonal epithelial origin of these malignancies [81–85] and some evidence suggests more aggressive behavior if the epithelial component consists of serous carcinoma [95, 111]. However, both hematogenous and lymphatic spread have been described [86, 87]. Radiation appears to offer local control [108, 109], but distant failure remains problematic. Results from GOG 150 (whole abdominal radiotherapy vs. combination chemotherapy with cisplatin and ifosfamide), showed that there was no advantage of one over the other [99]. The most active chemotherapeutic regimen to date is ifosfamide plus paclitaxel and due to its toxicity now serves as the control arm in GOG 261 which is comparing ifosfamide plus paclitaxel with carboplatin and paclitaxel [120].

Conclusions

- Serous carcinoma, carcinosarcoma, clear cell carcinoma, and mixed histology tumors, although representing 5–10 % of all endometrial cancers, are responsible for a significant percentage of endometrial cancer mortality.
- These tumors are understudied in randomized-controlled trials and available retrospective data are limited by nonstandardized surgical staging and variable treatment regimens applied.
- As significant risk of disease spread outside the uterus exists, comprehensive surgical staging is of paramount importance.
- High local and distant failure rates in patients with early-stage disease have prompted testing of combined modality therapy with chemotherapy and localized radiation, utilizing both high-dose rate brachytherapy to the vaginal cuff or IMRT to the pelvis.
- While multimodality treatment is preferred in USC, clear cell, and mixed histologies, chemotherapy with ifosfamide and paclitaxel has proven most efficacious in carcinosarcoma.

References

1. American Cancer Society. Cancer facts and figures 2015. Atlanta: G.A.C.S; 2015.
2. Hamilton CA et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94(5):642–6.
3. Lauchlan SC. Tubal (serous) carcinoma of the endometrium. Arch Pathol Lab Med. 1981;105 (11):615–8.
4. Hendrickson M et al. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982;6(2):93–108.
5. Kato DT et al. Uterine papillary serous carcinoma (UPSC): a clinicopathologic study of 30 cases. Gynecol Oncol. 1995;59(3):384–9.
6. Moore KN, Fader AN. Uterine papillary serous carcinoma. Clin Obstet Gynecol. 2011;54(2):278–91.
7. Cirisano Jr FD et al. The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. Gynecol Oncol. 2000;77 (1):55–65.

8. Fader AN et al. Uterine papillary serous carcinoma: epidemiology, pathogenesis and management. Curr Opin Obstet Gynecol. 2010;22(1):21–9.
9. Platz CE, Benda JA. Female genital tract cancer. Cancer. 1995;75(1 Suppl):270–94.
10. Grice J et al. Uterine papillary serous carcinoma: evaluation of long-term survival in surgically staged patients. Gynecol Oncol. 1998;69(1):69–73.
11. Goff BA et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecol Oncol. 1994;54(3):264–8.
12. Bristow RE et al. Extended surgical staging for uterine papillary serous carcinoma: survival outcome of locoregional (Stage I-III) disease. Gynecol Oncol. 2001;81(2):279–86.
13. Tay EH, Ward BG. The treatment of uterine papillary serous carcinoma (UPSC): are we doing the right thing? Int J Gynecol Cancer. 1999;9(6):463–9.
14. Abramovich D et al. Serum CA-125 as a marker of disease activity in uterine papillary serous carcinoma. J Cancer Res Clin Oncol. 1999;125 (12):697–8.
15. Gupta D et al. Performance of serum CA125 as a prognostic biomarker in patients with uterine papillary serous carcinoma. Int J Gynecol Cancer. 2011;21(3):529–34.
16. Olawaiye AB et al. Utility of pre-operative serum CA-125 in the management of uterine papillary serous carcinoma. Gynecol Oncol. 2008;110 (3):293–8.
17. Boruta 2nd DM et al. Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? Cancer. 2004;101(10):2214–21.
18. Bjorge T et al. Body size in relation to cancer of the uterine corpus in 1 million Norwegian women. Int J Cancer. 2007;120(2):378–83.
19. Gehrig PA et al. Association between uterine serous carcinoma and breast cancer. Gynecol Oncol. 2004;94(1):208–11.
20. Chan JK et al. Breast cancer followed by corpus cancer: is there a higher risk for aggressive histologic subtypes? Gynecol Oncol. 2006;102(3):508–12.
21. Geisler JP et al. Papillary serous carcinoma of the uterus: increased risk of subsequent or concurrent development of breast carcinoma. Gynecol Oncol. 2001;83(3):501–3.
22. Barakat RR et al. Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. Gynecol Oncol. 1994;55 (2):164–8.
23. Bergman L et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of liver and endometrial cancer risk following tamoxifen. Lancet. 2000;356(9233):881–7.
24. Fisher B et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97(22):1652–62.
25. Magriples U et al. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. J Clin Oncol. 1993;11(3):485–90.
26. Mignotte H et al. Iatrogenic risks of endometrial carcinoma after treatment for breast cancer in a large French case-control study. Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC). Int J Cancer. 1998;76(3):325–30.
27. Saadat M et al. Outcomes in patients with primary breast cancer and a subsequent diagnosis of endometrial cancer: comparison of cohorts treated with and without tamoxifen. Cancer. 2007;110 (1):31–7.
28. Silva EG, Tornos CS, Follen-Mitchell M. Malignant neoplasms of the uterine corpus in patients treated for breast carcinoma: the effects of tamoxifen. Int J Gynecol Pathol. 1994;13(3):248–58.
29. Goshen R et al. Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome? Gynecol Oncol. 2000;79 (3):477–81.
30. Lavie O et al. BRCA1 germline mutations in women with uterine serous papillary carcinoma. Obstet Gynecol. 2000;96(1):28–32.
31. Low JS et al. Adjuvant sequential chemotherapy and radiotherapy in uterine papillary serous carcinoma. Gynecol Oncol. 2005;97:171–7.
32. Fakiris AJ et al. Intraperitoneal radioactive phosphorous (32P) and vaginal brachytherapy as adjuvant treatment for uterine papillary serous carcinoma and clear cell carcinoma: the Indiana University experience. Brachytherapy. 2010;9(1):61–5.
33. Levine DA et al. Risk of endometrial carcinoma associated with BRCA mutation. Gynecol Oncol. 2001;80(3):395–8.
34. Boruta 2nd DM et al. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol. 2009;115(1):142–53.
35. Lax SF. Molecular genetic pathways in various types of endometrial carcinoma: from a phenotypical to a molecular-based classification. Virchows Arch. 2004;444(3):213–23.
36. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol. 2001;2 (2):127–37.
37. El-Sahwi KS, Schwartz PE, Santin AD. Development of targeted therapy in uterine serous carcinoma, a biologically aggressive variant of endometrial cancer. Expert Rev Anticancer Ther. 2012;12(1):41–9.
38. Fader AN, Santin AD, Gehrig PA. Early stage uterine serous carcinoma: management updates and genomic advances. Gynecol Oncol. 2013;129 (1):244–50.
39. Cancer Genome Atlas Research Network et al. Integrated genomic characterization of

endometrial carcinoma. Nature. 2013;497 (7447):67–73.
40. Slomovitz BM et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol. 2003;91(3):463–9.
41. Mendivil A, Schuler KM, Gehrig PA. Non-endometrioid adenocarcinoma of the uterine corpus: a review of selected histological subtypes. Cancer Control. 2009;16(1):46–52.
42. Chan JK et al. Significance of comprehensive surgical staging in noninvasive papillary serous carcinoma of the endometrium. Gynecol Oncol. 2003;90 (1):181–5.
43. Geisler JP et al. What staging surgery should be performed on patients with uterine papillary serous carcinoma? Gynecol Oncol. 1999;74(3):465–7.
44. ASTEC Study Group et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125–36.
45. Growdon WB et al. Prognostic determinants in patients with stage I uterine papillary serous carcinoma: a 15-year multi-institutional review. Int J Gynecol Cancer. 2012;22(3):417–24.
46. Turner BC et al. Effective treatment of stage I uterine papillary serous carcinoma with high dose-rate vaginal apex radiation (192Ir) and chemotherapy. Int J Radiat Oncol Biol Phys. 1998;40(1):77–84.
47. Carcangiu ML, Chambers JT. Uterine papillary serous carcinoma: a study on 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. Gynecol Oncol. 1992;47(3):298–305.
48. Fader AN et al. An updated clinicopathologic study of early-stage uterine papillary serous carcinoma (UPSC). Gynecol Oncol. 2009;115(2):244–8.
49. Lim P et al. Early stage uterine papillary serous carcinoma of the endometrium: effect of adjuvant whole abdominal radiotherapy and pathologic parameters on outcome. Cancer. 2001;91(4):752–7.
50. Sood BM et al. Patterns of failure after the multimodality treatment of uterine papillary serous carcinoma. Int J Radiat Oncol Biol Phys. 2003;57 (1):208–16.
51. Mehta N et al. Outcome and pattern of failure in pathologic stage I-II papillary serous carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys. 2003;57(4):1004–9.
52. Keys HM et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(3):744–51.
53. Havrilesky LJ et al. Outcomes in surgical stage I uterine papillary serous carcinoma. Gynecol Oncol. 2007;105(3):677–82.
54. Kwon J, Ackerman I, Franssen E. The role of abdominal-pelvic radiotherapy in the management of uterine papillary serous carcinoma. Int J Radiat Oncol Biol Phys. 2004;59(5):1439–45.
55. Martinez AA et al. Improved outcome at 10 years for serous-papillary/clear cell or high-risk endometrial cancer patients treated by adjuvant high-dose whole abdomino-pelvic irradiation. Gynecol Oncol. 2003;90(3):537–46.
56. Sutton G et al. Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2006;100(2):349–54.
57. Huh WK et al. Uterine papillary serous carcinoma: comparisons of outcomes in surgical Stage I patients with and without adjuvant therapy. Gynecol Oncol. 2003;91(3):470–5.
58. Hamilton CA et al. Impact of adjuvant therapy on survival of patients with early-stage uterine papillary serous carcinoma. Int J Radiat Oncol Biol Phys. 2005;63(3):839–44.
59. Thomas MB et al. Role of systematic lymphadenectomy and adjuvant therapy in stage I uterine papillary serous carcinoma. Gynecol Oncol. 2007;107(2):186–9.
60. Kiess AP et al. Five-year outcomes of adjuvant carboplatin/paclitaxel chemotherapy and intravaginal radiation for stage I-II papillary serous endometrial cancer. Gynecol Oncol. 2012;127 (2):321–5.
61. Kelly MG et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. Gynecol Oncol. 2005;98(3):353–9.
62. Abeler VM et al. Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern. Cancer. 1996;78(8):1740–7.
63. Hogberg T, et al. A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991). J Clin Oncol (Meeting Abstracts). 2007; 25(18_suppl): 5503.
64. Elit L et al. Optimal management for surgically Stage 1 serous cancer of the uterus. Gynecol Oncol. 2004;92(1):240–6.
65. Dietrich 3rd CS et al. The efficacy of adjuvant platinum-based chemotherapy in Stage I uterine papillary serous carcinoma (UPSC). Gynecol Oncol. 2005;99(3):557–63.
66. Ramondetta L et al. Treatment of uterine papillary serous carcinoma with paclitaxel. Gynecol Oncol. 2001;82(1):156–61.
67. Miller D et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2012;125:771–3.

68. Rosenberg P et al. Death rate and recurrence pattern among 841 clinical stage I endometrial cancer patients with special reference to uterine papillary serous carcinoma. Gynecol Oncol. 1993;51 (3):311–5.
69. Fields AL et al. Pilot phase II trial of radiation "sandwiched" between combination paclitaxel/platinum chemotherapy in patients with uterine papillary serous carcinoma (UPSC). Gynecol Oncol. 2008;108 (1):201–6.
70. Fader AN et al. Stage II uterine papillary serous carcinoma: carboplatin/paclitaxel chemotherapy improves recurrence and survival outcomes. Gynecol Oncol. 2009;112(3):558–62.
71. Hogberg T et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer. 2010;46 (13):2422–31.
72. Scully RE, Barlow JF. "Mesonephroma" of ovary. Tumor of Mullerian nature related to the endometrioid carcinoma. Cancer. 1967;20 (9):1405–17.
73. Kanbour-Shakir A, Tobon H. Primary clear cell carcinoma of the endometrium: a clinicopathologic study of 20 cases. Int J Gynecol Pathol. 1991;10 (1):67–78.
74. Craighead PS et al. Management of aggressive histologic variants of endometrial carcinoma at the Tom Baker Cancer Centre between 1984 and 1994. Gynecol Oncol. 2000;77(2):248–53.
75. Cirisano Jr FD et al. Epidemiologic and surgicopathologic findings of papillary serous and clear cell endometrial cancers when compared to endometrioid carcinoma. Gynecol Oncol. 1999;74 (3):385–94.
76. Christopherson WM, Alberhasky RC, Connelly PJ. Carcinoma of the endometrium: I. A clinicopathologic study of clear-cell carcinoma and secretory carcinoma. Cancer. 1982;49(8):1511–23.
77. Abeler VM, Kjorstad KE. Clear cell carcinoma of the endometrium: a histopathological and clinical study of 97 cases. Gynecol Oncol. 1991;40 (3):207–17.
78. Carcangiu ML, Chambers JT. Early pathologic stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinicopathologic features and survival. Int J Gynecol Pathol. 1995;14(1):30–8.
79. Creasman WT et al. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. Gynecol Oncol. 2004;95(3):593–6.
80. McMeekin DS et al. The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study. Gynecol Oncol. 2007;106(1):16–22.
81. Bitterman P, Chun B, Kurman RJ. The significance of epithelial differentiation in mixed mesodermal tumors of the uterus. A clinicopathologic and immunohistochemical study. Am J Surg Pathol. 1990;14(4):317–28.
82. Kounelis S et al. Carcinosarcomas (malignant mixed mullerian tumors) of the female genital tract: comparative molecular analysis of epithelial and mesenchymal components. Hum Pathol. 1998;29(1):82–7.
83. Emoto M et al. Characteristics of cloned cells of mixed mullerian tumor of the human uterus. Carcinoma cells showing myogenic differentiation in vitro. Cancer. 1993;71(10):3065–75.
84. Wada H et al. Molecular evidence that most but not all carcinosarcomas of the uterus are combination tumors. Cancer Res. 1997;57(23):5379–85.
85. Fujii H et al. Frequent genetic heterogeneity in the clonal evolution of gynecological carcinosarcoma and its influence on phenotypic diversity. Cancer Res. 2000;60(1):114–20.
86. Silverberg SG et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. Int J Gynecol Pathol. 1990;9(1):1–19.
87. Fleming WP et al. Autopsy findings in patients with uterine sarcoma. Gynecol Oncol. 1984;19 (2):168–72.
88. Amant F et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. Gynecol Oncol. 2005;98(2):274–80.
89. Gadducci A et al. The management of patients with uterine sarcoma: a debated clinical challenge. Crit Rev Oncol Hematol. 2008;65(2):129–42.
90. Brooks SE et al. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecol Oncol. 2004;93(1):204–8.
91. Inthasorn P et al. Analysis of clinicopathologic factors in malignant mixed Mullerian tumors of the uterine corpus. Int J Gynecol Cancer. 2002;12 (4):348–53.
92. McCluggage WG et al. Uterine carcinosarcomas in patients receiving tamoxifen. A report of 19 cases. Int J Gynecol Cancer. 2000;10(4):280–4.
93. Major FJ et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993;71(4 Suppl):1702–9.
94. Nielsen SN et al. Clinicopathologic analysis of uterine malignant mixed mullerian tumors. Gynecol Oncol. 1989;34(3):372–8.
95. Ramondetta LM et al. A phase II trial of cisplatin, ifosfamide, and mesna in patients with advanced or recurrent uterine malignant mixed mullerian tumors with evaluation of potential molecular targets. Gynecol Oncol. 2003;90(3):529–36.
96. Yamada SD et al. Pathologic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus. Cancer. 2000;88(12):2782–6.
97. NCCN clinical practice guidelines in oncology. Uterine neoplasms, version 2.2016. National Comprehensive Cancer Network (2015).

98. Schiavone MB et al. Survival of patients with uterine carcinosarcoma undergoing sentinel lymph node mapping. Ann Surg Oncol. 2016;23(1):196–202.
99. Wolfson AH et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol. 2007;107(2):177–85.
100. Page BR et al. Does the FIGO 2009 endometrial cancer staging system more accurately correlate with clinical outcome in different histologies? Revised staging, endometrial cancer, histology. Int J Gynecol Cancer. 2012;22(4):593–8.
101. Reed NS et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. 2008;44 (6):808–18.
102. Omura GA et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. J Clin Oncol. 1985;3 (9):1240–5.
103. Cantrell LA et al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma. Gynecol Oncol. 2012;127(1):22–6.
104. del Carmen MG, Birrer M, Schorge JO. Uterine papillary serous cancer: a review of the literature. Gynecol Oncol. 2012;127(3):651–61.
105. Brown LC et al. Vaginal brachytherapy for early-stage carcinosarcoma of the uterus. Brachytherapy. 2015;14(4):433–9.
106. Gerszten K et al. The impact of adjuvant radiotherapy on carcinosarcoma of the uterus. Gynecol Oncol. 1998;68(1):8–13.
107. Knocke TH et al. Results of primary and adjuvant radiotherapy in the treatment of mixed Mullerian tumors of the corpus uteri. Gynecol Oncol. 1999;73 (3):389–95.
108. Chi DS et al. The role of whole-pelvic irradiation in the treatment of early-stage uterine carcinosarcoma. Gynecol Oncol. 1997;65(3):493–8.
109. Le T. Adjuvant pelvic radiotherapy for uterine carcinosarcoma in a high risk population. Eur J Surg Oncol. 2001;27(3):282–5.
110. Sutton G et al. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol. 2005;96(3):630–4.
111. Resnik E et al. A phase II study of etoposide, cisplatin, and doxorubicin chemotherapy in mixed mullerian tumors (MMT) of the uterus. Gynecol Oncol. 1995;56(3):370–5.
112. Odunsi K et al. Efficacy of adjuvant CYVADIC chemotherapy in early-stage uterine sarcomas: results of long-term follow-up. Int J Gynecol Cancer. 2004;14(4):659–64.
113. Molpus KL et al. Postoperative pelvic irradiation in early stage uterine mixed mullerian tumors. Eur J Gynaecol Oncol. 1998;19(6):541–6.
114. Callister M et al. Malignant mixed Mullerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. Int J Radiat Oncol Biol Phys. 2004;58(3):786–96.
115. Sartori E et al. Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. Gynecol Oncol. 1997;67(1):70–5.
116. Sutton GP et al. Phase II trial of ifosfamide and mesna in mixed mesodermal tumors of the uterus (a Gynecologic Oncology Group study). Am J Obstet Gynecol. 1989;161(2):309–12.
117. Sutton G et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: a Gynecologic Oncology Group Study. Gynecol Oncol. 2000;79(2):147–53.
118. Curtin JP et al. Paclitaxel in the treatment of carcinosarcoma of the uterus: a gynecologic oncology group study. Gynecol Oncol. 2001;83 (2):268–70.
119. Miller DS et al. Phase II evaluation of topotecan in carcinosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol. 2005;98 (2):217–21.
120. Homesley HD et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25(5):526–31.
121. Toyoshima M et al. Clinical experience with combination paclitaxel and carboplatin therapy for advanced or recurrent carcinosarcoma of the uterus. Gynecol Oncol. 2004;94(3):774–8.
122. Powell MA et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. J Clin Oncol. 2010;28(16):2727–31.
123. Kohorn EI et al. Adjuvant therapy in mixed mullerian tumors of the uterus. Gynecol Oncol. 1986;23(2):212–21.
124. Manolitsas TP et al. Multimodality therapy for patients with clinical Stage I and II malignant mixed Mullerian tumors of the uterus. Cancer. 2001;91(8):1437–43.
125. Menczer J et al. A comparison between different postoperative treatment modalities of uterine carcinosarcoma. Gynecol Oncol. 2005;97 (1):166–70.
126. Fakiris AS et al. Intraperitoneal radioactive phosphorous and vaginal brachytherapy as adjuvant treatment for uterine papillary serous carcinoma and clear cell carcinoma the Indiana University experience. Brachytherapy, 2010. 9(1)61–5.
127. Low US et al. Adjuvant sequential chemotherapy and radiotherapy in uterine papillary serous carcinoma. Gynecol Oncol. 2005;97:171–177.

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Treatment of Advanced and Recurrent Carcinoma: Chemotherapy

Fernanda Musa

Abstract

Chemotherapy for endometrial cancer has evolved over the past two decades, with drug combinations convincingly showing to have a role in the treatment of advanced and recurrent endometrial cancer. Agents with established antitumor activity include doxorubicin, cisplatin, and paclitaxel. A combination of paclitaxel with the cisplatin analog carboplatin is currently the most commonly used regimen for first-line treatment of metastatic disease. Questions remain about the contribution of these regimens in adjuvant settings, about the role of drug therapy beyond first-line treatments, and about integration of targeted agents.

Keywords

Endometrial • Chemotherapy • Doxorubicin • Cisplatin • Paclitaxel • Carboplatin

Introduction

Advanced endometrial cancer is associated with adverse outcomes compared to early-stage disease, with a 5-year survival of 59.6 % for stage III disease and 28.6 % for stage IV disease. The prognosis, however, is impacted by the degree of tumor differentiation and histology. Women with stage III disease and grade 1 adenocarcinomas have an 83 % 5-year survival compared to 48 % for women with grade 3 adenocarcinomas. Similarly, papillary serous and clear cell histologies are well-described poor prognostic indicators associated with decreased survival, comparable to that of ovarian cancer. SEER data suggests that the 5-year survival for patients with stage III papillary serous endometrial cancer is 33.3 % and 18.3 % for stage IV, compared to 66.9 % and 36.8 % for stage III and IV endometrioid tumors, respectively (all grades) [1].

Recurrent endometrial cancer presents with differing patterns ranging from localized to diffuse, and involvement of nodal and visceral areas. Therapeutic options vary depending on whether the metastatic focus is in a previously

F. Musa (✉)
Division of Gynecologic Oncology, New York University Langone Medical Center, New York, NY, USA
e-mail: fernanda.musa@nyumc.org

irradiated field or not. The choice of chemotherapy in recurrent endometrial cancer, particularly in papillary serous tumors, is largely extrapolated from the ovarian cancer literature. Similarly to ovarian cancer, recurrences can be categorized as platinum-sensitive versus platinum-resistant depending on their temporal relationship to the completion of a previous platinum-containing treatment. This status provides a guide to the selection of the chemotherapeutic agent of choice; however, response rates are generally lower than those observed in recurrent ovarian cancer. Chemotherapy in this setting is palliative and mindfulness of the patient's quality of life while undergoing treatment is imperative in any therapeutic intervention.

Development of Systemic Therapies

The systemic treatment of endometrial carcinoma was first developed around progestins and doxorubicin and then mostly evolved from phase III studies by the Gynecologic Oncology Group (GOG) that have been performed since the 1970s. GOG 122, the first randomized phase III study demonstrating the superiority of chemotherapy (doxorubicin plus cisplatin, AP) over radiation (whole-abdominal radiation, WAI) in endometrial cancer, served as a powerful stimulus for extending the use of adjuvant systemic therapy for this disease. In GOG 122, women with stage III and low-volume (<2 cm residual disease after debulking surgery) stage IV endometrial carcinoma were randomized to receive WAI with a pelvic boost or AP chemotherapy with no radiotherapy. Seventy-five percent of women had stage III disease. Twenty percent had serous tumors. The hazard ratio for progression was 0.71 favoring AP (95 % CI, 0.55–0.91; $p < 0.01$). Women with both stage III and stage IV disease appeared to benefit from treatment. No prognostic feature including age, substage, or histology predicted lack of benefit from chemotherapy [2].

The adoption of chemotherapy as a preferred modality over pelvic irradiation was initially controversial. An Italian randomized phase III trial of lower risk patients compared to GOG 122 demonstrated no difference in PFS or OS between adjuvant chemotherapy and pelvic radiation therapy at 95-month follow-up. The study did demonstrate fewer distant relapses in the chemotherapy group and local relapses in the radiotherapy group [3]. The Japanese GOG reported similar findings and no difference when comparing cisplatin, doxorubicin, and cyclophosphamide versus whole pelvic radiotherapy in patients with stage IC–IIIC endometrioid adenocarcinoma [4].

Integration of Chemotherapy and Radiation for Early-Stage Disease

The results of the Nordic Society of Gynecologic Oncology (NSGO), European Organization for Research and Treatment Center (EORTC), and ILIADE-III (MaNGO group) trials randomizing women to receive pelvic radiation therapy with and without chemotherapy were published together. Several different chemotherapy regimens were allowed including doxorubicin, cisplatin, and carboplatin–paclitaxel. The pooled results including 534 evaluable patients with surgically resected high-risk FIGO stage I–III endometrial cancers showed that combined modality treatment was associated with a 36 % reduction in the risk of relapse or death (HR 0.64, CI 0.41–0.99, $p = 0.04$). The pooled results also demonstrate an improvement in the cancer-specific survival (HR 0.55, CI 0.35–0.88, $p = 0.01$) [5]. The study concluded that addition of chemotherapy to radiation improves PFS in endometrial cancer patients with no postoperative residual tumor and a high-risk profile.

Many women with endometrial cancer are elderly (median age at diagnosis is 60–65 years) and dose-intense regimens need to be approached cautiously. GOG 184 randomly assigned women with stage III and IV disease who underwent volume-directed or involved-field radiation therapy to chemotherapy containing either doxorubicin plus cisplatin or doxorubicin, cisplatin, and paclitaxel. Both arms required granulocyte colony-stimulating factor support given limited

hematologic reserve following RT. The study concluded that addition of paclitaxel to doxorubicin and cisplatin was not associated with an improvement in recurrence-free survival but was associated with increased toxicity [6]. A recently published review by the Cochrane Library pooling the results of four major randomized controlled trials [2–4, 6] concluded that there is moderate-quality evidence that chemotherapy increases survival time after primary surgery in endometrial cancer by approximately 25 % relative to radiotherapy in stage III and IV disease. There is insufficient evidence at this time relative to the risks and benefits of adjuvant chemo-radiation versus chemotherapy alone in this setting [7]. In an attempt to answer this important question, the GOG has an ongoing phase III study which randomizes women with optimally cytoreduced advanced-stage endometrial cancer to carboplatin and paclitaxel with or without tumor volume-directed irradiation preceding the chemotherapy (GOG 258).

Chemotherapy for Metastatic or Recurrent Disease

The amount of residual disease after surgery for advanced endometrial cancer has an impact on median survival and progression-free interval [8–13]. For women who present with extensive metastatic disease and/or are not candidates for surgical therapy, chemotherapy is a mainstay of treatment. Stage III–IV endometrial cancer is comprised of a diverse patient population with a small proportion of women with well-differentiated endometrioid cancers and a larger proportion of high-risk disease subtypes such as uterine papillary serous carcinoma, clear-cell carcinomas, or carcinosarcoma of the uterus.

The overall poor prognosis of this group is highlighted by the Cochrane Library meta-analysis comparing different treatment strategies in this population. The review discusses the findings of 14 randomized clinical trials and offers multiple comparisons: administration of multi-agent combinations ("more intensive") versus fewer agents ("less intensive"), comparison across different chemotherapy doublets, and a comparison across different single chemotherapeutic agents. The conclusions are sobering. Compared with the administration of "less intensive" regimens, the use of "more intensive" regimens (eight trials including 1519 patients) resulted in improved PFS from 6 to 7 months (HR 0.82, CI 0.74–0.90) and OS from 9 to 10.5 months (HR 0.86, CI 0.77–0.96). Trials that compared doxorubicin (plus or minus cisplatin) with or without additional drugs favored the arms incorporating additional chemotherapy at the cost of additional toxicity. No single agent or combination chemotherapy regimen or schedule stood out.

Neoadjuvant chemotherapy is an interesting strategy that allows the identification of chemosensitive disease that is more likely to benefit from debulking surgery when compared to chemoresistant disease. It also provides a feasible up-front strategy for patients with unresectable disease or who are not otherwise candidates for cytoreductive surgery due to medical comorbidities. Given the considerable risk of postoperative complications associated with primary debulking reported at 36–39 % in the endometrial cancer population [10, 11], coupled with the older age and increased medical comorbidities associated with this disease, neoadjuvant chemotherapy may be a reasonable first approach in patients with advanced disease. In a prospective clinical trial including 30 patients who received 3–4 cycles of neoadjuvant chemotherapy prior to an attempt at cytoreduction, the Leuven Group concluded that the degree of tumor regression after NACT for advanced-stage endometrial cancer was a new prognostic marker. In their study, carboplatin and paclitaxel chemotherapy achieved a response rate of 74 %, with 2 complete responses and 20 partial responses. They did not operate on patients with progression of disease. Their optimal cytoreduction rate was 80 % ($\leq$1 cm) with a low postoperative morbidity rate [14].

The most active drugs in women with no prior chemotherapy are platinum agents, taxanes, and anthracyclines, all producing response rates of

20–30 % as single agents. Combination chemotherapy has produced higher response rates and improved survival in randomized trials. Several combination regimens have been tested in phase III trials and are summarized in Table 1. Based on phase II evidence reporting response rates between 40 and 74 % at acceptable toxicity for carboplatin and paclitaxel in both a chemo-naïve and a pretreated population, this combination was further studied in the phase III setting [14, 22–25]. Notably, in GOG 209, which utilized a non-inferiority design, carboplatin and paclitaxel (CT) as a doublet was not inferior to paclitaxel, doxorubicin, and cisplatin (TAP) with a more favorable toxicity profile, leading to its adoption as the standard doublet moving forward in clinical trials [21]. Interestingly, both treatment arms were associated with more than doubled median OS compared with previous studies. The marked improvement in median OS when compared to previous studies is likely to be multifactorial and reflect differential inclusion of a group of patients with improved prognosis, improvements in subsequent therapy, wider availability of imaging studies, and possible earlier detection of recurrences [26].

Single-Agent Chemotherapy

A large number of cytotoxic agents have been tested in endometrial carcinoma since the early 1960s. Results of single-agent trials for drugs that are commercially available are presented in Table 2.

Anthracyclines were among the first agents proven to be effective. Doxorubicin has been studied in phase II and III clinical trials at doses of 50–60 mg/m^2, yielding overall response rates between 25 and 37 % (see Table 2). Epirubicin produced a similar response rate of 26 % in one small phase II study [40]. Pegylated liposomal doxorubicin (Doxil®) proved disappointing in first-line treatment, producing a response rate of only 11.5 % [42]. However, additional data demonstrated RR of 36 % in the first line and 22 % in second line [43, 44]. Moreover, activity in combination with carboplatin is encouraging [26].

Platinum agents also have good activity. Cisplatin and its less neurotoxic analog, carboplatin, have produced response rates between 20 and 42 % in a number of single-agent trials (see Table 2). A trial of oxaliplatin by the GOG in patients with prior platinum therapy reported a response rate of 13.5 % [41]. The taxanes, paclitaxel and docetaxel, are the only agents ever shown to have meaningful activity in previously treated patients and have, therefore, now been incorporated into most frontline regimens (see Table 2). The data for agents beyond taxanes, anthracyclines, and platinum is summarized below [15, 32, 34, 35, 51, 52]. The combination of cisplatin and gemcitabine achieved 50 % RR in a population of chemo-naïve patients with recurrent disease [53]. The response rate observed for single-agent chemotherapy is rarely over 20 %. Ixabepilone appeared promising but a subsequent phase III trial did not see any benefit over the control arm (doxorubicin or paclitaxel) [54]. New treatment strategies including further developing the "chemotherapy backbone" are urgently needed for this disease [26] (Table 3).

Carcinosarcomas

Uterine carcinosarcomas (malignant mixed müllerian tumors) have been traditionally classified as a subtype of uterine sarcoma but accumulating molecular evidence has reclassified these tumors as more closely related to carcinomas and frequently it is the carcinoma component that will metastasize.

Response rates for single-agent chemotherapy in carcinosarcomas range from 0 to 10 % for doxorubicin [55, 56], 18 to 42 % for cisplatin [57, 58], 32 % for ifosfamide, and 18 % for paclitaxel [59, 60]. As with endometrial carcinomas, combination chemotherapy regimens have been shown to improve response rates at the expense of added toxicity. GOG 194 randomized women with advanced, recurrent, or persistent carcinosarcoma to treatment with ifosfamide alone or ifosfamide plus cisplatin

Table 1 Landmark trials of combination chemotherapy for endometrial cancer

Reference	Accrual	Phase	Intervention	*N*	Study population	ORR (%)	PFS (mo)	OS (mo)
Thigpen GOG-048 [15]	1979–1985	3	Doxorubicin 60 mg/m^2 Q21D Doxorubicin 60 mg/m^2 + cyclophosphamide 500 mg/m^2 Q21D	132 144	Chemo-naïve	22 30	3.2 3.9	6.7 7.3
Thigpen GOG-107 [16]	12/1988–12/1991	3	Doxorubicin 60 mg/m^2 Q21D Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q21D	150 131	Chemo-naïve	25 42	4 6	9 9
Aapro EORTC-55872 [17]	9/1988–6/1994	3	Doxorubicin 60 mg/m^2 Q28D Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q28D	87 90	Chemo-naïve	17 43	7 8	7 9 ($p = 0.06$)
Gallion GOG-139 [18]	3/1993–8/1996	3	Doxorubicin 60 mg/m^2 + cisplatin 60 mg/m^2 Q21D Doxorubicin 60 mg/m^2 (6 am) + cisplatin 60 mg/m^2 (6 pm) Q21D	169 173	Chemo-naïve	46 49	6.5 5.9	11.2 13.2
Fleming GOG-163 [19]	8/1996–11/1998	3	Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q21D Doxorubicin 50 mg/m^2 + paclitaxel 150 mg/m^2/24 h Q21D + G-CSF	157 160	Chemo-naïve	40 43	7.2 6.0	12.6 13.6
Fleming GOG-177 [20]	12/1998–8/2000	3	Doxorubicin 60 mg/m^2 + cisplatin 50 mg/m^2 Q21D Doxorubicin 45 mg/m^2 + cisplatin 50 mg/m^2 + paclitaxel 160 mg/m^2 Q21D + G-CSF	129 134	Chemo-naïve	34 57	5 8	12 15 ($p = 0.03$)
Miller GOG-209 [21]	8/2003–4/2009	3	Carboplatin AUC 6 + paclitaxel 175 mg/m^2 Doxorubicin 45 mg/m^2 + cisplatin 50 mg/m^2 + paclitaxel 160 mg/m^2 Q21D + G-CSF	663 642	Chemo-naïve	NR NR	14 14	32 38

Reference arms listed first. p value only listed for significant differences

Table 2 Single-agent chemotherapy for endometrial cancer: anthracyclines, taxanes, and platinum

Chemotherapy	Dose	Population	*N*	RR (%)
Carboplatin [27]	300 mg/m^2 q 4 weeks	Prior chemo	17	0
Carboplatin [27]	400 mg/m^2 q 28 days	Chemo-naïve	33	24
Cisplatin [28]	50 mg/m^2 q 3 weeks	Chemo-naïve	11	36
Cisplatin [29]	50 mg/m^2 q 3 weeks	Prior chemo	25	4
Cisplatin [30]	50 mg/m^2 q 3 weeks	Chemo-naïve	49	20
Cisplatin [31]	50–100 mg/m^2 q 4 weeks	Chemo-naïve	26	42
Cisplatin [32]	60 mg/m^2 q 21 days	Chemo-naïve	14	21
Cisplatin [33]	3 mg/kg q 3 weeks	Prior chemo	13	31
Cyclophosphamide [34]	666 mg/m^2 q 3 weeks	Chemo-naïve	19	0
Cyclophosphamide [35]	1200 mg/m^2/24 h q 3 weeks	Chemo-naïve	14	14
Cyclophosphamide [35]	1200 mg/m^2/24 h q 3 weeks	Prior chemo	15	0
Dactinomycin [36]	2 mg/m^2 q 4 weeks	Prior chemo	25	12
Docetaxel [37]	35 mg/m^2 q week	Chemo-naïve	34	21
Docetaxel [38]	70 mg/m^2 q 3 weeks	Chemo-naïve	19	37
Docetaxel [38]	70 mg/m^2 q 3 weeks	Prior chemo	13	23
Doxorubicin [34]	50 mg/m^2 q 3 weeks	Chemo-naïve	21	19
Doxorubicin [34]	50 mg/m^2 q 3 weeks	Prior chemo	9	11
Doxorubicin [39]	60 mg/m^2 q 3 weeks	Chemo-naïve	43	37
Epirubicin [40]	80 mg/m^2 q 3 weeks	Chemo-naïve	27	26
Oxaliplatin [41]	130 mg/m^2 q 21 days	Prior chemo	52	13.5
Liposomal doxorubicin [42]	40 mg/m^2 q 4 weeks	Chemo-naïve	52	11.5
Liposomal doxorubicin [43]	40 mg/m^2 q 4 weeks	Chemo-naïve	22	36
Liposomal doxorubicin [44]	40 mg/m^2 q 4 weeks	Prior chemo	19	22
Liposomal doxorubicin [45]	50 mg/m^2 q 4 weeks	Prior chemo	42	9.5
Paclitaxel [46]	175 mg/m^2 q 3 weeks	Prior chemo	19	37
Paclitaxel [47]	170 mg/m^2 q 3 weeks	Prior chemo	7	43
Paclitaxel [48]	200 mg/m^2 q 3 weeks	Prior chemo	44	27
Paclitaxel [49]	210 mg/m^2 q 3 weeks	Chemo-naïve	10	60
Paclitaxel [49]	210 mg/m^2 q 3 weeks	Prior chemo	13	7.7
Paclitaxel [50]	250 mg/m^2/24 h + G-CSF q 21 days	Chemo-naïve	28	36

RR response rate
G-CSF granulocyte colony-stimulating factor

[61]. The combination regimen produced better response rates (54 % versus 36 %), but there was no significant difference in OS (7.6 months versus 9.4 months, $p = 0.071$). A subsequent study randomized chemotherapy-naïve women with stage III or IV disease to ifosfamide alone or ifosfamide plus paclitaxel [62]. The combination arm produced a significant improvement in response rate, PFS, and OS (HR 0.69; 95 % CI 0.49–0.97; $p = 0.03$). In the phase II setting, carboplatin and paclitaxel have demonstrated an RR of 54 % with acceptable toxicity in 55 patients [63]. An ongoing phase III clinical trial is comparing the combination of carboplatin and paclitaxel to the standard ifosfamide and paclitaxel in this disease (GOG 261).

New Directions

A greater understanding of cancer biology and major advances in biotechnology in the last decade have led to the development of agents targeted against specific abnormalities in cancers, especially to aberrant growth signal transduction and microenvironment factors. A number of these novel therapeutic agents are currently being investigated in advanced endometrial cancer. Agents of interest include erlotinib (an EGFR tyrosine kinase inhibitor), trastuzumab (an epidermal growth factor receptor inhibitor), antiangiogenics (bevacizumab, cediranib among others), and mTOR inhibitors

Table 3 Chemotherapy for endometrial cancer: beyond TAP

Chemotherapy	Dose	Population	*N*	RR (%)
Etoposide IV [66]	100 mg/m^2 days 1, 3, 5 q 28 days	Prior chemo	29	3
Etoposide PO [67]	50 mg/day × 21 days q 28 days	Chemo-naïve	44	14
Etoposide PO [68]	50 mg/m^2 × 21 q 28 days	Prior chemo	22	0
Ifosfamide [69]	1.2 g/m^2/day × 5 days q 4 weeks	Chemo-naïve	33	24
Gemcitabine [70]	800 mg/m^2 IV q 21 days	Prior chemo	24	4
Cisplatin + Gemcitabine [53]	P: 30 mg/m^2 IV, G: 900 mg/m^2 IV q 21 days	Prior chemo	21	50
Ifosfamide [71]	1.2 g/m^2/day × 5 q 4 weeks	Prior chemo	40	15
Ifosfamide [35]	5 g/m^2/24 h q 3 weeks	Chemo-naïve	16	25
Ifosfamide [35]	5 g/m^2/24 h q 3 weeks	Prior chemo	16	0
Ixabepilone [72]	40 mg/m^2 IV q 21 days	Prior chemo	52	12
Methotrexate [73]	40 mg/m^2/week	Chemo-naïve	33	6
Topotecan [51]	0.5–1.5 mg/m^2 × 5 q 21 days	Prior chemo	22	9
Topotecan [52]	0.8–1.5 mg/m^2 × 5 days q 21 days	Chemo-naïve	40	20
Vinblastine [57]	1.5 mg/m^2/24 h × 5 days q 3 weeks	Chemo-naïve	34	12
Vincristine [74]	1.4 mg/m^2 q week × 4 then q 2 weeks	Chemo-naïve	33	18
Vincristine [75]	0.25–0.5 mg/m^2 CIV × 5 days	Prior chemo	5	0

RR response rate
G-CSF granulocyte colony-stimulating factor

Table 4 Targeted therapies for recurrent endometrial cancer

Biologic agent	Dose	Population	*N*	RR (%)
Bevacizumab	15 mg/kg IV q 21 days	Prior chemo	56	13.5
Bevacizumab + temsirolimus [76]	B: 10 mg/kg q 14 days, T: 25 mg IV weekly	Prior chemo	53	24.5
Erlotinib [77]	150 mg daily	Chemo-naïve	34	12.5
Everolimus + Letrozole [65]	E: 10 mg PO daily, L: 2.5 mg PO daily	Prior chemo	38	32
Pilaralisib [64]	600 mg PO daily or 400 mg PO daily	Prior chemo	67	6
Trastuzumab [78]	4 mg/kg week 1 then 2 mg/kg weekly	Prior chemo	34	0

(everolimus, temsirolimus, and the novel dual-mTOR inhibitors). PI3K, AKT, and dual-mTOR inhibitors are also under investigation for this disease, some with disappointing results as single agents [64]. Metformin, a widely available oral biguanide, is also being studied in GOG protocol 286 in combination with chemotherapy for advanced endometrial cancer. In addition to its role in inhibiting gluconeogenesis, metformin is postulated to act as a dual-mTOR inhibitor in endometrial cancer cells. A recently published phase II study of the combination of everolimus and letrozole reports an objective response rate of 32 % in 38 patients who were previously considered incurable, with up to two prior cytotoxic chemotherapies. Nine complete responses were achieved with 15 cycles as the median number of cycles among responders. None of the patients in this promising trial discontinued therapy based on toxicity [65]. There is increasing opportunity to incorporate biologic agents in the treatment of women with advanced endometrial cancer; future directions include implementing small-molecule inhibitors to extend the role of systemic therapies and further improve patient outcomes (Table 4).

Conclusions

- Patients with advanced or recurrent endometrial carcinoma have a median survival of about a year.

- Platinum/taxane-based chemotherapy produces response rates between 40 and 60 % in the setting of metastatic endometrial carcinoma.
- A survival benefit has recently been demonstrated for the use of adjuvant chemotherapy in stage III endometrial carcinoma.
- Uterine carcinosarcomas are aggressive cancers with a 35 % overall 5-year survival. Preliminary data suggest a benefit to adjuvant chemotherapy.

References

1. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. Semin Surg Oncol. 1994;10:31–46.
2. Randall ME, Spirtos NM, Dvoretsky P. Whole abdominal radiotherapy versus combination chemotherapy with doxorubicin and cisplatin in advanced endometrial carcinoma (phase III): Gynecologic Oncology Group Study No. 122. J Natl Cancer Inst Monogr. 1995;19:13–5.
3. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer. 2006;95:266–71.
4. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol. 2008;108:226–33.
5. Hogberg T. Adjuvant chemotherapy in endometrial cancer. Int J Gynecol Cancer. 2010;20:S57–9.
6. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. Gynecol Oncol. 2009;112:543–52.
7. Galaal K, Al Moundhri M, Bryant A, Lopes AD, Lawrie TA. Adjuvant chemotherapy for advanced endometrial cancer. Cochrane Database Syst Rev. 2014;5, CD010681.
8. Goff BA, Goodman A, Muntz HG, Fuller Jr AF, Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol. 1994;52:237–40.
9. Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in stage IV endometrial carcinoma. Gynecol Oncol. 1997;67:56–60.
10. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. 2000;78:85–91.
11. Memarzadeh S, Holschneider CH, Bristow RE, et al. FIGO stage III and IV uterine papillary serous carcinoma: impact of residual disease on survival. Int J Gynecol Cancer. 2002;12:454–8.
12. Lambrou NC, Gomez-Marin O, Mirhashemi R, et al. Optimal surgical cytoreduction in patients with stage III and stage IV endometrial carcinoma: a study of morbidity and survival. Gynecol Oncol. 2004;93:653–8.
13. Thomas MB, Mariani A, Cliby WA, Keeney GL, Podratz KC, Dowdy SC. Role of cytoreduction in stage III and IV uterine papillary serous carcinoma. Gynecol Oncol. 2007;107:190–3.
14. Vandenput I, Van Calster B, Capoen A, et al. Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment? Br J Cancer. 2009;101:244–9.
15. Thigpen JT, Blessing JA, DiSaia PJ, Yordan E, Carson LF, Evers C. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 1994;12:1408–14.
16. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2004;22:3902–8.
17. Aapro M. Docetaxel versus doxorubicin in patients with metastatic breast cancer who have failed alkylating chemotherapy: a preliminary report of the randomized phase III trial. 303 Study Group. Semin Oncol. 1998;25:7–11.
18. Gallion HH, Brunetto VL, Cibull M, et al. Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2003;21:3808–13.
19. Fleming GF, Filiaci VL, Bentley RC, et al. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. Ann Oncol. 2004;15:1173–8.
20. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial

carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2004;22:2159–66.
21. Miller DFV, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2012;3:771–3.
22. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. J Clin Oncol. 2001;19:4048–53.
23. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. Int J Gynecol Cancer. 2008;18:803–8.
24. Scudder SA, Liu PY, Wilczynski SP, et al. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. Gynecol Oncol. 2005;96:610–5.
25. Arimoto T, Nakagawa S, Yasugi T, et al. Treatment with paclitaxel plus carboplatin, alone or with irradiation, of advanced or recurrent endometrial carcinoma. Gynecol Oncol. 2007;104:32–5.
26. Goldfinger M, Diaz I, Muggia F. Systemic treatment of endometrial cancer: what is doxorubicin's role? J Clin Oncol. 2014;32:2181–2.
27. van Wijk FH, Lhomme C, Bolis G, et al. Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynaecological Cancer Group. Eur J Cancer. 2003;39:78–85.
28. Trope C, Grundsell H, Johnsson JE, Cavallin-Stahl E. A phase II study of Cis-platinum for recurrent corpus cancer. Eur J Cancer. 1980;16:1025–6.
29. Thigpen JT, Blessing JA, Lagasse LD, DiSaia PJ, Homesley HD. Phase II trial of cisplatin as second-line chemotherapy in patients with advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group study. Am J Clin Oncol. 1984;7:253–6.
30. Thigpen JT, Blessing JA, Homesley H, Creasman WT, Sutton G. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 1989;33:68–70.
31. Seski JC, Edwards CL, Herson J, Rutledge FN. Cisplatin chemotherapy for disseminated endometrial cancer. Obstet Gynecol. 1982;59:225–8.
32. Edmonson JH, Krook JE, Hilton JF, et al. Randomized phase II studies of cisplatin and a combination of cyclophosphamide-doxorubicin-cisplatin (CAP) in patients with progestin-refractory advanced endometrial carcinoma. Gynecol Oncol. 1987;28:20–4.
33. Deppe G, Cohen CJ, Bruckner HW. Treatment of advanced endometrial adenocarcinoma with cis-dichlorodiamine platinum (II) after intensive prior therapy. Gynecol Oncol. 1980;10:51–4.
34. Horton J, Begg CB, Arseneault J, Bruckner H, Creech R, Hahn RG. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. Cancer Treat Rep. 1978;62:159–61.
35. Pawinski A, Tumolo S, Hoesel G, et al. Cyclophosphamide or ifosfamide in patients with advanced and/or recurrent endometrial carcinoma: a randomized phase II study of the EORTC Gynecological Cancer Cooperative Group. Eur J Obstet Gynecol Reprod Biol. 1999;86:179–83.
36. Moore DH, Blessing JA, Dunton C, Buller RE, Reid GC. Dactinomycin in the treatment of recurrent or persistent endometrial carcinoma: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 1999;75:473–5.
37. Gunthert AR, Ackermann S, Beckmann MW, et al. Phase II study of weekly docetaxel in patients with recurrent or metastatic endometrial cancer: AGO Uterus-4. Gynecol Oncol. 2007;104:86–90.
38. Katsumata N, Noda K, Nozawa S, et al. Phase II trial of docetaxel in advanced or metastatic endometrial cancer: a Japanese Cooperative Study. Br J Cancer. 2005;93:999–1004.
39. Thigpen JT, Buchsbaum HJ, Mangan C, Blessing JA. Phase II trial of adriamycin in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Cancer Treat Rep. 1979;63:21–7.
40. Calero F, Asins-Codoner E, Jimeno J, et al. Epirubicin in advanced endometrial adenocarcinoma: a phase II study of the Grupo Ginecologico Espanol para el Tratamiento Oncologico (GGETO). Eur J Cancer. 1991;27:864–6.
41. Fracasso PM, Blessing JA, Molpus KL, Adler LM, Sorosky JI, Rose PG. Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2006;103:523–6.
42. Homesley HD, Blessing JA, Sorosky J, Reid G, Look KY. Phase II trial of liposomal doxorubicin at 40 mg/m(2) every 4 weeks in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2005;98:294–8.
43. Balbi G, Visconti S, Monteverde A, Manganaro MA, Cardone A. Liposomal doxorubicin: a phase II trial. Acta Biomed. 2007;78:210–3.
44. Escobar PF, Markman M, Zanotti K, Webster K, Belinson J. Phase 2 trial of pegylated liposomal doxorubicin in advanced endometrial cancer. J Cancer Res Clin Oncol. 2003;129:651–4.
45. Muggia FM, Blessing JA, Sorosky J, Reid GC. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2002;20:2360–4.
46. Lissoni A, Zanetta G, Losa G, Gabriele A, Parma G, Mangioni C. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol. 1996;7:861–3.

47. Woo HL, Swenerton KD, Hoskins PJ. Taxol is active in platinum-resistant endometrial adenocarcinoma. Am J Clin Oncol. 1996;19:290–1.
48. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2003;88:277–81.
49. Hirai Y, Hasumi K, Onose R, et al. Phase II trial of 3-h infusion of paclitaxel in patients with adenocarcinoma of endometrium: Japanese Multicenter Study Group. Gynecol Oncol. 2004;94:471–6.
50. Ball HG, Blessing JA, Lentz SS, Mutch DG. A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group Study. Gynecol Oncol. 1996;62:278–81.
51. Miller DS, Blessing JA, Lentz SS, Waggoner SE. A phase II trial of topotecan in patients with advanced, persistent, or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2002;87:247–51.
52. Wadler S, Levy DE, Lincoln ST, Soori GS, Schink JC, Goldberg G. Topotecan is an active agent in the first-line treatment of metastatic or recurrent endometrial carcinoma: Eastern Cooperative Oncology Group Study E3E93. J Clin Oncol. 2003;21:2110–4.
53. Brown J, Smith JA, Ramondetta LM, et al. Combination of gemcitabine and cisplatin is highly active in women with endometrial carcinoma: results of a prospective phase 2 trial. Cancer. 2010;116:4973–9.
54. McMeekin S, Dizon D, Barter J, et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. Gynecol Oncol. 2015;138:18–23.
55. Gershenson DM, Kavanagh JJ, Copeland LJ, Edwards CL, Freedman RS, Wharton JT. High-dose doxorubicin infusion therapy for disseminated mixed mesodermal sarcoma of the uterus. Cancer. 1987;59:1264–7.
56. Omura GA, Major FJ, Blessing JA, et al. A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer. 1983;52:626–32.
57. Thigpen JT, Kronmal R, Vogel S, et al. A phase II trial of vinblastine in patients with advanced or recurrent endometrial carcinoma. A Southwest Oncology Group Study. Am J Clin Oncol. 1987;10:429–31.
58. Thigpen JT, Blessing JA, Orr Jr JW, DiSaia PJ. Phase II trial of cisplatin in the treatment of patients with advanced or recurrent mixed mesodermal sarcomas of the uterus: a Gynecologic Oncology Group Study. Cancer Treat Rep. 1986;70:271–4.
59. Sutton GP, Blessing JA, Rosenshein N, Photopulos G, DiSaia PJ. Phase II trial of ifosfamide and mesna in mixed mesodermal tumors of the uterus (a Gynecologic Oncology Group Study). Am J Obstet Gynecol. 1989;161:309–12.
60. Curtin JP, Blessing JA, Soper JT, DeGeest K. Paclitaxel in the treatment of carcinosarcoma of the uterus: a gynecologic oncology group study. Gynecol Oncol. 2001;83:268–70.
61. Sutton G, Brunetto VL, Kilgore L, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: a Gynecologic Oncology Group Study. Gynecol Oncol. 2000;79:147–53.
62. Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25:526–31.
63. Powell MA, Filiaci VL, Rose PG, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group Study. J Clin Oncol. 2010;28:2727–31.
64. Matulonis U, Vergote I, Backes F, et al. Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. Gynecol Oncol. 2015;136:246–53.
65. Slomovitz BM, Jiang Y, Yates MS, et al. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol. 2015;33:930–6.
66. Slayton RE, Blessing JA, Delgado G. Phase II trial of etoposide in the management of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Cancer Treat Rep. 1982;66:1669–71.
67. Poplin EA, Liu PY, Delmore JE, et al. Phase II trial of oral etoposide in recurrent or refractory endometrial adenocarcinoma: a Southwest Oncology Group Study. Gynecol Oncol. 1999;74:432–5.
68. Rose PG, Blessing JA, Lewandowski GS, Creasman WT, Webster KD. A phase II trial of prolonged oral etoposide (VP-16) as second-line therapy for advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 1996;63:101–4.
69. Sutton GP, Blessing JA, DeMars LR, Moore D, Burke TW, Grendys EC. A phase II Gynecologic Oncology Group trial of ifosfamide and mesna in advanced or recurrent adenocarcinoma of the endometrium. Gynecol Oncol. 1996;63:25–7.
70. Tait DL, Blessing JA, Hoffman JS, et al. A phase II study of gemcitabine (gemzar, LY188011) in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2011;121:118–21.
71. Sutton GP, Blessing JA, Homesley HD, McGuire WP, Adcock L. Phase II study of ifosfamide and mesna in refractory adenocarcinoma of the endometrium. A Gynecologic Oncology Group Study. Cancer. 1994;73:1453–5.
72. Dizon DS, Blessing JA, McMeekin DS, Sharma SK, Disilvestro P, Alvarez RD. Phase II trial of ixabepilone as second-line treatment in advanced

endometrial cancer: gynecologic oncology group trial 129-P. J Clin Oncol. 2009;27:3104–8.
73. Muss HB, Blessing JA, Hatch KD, Soper JT, Webster KD, Kemp GM. Methotrexate in advanced endometrial carcinoma. A phase II trial of the Gynecologic Oncology Group. Am J Clin Oncol. 1990;13:61–3.
74. Broun GO, Blessing JA, Eddy GL, Adelson MD. A phase II trial of vincristine in advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group Study. Am J Clin Oncol. 1993;16:18–21.
75. Jackson Jr DV, Jobson VW, Homesley HD, et al. Vincristine infusion in refractory gynecologic malignancies. Gynecol Oncol. 1986;25:212–6.
76. Alvarez T, Miller E, Duska L, Oliva E. Molecular profile of grade 3 endometrioid endometrial carcinoma: is it a type I or type II endometrial carcinoma? Am J Surg Pathol. 2012;36:753–61.
77. Oza AM, Eisenhauer EA, Elit L, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. J Clin Oncol. 2008;26:4319–25.
78. Fleming GF, Sill MW, Darcy KM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2010;116:15–20.

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Treatment for Advanced and Recurrent Carcinoma: Combined Modalities

Marcela G. del Carmen and Neil S. Horowitz

Abstract

The use of chemotherapy has provided new opportunities for exploring the combination of local and systemic modalities in the treatment of both early and advanced stages of endometrial carcinoma. The following circumstances are discussed: (1) radiation therapy for locally recurrent endometrial cancer; (2) surgery for stage IV and recurrent endometrial cancer; and (3) advanced stage endometrial cancer consolidating with postoperative and post-chemotherapy radiation therapy. Integration of hormones is also discussed.

Keywords

Endometrial cancer • Radiation • Surgery in stage IV and recurrences • Chemotherapy • Hormones

Endometrial cancer is generally associated with a good prognosis. This is largely due to the fact that approximately 75 % of patients present with stage I disease and 13 % of patients present with stage II disease [1]. For these women, surgery alone or in combination with local therapy is generally curative. For patients with stage III or IV disease or for those with recurrent endometrial cancer, prognosis remains poor and the optimal adjuvant therapy is yet to be established (Table 1). A subset of these patients may benefit from hormonal manipulation, systemic chemotherapies, or combination treatment with volume directed radiotherapy and systemic chemotherapy. The choice of therapy depends on the extent of residual disease after initial surgery, site and nature of the recurrence, the prior therapy used, and the intent of treatment, be it curative or palliative. As the use of hormonal therapy and chemotherapy for treatment of advanced or recurrent carcinoma is addressed elsewhere in this book, the aim of this chapter is to focus on combined treatment modalities for this group of women.

M.G. del Carmen, M.D., M.P.H. (✉) and
N.S. Horowitz, M.D.
Division of Gynecologic Oncology, Vincent Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Yawkey 9 E, Boston, MA 02114, USA
e-mail: mdelcarmen@partners.org

Table 1 Five-year survival for patients with endometrial cancer by FIGO staging

FIGO staging	Five-year survival (percent)
IA	88.9
IB	90.0
IC	80.7
IIA	79.9
IIB	72.3
IIIA	63.4
IIIB	38.8
IIIC	51.1
IVA	19.9
IVB	17.2

FIGO: International Federation of Gynecology and Obstetrics
Adapted from J Epidemiol Biostat 2000;5:221 and using 1988 FIGO staging system

Radiation Therapy for Locally Recurrent Endometrial Cancer

Site of recurrence, previous treatment with radiation therapy, relapse-free interval, and histology are important prognostic factors affecting survival in patients with recurrent endometrial cancer. A longer relapse-free interval, low-grade histology, isolated vaginal recurrence, and endometrioid adenocarcinomas are factors associated with improved survival in recurrent endometrial cancer [2, 3]. In general, women with non-endometrioid histologies have a worse prognosis than those with endometrioid histologies. For women with a recurrent endometrial cancer following primary treatment with surgery alone, radical radiation therapy may be appropriate.

For a select group of patients not previously radiated and with small vaginal recurrences, radiation therapy may be curative. The use of radiation therapy, as part of primary treatment, influences sites of recurrence and survival after relapse. As documented by the PORTEC trial, survival was longer for women with recurrent disease who had not been treated with adjuvant radiation following primary surgical therapy [4, 5]. This trial included women with stage I disease, not all of whom had complete surgical staging, and randomized them to surgery alone or adjuvant pelvic radiation therapy [4, 5]. At 3 years, the actuarial survival for women, after any relapse, in the non-radiation therapy group was 51 %, compared to 19 % for women in the adjuvant radiation therapy group [4, 5]. After an isolated vaginal cuff recurrence, 5-year survival for the nonradiated group was 65 %, compared to 43 % for women randomized to the adjuvant radiation therapy arm of the study [4, 5]. For women treated with radiation therapy in the recurrent setting, long-term survival is reported to range from 18 to 71 % [6–9]. Five-year survival for these women is documented to range from 25 to 50 % [9–11].

Successful local control depends on anatomic site of recurrence and tumor size at relapse. Local control is possible in 40–75 % of women treated with salvage radiation therapy [3, 7, 9, 11]. In a series of 91 patients with isolated vaginal recurrences, local control was seen in 75 % of those treated with salvage radiation therapy [9]. Tumor size at the time of recurrence also influences local control. In a series of 58 women with recurrent endometrial cancer, 5-year local control was 80 % for those with tumors ≤ 2 cm compared to 54 % for those with larger tumors ($p = 0.02$) [11]. Women with noncentral recurrences have a worse prognosis than those with isolated vaginal relapse. Although only a limited experience exists, salvage radiation therapy may be appropriate in the setting of a noncentral recurrence [12]. For women with a pelvic recurrence, 3-year survival is reported to be 8 %, compared to 73 % for those with an isolated vaginal recurrence [4, 5]. This survival is comparable to the 3-year survival in patients with distant metastases [4, 5].

Patients with vaginal recurrences are usually treated with a combination of pelvic radiation and brachytherapy. For women with a previous history of pelvic radiation therapy, brachytherapy alone is utilized [13]. In the presence of bulky disease, interstitial brachytherapy has been reported to result in excellent pelvic control rates [13, 14]. It is important to underscore that in the recurrent setting, higher doses of radiation therapy are required than the doses used in the

adjuvant setting. As a result, 3–12 % of patients suffer from severe treatment-related side effects, especially in the gastrointestinal tract [3, 6, 9, 14]. Patients with a previous history of radiation therapy are especially susceptible to severe toxicity at the time of radiation therapy in the recurrent setting [6, 14].

The role of concurrent chemotherapy with radiation remains investigational. The Gynecologic Oncology Group (GOG) is conducting a randomized trial (GOG 238) evaluating the role of cisplatin as a radiation sensitizer in this setting.

Surgery for Stage IV and Recurrent Endometrial Cancer

Cytoreductive surgery may play a role in the management of stage IV endometrial cancer. There are several retrospective reviews that suggest a survival advantage in those patients who have their tumor optimally cytoreduced (Table 2) [15–17]. In all three series successful cytoreduction was a statistically significant prognostic variable by multivariant analysis. In the work by Bristow et al., young age (<58 years old) and a good performance status were also predictive of survival [15]. Chi and his colleagues saw no difference in survival for those women who presented with optimal stage IV disease and those that were surgically cytoreduced to an optimal extent of disease suggesting the importance of aggressive surgery in addition to the biology of the tumor plays a role in survival [16].

Recurrent disease isolated to the central pelvis following radiation therapy is seen rarely. Selected patients with such a recurrence may be candidates for pelvic exenteration [18, 19]. Pelvic exenteration has been associated with significant operative morbidity and poor overall survival in the setting of recurrent endometrial cancer [18, 19]. In a series of 44 patients, nine long-term survivors were seen [19]. In this study, the reported median OS was 10.2 % and 5-year OS was 20 %, following pelvic exenteration [19]. This highly morbid procedure may be the only potentially curative alternative for selected patients with a central recurrence following initial surgery and radiation therapy. However, radical pelvic resection and extended pelvic resection in conjunction with intraoperative radiation have also been described [20].

Other than pelvic exenteration for central recurrences, surgery does not have a definitive role in the treatment of patients with recurrent endometrial cancer. Two recent retrospective analyses have explored the role of surgery in this setting. Scarabelli and his colleagues operated on 20 women at the time of their first pelvic or abdominal recurrence [21]. Patients were classified as having no residual tumor or having tumor at the end of surgery [21]. Postoperative therapy was at the discretion of the treating surgeon but included both radiation and chemotherapy. Sixty-five (65 %) of patients were left with no residual disease and had a median progression-free and overall survival of 9.1 months and 11.8 months respectively. This was statistically significantly better than those who were left with disease. The PFS for this

Table 2 Surgical cytoreduction for stage IV endometrial cancer

Author	Reference number	Number of patients	Residual tumor diameter (cm)	Median survival (months)
Goff et al., 1994	[17]	47	Resected	18
			Unresected	8
Chi et al., 1997	[16]	55	≤2 cm	31
			>2 cm	12
			Unresected	3
Bristow et al., 2000	[15]	65	Microscopic	40
			≤1 cm	15
			>1 cm	11

group of women was 1.5 months and none were alive 9 months after surgery. There were two perioperative deaths but otherwise morbidity was acceptable [21]. The other review by Campagnutta et al. is an updated analysis from the same group in Italy [22]. In this series of 75 patients, 56 (75 %) were left with no residual disease but at a significant cost with a 30 % major surgical complications and 8 % postoperative mortality rate [22]. Those patients that did achieve optimal tumor cytoreduction did have an improvement in their cumulative 5-year survival 36 % versus 0 % when compared to those with residual disease [22]. Two additional series of surgical resection or recurrent endometrial cancer showed median survival for those who had optimal or complete cytoreduction was roughly 40 months compared to less than 15 months for those with suboptimal resection. In multivariate analysis size of residual disease was a significant factor associated with survival [23, 24]. Given the modest improvements in survival in both of these reviews and the morbidity and mortality of surgery, appropriate patient selection is critical prior to embarking on this management of recurrent disease.

Advanced Stage Endometrial Cancer

Approximately 5–10 % of patients with endometrial cancer present with clinical stage III disease [25]. Unfortunately, stage III disease includes women with quite varying risks as the ultimate outcome for women with positive cytology as their only risk factor is obviously quite different from those with multiple positive pelvic or para-aortic lymph nodes. This risk stratification is addressed in the new FIGO staging. Radiotherapy alone as primary treatment for these patients carries a 5-year survival rate of 15–40 % and is associated with a high rate of distant failures and as such, surgery is often the mainstay of therapy [25]. The role of adjuvant therapy and more importantly the type of adjuvant treatment for women with stage III disease remain controversial.

The new 2009 FIGO staging system continues to require the collection of peritoneal cytology. However, under this new system, positive pelvic washings are no longer formally considered part of the staging system, and consequently, do not alter staging. The management of patients with positive peritoneal cytology as their only risk factor remains a challenge. These patients, with FIGO stage IIIA, per 1988 staging criteria, have been treated via numerous modalities including observation, hormonal treatment, whole abdominal radiation therapy, and intraperitoneal chromic phosphate. In a series of 22 patients with stage IIIA endometrial cancer, defined as either positive peritoneal cytology and/or adnexal metastases, the reported 5-year disease-free survival was 90 % with the use of whole abdominal radiation therapy [25].

Historically, intraperitoneal chromic phosphate has been used in the treatment of stage III endometrial cancer [26–29]. In a study of 65 patients with clinical stage I–III, the reported 2-year disease-free survival, following the administration of intraperitoneal chromic phosphate, for patients with stage I disease and positive peritoneal cytology, was documented to be 94 % [26]. It is of note that in this study, the administration of intraperitoneal chromic phosphate with whole pelvic radiation therapy led to gastrointestinal tract toxicity, requiring surgical intervention in 29 % of patients [26]. Although intraperitoneal chromic phosphate resulted in adequate disease-free survival, its concomitant use with radiation therapy is not appropriate, given the toxicity profile noted above. In a study by Creasman et al. of 23 patients with positive peritoneal cytology treated with intraperitoneal chromic phosphate, the recurrence rate was documented to be 13 %, with a mortality rate of 9 % [29]. The highly controversial issue with positive peritoneal cytology as an isolated risk factor is evident in this study. Forty-six percent of patients with positive peritoneal cytology as an isolated factor were noted to be at risk of carcinomatosis recurrence and death [29].

The use of hormonal therapy is an appropriate treatment approach to patients with malignant

cytology. In a series of 45 patients with malignant cytology as their only risk factor for adjuvant treatment, all treated with progesterone therapy, 80 % were noted to have estrogen receptor positive (ER+) tumors and 90 % were documented to have progesterone positive tumors (PR+) [30]. Thirty six of them underwent a second-look laparoscopic procedure with 94.5 % of them having no evidence of disease [30]. The remaining two patients were treated with progesterone therapy for an additional 2 years and had a negative third-look laparoscopy [30]. Importantly, there were no documented recurrences or disease-related death [30].

The role of observation for those women with positive cytology as their only risk factor is controversial. The risk of recurrence with positive cytology is often associated with other intrauterine risk factors that help form the basis of recommending additional treatment [27–30]. In a multicenter retrospective analysis of 98 women with stage IIIA disease, 40 women had stage IIIA1 disease and of those 24 met NCCN's guidelines for observation (IIIA1, nonserous histology, and FIGO grade 1–2). None of 12 patients receiving adjuvant therapy recurred while 1 of 12 patients not receiving adjuvant therapy recurred thus suggesting there is a subset of low-risk women with positive cytology that can be observed [28].

The role of postoperative radiation therapy in conferring a survival advantage in patients with stage III endometrial cancer may be related to the impact of gross residual lymph nodal disease prior to initiating radiation therapy. GOG 33, the documented 5-year survival for patients with para-aortic radiation therapy, was noted to be 36 % [31]. In this series, 16 patients had pathologically confirmed para-aortic nodal and pelvic nodal disease prior to initiation of radiation therapy [31]. The radiation dose administered ranged from 4500 to 5075 cGy, delivered through 8 cm wide by 18 cm long portals, starting from the pelvic brim [31]. The documented 5-year survival for patients with both para-aortic and pelvic nodal disease was 43 %, compared to 47 % for those with para-aortic nodal disease only [31]. In a series of 18 patients with para-aortic nodal disease treated with radiation therapy, the 5-year overall survival for patients with microscopic nodal disease was noted to be 67 %, compared to 17 % for patients with gross para-aortic nodal disease prior to commencing radiation therapy [32].

Trying to improve on the outcome of radiation alone, many authors have tried to combine cytotoxic chemotherapy with radiation. The safety and efficacy of combined postoperative chemoradiation have been demonstrated in both ovarian and cervical carcinoma [33–35]. The use of multimodality therapy in endometrial cancer addresses the fact that most relapses after adjuvant radiation occur outside the radiated field. Clearly there is a need for both local and systemic control in advanced staged endometrial cancer. Multiple different chemotherapy agents have been combined with both volume directed and whole abdominal chemotherapy with acceptable toxicity and response rates (Table 3) [36–41]. Unfortunately all of these studies are limited by their small size.

The GOG published the results of a phase III randomized trial for women with stage III with low-volume stage IV disease (<2 cm of residual disease following surgical resection) [42]. In this trial, patients were randomized to either whole abdominal radiation therapy versus combination chemotherapy (cisplatin plus doxorubicin) [42]. The study documented a significant progression-free and overall survival benefiting the patients treated with combination chemotherapy when compared to the patients treated with whole abdominal radiation (hazard for death, 0.68; 95 % CI, 0.52–0.89; $p < 0.01$) [42]. It is important to note that this trial commenced accrual in 1992 and since then radiation techniques, chemotherapeutic regimens, and supportive care measures have improved so that these patients have more options than available in the early 1990s [43]. As noted by Fleming, GOG 122 raised the question of the appropriateness of combining radiation therapy and chemotherapy for these patients [43]. GOG 184 (Table 4) administered radiation therapy to the involved fields (either the pelvis or the pelvis

Table 3 Phase I and II trials evaluating combination chemotherapy and radiation therapy in the management of stage III/IV and high-risk endometrial carcinoma

Author	Stages	Patients	Regimen	Comments
Duska [36]	III/IV, HR	20	TAC f/b 45 Gy WPRT	SBO X2
				13 NED @ median f/u 16 months
Soper [26]	III/IV	10	30 Gy WART + CDDP f/b Dox + CDDP	7 of 10 received chemo
				10/10 grade 4 neutropenia
				5 episodes FN
				Median survival 14 months
Bruzzone [38]	III/IV	45	CDDP + Epidox + Cytoxan f/b 50 Gy WPRT	8 % grade 4 neutropenia
				9 years PFS—30 %, OS—53 %
Frigerio [39]	HR	13	Paxlitaxel + 50 Gy WPRT	Minimal toxicity
				No survival data
Greven [40]	HR	46	45 Gy WPRT + CDDP f/b CDDP + Paclitaxel	2 % grade 4 heme tox w/RT
				62 % grade 4 heme tox w/ CT
				2 years DFS—83 %, OS—90 %
Wilkinson-Ryan [41]	III/IV	51	Carboplatin, Taxol, IMRT 48–52 Gy	80 % 3 years OS; median PFS 42.8, OS—44.9

HR = high-risk endometrial cancer (papillary serous, clear cell, advanced stage); TAC = Paclitaxel 160 mg/m^2, Doxorubicin 45 mg/m^2, Carboplatin AUC 5; f/b = followed by; WPRT = whole pelvic radiotherapy; WART = whole abdominal radiotherapy; CDDP = cisplatin; Dox = Doxorubicin; Epidox = epidoxorubicin; PFS = progression-free survival; OS = overall survival; FN = febrile neutropenia; Duska—TAC = Paclitaxel 160 mg/m^2, Doxorubicin 45 mg/m^2, Carboplatin AUC 5; Soper—CDDP 15 mg/m^2 with RT, Doxorubicin 50 mg/m^2, CDDP 50 mg/m^2; Bruzzone—CDDP 50 mg/m^2, Epidoxorubicin 60 mg/m^2, Cytoxan 600 mg/m^2; Frigerio—Paclitaxel 60 mg/m^2; Greven—CDDP 50 mg/m^2 Day 1 and 28 of WPRT, CDDP 50 mg/m^2, Paclitaxel 175 mg/m^2

Table 4 Current Gynecologic Oncology Group trials for patients with stage III/IV endometrial cancer

Study number	Eligibility	Regimen
184	Stage III, <2 cm	WPRT +/− PA or VB f/b CDDP and Doxorubicin +/− Paclitaxel
209	Stage III/IV, measurable disease	CDDP 50 mg/m^2 + Doxorubicin 45 mg/m^2 + Paclitaxel 160 mg/m^2 v/s Carboplatin AUC 6 + Paclitaxel 175 mg/m^2
9907	Stage III/IV, <2 cm	WART with weekly CDDP 25 mg/m^2 + Paclitaxel 20 mg/m^2
9908	Stage III/IV, <2 cm	Doxorubicin + CDDP f/b WART

WPRT = whole pelvic radiotherapy, WART = whole abdominal radiotherapy, CDDP = cisplatin, PA = Para-aortic, VB = vault brachytherapy, F/b = followed by

and the para-aortic lymph nodes) with subsequent delivery of six cycles of chemotherapy. The randomization in GOG 184 was to different chemotherapeutic regimen, doxorubicin plus cisplatin versus doxorubicin, cisplatin, and paclitaxel [44]. There was no significant improvement in recurrence-free survival with the addition of paclitaxel to cisplatin and doxorubicin, following surgery and radiation therapy [44]. However, the three-drug regimen was associated with increased toxicity [44].

Bevacizumab, the anti-VEGF monoclonal antibody, is active in the treatment of endometrial cancer. In a study of 53 patients, previously treated with up to two prior lines of therapy, the reported overall response rate was 15 %, with a 36 % progression-free interval at 6 months [45]. The reported median PFS and OS were 4 months and 11 months, respectively. There were no gastrointestinal perforation events reported [45]. The role of bevacizumab has been further evaluated in patients with advanced or recurrent endometrial cancer in a three-arm, randomized phase II study (GOG 86P). Patients were randomized to one of three arms: (1) carboplatin and paclitaxel plus bevacizumab;

(2) carboplatin and paclitaxel plus temsirolimus (an mTOR inhibitor); or (3) carboplatin and ixabepilone plus bevacizumab. Accrual to this study has been completed and results will be available for publication in the near future. Finally, in a small feasibility study, Viswanathan and colleagues evaluated the toxicity of combining bevacizumab with radiation in patients with recurrent endometrial cancer. Fifteen women with recurrent endometrial cancer involving the vaginal cuff or retroperitoneal nodes received bevacizumab every 2 weeks during radiation. All patients finished radiation on time and there was excellent short-term PFS and OS. Toxicities were minimal with one thromboembolic event and no GI perforations [46].

Still controversial, however, is the timing of the chemotherapy and the most appropriate agents to use. It is unclear whether systemic treatment should be delivered prior to, after radiation, or delivered as a "sandwich" technique with some chemotherapy delivered before and after radiation. The GOG continues to investigate multimodality therapy and until the results of these studies mature, the answers to many of these questions will not be answered (Table 4).

Combination Hormonal Therapy

The knowledge that the development of endometrial cancer is associated with excess estrogen production has resulted in the use of a variety of progestational agent in the treatment of endometrial cancer [47, 48]. A number of such agents have been used in the setting of recurrent and metastatic endometrial cancer. These agents include medroxyprogesterone acetate (MPA), hydroxyprogesterone caproate, and megestrol acetate. Reported response rates include 14–53 % for MPA, 9–34 % for hydroxyprogesterone caproate, and 11–56 % for megestrol acetate [47–52]. Overall, response rates of 30–35 % have been reported [47–54]. Recent data suggest that response rate to progestational therapy may be only 15–20 % [51, 53]. Response to progestational agents is usually of short duration, with an observed median time of 4 months [55]. The use of these individual agents as hormonal therapy in advanced or recurrent endometrial cancer is discussed in detail in a different section.

The effectiveness of progestational agents has been theorized to be increased with the use of estrogenic compounds, such as tamoxifen [56, 57]. Estrogenic substances have been documented to increase progesterone receptors (PRs) in human endometrial cancers [56, 57]. Progestins may downregulate PRs concentration so that the reduced effectiveness of progestational agents and their short duration may be the result of PRs depletion in tumors treated with these agents [56]. It has also been postulated that agents augmenting PRs concentration, such as tamoxifen, may potentiate the effectiveness of progestin-based therapy [56]. Tamoxifen has been associated with a 10–22 % response rate in the treatment of endometrial cancer [58, 59].

Several studies have investigated the combination therapy of progestational agents with tamoxifen in recurrent and advanced endometrial cancer. In the Eastern Cooperative Oncology Group (ECOG) study, there was no difference in the response rate between megestrol acetate as a single agent versus the combination of tamoxifen and megestrol acetate [60]. In the Gynecologic Oncology Group (GOG) study of alternating tamoxifen and megestrol in the treatment of advanced or recurrent endometrial cancer, an overall response rate of 26 % was noted [61]. In this trial, megestrol (80 mg twice daily) was given for 3 weeks, followed by tamoxifen (20 mg twice daily) for 3 weeks [61]. In another recent GOG study, patients with advanced endometrial cancer were treated with tamoxifen (20 mg twice daily) plus alternating weekly cycles of medroxyprogesterone (100 mg twice daily) [62]. The response rate was 33 %, with a median progression-free survival of 3 months and median overall survival of 13 months [62]. The results of this trial demonstrate the promising activity of combination daily tamoxifen and intermittent weekly medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial cancer [62]. The progression-free survival and median survival

in this trial are similar to those reported for progestin therapy alone [48, 50, 54]. The reported adverse effects were also comparable to those reported in a series of patients treated with hormonal therapy. However, the reported 33 % response rate is one of the highest seen among the GOG trials investigating the use of hormonal therapy in patients with advanced or recurrent endometrial cancer. Combination hormonal therapy for advanced or recurrent endometrial cancer is an attractive treatment alternative for selected patients, especially those with hormone receptor positive tumors. The potential response rate and the low toxicity profile associated with these agents make them a suitable therapeutic first choice for many such patients.

Combination Chemohormonal Therapy

Combination regimens utilizing chemotherapy with hormonal therapy have also been investigated in the treatment of advanced and recurrent endometrial cancer. The use of chemotherapy alone for recurrent or advanced endometrial cancer is discussed in detail in a different section. It is important to highlight the fact that only a few studies have evaluated the use of chemotherapy concurrently with hormonal therapy. These investigations have several, serious methodological errors, are underpowered, and have not included the most active chemotherapeutic agents in endometrial cancer. Only a few of the phase II clinical trials have accrued an excess of 20 patients. These trials document response rates ranging from 40 to 50 %, similar to the response rates seen with combination chemotherapeutic regimens without hormonal therapy [63, 64]. A limited number of randomized trials have compared two different chemotherapeutic regimens containing progestins [63, 65]. In the study by Ayoub et al., the use of cyclophosphamide, doxorubicin, and 5-fluorouracil is compared with and without sequential medroxyprogesterone acetate alternating with tamoxifen [66]. In this study of 43 patients, the response rate in the hormone-containing regimen was 43 %, compared to 15 % in the chemotherapy-only arm [66]. The documented median survival in the combination chemotherapy-hormone therapy arm was noted to be 14 months, compared to 11 months for the chemotherapy-only arm [54]. This difference in median survival was not statistically significant [66].

In the study by Cornelison et al., 50 consecutive patients were treated with melphalan, 5-fluorouracil, and medroxyprogesterone acetate as first-line therapy [67]. Fifty additional patients were treated prospectively and at a later time with cisplatin, doxorubicin, etoposide, and megestrol acetate [67]. The response rate for the two regimens was similar [67]. A significant advantage in 2-year (45 % versus 14 %), 5-year (30 % versus 5 %), and median survival (22 months versus 9 months) was seen with the second regimen (cisplatin, doxorubicin, etoposide, and megestrol acetate), when compared to the first regimen (melphalan, 5-fluorouracil, and medroxyprogesterone acetate) [67].

In a recent study, 23 patients were treated with carboplatin, methotrexate, and 5-fluorouracil, in combination with medroxyprogesterone acetate [68]. Seventy-four percent of patients had an objective response, with a long-lasting response seen in two patients (9 %) [68]. The documented median response duration was longer than 10 months (3–45+), with a median survival longer than 16 months (2–45+) [68]. The earlier trials failed to show that simultaneous chemotherapy and hormonal therapy is superior to the more traditional treatment strategy of utilizing hormonal therapy followed by chemotherapy at the time of disease progression.

Finally, Bevis and colleagues evaluated paclitaxel, carboplatin, and megestrol acetate in the management of advanced stage or recurrent carcinoma of the endometrium [69]. In this phase II trial, 28 patients received paclitaxel (175 mg/m^2), carboplatin AUC-6 every 21 days for six cycles, and megestrol acetate 40 mg four times daily for up to 5 years. Mean PFI was 40.2 months and mean OS was 50.1 months. Myelosuppression was the most common toxicity but there were four thromboembolic events

noted [69]. The authors concluded that this regimen was active and raised the question of whether the addition of hormonal therapy to cytotoxic chemotherapy could improve survival [69].

The most recent trials are promising. However, the question of whether these regimens are better than paclitaxel-containing combination chemotherapy is not known and will require further investigation through a randomized trial.

In efforts to overcome resistance to hormonal therapies, current investigations are evaluating alternatives to progesterones. Aromatase inhibitors such as arimidex and letrozole have shown minimal activity as single agents, but when combined with targeted agents such as mTOR inhibitors, they have shown more impressive results and are the focus of ongoing or planned clinical trials [70–73].

Conclusions

Locally advanced or recurrent endometrial cancer can be treated via surgery, radiation therapy, hormonal therapy, or chemotherapy. The treatment modality choice largely depends on the localization of disease, the patient's performance status and previous treatment history, and the tumor's hormonal receptor status. Isolated vaginal recurrences in patients with no previous history of radiation therapy are amenable to primary treatment with radiation therapy. Patients with recurrent low-grade tumors that express estrogen and progesterone receptors may be treated with progestin therapy for prolonged periods of time, with adequate response rates and low toxicity. In the setting of hormone receptor negative tumors or for lesions that have progressed after hormonal therapy, chemotherapy offers another treatment alternative with modest response rates. Higher response rates, and potentially, a longer survival time, may be reached through the use of combination chemotherapy, especially regimens containing paclitaxel, or with combinations of chemotherapy and hormonal therapy [73]. The best regimen is still unknown and the treatment choice should be based, again, on the extent of disease recurrence, prior treatment history, and patient preference and performance status.

References

1. Tarone RE, Chu KC. Age-period-cohort analyses of breast, ovarian, endometrial and cervical cancer mortality rates for Caucasian women in the USA. J Epidemiol Biostat. 2000;5:221–31.
2. Morgan JD, Reddy S, Sarin P, et al. Isolated vaginal recurrences of endometrial carcinoma. Radiology. 1993;189:609–13.
3. Hoekstra CJ, Koper PC, van Putten WL. Recurrent endometrial adenocarcinoma after surgery alone: prognostic factors and treatment. Radiother Oncol. 1998;27:164–6.
4. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage 1 endometrial carcinoma: multicenter randomised trial. PORTEC study group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355:1404–11.
5. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial small star, filled. Gynecol Oncol. 2003;89:201–9.
6. Kuten A, Grigsby PW, Perez CA, et al. Results of radiotherapy in recurrent endometrial carcinoma: a retrospective analysis of 51 patients. Int J Radiat Oncol Biol Phys. 1989;17:29–34.
7. Curran WJ, Whittington R, Peters AJ, Fanning J. Vaginal recurrences of endometrial carcinoma: the prognostic value of staging by a primary vaginal carcinoma system. Int J Radiat Oncol Biol Phys. 1988;15:803–8.
8. Pai HH, Souhami L, Clark BG, Roman T. Isolated vaginal recurrences in endometrial carcinoma: treatment results using high-dose-rate intracavitary brachytherapy and external beam radiotherapy. Gynecol Oncol. 1997;66:300–7.
9. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol Biol Phys. 2003;56:1366–72.
10. Jereczek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy. Int J Radiat Oncol Biol Phys. 2000;48:405–13.
11. Wylie J, Irwin C, Pintilie M, et al. Results of radical radiotherapy for recurrent endometrial cancer. Gynecol Oncol. 2000;77:66–72.
12. Monk BJ, Tewari KS, Puthawala AA, et al. Treatment of recurrent gynecologic malignancies with iodine-125 permanent interstitial irradiation. Int J Radiat Oncol Biol Phys. 2002;52:806–15.

13. Nag S, Yacoub S, Copeland LS, Fowler JM. Interstitial brachytherapy for salvage treatment of vaginal recurrences in previously unirradiated endometrial cancer patients. Int J Radiat Oncol Biol Phys. 2002;54:1153–9.
14. Tewari K, Cappuccini F, Brewster WR, et al. Interstitial brachytherapy for vaginal recurrences of endometrial carcinoma. Gynecol Oncol. 1999;74:416–22.
15. Bristow RE, Zerbe MJ, Rosenshein NB, et al. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. 2000;2:85–91.
16. Chi DS, Welshinger M, Venkatraman ES, et al. The role of surgical cytoreduction in Stage IV endometrial cancer. Gynecol Oncol. 1997;1:56–60.
17. Goff BA, Goodman A, Muntz HG, Fuller AF, Nikrui N, Rice L. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol. 1994;52:237–40.
18. Morley GW, Hopkins MP, Lindenauer SM, et al. Pelvic exenteration, University of Michigan: 100 patients at 5 years. Obstet Gynecol. 1989;74:934–43.
19. Barakat RR, Goldman NA, Patel DA, et al. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol. 1999;75:99–102.
20. Dowdy SC, Mariani A, Cliby WA, Haddock MG, Petersen IA, Sim FH, Podratz KC. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. Gynecol Oncol. 2006;101:280–6.
21. Scarabelli C, Campagnutta E, Giorda G, DePiero G, Sopracordevole F, Quaranta M, DeMarco L. Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma. Gynecol Oncol. 1998;70:90–3.
22. Campagnutta E, Giorda G, Depiero G, Sopracoreveole F, Visentin MC, Martella L, Scarabelli C. Surgical treatment of recurrent endometrial carcinoma. Cancer. 2004;100(1):89–96.
23. Awtrey CS, Sadungog MG, Leitao MM, Alektiar KM, Aghajanian C, Hummer AJ, Barakat RR, Chi DS. Surgical resection of recurrent endometrial carcinoma. Gynecol Oncol. 2006;102(3):480–8.
24. Bristow RE, Santillan A, Zahurak ML, Gardner GJ, Giuntoli 2nd RL, Armstrong DK. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol. 2006;103(1):281–7.
25. Potish RA, Twiggs LB, Adcock LL, Prem KA. Role of whole abdominal radiation therapy in the management of endometrial cancer: prognostic importance of factors indicating peritoneal metastases. Gynecol Oncol. 1985;21:80–6.
26. Soper JT, Creasman WT, Clarke-Pearson DL, Sullivan DC, et al. Intraperitoneal chromic phosphate P 32 suspension therapy of malignant peritoneal cytology in endometrial carcinoma. Am J Obstet Gynecol. 1985;153:191–6.
27. Wethington SL, Barrena Medel NI, Wright JD, Herzog TJ. Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: unraveling a mystery. Gynecol Oncol. 2009;115(1):18–25.
28. Havrilesky LJ, Secord AA, O'Malley DM, Broadwater G, Bae-Jump V, Cohn DE, Gehrig PA. Multicenter analysis of recurrence and survival in stage IIIA endometrial cancer. Gynecol Oncol. 2009;114(2):279–83.
29. Creasman WT, Disaia PJ, Blessing J, et al. Prognostic significance of peritoneal cytology in patients with endometrial cancer and preliminary data concerning therapy with intraperitoneal radiopharmaceuticals. Am J Obstet Gynecol. 1981;141:921–9.
30. Yazigi R, Piver MS, Blumenson L. Malignant peritoneal cytology as prognostic indicator in stage I endometrial cancer. Gynecol Oncol. 1983;62:359–62.
31. Potish RA, Twigs LB, Adcock LL, et al. Paraaortic lymph node radiotherapy in cancer of the uterine corpus. Obstet Gynecol. 1985;65:251–6.
32. Feuer GA, Calanog A. Endometrial carcinoma: treatment of positive paraaortic nodes. Gynecol Oncol. 1987;27:104–9.
33. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL, Insalaco S. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144–53.
34. Peters WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W, Alberts DS. Concurrent chemotherapy and pelvic radiation therapy compared to pelvic radiation therapy alone as adjuvant therapy after radical surgery in high risk early stage cancer of the cervix. J Clin Oncol. 2000;18 (8):1606–13.
35. Pickel H, Lahousen M, Petru E, Stettner H, Hackl A, Kapp K, Winter R. Consolidation radiotherapy after carboplatin-based chemotherapy in radically operated advanced ovarian cancer. Gynecol Oncol. 1999;72 (2):215–9.
36. Duska LR, Berkowitz R, Matulonis U, Muto M, Goodman A, Mcintyre JF, Klein A, Atkinson T, Seiden MV, Campos S. A pilot trial of TAC (paclitaxel, doxorubicin, and carboplatin) chemotherapy with Filgrastim (r-met HuG-CSF) support followed by radiotherapy in patients with "high risk" endometrial cancer. Gynecol Oncol. 2005; 96:198–203.
37. Soper JT, Reisinger SA, Ashbury R, Jones E, Clarke-Pearson DL. Feasibility study of concurrent weekly cisplatin and whole abdominopelvic irradiation followed by doxorubicin/cisplatin chemotherapy for advanced stage endometrial carcinoma: a Gynecologic Oncology Group trial. Gynecol Oncol. 2004;95:95–100.
38. Bruzzone M, Miglietta L, Frazone P, Gadducci A, Boccardo F. Combined treatment with chemotherapy and radiotherapy in high-risk FIGO stage III-IV

endometrial cancer patients. Gynecol Oncol. 2004;93 (2):345–52.
39. Frigerio L, Mangili G, Aletti M, Carnelli M, Garavaglia E, Beatrice S, Ferrari A. Concomitant radiotherapy and paclitaxel for high-risk endometrial cancer: first feasibility study. Gynecol Oncol. 2001;81:53–7.
40. Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T. Preliminary analysis of RTOG 9708: adjuvant postoperative radiotherapy combined with cisplatin/paclitaxel chemotherapy after surgery for patients with high-risk endometrial cancer. Int J Radiat Oncol Biol Phys. 2004;59 (1):168–73.
41. Wilkinson-Ryan I, Binder PS, Pourabolghassem S, Al-Hammadi N, Fuh K, Hagemann A, THaker P, Scharz J, Grigsby P, Mutch D, Powell M. Concomitant chemotherapy and radiation for the treatment of advanced stage endometrial cancer. Gynecol Oncol. 2014;134(1):24–8.
42. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, Thigpen JT, Benda JA. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2006;24:34–44.
43. Fleming GF. Major progress for a less common cancer. J Clin Oncol. 2006;24:6–8.
44. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. Gynecol Oncol. 2009;112:543–52.
45. Aghajanian C, Sill MW, Darcy KM, Greer B, McMeekin DS, Rose PG, Rotmensch J, Barnes MN, Hanjani P, Leslie KK. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011;29 (16):2259–65.
46. Viswanathan AN, Lee H, Berkowitz R, Berlin S, Campos S, Feltmate C, Horowitz N, Muto M, Sadow CA, Matulonis U. A prospective feasibility study of radiation and concurrent bevacizumab for recurrent endometrial cancer. Gynecol Oncol. 2014;132 (1):55–60.
47. Kelley RM, Baker WH. Progestational agents in the treatment of carcinoma of the endometrium. N Engl J Med. 1961;264:216–22.
48. Piver MS, Barlow JJ, Luain JR, et al. Medroxyprogesterone acetate versus hydroxyprogesterone caproate in women with metastatic endometrial adenocarcinoma. Am J Clin Oncol. 1980;45:268–72.
49. Bonte J. Medroxyprogesterone in the management of primary and recurrent endometrial adenocarcinoma. Acta Obstet Gynecol Scand Suppl. 1972;19:21–4.
50. Reifenstein EC. The treatment of advanced endometrial cancer with hydroxyprogesterone caproate. Gynecol Oncol. 1974;2:337–414.
51. Geisler HE. The use of megestrol acetate in the treatment of advanced malignant lesions of the endometrium. Gynecol Oncol. 1979;1:340–6.
52. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999;17:1736–44.
53. Quinn MA, Cauchi M, Fortune D. Endometrial carcinoma: steroid receptors and response to medroxyprogesterone acetate. Gynecol Oncol. 1985;21:314–9.
54. Thigpen JT, Blessing J, Disaia P. Oral medroxyprogesterone acetate in advanced or recurrent endometrial carcinoma: results of therapy and correlation with estrogen and progesterone receptor levels. In: Iacobelli S, editor. Endocrinology and malignancy: basic and clinical issues, The Proceedings of the First International Congress on Cancer and Hormones. Rome: CRC Press, Parthenon Publishers; 1986. p. 446–7.
55. Barakat RR, Grigsby PW, Sabbatini P, et al. Corpus epithelial tumors. In: Hoskins WJ, Perez CA, Young RC, editors. Principles and practices of gynecologic oncology. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1997. p. 880–4.
56. Mortel R, Levy C, Wolff JP, et al. Female sex steroid receptors in postmenopausal endometrial carcinoma and biochemical response to an antiestrogen. Cancer Res. 1981;41:1140–7.
57. Carlson JA, Allegra JC, Day TG, et al. Tamoxifen and endometrial carcinoma: alterations in estrogen and progesterone receptors in untreated patients and combination hormonal therapy in advanced neoplasia. Am J Obstet Gynecol. 1984;149:149–53.
58. Thigpen JT, Brady MF, Homesley HD. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma. A Gynecologic Oncology Group study. J Clin Oncol. 2001;19:364–7.
59. Moore TD, Phillips PH, Nerenstone SR, et al. Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. J Clin Oncol. 1991;9:1071–7.
60. Pandya KJ, Yeap BY, Davis TE. Phase II study of megestrol and mestrol and tamoxifen in advanced endometrial carcinoma: an Eastern Cooperative Oncology Group (ECOG) study. Am J Clin Oncol. 2001;24:43–6.
61. Fiorca JV, Brunetto VL, Hanjani P, et al. A phase II study of recurrent and advanced endometrial carcinoma treated with alternating courses of megestrol acetate (Megace) and tamoxifen citrate (Nolvadex). Gynecol Oncol. 2004;92(1):10–4.
62. Whitney CW, Brunetto VL, Zaine RJ, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology study. Gynecol Oncol. 2004;92:4–9.
63. Horton J, Elson P, Gordon P, et al. Combination chemotherapy for advanced endometrial cancer. An evaluation of three regimens. Cancer. 1982;49:2441–5.

64. Piver MS, Lele SB, Patsner B, et al. Melphalan, 5-fluorouracil, and medroxyprogesterone acetate in metastatic endometrial carcinoma. Obstet Gynecol. 1986;67:261–7.
65. Cohen CJ, Bruckner HW, Deppe G, et al. Multidrug treatment of advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Obstet Gynecol. 1984;63:719–26.
66. Ayoub J, Audet-Lapointe P, Methot Y, et al. Efficacy of sequential cyclical hormonal therapy in endometrial cancer and its correlation with steroid hormone receptor status. Gynecol Oncol. 1988;31:327–37.
67. Cornelison TL, Baker TR, Piver MS, et al. Cisplatin, adriamycin, etoposide, megestrol acetate versus melphalan, 5-fluorouracil, medroxyprogesterone acetate in the treatment of endometrial carcinoma. Gynecol Oncol. 1995;59:243–8.
68. Bafaloukos D, Aravantinos G, Samonis G, et al. Carboplatin, methotrexate and 5-fluorouracil in combination with medroxyprogesterone acetate (JMF-M) in the treatment of advanced or recurrent endometrial carcinoma: a Hellenic cooperative oncology group study. Oncology. 1999;56:198–201.
69. Bevis KS, Kilgore LC, Alvarez RD, Straughn Jr JM, Leath 3rd CA. Combination therapy with paclitaxel, carboplatin, and megestrol acetate for the management of advanced stage or recurrent carcinoma of the endometrium: a phase II study. J Reprod Med. 2014;59(3-4):113–20.
70. Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2000;78(2):212–6.
71. Gallion HH, Brunetto VL, Cibull M, et al. Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2003;21:3808–13.
72. Ma BB, Oza A, Eisenhauer E, Stanimir G, Carey M, Chapman W, Latta E, Sidu K, Powers J, Walsh W, Fyles A. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers- a study of the National Cancer Institute of Canada Clinical Trials Group. Int J Gynecol Cancer. 2004;14(4):650–8.
73. Slomovitz BM, Jiang Y, Yates MS, Soliman PT, Johnston T, Nowakowski M, et al. A phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol. 2015; 33:930.

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Management of Uterine Sarcomas

Leslie R. Boyd

Abstract

Uterine sarcomas, including the subtypes leiomyosarcoma, endometrial stromal sarcoma, and adenosarcoma, are a heterogenous group of tumors which vary widely in their biology and prognosis. Surgery is the mainstay of treatment. The roles of chemotherapy, radiation therapy and hormonal therapy are poorly defined, in large part due to the rarity of these tumors. Prior clinical trials grouped uterine sarcomas together, which helped trial accrual but hampered applicability of trial results. Today's trials are specific to each histology, and are often supplemented by molecular studies to improve interpretation of results. Continued investigations should point the way for future therapies directed towards these tumors.

Keywords

Adenosarcoma • Endometrial stromal sarcoma • Gemcitabine • Docetaxel • Hormonal therapy • Leiomyosarcoma • Undifferentiated endometrial sarcoma • Uterine sarcomas

Introduction

Malignant mesenchymal tumors of the uterine corpus are rare tumors. They comprise less than 3% of all uterine corpus tumors [1], yet account for a disproportionate percentage of deaths from uterine cancers, as high as 29% in one series [2]. Historically, uterine sarcomas have been grouped together for the purposes of clinical trials. While this grouping aided accrual, and allowed for relatively rapid testing of promising therapeutic drugs, the heterogeneous origins and behavior of these tumors limited clinical applicability of the results. Carcinosarcoma, which has been previously classified as a uterine sarcoma, is now widely believed to be a metaplastic, high grade endometrial adenocarcinoma, and is covered separately [see Chap. 10]. Leiomyosarcoma is the most common uterine sarcoma, followed by endometrial stromal sarcomas, undifferentiated endometrial sarcomas and müllerian

L.R. Boyd (✉)
Division of Gynecologic Oncology,
Department of Obstetrics and Gynecology,
NYU School of Medicine, New York, NY, USA
e-mail: Leslie.Boyd@nyumc.org

adenosarcomas. These are all rare tumors: a recent study using Scandinavian databases found a rate of leiomyosarcoma of 0.4 per 100,000 women, and of endometrial stromal sarcoma of 0.3 per 100,000 women. Over the study period of 1978–1997, the rates of both diseases were constant [3]. Risk factors for uterine sarcoma include obesity, diabetes mellitus, and younger age at menarche [4].

Preoperative diagnosis of uterine sarcoma is often difficult. Women with early stage uterine sarcoma will present with the same set of symptoms associated with the much more common benign uterine leiomyomata. Unfortunately, no imaging modality has been shown to accurately differentiate between the two diagnoses.

Primary Surgery

Whenever possible, surgery should be undertaken in patients with uterine sarcoma, in order to remove all sites of disease and surgically stage the patient. In 2009, the International Federation of Gynecologists and Obstetricians (FIGO) released a staging system specific for uterine sarcomas. This classification defines two different staging systems: one for leiomyosarcoma and endometrial stromal sarcoma, and another for adenosarcoma [5]. Carcinosarcoma should be staged using the endometrial cancer staging system [see Chap. 10]. The extent of the surgery depends on the histologic subtype. Similarly, adjuvant therapy is strongly informed by the histologic diagnosis and careful pathology review is critical since sarcoma histologic subtypes vary in prognosis and management.

Leiomyosarcoma

Primary surgical management for early stage leiomyosarcoma is total hysterectomy with bilateral salpingo-oophorectomy. Lymph node status is part of the staging algorithm, but is not therapeutic. Normal appearing lymph nodes are unlikely to be involved, making routine lymphadenectomy unnecessary [6–9]. For patients with leiomyosarcoma, only suspicious lymph nodes need be removed [9]. It is unclear if oophorectomy is an important aspect of treatment; a SEER study including over 1300 patients showed no survival advantage to oophorectomy in women with leiomyosarcoma [10].

The widespread use of minimally invasive surgical techniques for leiomyomata, including power morcellation, has led to increasing concerns for the inadvertent anatomic disruption of undiagnosed leiomyosarcoma. Several studies confirm that patients who undergo myomectomy for presumed benign disease, and are subsequently diagnosed with leiomyosarcoma, have worse outcomes compared to women who undergo hysterectomy [11–13]. For women who underwent myomectomy for what was presumed to be leiomyomata, completion hysterectomy is indicated in the case of high-grade leiomyosarcoma. In one report, two-thirds of patients had residual disease at completion hysterectomy [14].

Endometrial Stromal Sarcoma (ESS): Low Grade ESS and Undifferentiated Endometrial Sarcoma

In 2014, the World Health Organization reorganized the classification schema for endometrial stromal tumors. The designation of low-grade endometrial stromal sarcoma has been maintained, but the entity previously referred to as high grade endometrial stromal sarcoma is now referred to as undifferentiated endometrial sarcoma (IARC). Low-grade ESS is characterized by its hormonal sensitivity and indolent behavior, with long disease-free intervals interspersed by resectable recurrent disease. Undifferentiated endometrial sarcoma is an aggressive malignancy, with few clinical options for treatment. Recurrent genetic fusion involving the transcriptional repressor JAZF1, was first identified in these tumors in 2001, and has since been replicated involving multiple oncoproteins [15, 16]. The JAZF1-SUZ12 gene fusion is the most common rearrangement, though rarely fusions of EPC1-PHF1 and JAZF1-PHF1 have been identified [17].

Low-grade endometrial stromal sarcoma is often cured by surgery alone. Extended surgical

staging is not generally recommended [9], and lymphadenectomy does not seem to affect outcomes [18, 19]. These are generally hormonally responsive tumors, and ovarian retention has been shown to decrease progression-free survival [20, 21], though large series have shown no decrease in overall survival for those patients retaining their ovaries [22, 23]. Though bilateral salpingo-oophorectomy is the general rule, ovarian conservation may be considered in young women. The benefit of adjuvant therapy is uncertain in patients with fully resected, early stage disease.

Mullerian Adenosarcoma

Adenosarcomas are rare tumors with mixed elements: a malignant, but often low-grade mesenchymal component, with a benign glandular epithelium. Most patients are diagnosed with early stage disease, and have favorable long-term survival [24]. However, the presence of sarcomatous overgrowth or myometrial invasion are negative prognostic factors [25, 26]. Recent molecular analysis has confirmed that these tumors originate as mesenchymal neoplasms, with unrelated epithelial components [27]. Most adenosarcomas exhibit ER and/or PR expression, though tumors with sarcomatous overgrowth exhibit less expression [28].

Standard surgical treatment involves hysterectomy with bilateral salpingo-oophorectomy, though ovarian conservation appears safe in premenopausal patients with low-risk features [26, 29]. Adjuvant therapy is not warranted in cases without myometrial invasion. Myometrial invasion and/or sarcomatous overgrowth carry an increased risk of recurrence, but there is no proven adjuvant regimen. Both radiation therapy (RT) and hormonal therapy have been used.

Adjuvant Therapy

With the widespread use of computerized tomography, both intra-pelvic and intra-abdominal spread can be readily identified. If not performed preoperatively, a CT of the chest is essential in patients after diagnosis, as these tumors commonly metastasize to the lungs. Most available adjuvant data pertains to patients with leiomyosarcoma.

Adjuvant Pelvic Radiation

Stage I and II leiomyosarcomas have a 50–70% risk of recurrence, with >50% being extra-pelvic recurrences [6, 7, 30]. The use of adjuvant pelvic RT has been debated, with the majority of the literature limited to retrospective reviews. Despite the bias inherent with retrospective studies, with rare exceptions [31], these trials have shown improved local control with no change in overall survival [32–34].

The EORTC protocol 55874 evaluated the role of adjuvant RT in patients with stage I and II uterine sarcoma. Patients were randomized to either observation or pelvic RT after undergoing a minimum surgery of hysterectomy, bilateral salpingo-oophorectomy and pelvic washings. Of the 224 patients accrued, 103 patients had a leiomyosarcoma. As expected, there was improvement in local control overall, but no improvement in overall survival. Of note, a subgroup analysis of the LMS patients showed no benefit to RT in achieving either local control or overall survival [35]. This prospective trial shows no clear benefit to adjuvant pelvic RT for patients with resected uterine LMS. A SEER analysis which included 1088 patients with LMS, also concluded no survival benefit to the addition of adjuvant RT [36]. Its role as adjuvant therapy in ESS is also uncertain [37].

Adjuvant Chemotherapy

For early stage leiomyosarcoma, adjuvant chemotherapy remains unproven, despite several trials designed to address this question [38, 39].

GOG 20 was designed before the widespread availability of CT scans, and in retrospect, naively conceived that a drug with limited activity such as doxorubicin could prove useful in patients with stage I or II uterine sarcoma (all types): they were randomly assigned to doxorubicin versus observation. Pelvic RT was optional, and could be used before or after the chemotherapy. Despite a 9-year accrual, only 156 patients were evaluable, 48 with leiomyosarcoma.

There was no difference in OS or PFS between the two groups [40] with recurrence noted in 44% (11/25) on doxorubicin (Adriamycin) versus 61% (14/23) on the observation arm. The low patient number and other study limitations inhibited further group studies in the adjuvant setting in spite of reportedly more active chemotherapy regimens from single institution trials that often included carcinosarcomas and ESS [41]. Ifosfamide [42], cisplatin, doxorubicin, or other antitumor antibiotics formed part of a large number of regimens studied [43–45]—some of these also including radiation [46]. More recently, attention has shifted to gemcitabine and docetaxel [47] after confirmatory results from a GOG study [48].

The combination of gemcitabine–docetaxel, followed by doxorubicin was evaluated by the Sarcoma Alliance for Research (SARC) as adjuvant therapy for resected stage I and II leiomyosarcoma [49]. Median follow-up was 39.8 months, with 46% of patients developing recurrent disease; 78% of patients were progression-free at 2 years, and 57% were progression-free at 3 years. Though these results are promising compared to historical controls, we await results of an ongoing prospective, phase III trial comparing this regimen to observation.

Adjuvant Hormonal Therapy

Stromal neoplasms derive from endometrial stromal cells: there are multiple analyses documenting the presence of steroid receptors (ER and PR) in these tumors [50–52]. The fact that hysterectomy with BSO seems to be associated with longer remissions than if the ovaries are preserved supports the hormonal sensitivity of these tumors. One study showed rates of ER expression of 48.3% and PR expression of 30% [51]. Analogous to the treatment of hormone-sensitive breast cancer, initial favorable results were reported after treatment of low-grade endometrial stromal sarcomas with progestational agents such as megestrol acetate [53], and subsequently these have often been replaced by aromatase inhibitors and GnRH agonists [53–57]. Excellent long-term outcomes have been documented in advanced disease settings when using each of the aforementioned hormonal options in sequence [52]. Given the favorable toxicity profile of such agents, it is reasonable to consider using them in the adjuvant setting.

Treatment of Recurrent/Metastatic Disease

Metastases most commonly occur in the abdomen (intraperitoneal and spread to adjacent organs) and distally most often to the lungs, bone, liver and central nervous system. There are few effective systemic treatment options for patients with advanced or recurrent uterine sarcoma. As a result, surgical resection should be considered if complete resection can be achieved without significant morbidity.

Metastatectomy

Several institutions have reported successful case series involving metastatectomy for patients with leiomyosarcoma, in particular for lung metastases [58–61]. A prolonged progression-free interval, an isolated site of recurrence, and optimal cytoreduction are associated with prolonged survival following resection [60, 61]. These favorable reports need to be interpreted cautiously, given the selection bias inherent in case series. A subsequent retrospective review of patients undergoing radical surgery examined prognostic factors associated with improved PFS (but not OS) when compared to patients who did not have up front surgery [62] In spite of the limitations inherent in these data, metastatectomy represents an option for selected patients with resectable metastases.

Radiation Therapy (RT)

Radiation plays a role in palliating tumor-related symptoms in patients with advanced uterine sarcoma. In patients with unresectable disease, radiation may be used to shrink the tumor sufficiently to reduce bleeding, obstruction and pain. The current standard palliative RT schedule was described in RTOG 8502. This study utilized a total of 44.4 Gy in 12 fractions with two treatment breaks [63]. The risk of long term radiation

related complications was 7%, which is tolerable given the acuity of the patient population [64].

Systemic Non-hormonal Therapy

The initial trials of chemotherapy for recurrent disease took place without a distinction to the type of sarcomas, and historically followed "broad phase II studies" with new anticancer agents. Objective responses in soft tissue sarcomas noted with doxorubicin prompted the development of combinations with this drug, strongly influencing the early trials. These studies, noted in Tables 1 and 2, generally included most histologic types, and ultimately separated carcinosarcomas (which are more chemosensitive) from leiomyosarcomas.

Systemic therapy for these patients is considered palliative, with goals to relieve symptoms and extend time to progression. There are no randomized controlled trials comparing chemotherapy to best supportive care in this patient population. Patients should understand the palliative nature of their treatment, and the toxicity of the chosen regimen should be taken into consideration.

After favorable results as a second line agent, gemcitabine plus docetaxel was evaluated as first line treatment for metastatic leiomyosarcoma. Patients received gemcitabine 900 mg/m^2 days 1 and 8 IV, followed by docetaxel 100 mg/m^2 IV on day 8. Marrow support was standard on the regimen, and patients with a history of pelvic RT had a dose reduction of both drugs. Of 42 evaluable patients, an objective response was seen in 15 patients (36%, CR: 5%, PR: 31%). The most common grade 3 or 4 toxicities were

Table 1 Early randomized trials for advanced "gynecologic" sarcomas

Regimen	N	Response Rate (%)	PFS (m)	OS (m)	References
Doxorubicin	120	16		6.3	[65]
Doxorubicin, Dacarazine	106	24		5.8	
Doxorubicin	50	19	5.1	11.6	[66]
Doxorubicin, Cyclophosphamide	54	20	4.9	10.9	

Table 2 Results for uterine leiomyosarcoma patients in selected combination trials

Leiomyosarcoma Combination	Dosing	N	Response rate (%)	References
Ifosfamide	5 g/m^2 over 24 h	18	17	[67]
Doxorubicin	50 mg/m^2			
Dacarbazine	250 mg/m^2/day × 5	31	30	[68]
Doxorubicin	60 mg/m^2			
Cyclophosphamide	500 mg/m^2	17	13[a]	[66]
Doxorubicin	60 mg/m^2			
Hydroxyurea	500 mg q 6 h × 4	38	19	[69]
Dacarbazine	700 mg/m^2			
Etoposide	100 mg/m^2/day × 3			
Vincristine	1.5 mg/m^2 weekly	14	29[b]	[70]
Actinomycin D	0.5 mg/m^2/day × 5			
Cyclophosphamide	300 mg/m^2/day × 5			
Gemcitabine	900 mg/m^2 days 1 and 8	34	53	[47]
Docetaxel	100 mg/m^2 day 8			
Trabectedin	1.1 mg/m^2	47	60	[71]
Doxorubicin	60 mg/m^2			

[a]Includes response rate of patients on comparator arm, doxorubicin alone
[b]Includes two patients with ESS, one of whom had an objective response

neutropenia, anemia, thrombocytopenia, and fatigue [48]. The combination of dose-rate-based gemcitabine plus docetaxel is now standard first line therapy for patients with metastatic or recurrent disease. The addition of bevacizumab to this backbone does not improve response or survival [72].

The combination of gemcitabine plus docetaxel has been evaluated as second line treatment following prior therapy: the TAXOGEM study was a randomized, multicenter phase II trial evaluating gemcitabine versus gemcitabine and docetaxel for second line treatment of leiomyosarcoma after anthracycline treatment. Non-uterine leiomyosarcoma patients were included. The dosing of gemcitabine as a single agent was 1000 mg/m^2 days 1, 8, and 15; dosing on the comparator arm was gemcitabine 900 mg/m^2 days 1 and 8, with docetaxel 100 mg/m^2 day 8. The combination did not improve PFS or OS, and the toxicity profile favored gemcitabine alone [73].

The combination of trabectedin and doxorubicin for first line treatment of advanced leiomyosarcoma was evaluated in a phase II study. Both uterine and soft tissue sarcomas were entered, though separate analysis of the 47 uterine leiomyosarcoma patients was given. For the uterine leiomyosarcoma patients, the overall RR was 60%, with median progression-free survival of 8 months [71].

The combination of doxorubicin, ifosfamide and cisplatin was reported as a single-institution's experience of an aggressive treatment protocol including additional radiation and surgery for patients with advanced or recurrent leiomyosarcoma [74]. Treatment was limited to patients under the age of 65, and toxicity was as expected for a combination regimen.

Agents with modest response rates include doxorubicin (24%) [65], pegylated liposomal doxorubicin (RR 16.1%) [75], ifosfamide (RR 17%) [73, 76], gemcitabine (RR 20%) [74, 77], and single agent trabectedin (ecteinascidin or ET-743) (RR 8% as second line and 17% as first line treatment) [78, 79, 82, 83]. Cisplatin, which is often added to combinations because of its activity against carcinosarcoma, [80] and a number of other agents (etoposide, paclitaxel, topotecan, ixabepilone) have been studied by the GOG in their #87 protocol series. These combinations have been minimally active, and subsequently studies focusing on "targeted" agents (thalidomide, imatinib mesylate) within the GOG#230 series have all yielded disappointing results in persistent or recurrent leiomyosarcoma [81–83].

Undifferentiated endometrial sarcoma (previously referred to as high grade endometrial stromal sarcoma) is quite different from low-grade endometrial stromal sarcoma, with rapid recurrences and rare responses to chemotherapy. These tumors may be partitioned into two prognostic groups, a high mitotic index group and a low mitotic index group. The latter group is more likely to show expression of ER, PR or presence of the YWHAE-FAM 22 translocation [84]. ESS associated with the YWHAE-FAM22 fusion are much more aggressive than other ESS and should be treated similarly to other high grade sarcomas. Cyclin D1 may help differentiate these tumors, and inform subsequent treatment decisions [85, 86].

Few studies have been directed specifically to improve the outcome of advanced or recurrent undifferentiated endometrial sarcoma [87, 88]. A single phase II GOG study showed a 33% response rate to ifosfamide [89]. There have also been reports of responses to doxorubicin [87, 88], etoposide [90], and gemcitabine with docetaxel [88, 91].

Low-grade ESS respond to hormones as discussed under adjuvant therapy; response to imatinib mesylate has also been reported [92]. For the rare advanced or recurrent mullerian adenosarcoma, systemic treatments for the rare patients who progress on hormonal interventions have been adopted from other sarcomas, utilizing doxorubicin, gemcitabine/docetaxel, ifosfamide and platinum combinations [24–26].

Hormonal Therapy

For patients with advanced stage or recurrent low-grade ESS, hormonal therapy is the mainstay of treatment [93–95]. In this disease,

hormonal therapy generally offers long-term stabilization of disease with tolerable side effects.

Hormonal therapy has been explored in uterine leiomyosarcoma, given the limited efficacy of other therapies and that between 40 and 80% of patients will have ER and/or PR receptors [96]. One retrospective study showed a partial response rate of 9%, but prolonged stabilization of disease [97]. A phase II study evaluated the use of letrozole in uterine leiomyosarcoma patients with advanced or metastatic disease with ER/PR expression documented in their tumors. A total of 26 patients received study drug, with a best response of stable disease in 14 patients (54%). The 12 week PFS rate was 47%, exceeding protocol expectations, however without a no treatment control arm, the impact of hormonal therapy is unclear [98].

Biologic Therapy

The GOG has run several trials using systemic non-hormonal therapies for leiomyosarcoma. These include antiangiogenic biologic agents such as Aflibercept—an inhibitor of VEGF-A and -B, as well as Placental Growth Factor 1 and 2. This biologic has been evaluated in a phase II trial for patients with uterine sarcomas, including those with recurrent or metastatic uterine LMS (41 patients) [99]. Sunitinib, a small molecule multi-kinase inhibitor, with activity against VEGF and platelet-derived growth factor (PDGF), has also been investigated in women with advanced or recurrent LMS [83]; eligibility was confined to women with measurable disease after one or two prior cytotoxic regimens. Of the 23 patients evaluable, two achieved a partial response (9%), and median PFS was only 1.5 months. Limited experience is available with pazopanib, another tyrosine kinase inhibitor with antiangiogenic properties in uterine leiomyosarcoma.

The role of biologics in the treatment of ESS remains under investigation. One study identified c-abl by immunohistochemistry on all tested ESS specimens [100]. A radiologic complete response was reported in a patient with low-grade ESS following treatment with imatinib mesylate [92]. More data is needed to determine if these agents will provide another arm of therapy.

Immunologic interventions are being widely explored in gynecologic cancers, and reports from mostly phase I expansion cohorts are awaited.

New Directions

The rise in personalized medicine and the availability of genomic profiling for these tumors will lead to a watershed of information. Targeted therapy will be applied to these tumors in increasing numbers. The trials to date on biologic agents have had lackluster results; however, novel agents and combinations may still hold promise. In order to move the field forward, it will be critical to aggregate genomic and pathway data so that druggable targets can be evaluated in a methodical way. If correctly categorized and shared, this influx of information can increase the likelihood that new, effective systemic therapies are identified.

Conclusions

Surgery remains the mainstay of treatment for uterine sarcomas. Careful histologic review should be undertaken for each of these diagnoses to appropriately guide further therapy.

Adjuvant treatment for uterus-limited leiomyosarcoma remains unproven. The combination of gemcitabine and docetaxel is now the mainstay of treatment for advanced or recurrent disease.

Low-grade endometrial stromal sarcoma is an indolent tumor with a favorable prognosis. Undifferentiated stromal sarcoma is an aggressive, rare tumor. Identification of genomic translocations may identify high-risk groups and aid in adjuvant treatment decisions.

Patients should be encouraged to engage in clinical trials given our current limitations in treatment for many of these tumors.

References

1. Siegel R, et al. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.
2. Nordal RR, Thoresen SO. Uterine sarcomas in Norway 1956–1992: incidence, survival and mortality. Eur J Cancer. 1997;33(6):907–11.
3. Koivisto-Korander R, et al. Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA databases. Maturitas. 2012;72:56–60.
4. Felix AS, et al. The etiology of uterine sarcomas: a pooled analysis of the epidemiology of endometrial cancer consortium. Br J Cancer. 2013;108:727–34.
5. FIGO Committee on Gynecologic Oncology. FIGO staging for uterine sarcomas. Int J Gynecol Obstet. 2009;104:179.
6. Giuntoli RL 2nd, Metzinger DS, DiMarco CS, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol. 2003;89:460–9.
7. Yamada SD, Burger RA, Brewster WR, Anton D, Kohler MF, Monk BJ. Pathologic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus. Cancer. 2000;88:2782–6.
8. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994;83(3):414–8.
9. Goff BA, Rice LW, Fleischhacker D, et al. Uterine leiomyosarcoma and endometrial stromal sarcoma: lymph node metastases and sites of recurrence. Gynecol Oncol. 1993;50:105–9.
10. Kapp DS, et al. Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. 2008;112:820–30.
11. George S, et al. Retrospective cohort study evaluating the impact of intraperitoneal morcellation of outcomes of localized uterine leiomyosarcoma. Cancer. 2014;120:3154–8.
12. Park JY, et al. The impact of tumor morcellation during surgery on the prognosis of patients with apparent early uterine leiomyosarcoma. Gynecol Oncol. 2011;122:255–9.
13. Morice P, et al. Prognostic value of initial surgical procedure for patients with uterine sarcoma: analysis of 123 patients. Eur J Gynaecol Oncol. 2003;24:237–40.
14. Berchuck A, Rubin SC, Hoskins WJ, Saigo PE, Pierce VK, Lewis JLJR. Treatment of uterine leiomyosarcoma. Obstet Gynecol. 1988;71:845–50.
15. Koontz JI, et al. Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. PNAS. 2001;98:6348–53.
16. Micci F. Consistent rearrangement of chromosomal band 6p21 with generation of fusion genese JAZF1/PHF1 and EPC/PHF1 in endometrial stromal sarcoma. Cancer Res. 2006;66:107–12.
17. Chiang S, et al. Frequency of known gene rearrangements in endometrial stromal tumors. Am J Surg Pathol. 2011;35(9):1364–72.
18. Signorelli M, et al. Lymphadenectomy in uterine low-grade endometrial stromal sarcoma: an analysis of 19 cases and a literature review. Int J of Gynecol. Cancer. 2010;20(8):1363–6.
19. Barney B, et al. Does radiotherapy or lymphadenectomy improve survival in endometrial stromal sarcoma? Int J Gynecol Cancer. 2009;19(7):1232–8.
20. Yoon A, et al. Prognostic factors and outcomes in endometrial stromal sarcoma with the 2009 FIGO staging system: a multicenter review of 114 cases. Gynecol Oncol. 2014;132:70–5.
21. Feng W, et al. Stage I to II WHO-2003 defined low-grade endometrial stromal sarcoma: how much primary therapy is needed and how little is enough? Int J Gynecol Cancer. 2013;23(3):488–93.
22. Shah JP, et al. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. Obstet Gynecol. 2008;112:1102–8.
23. Chan JK, et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer. 2008;99:1210–5.
24. Arend R, et al. Long-term outcome and natural history of uterine adenosarcomas. Gynecol Oncol. 2010;119:305–8.
25. Bernard B e. Uterine adenosarcomas: a dual-institution update on staging, prognosis and survival. Gynecol Oncol. 2013;131:634–9.
26. Tanner EJ, et al. Management of uterine adenosarcomas with and without sarcomatous overgrowth. Gynecol Oncol. 2013;129:140–4.
27. Piscuoglio S, et al. Uterine adenosarcomas are mesenchymal neoplasms. J Pathol. 2016;238:381–8.
28. Soslow R, et al. Mullerian adenosarcomas: an immunophenotypic analysis of 35 cases. Am J Surg Pathol. 2008;32(7):1013–21.
29. Michener C, Simon NL. Ovarian conservation in a woman of reproductive age with mullerian adenosarcoma. Gynecol Oncol. 2001;83:424–7.
30. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993;71:1702–9.
31. Ferrer F, Sabater S, Farrus B, et al. Impact of radiotherapy on local control and survival in uterine sarcomas: a retrospective study from the Group Oncologic Catala-Occita. Int J Radiat Oncol Biol Phys. 1999;44:47–52.
32. Sampath S, et al. The role of adjuvant radiation in uterine sarcomas. Int J Radiat Oncol Biol Phys. 2010;76(3):728–34.

33. Magnuson WJ, et al. Impact of adjuvant pelvic radiotherapy in stage I uterine sarcoma. Anticancer Res. 2015;35(1):365–70.
34. Mahdavi A, et al. Pelvic radiation improves local control after hysterectomy for uterine leiomyosarcoma: A 20 year experience. Int J Gynecol Cancer. 2009;19:1080–4.
35. Reed NS, et al. Phase III randomized study to evaluate the role of adjuvant pelvic in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. 2008;44:808–18.
36. Wright JD, et al. The role of radiation in improving survival for early stage carcinosarcoma and leiomyosarcoma. Am J Obstet Gynecol. 2008;199:536.e1–8.
37. Weitmann HD, Knocke TH, Kucera H, Potter R. Radiation therapy in the treatment of endometrial stromal sarcoma. Int J Radiat Oncol Biol Phys. 2001;49(3):739–48.
38. Ricci S, et al. Does adjuvant chemotherapy improve survival for women with early-stage uterine leiomyosarcoma? Gynecol Oncol. 2013;131:629–33.
39. Mancari R, et al. Adjuvant chemotherapy in stage I – II uterine leiomyosarcoma: a multicentric retrospective study of 140 patients. Gynecol Oncol. 2014;133:531–6.
40. Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. J Clin Oncol. 1985;3:1240–5.
41. Peters WA 3rd, Rivkin SE, Smith MR, Tesh DE. Cisplatin and adriamycin combination chemotherapy for uterine stromal sarcomas and mixed mesodermal tumors. Gynecol Oncol. 1989;34:323–7.
42. Kushner DM, Webster KD, Belinson JL, Rybicki LA, Kennedy AW, Markman M. Safety and efficacy of adjuvant single-agent ifosfamide in uterine sarcoma. Gynecol Oncol. 2000;78:221–7.
43. van Nagell JR Jr, Hanson MB, Donaldson ES, Gallion HH. Adjuvant vincristine, dactinomycin, and cyclophosphamide therapy in stage I uterine sarcomas. A pilot study. Cancer. 1986;57:1451–4.
44. Hannigan EV, Freedman RS, Elder KW, Rutledge FN. Treatment of advanced uterine sarcoma with adriamycin. Gynecol Oncol. 1983;16:101–4.
45. Hannigan EV, Freedman RS, Elder KW, Rutledge FN. Treatment of advanced uterine sarcoma with vincristine, actinomycin D, and cyclophosphamide. Gynecol Oncol. 1983;15:224–9.
46. Pautier P, Rey A, Haie-Meder C, et al. Adjuvant chemotherapy with cisplatin, ifosfamide, and doxorubicin followed by radiotherapy in localized uterine sarcomas: results of a case-control study with radiotherapy alone. Int J Gynecol Cancer. 2004;14:1112–7.
47. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: Results of a Phase II Trial. J Clin Oncol. 2002;20:2824–31.
48. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol. 2008;109(3):329–34.
49. Hensley ML, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). Cancer. 2013;119:1555–61.
50. Chu MC, Mor G, Lim C, Zheng W, Parkash V, Schwartz PE. Low-grade endometrial stromal sarcoma: hormonal aspects. Gynecol Oncol. 2003;90:170–6.
51. Wade K, Quinn MA, Hammond I, Williams K, Cauchi M. Uterine sarcoma: steroid receptors and response to hormonal therapy. Gynecol Oncol. 1990;39:364–7.
52. Thanopoulou E, et al. Hormonal treatments in metastatic endometrial stromal sarcomas: the 10-year experience of the sarcoma unit of Royal Marsden Hospital. Clin Sarcoma Res. 2015;5:8.
53. Mizuno M, et al. Long-term medroxyprogesterone acetate therapy for low-grade endometrial stromal sarcoma. Int J Clin Oncol. 2012;17:348–54.
54. Spano JP, Soria JC, Kambouchner M, et al. Long-term survival of patients given hormonal therapy for metastatic endometrial stromal sarcoma. Med Oncol. 2003;20:87–93.
55. Maluf FC, Sabbatini P, Schwartz L, Xia J, Aghajanian C. Endometrial stromal sarcoma: objective response to letrozole. Gynecol Oncol. 2001;82:384–8.
56. Leunen M, Breugelmans M, De Sutter P, et al. Low-grade endometrial stromal sarcoma treated with the aromatase inhibitor letrozole. Gynecol Oncol. 2004;95:769.
57. Mesia AF, Demopoulos RI. Effects of leuprolide acetate on low-grade endometrial stromal sarcoma. Am J Obstet Gynecol. 2000;182:1140–1.
58. Burt BM, et al. Repeated and aggressive pulmonary resections for leiomyosarcoma metastases extends survival. Ann Thorac Surg. 2011;92:1202–7.
59. Clavero JM. Gynecologic cancers: factors affecting survival after pulmonary metastasectomy. Ann Thorac Surg. 2006;81:2004–7.
60. Giuntoli R, et al. Secondary cytoreduction in the management of recurrent uterine leiomyosarcoma. Gynecol Oncol. 2007;106:82–8.
61. Leitao MM, et al. Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. Gynecol Oncol. 2002;87:287–94.
62. Leitao MM, et al. Surgical cytoreduction in patients with metastatic uterine leiomyosarcoma at the time of initial diagnosis. Gynecol Oncol. 2012;125:409–13.

63. Spanos W, Guse C, Perez C, Grisby P, Doggett RL, Poulter C. Phase II study of multiple daily fractionations in the palliation of advanced pelvic malignancies: preliminary report of RTOG 8502. Int J Radiat Oncol Biol Phys. 1989;17:659–61.
64. Spanos WJ, et al. Late effect of multiple daily fraction palliation schedule for advanced pelvic malignancies (RTOG 8502). Int J Radiat Oncol Biol Phys. 1994;29(5):961–7.
65. Omura GA, Major FJ, Blessing JA, et al. A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer. 1983;52:626–32.
66. Muss HB, Bundy B, DiSaia PJ, et al. Treatment of recurrent or advanced uterine sarcoma. A randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a Phase III trial of the Gynecologic Oncology Group). Cancer. 1985;55:1648–53.
67. Loehrer PJ, Sledge GW, Nicaise C, et al. Ifosfamide plus doxorubicin in metastatic adult sarcomas: a multi-institutional phase II trial. J Clin Oncol. 1989;7:1655–9.
68. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol. 1993;11:1276–85.
69. Currie J, Blessing JA, Muss HB, Fowler J, Berman M, Burke TW. Combination chemotherapy with hydroxyurea, dacarbazine (DTIC), and etoposide in the treatment of uterine leiomyosarcoma: a Gynecologic Oncology Group study. Gynecol Oncol. 1996;61:27–30.
70. Piver MS, DeEulis TG, Lele SB, Barlow JJ. Cyclophosphamide, vincristine, adriamycin and dimethyl-triazeno imidazole carboxamide (CYVADIC) for sarcomas of the female genital track. Gynecol Oncol. 1982;14:319–23.
71. Pautier P, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS- 02): a non-randomised, multicenter, phase 2 trial. Lancet Oncol. 2015;16:457–64.
72. Hensley ML, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first line treatment for metastatic uterine leiomyosarcoma: An NRG Oncology/Gynecologic Oncology Group study. J Clin Oncol. 33:1180–5.
73. Pautier P et al. Randomized multicenter and stratified phase II study of Gemcitabine alone vs gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a federation nationale de Centres de Lutte Contre Le Cancer (FNCLCC) French Sarcoma Group (TAXOGEM) study.
74. Hadoux J, et al. Multimodal treatment with doxorubicin, cisplatin and ifosfamide for the treatment of advanced or metastatic uterine leiomyosarcoma: a unicentric experience. Int J Gynecol Cancer. 2015;25(2):296–302.
75. Sutton G, Blessing J, Hanjani P, Kramer P, Gynecologic Oncology Group. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol. 2005;96:749–52.
76. Sutton GP, Blessing JA, Barrett RJ, McGehee R. Phase II trial of ifosfamide and mesna in leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Am J Obstet Gynecol. 1992;166:556–9.
77. Look KY, Sandler A, Blessing JA, et al. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) study. Gynecol Oncol. 2004;92:644–7.
78. Garcia-Carbonero R, Supko JG, Manola J, et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol. 2004;22:1480–90.
79. Delaloge S, Yovine A, Taamma A, et al. Ecteinascidin-743: a marine-derived compound in advanced, pretreated sarcoma patients--preliminary evidence of activity. J Clin Oncol. 2001;19:1248–55.
80. Thigpen T, Blessing JA, Beecham J, Homesley H, Yordan E. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent uterine sarcomas: a Gynecologic Oncology Group study. J Clin Oncol. 1991;9:1962–6.
81. McMeekin DS, et al. A phase II trial of thalidomide in patients with refractory leiomyosarcoma of the uterus and correlation with biomarkers of angiogenesis: a gynecologic oncology group study. Gyn Oncology. 2007;106(3):596–603.
82. Duska LR, et al. A phase II evaluation of ixabepilone in the treatment of recurrent or persistent leiomyosarcoma of the uterus: an NRG Oncology/Gynecologic Oncology Group Study. Gyn Oncology. 2014;135:44–8.
83. Hensley ML, et al. Sunitinib malate in the treatment of recurrent or persistent uterine leiomyosarcoma: A Gynecologic Oncology Group phase II study. Gyn Oncology. 2009;115:460–5.
84. Gremel G, et al. A prognosis based classification of undifferentiated uterine sarcomas: identification of mitotic index, hormone receptors and YWHAE-FAM22 translocation status as predictors of survival. Int J Cancer. 2015;136(7):1608–18.
85. Lee CH, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: a histologically high grade and clinically aggressive tumor. Am J Surg Pathol. 2012;36(5):641–53.
86. Lee CH, et al. Cyclin D1 as a diagnostic immunomarker for endometrial stromal sarcoma

with YWHAE-FAM22 rearrangement. Am J Surg Pathol. 2012;36(10):1562–70.
87. Malouf GG, et al. Prognostic factors and outcome of undifferentiated endometrial sarcoma treated by multimodal therapy. Int J Gynecol Obset. 2013;122 (1):57–61.
88. Tanner EJ, et al. High grade undifferentiated uterine sarcoma: surgery, treatment, and survival outcomes. Gynecol Oncol. 2012;127:27–31.
89. Sutton G, Blessing JA, Park R, DiSaia PJ, Rosenshein N. Ifosfamide treatment of recurrent or metastatic endometrial stromal sarcomas previously unexposed to chemotherapy: a study of the Gynecologic Oncology Group. Obstet Gynecol. 1996;87:747–50.
90. Lin YC, Kudelka AP, Tresukosol D, et al. Prolonged stabilization of progressive endometrial stromal sarcoma with prolonged oral etoposide therapy. Gyencol Oncol. 1995;58:262–5.
91. Takano T, et al. Feasibility study of gemcitabine plus docetaxel in advanced or recurrent uterine leiomyosarcoma in undifferentiated endometrial sarcoma in Japan. Int J Clin Oncol. 2014;19:897–905.
92. Kalender ME, et al. Detection of complete response to imatinib mesylate (Glivec/Gleevec) with 18F-FDG PET/CT for low grade endometrial stromal sarcoma. Cancer Chemother Parmacol. 2009;63 (3):555–9.
93. Amant F, et al. Gynecologic Cancer InterGroup consensus review for endometrial stromal sarcoma. Int J Gynecol Cancer. 2014;24(9):S67–72.
94. Rauh-Hain JA, et al. Endometrial stromal sarcoma: a systematic review. Obstet Gynecol. 2013;122:676–83.
95. Tanz R, et al. Endometrial stromal sarcoma: prognostic factors and impact of adjuvant therapy in early stages. Hematol Oncol Stem Cell Ther. 2012;5 (1):31–5.
96. Leitao MM, Soslow RA, Nonaka D, et al. Tissue microarray immunohistochemical expression of estrogen, progesterone, and androgen receptors in uterine leiomyomata and leiomyosarcoma. Cancer. 2004;101:1455–62.
97. O'Cearbhaill R, et al. Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors. Gynecol Oncol. 2010;116:424–9.
98. George et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. Cancer. 2014;120:738–43.
99. Mackay HJ, Buckanovich RJ, Hirte H, et al. A phase II study of single agent aflibercept (VEGF trap) in metastatic gynecologic carcinosarcomas and uterine leiomyosarcomas: a trial of the Princess Margaret Hospital, Chicago and Californai Cancer Consortia. Gynecol Oncol. 2012;125:136–40.
100. Cheng X, et al. Recurrence patterns and prognosis of endometrial stromal sarcoma and the potential of tyrosine kinase-inhibiting therapy. Gynecol Oncol. 2011;121:323–7.

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Future Directions and New Targets in Endometrial Cancer

Jonathan D. Black, Dana M. Roque, Leslie I. Gold, and Alessandro D. Santin

Abstract

Recent advances in next generation sequencing (NRG) have provided compelling evidence that endometrial cancers result from heterogeneous somatic mutations. These findings argue that a catalog of molecular aberrations that cause endometrial cancer is critical for the proper classification of these tumors and for developing novel and more effective targeted therapies against this disease. This chapter summarizes the recent advances made toward the elucidation of underlying pathway aberrations and the development of targeted therapies that exploit the unique molecular characteristics of endometrial cancers.

Keywords

Endometrial cancer • Uterine serous carcinoma • Targeted therapy • Immunotherapy • Novel therapies

Introduction

Endometrial cancers have historically been designated as Type I or Type II [1]. Type I endometrial cancer account for 65–70 % of cases and is associated with grade 1–2 endometrioid histology, younger age of onset, retention of estrogen receptor (ER), and progesterone receptor (PR) status, a history of unopposed estrogen, and deletions in k-Ras, PTEN, or mismatch repair mechanisms [2–4]. In contrast, Type II endometrial cancer is associated with serous, clear cell or grade 3 endometrioid histology, loss of ER/PR, black race, absence of unopposed estrogen, presentation at later stage, reduced

J.D. Black and A.D. Santin (✉)
Division of Gynecologic Oncology, Yale University, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA
e-mail: alessandro.santin@yale.edu

D.M. Roque
Department of Obstetrics, University of Maryland School of Medicine, Baltimore, MD 21201, USA

L.I. Gold
Gynecology & Reproductive Sciences, New York University School of Medicine, New York, NY 10016, USA

E-cadherin expression, aneuploidy, mutations in p53, and HER2/Neu overexpression [5–9]. Type II endometrial cancer is typically more aggressive than type I cancer and has a poorer prognosis.

Recently, using an integrated genomic, epigenomic, transcriptomic, and proteomic approach, The Cancer Genome Atlas (TCGA) Research Network provided compelling evidence that endometrial cancers result from heterogeneous somatic mutations and, accordingly, classified endometrial cancers into four categories: (1) polymerase epsilon (POLε)-ultramutated, (2) microsatellite instability hypermutated, (3) copy-number low, and (4) copy-number high, serous-like [10]. The genetic aberrations of endometrial carcinomas may therefore represent a better tool to classify these tumors and guide adjuvant treatment for women harboring biologically aggressive disease. In this chapter, we discuss some of the new molecular pathways/targets identified in endometrial cancer and the state-of-the-art of both preclinical and clinical achievements in molecular-targeted therapy.

Molecular Pathways and Targets

Mismatch Repair Genes and POLε Mutations

Microsatellite instability (MSI), or alterations in the length of short repetitive deoxyribonucleic acid (DNA) sequences, is a result of the lack of intact DNA mismatch repair (MMR), which is an essential system for correcting DNA sequence errors during replication. The DNA MMR system may become disabled through intragenic mutations or promoter hypermethylation of one of the DNA MMR genes (e.g., *MLH1*, *MSH2*, *MSH6*, *PMS2*). POLε and polymerase δ (POLD) constitute the two nuclear DNA polymerases present in eukaryotic cells endowed with intrinsic proofreading activity [11, 12]. These polymerases are responsible for the bulk of chromosomal DNA synthesis during cell division, and multiple studies in yeast and mammalian cells have shown that polymerase proofreading and postreplication mismatch repair represent the primary guardians of DNA replication fidelity [11, 12]. In addition, loss of function in one or both of these genes dramatically increases the number of spontaneous mutations [11, 12]. Recent TCGA Research Network data demonstrated that 40 % of endometrial endometrioid tumors (i.e., Type I) and 2 % of the high-copy number serous-like tumors (i.e., Type II) are MSI hypermutated while about 10 % of endometrial cancers harbor POLε driver mutations [10]. In this study, MSI endometrial cancers were characterized by endometrioid histology, a lower MLH1 mRNA expression, and high frequency of somatic mutations (i.e., approximately tenfold greater than microsatellite stable (MSS) endometrial tumors) [10]. In contrast, POLε mutations were common in both type I and type II endometrial cancers [10, 12–14] and conferred an ultramutator phenotype that allowed incipient cancer cells to accumulate additional cancer-promoting mutations (i.e., the number of somatic mutations in POLε-mutated tumors exceed by far those found in MSI-mutated patients) [10]. Importantly, MSI hypermutated and POLε ultramutated endometrial cancer patients experienced a very good prognosis regardless of the fact that a large number of these patients harbored poorly differentiated endometrial tumors [10, 12–14]. It is currently not understood why patients developing MSI hypermutated or POLε ultramutated phenotypes may have such a good outcome; however, it is possible that the large number of somatic mutations present in these tumors may render these cancers highly immunogenic for the host due to the large number of mutated epitopes [15]. Thus, it may be unlikely to spread or metastasize due to their extremely high number of mutations [16]. Importantly, if the former hypothesis proves to be correct, the high mutation burden of these tumors, similar to what was recently demonstrated for melanoma and lung cancer patients, may confer clinical benefit to these patients if/when novel immunotherapeutic approaches based on blocking immune checkpoints antibodies (i.e., anti-CTLA4-ipilimumab, anti-PD1-nivolumab, Bristol

Meyers Squibb, Wallingford, CT) are implemented [17]. Alternatively, if the latter hypothesis is correct, as with breast and ovarian cancer patients harboring homologous recombination defects (i.e., BRCA1/2 mutations), synthetic lethality might be explored to develop targeted therapy effective in MSI and POLε-mutated endometrial cancers [18, 19].

Phosphatase and Tensin Homolog (PTEN) and Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha (*PI3KCA*) and Regulatory Subunit (PI3KR1)

Cancer genetic studies suggest that the *Phosphatase and Tensin Homolog* (*PTEN*) and the *phosphatidylinositol 3-kinase* (*PI3K*) genes are two of the most frequently mutated genes in human tumors. TCGA data showed that up to 93 % of endometrial tumors had mutations in the PTEN/PI3K pathway suggesting the potential for targeted therapy with inhibitors against PI3K, AKT, or mTOR pathways in these tumors [10].

PTEN gene loss of activity is due to mutations in up to 61% [20–22] and due to a loss of heterozygosity in 40 % of cases [23]. PTEN protein acts as a lipid and protein phosphatase, and functions and behaves similar to a tumor suppressor gene. The lipid phosphatase activity of PTEN causes cell cycle arrest at the G1/S checkpoint; the protein phosphatase activity of PTEN is involved in the inhibition of adhesion formation, cell migration, and the inhibition of growth factor-stimulated MAPK signaling. PTEN protein also antagonizes the phosphatidylinositol 3-kinase (PI3K/AKT/mTOR) pathway by dephosphorylating phosphatidylinositol (3,4,5)-trisphosphate (PIP3). This dephosphorylation results in inhibition of AKT. Thus, loss of PTEN function leads to increased levels of phospho-AKT, activation of anti-apoptotic proteins, and ultimately an increase in cell cycle progression [24]. In atypical hyperplasia, PTEN inactivation occurs in up to 50 % of the cases. PTEN mutations are also found in simple hyperplasia and are partially associated with monoclonality [25]. Therefore, PTEN inactivation and mutations may be identified in endometrioid adenocarcinoma precursor lesions.

The *phosphatidylinositol-3-kinase* (*PI3KCA*) gene encodes for a heterodimeric protein with an 85-kDa regulatory subunit (PI3KR1) and a 110-kDa catalytic subunit (*PI3KCA*) [26, 27]. In endometrial cancers, unlike other human tumors, *PI3KCA* and PI3KR1 mutations are often associated with PTEN mutations. This is common in both type I and type II tumors [28]. PI3K phosphorylates a series of membrane phospholipids, catalyzing the transfer of ATP (adenosine triphosphate)-derived phosphate thereby forming secondary messenger lipids phosphatidylinositol-3,4-bisphosphate and phosphatidylinositol-3,4,5-trisphosphate [25–28]. PI3K plays a central role in cellular proliferation, growth, survival, mobility, and metabolism via activation of the PTEN/AKT pathway. PI3K is activated via the binding of a ligand to its cognate receptor, which attracts a series of kinases to the plasma membrane thereby initiating the downstream AKT/mTOR signaling cascade that regulates cell growth.

The central role of PI3K activation in tumor cell biology has prompted an effort to target PI3K and/or downstream kinases such as AKT and mammalian target of rapamycin (mTOR) in endometrial cancer. As a result, apitolisib (GDC-0980, Genentech, South San Francisco, CA), a potent inhibitor of class I PI3K and mTOR kinase (TORC1/2), has recently been tested in preclinical studies and not-surprisingly, has shown significant activity in vitro and in vivo against endometrial tumors harboring PI3K driver mutations [29]. Furthermore, AZD8055, a novel dual mTORC1/2 inhibitor, showed significant tumor growth inhibition in high HER-2/neu-expressor endometrial cancers in vitro [30] and caused in vivo regression in breast, lung, colon, prostate, and uterine xenograft models [31]. Taselisib, GDC-0032 (Genentech, South San Francisco, CA), a novel, oral, selective inhibitor of PI3K, has been shown to be highly active in vivo in uterine serous carcinoma (USC) mouse xenografts harboring *PI3KCA* mutations and overexpressing HER2/

neu ($p = 0.007$) [32]. Multiple phase I, II, and III clinical trials with inhibitors targeting PI3K, AKT, or mTOR pathways are currently ongoing or have been recently completed [33]. Unfortunately, emerging clinical data show limited single-agent activity of such inhibitors at tolerated doses [34–36]. However, it is important to note that the response rate for patients with heavily pretreated, advanced cancers and *PI3KCA* mutations who were given PI3K/AKT/mTOR axis inhibitors was significantly higher than that for patients without documented *PI3KCA* mutations treated on the same trials [36]. This observation is consistent with data that demonstrate low response rates on traditional phase I and II trials, in which molecular testing is not used, and suggests that selecting *PI3KCA*-mutant patients for treatment with PI3K/AKT/mTOR axis inhibitors may potentially predict response. Taken together, these results imply that screening for *PI3KCA* and PI3KR1 mutations may warrant further investigation in the application of targeted PI3K/AKT/mTOR inhibitors to the clinic in endometrial cancer patients.

Epidermal Growth Factor Receptor (*EGFR*; ErbB-1; HER1)

The ErbB receptor tyrosine kinase family consists of four cell surface receptors: ErbB-1 or epidermal growth factor receptor (*EGFR*) or HER1, ErbB2 or HER2/neu, ErbB-3, and ErbB4. Type I tumors are more likely to exhibit mutations in *EGFR* when compared to Type II tumors (46 % versus 34 %) [37]. *EGFR* is a membrane receptor that lies upstream to the PI3K/AKT/mTOR and Ras-Raf-MEK-ERK pathways. After ligand binding, *EGFR* becomes active as a homodimer. It may also pair with another member of the ErbB receptor family, such as ErbB2/Her2/neu, and become an activated heterodimer. In type II tumors, *EGFR* expression correlates with survival ($p = 0.028$) [38]. Therefore, *EGFR* is a therapeutic target of significant interest.

As reported by Schwab et al., the tyrosine kinase inhibitors (TKI) afatinib (Gilotrif™, Boehringer Ingelheim, Ridgefield, CT) and neratinib (Puma Biotechnology, Los Angeles, CA) both exhibit significant tumor growth inhibition both in vitro and in vivo models of USC harboring overexpression of *EGFR* and HER2/neu [39, 40]. In addition, in vivo models showed improved survival when using both agents independently. Afatinib works by covalently binding to intracellular phosphorylation sites of ErbB1, ErbB2, and ErbB4, as well as inhibiting transphosphorylation of ErbB3. Neratinib is an irreversible inhibitor of ErbB1 and HER2/neu, and prevents activation of the signaling pathways brought about by receptor dimerization.

HER2/neu (ErbB-2)

The HER2 protein has a cysteine-rich extracellular ligand-binding domain, a hydrophobic membrane-spanning region, and an intracellular tyrosine kinase domain. In HER2-amplified cells, there may be up to 100 *C-ErBB2* gene copies per tumor cell [41] compared with two copies present in normal cells. This overamplification results in HER2 overexpression at both the mRNA and protein levels and a resultant phosphorylation of intracellular tyrosine kinase residues [42]. This modulates cell proliferation, differentiation, migration, and survival in addition to upregulating the Ras/Raf/MAPK and PI3K/AKT/mTOR pathways. In many solid tumors, HER2 expression status is now determined using immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) assays in instances of equivocal IHC results, though no standard guidelines exist for HER2 testing in endometrial cancer [43]. HER2 overexpression correlates with prognosis [44]. Thus, given that up to 69 % of all endometrial cancers and up to 80 % of type II endometrial tumors overexpress HER2, it is an important molecular target for therapy.

Trastuzumab (Herceptin®, Genentech, South San Francisco, CA) is an FDA-approved

HER2-targeting antibody that is approved for use as an adjuvant in early-stage, HER2-positive, node-positive breast cancer [45]. There have been multiple encouraging case reports using trastuzumab in USC [46–48], and the effect on progression-free survival in advanced or recurrent USC is currently being evaluated in a multi-institutional phase II trial of trastuzumab combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone [49]. Pertuzumab (Omnitarg®, Genentech, South San Francisco, CA) is a humanized IgG1 monoclonal antibody heterodimerization inhibitor that binds domain II of the ErbB2 receptor. When compared to trastuzumab, pertuzumab inhibits broader downstream signal transduction pathways through abrogation of lateral signal transduction [50–52]. Lapatinib (Tykerb®, GlaxoSmithKlein, Philadelphia, PA), a reversible dual inhibitor of both HER2 and *EGFR*, has shown the ability to restore trastuzumab sensitivity in cells that have previously shown resistance to trastuzumab therapy [53]. As clinical trials move forward, these agents will play a significant role in targeted therapy.

Trastuzumab is also used as a vehicle in the antibody-drug-conjugate trastuzumab emtansine (Kadcyla®, T-DM1, Genentech, South San Francisco, CA). DM1 belongs to the maytansine class of cytotoxic agents. T-DM1 is internalized by HER2 receptor-mediated endocytosis, offering selective effects on HER2-overexpressing cells. After internalization, T-DM1 is degraded by lysosomes, resulting in the release of free intracellular DM1. DM1 is a microtubule assembly inhibitor and its action leads to cell death as a result of G2/M phase cell cycle arrest. [54, 55] T-DM1 also has action similar to trastuzumab alone with regard to reducing signaling in the HER2 pathway and initiation of antibody-dependent cell-mediated cytotoxicity [56–58]. In 2014, English et al. showed significant activity of T-DM1 in vitro and in vivo in USC [59]. T-DM1 was more effective than trastuzumab in inhibiting cell proliferation and causing apoptosis ($p = 0.004$) in USC overexpressing HER2. T-DM1 was highly active at reducing tumor formation in USC xenografts overexpressing HER2 ($p = 0.04$) and mice treated with TDM-1 had significantly longer survival when compared to mice treated with trastuzumab alone and untreated control mice ($p \leq 0.0001$). These are promising results that will undoubtedly be further evaluated in clinical trials.

Vascular Endothelial Growth Factor (VEGF)

When the core of a tumor attains a critical level of hypoxia, neoangiogenesis occurs as an effort to promote tumor growth, progression, and metastasis. Vascular endothelial growth factor (VEGF) enhances vascular permeability, vasodilation, and capillary fenestration and is a prime target for modulation. The VEGF family consists of six members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and PIGF and their respective receptors (VEGFR) [60]. In endometrial cancer, VEGF-A overexpression is a poor prognostic indicator and is associated with advanced grade, lymphovascular space invasion and spread [61, 62], and upregulation of p53 [63].

Bevacizumab (Avastin®, Genentech, South San Francisco, CA) is a recombinant IgG1 monoclonal antibody that neutralizes VEGF and has shown promising results in multiple phase II trials for recurrent endometrial adenocarcinoma. For example, in Gynecologic Oncology Group (GOG) trials 229G and 229E, bevacizumab was used alone [64] and in combination with temsirolimus [65], respectively. As a standalone treatment of 15 mg/kg every 3 weeks in patients with two or three prior lines of chemotherapy, bevacizumab exhibited a 13.5 % response rate [64]. Bevacizumab, 10 mg/kg given biweekly as a combination with temsirolimus 25 mg weekly, showed improved outcomes; 24.5 % of patients exhibited a clinical response and 46.9 % of patients achieved a progression free survival of 6 months or more [65]. A three-arm randomized phase II study of paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, and ixabepilone/carboplatin/bevacizumab as initial therapy for measurable stage III/IV or recurrent endometrial

cancer is ongoing [66]. The results of this study are eagerly awaited by the oncology community.

Other VEGF-related therapies are being developed as well. VEGF Trap (Eylea®, afibercept, Sanofi-Aventis, Paris, France) is a monocolonal IgG fusion protein that serves as a decoy receptor for VEGFR-1 and -2; ramucirumab (Cyramza®, Eli Lilly, Indianapolis, IN) is a mononcolonal antibody that targets VEGFR-2. In a phase II study of 44 women with recurrent or persistent uterine cancer using aflibercept, 6-month progression-free survival was 41 % and overall response rate was 7 % (all partial responses); there were two treatment-related deaths due to gastrointestinal perforation and arterial rupture [67]. While not yet reported in endometrial adenocarcinomas, Cyramza® yielded promising improvements in progression-free survival relative to placebo in the phase III REGARD trial in patients with locally advanced or metastatic gastric or GE junction adenocarcinoma who had progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy [68]. Powell et al. recently reported a response rate of 18.6 % in patients with recurrent or persistent endometrial carcinoma who received brivaniv, an oral dual anti-VEGF and weak anti-fibroblast growth factor receptor (FGFR) agent [69].

FBXW7/Cyclin E/PPP2RA1

In uterine serous carcinoma, whole-exome and Sanger sequencing have revealed mutations in *FBXW7* (19 %) and *PPP2R1A* (18 %) in both carcinomas and matched precursor endometrial intraepithelial carcinoma [70]. FBXW7 is an F-box protein that is critical in the ubiquitination of the tumor-promoting proteins cyclin E and PPP2R1A [71–73]. *CCNE1* encodes cyclin E1, the upregulation of which promotes cell cycle progression through the G1 phase via interactions with CDK-1 [71]. PPP2R1A is a regulatory unit of serine/threonine protein phosphatase 2, which regulates growth. In USC, mutations in *PPP2R1A* have been reported in up to 32 % of tumors and somatic amplifications of *CCNE1* were identified in up to 44 % [74–76]. Cyclin-dependent kinase inhibitors may have a role for use in USC. In addition, curcumin has been proposed as a regulator of the proteasome and cyclin family of cell cycle proteins [77], yielding yet another potential therapeutic intervention.

Skp2 E3 Ligase Inhibitors

The F-box protein, Skp2, a component of the SCF-Skp2/Cks1 E3 ligase complex, has specificity for the tumor suppressor and cyclin-dependent kinase inhibitor, $p27^{kip1}$ (p27) causing its ubiquitylation and subsequent degradation by the 26S proteasome [78, 79]. Normally, the levels of p27 increase in the nucleus and bind to and inactivate CyclinE/Cdk2 maintaining the retinoblastoma protein (pRb) in a hypophosphorylated state for cell cycle arrest [80]. Accordingly, p27 nuclear expression is low in proliferative phase endometrium and high in the secretory phase [81–84]. In endometrial cancer and other cancers, there is a statistically significant decrease in p27 with a concomitant increase in Skp2 [85–88]. This loss of p27 is caused by its perpetual degradation in the nucleus due to high Skp2/Cks1 E3 ligase activity ultimately leading to uncontrolled proliferation [89]. Knocking down Skp2 in endometrial cancer cell lines completely obviates estrogen-induced degradation of p27 and growth stimulation. Moreover, estrogen causes MAPK-dependent phosphorylation of p27 on threonine 187, which is essential for its identification and ubiquitylation by SCF-Skp2/Cks1 [89]. These results purport a pathogenic mechanism for estrogen-induced type I endometrial cancer, representing 85 % of uterine cancers and thus, blocking nuclear p27 degradation by Skp2/Cks1 is a rational molecular target for this cancer [90, 91].

Whereas unopposed estrogen increases the risk for developing endometrial hyperplasia, the precursor to type I endometrial cancer [91], ostensibly due to degradation of p27, progesterone treatment increases the level of nuclear p27

with concomitant inhibition of proliferation in primary endometrial cancer cells [84, 89]. Progesterone therapy (Megace®) for hyperplasia and cancer is associated with an increase in nuclear p27 [92, 93], thereby underscoring the significance of p27 as a molecular target forendometrial growth. Of note, the PTEN tumor suppressor and p27, which both negatively control cell cycle progression, malfunction as an early event in endometrial cancer oncogenesis [94], and it has been shown that Skp2 functions in the regulation of p27 and cell proliferation by the PTEN/PI3K pathway [95]. Rather than regulation of cell proliferation by transcription and translation [89], the studies point to the Ubiquitin Proteasome System as the essential regulator of normal and malignant endometrial epithelial cell growth supporting the use of proteasome inhibitors as a rational therapeutic approach for endometrial cancer and others with loss of p27 due to high Skp2/Cks1 E3 ligase activity.

The first general proteasome inhibitor for cancer therapy, bortezomib (Velcade, PS-431) was approved for multiple myeloma [96], but is marginally effective and failed for other cancers because they ostensibly blocked the degradation of both oncogenes and tumor suppressors [97]. Aided by X-ray crystallographic studies, Skp2 and Cks1 of the SCF complex form a structural druggable pocket where p27 is ubiquitylate [98–100]. Computational ligand docking of the structure of the interface between Skp2/Cks1 and p27, and a virtual ligand screen (VLS) was used to identify small molecule inhibitors that specifically block degradation of p27 phosphorylated on Threonine 187 [100]. Unlike other SCF-Skp2 complexes that target a variety of proteins for degradation, importantly, the pocket formed by Skp2/Cks1 has substrate specificity for ubiquitylating only the cyclin-dependent kinase inhibitors p27 and p21 [99]. Another means for disabling p27 from arresting cell growth is its sequestration in the cytoplasm in some cancers including endometrial cancer [87, 101, 102]. Cytoplasmic mislocalization occurs when p27 is phosphorylated on threonine 157 by Akt kinase activity. This aligns with the loss of PTEN phosphatase function in blocking PI3K/Akt in endometrial cancers [91]. In the cytoplasm, p27 not only loses its nuclear antiproliferative effect but assumes an oncogenic phenotype mediating migration/metastasis [101, 102]. Fortuitously, certain Skp2 inhibitors increase nuclear p27 while decreasing cytoplasmic p27 in endometrial carcinoma patient primary cells [103]. Thus, these inhibitors might have dual therapeutic advantages as both cytostatic as well as anti-metastatic agents.

In vitro, the novel small molecule inhibitors of Skp2/Cks1 E3 ligase activity, named Skp2E3LIs, block phosphorylation of pRb, the downstream molecular target for cell cycle arrest in G1 and stabilize nuclear p27 by markedly increasing its half-life [103]. Skp2E3LIs blocked both estrogen stimulation of proliferation and degradation of nuclear p27 to the same extent as blocking estrogen receptor activation with ICI 182,780. In vivo, Skp2E3LIs injected into estrogen-primed mice, obviated estrogen-induced hyperplasia, increased nuclear p27, and decreased the number of mitotic endometrial epithelial cells by 62 % [103]. These studies provide functional proof of principle that Skp2E3LIs act in the nucleus to prevent estrogen-induced degradation of p27 thereby regaining growth control by directly blocking Skp2/Cks1 ubiquitylation. The activity in mice suggests that the Skp2E3LIs might have utility in the treatment of complex atypical endometrial hyperplasia to prevent the development of endometrial carcinoma. Human endometrial cancer xenograft studies in immunocompromised mice using genetically defined patient cells with respect to PTEN, Akt, *PI3KCA*, Her2 amplification/mutations, are underway with the current Skp2E3LIs. Together with screening for Skp2 levels, these studies should aid in tailoring patient-specific Skp2E3LI therapy while these compounds are clinically developed.

The apparent critical importance and enthusiasm for developing specific inhibitors of Skp2 E3ligase activity to advance the field by supplanting the current non-specific anti-proteasome therapy has been shared by others [104, 105]. In one study, a Skp2 inhibitor discovered through a high throughput in silico screen was shown to suppress human prostate and lung

cancer xenograft growth in immunocompromised mice [106]. The Skp2E3LIs are distinguished from other Skp2 inhibitors as they stabilize p27 in the nucleus to prevent cell cycle progression by pharmacologically targeting the binding interaction between the E3 ligase, SCF-Skp2/Cks1, and p27 [106]. As an advantage for endometrial carcinoma prevention and therapy, Skp2E3LIs target the etiologic agent for this cancer by stabilizing p27 in the presence of estrogen. Moreover, Sp2E3LIs subvert the need for progesterone receptors, lacking in higher grade cancers that cannot respond to progestin therapy.

Claudins

Claudins are membrane proteins that are involved in the formation of tight junctions, which block the diffusion of protein and lipids through the plasma membrane [68, 69], and which are associated with epithelial breakdown. They also assist in recruiting cell-signaling proteins, regulate cell proliferation, cell differentiation, and neoplastic transformation [107]. One of the extracellular loops of the claudins acts a binding site for *Clostridium perfringens* toxin (CPE) [108]. Claudin-3 is a low-affinity receptor for CPE, and claudin-4 is a high-affinity receptor for CPE. Claudin-3 and -4 have been found to be among the highest differentially expressed genes in USC [109], in addition to a variety of other cancers [110, 111]. Claudin-3 and -4 may represent markers for biological aggressiveness; in one study of 20 USC samples, CPE receptors were identified in 100 % of samples and significantly higher levels ($p < 0.05$) in metastatic USC when compared with primary tumor sites. Thus, USC that are recurrent or refractory to standard treatments may be susceptible to CPE-based therapeutic approaches.

Tubulin

Class III β-tubulin heterodimerizes with α-tubulin to form microtubules critical to cell division. Resistance to paclitaxel has been tied to the upregulation of class III β-tubulin [112], and loss of PTEN appears to confer enhanced tubulin-based metastatic cell reattachment [113]. Paclitaxel binds preferentially to class I β-tubulin [114], and higher class III β-tubulin expression reduces the rate of microtubule assembly, rendering cells less susceptible to paclitaxel [115]. Aggressive histologic subtypes of gynecologic cancer, such as USC, clear cell carcinomas, and other solid tumors, have been associated with high levels of class III β-tubulin [116–118].

Epothilones are microtubule-stabilizing macrolides isolated from the bacteria *Sorangium cellulosum* [119], which exhibit activity against paclitaxel-resistant malignancies due in part to equal binding affinity for class I and class III β-tubulin [120]. Patupilone (Novartis, Basel, Switzerland) and ixabepilone (Ixempra®/BMS-247550; Bristol-Meyers-Squibb, NY, USA) are notable members. In vitro, patupilone has shown good efficacy in the inhibition of tumor cell growth in uterine cancer cell lines [117, 121, 122]. Ixabepilone has shown activity at the phase II level for advanced or recurrent endometrial adenocarcinomas [123], but not for uterine leiomyosarcomas previously treated with a taxane [124]. Importantly, class III β-tubulin has not yet been shown to be upregulated in leiomyosarcoma. Ixabepilone remains under evaluation as first-line therapy with carboplatin and bevacizumab in stage III/IV primary or recurrent endometrial cancer.

Future Directions

Recent reports on the genetic landscape of somatic single-nucleotide and copy-number mutations in endometrial cancers have greatly contributed to a deeper understanding of the molecular aberrations underlying these tumors and provided opportunities for genome-guided clinical trials. Novel immunotherapy approaches based on immune checkpoint-antibodies in hypermutated and ultramutated tumors and tumor-specific drug delivery; small molecule inhibitors against PI3K, AKT, or mTOR

pathways; anti-angiogenic and novel cytotoxic agents such as the epothilones against MSS and biologically aggressive copy-number high; serous-like endometrial tumors are among the most promising developments for this disease. With growing recognition of the importance of individual tumor biology, in the next few years, we hope that targeted therapies will allow for the genuine practice of personalized molecular medicine in endometrial cancer.

References

1. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15:10–7.
2. Lax SF, Pizer ES, Ronnett BM, Kurman RJ. Comparison of estrogen and progesterone receptor, Ki-67, and p53 immunoreactivity in uterine endometrioid carcinoma and endometrioid carcinoma with squamous, mucinous, secretory, and ciliated cell differentiation. Hum Pathol. 1998;29:924–31.
3. Voss MA, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer—a clinical and pathological evaluation. Gynecol Oncol. 2012;124:15–20.
4. Goff BA, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecol Oncol. 1994;54:264–8.
5. Mutch DG. The more things change the more they stay the same. Gynecol Oncol. 2012;124:3–4.
6. Wilson TO, et al. Evaluation of unfavorable histologic subtypes in endometrial adenocarcinoma. Am J Obstet Gynecol. 1990;162:418–23. discussion 423–6.
7. Emons G, Fleckenstein G, Hinney B, Huschmand A, Heyl W. Hormonal interactions in endometrial cancer. Endocr Relat Cancer. 2000;7:227–42.
8. Hameed K, Morgan DA. Papillary adenocarcinoma of endometrium with psammoma bodies. Histology and fine structure. Cancer. 1972;29:1326–35.
9. Hamilton CA, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94:642–6.
10. Cancer Genome Atlas Research Network, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497:67–73.
11. Albertson TM, et al. DNA polymerase epsilon and delta proofreading suppress discrete mutator and cancer phenotypes in mice. Proc Natl Acad Sci U S A. 2009;106:17101–4.
12. Palles C, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45:713.
13. Meng B, et al. POLE exonuclease domain mutation predicts long progression-free survival in grade 3 endometrioid carcinoma of the endometrium. Gynecol Oncol. 2014;134:15–9.
14. Santin AD, et al. Improved survival of patients with hypermutation in uterine serous carcinoma. Gynecol Oncol Report. 2015;12:3–4.
15. Boussiotis VA. Somatic Mutations and Immunotherapy Outcome with CTLA-4 Blockade in Melanoma. N Engl J Med. 2014. doi:10.1056/NEJMe1413061.
16. Loeb LA. Human cancers express mutator phenotypes: origin, consequences and targeting. Nat Rev Cancer. 2011;11:450–7.
17. Snyder A, et al. Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma. N Engl J Med. 2014. doi:10.1056/NEJMoa1406498.
18. Martin SA, et al. DNA polymerases as potential therapeutic targets for cancers deficient in the DNA mismatch repair proteins MSH2 or MLH1. Cancer Cell. 2010;17:235–48.
19. Hewish M, et al. Cytosine-based nucleoside analogs are selectively lethal to DNA mismatch repair-deficient tumour cells by enhancing levels of intracellular oxidative stress. Br J Cancer. 2013;108:983–92.
20. Risinger JI, Hayes AK, Berchuck A, Barrett JC. PTEN/MMAC1 mutations in endometrial cancers. Cancer Res. 1997;57:4736–8.
21. Tashiro H, et al. Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. Cancer Res. 1997;57:3935–40.
22. Samarnthai N, Hall K, Yeh I-T. Molecular profiling of endometrial malignancies. Obstet Gynecol Int. 2010;2010:162363.
23. Prat J, Gallardo A, Cuatrecasas M, Catasús L. Endometrial carcinoma: pathology and genetics. Pathology. 2007;39:72–87.
24. Mutter GL, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92:924–30.
25. Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, Bilanges B. The emerging mechanisms of isoform-specific PI3K signalling. Nat Rev Mol Cell Biol. 2010;11:329–41.
26. Matias-Guiu X, Prat J. Molecular pathology of endometrial carcinoma. Histopathology. 2013;62:111–23.
27. Oda K, Stokoe D, Taketani Y, McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. Cancer Res. 2005;65:10669–73.
28. Doll A, et al. Novel molecular profiles of endometrial cancer—new light through old windows. J Steroid Biochem Mol Biol. 2008;108:221–9.
29. Pavlidou A, Vlahos NF. Molecular alterations of PI3K/Akt/mTOR pathway: a therapeutic target in

endometrial cancer. ScientificWorldJournal. 2014;2014:709736.
30. English DP, et al. Oncogenic PIK3CA gene mutations and HER2/neu gene amplifications determine the sensitivity of uterine serous carcinoma cell lines to GDC-0980, a selective inhibitor of Class I PI3 kinase and mTOR kinase (TORC1/2). Am J Obstet Gynecol. 2013;209:465.e1–9.
31. English DP, et al. HER2/neu gene amplification determines the sensitivity of uterine serous carcinoma cell lines to AZD8055, a novel dual mTORC1/2 inhibitor. Gynecol Oncol. 2013;131:753–8.
32. Chresta CM, et al. AZD8055 is a potent, selective, and orally bioavailable ATP-competitive mammalian target of rapamycin kinase inhibitor with in vitro and in vivo antitumor activity. Cancer Res. 2010;70:288–98.
33. Lopez S, et al. Taselisib, a selective inhibitor of PIK3CA, is highly effective on PIK3CA-mutated and HER2/neu amplified uterine serous carcinoma in vitro and in vivo. Gynecol Oncol. 2014. doi:10.1016/j.ygyno.2014.08.024.
34. Dancey JE. Therapeutic targets: MTOR and related pathways. Cancer Biol Ther. 2006;5:1065–73.
35. Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K inhibitors: lessons learned from early clinical trials. Nat Rev Clin Oncol. 2013;10:143–53.
36. Janku F, et al. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol. 2012;30:777–82.
37. Llauradó M, et al. Molecular bases of endometrial cancer: new roles for new actors in the diagnosis and the therapy of the disease. Mol Cell Endocrinol. 2012;358:244–55.
38. Konecny GE, et al. HER2 gene amplification and EGFR expression in a large cohort of surgically staged patients with nonendometrioid (type II) endometrial cancer. Br J Cancer. 2009;100:89–95.
39. Schwab CL, et al. Afatinib demonstrates remarkable activity against HER2-amplified uterine serous endometrial cancer in vitro and in vivo. Br J Cancer. 2014;111:1750–6.
40. Schwab CL, et al. Neratinib shows efficacy in the treatment of HER2/neu amplified uterine serous carcinoma in vitro and in vivo. Gynecol Oncol. 2014;135:142–8.
41. Kallioniemi OP, et al. ERBB2 amplification in breast cancer analyzed by fluorescence in situ hybridization. Proc Natl Acad Sci. 1992;89:5321–5.
42. Graus-Porta D, Beerli RR, Daly JM, Hynes NE. ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. EMBO J. 1997;16:1647–55.
43. Buza N, Roque DM, Santin AD. HER2/ neu in endometrial cancer: a promising therapeutic target with diagnostic challenges. Arch Pathol Lab Med. 2014;138:343–50.
44. Black JD, English DP, Roque DM, Santin AD. Targeted therapy in uterine serous carcinoma: an aggressive variant of endometrial cancer. Womens Health. 2014;10:45–57.
45. Piccart-Gebhart MJ, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:1659–72.
46. Jewell E, Secord AA, Brotherton T, Berchuck A. Use of trastuzumab in the treatment of metastatic endometrial cancer. Int J Gynecol Cancer. 2006;16:1370–3.
47. Santin AD, Bellone S, Roman JJ, McKenney JK, Pecorelli S. Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. Int J Gynaecol Obstet. 2008;102:128–31.
48. Villella JA, Cohen S, Smith DH, Hibshoosh H, Hershman D. HER-2/neu overexpression in uterine papillary serous cancers and its possible therapeutic implications. Int J Gynecol Cancer. 2006;16:1897–902.
49. Clinical trials. Evaluation of carboplatin/paclitaxel with and without Trastuzumab (Herceptin) in Uterine serous cancer. http://clinicaltrials.gov/show/NCT01367002
50. Nagumo Y, et al. Trastuzumab and pertuzumab produce changes in morphology and estrogen receptor signaling in ovarian cancer xenografts revealing new treatment strategies. Clin Cancer Res. 2011;17:4451–61. at <http://clincancerres.aacrjournals.org/content/17/13/4451.short>.
51. Bellone M, et al. In vitro activity of pertuzumab in combination with trastuzumab in uterine serous papillary adenocarcinoma. Br J Cancer. 2010;102:134–43. at <http://www.nature.com/bjc/journal/v102/n1/abs/6605448a.html>.
52. Mullen P, Cameron DA, Hasmann M, Smyth JF, Langdon SP. Sensitivity to pertuzumab (2C4) in ovarian cancer models: cross-talk with estrogen receptor signaling. Mol Cancer Ther. 2007;6:93–100.
53. Kim JW, et al. The growth inhibitory effect of lapatinib, a dual inhibitor of EGFR and HER2 tyrosine kinase, in gastric cancer cell lines. Cancer Lett. 2008;272:296–306.
54. Lewis Phillips GD, et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res. 2008;68:9280–90.
55. Remillard S, Rebhun LI, Howie GA, Kupchan SM. Antimitotic activity of the potent tumor inhibitor maytansine. Science. 1975;189:1002–5.
56. Junttila TT, Li G, Parsons K, Phillips GL, Sliwkowski MX. Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib

insensitive breast cancer. Breast Cancer Res Treat. 2011;128:347–56.
57. Wilken JA, Maihle NJ. Primary trastuzumab resistance: new tricks for an old drug. Ann N Y Acad Sci. 2010;1210:53–65.
58. Boyraz B, et al. Trastuzumab emtansine (T-DM1) for HER2-positive breast cancer. Curr Med Res Opin. 2013;29:405–14.
59. English DP, et al. T-DM1, a novel antibody-drug conjugate, is highly effective against primary HER2 overexpressing uterine serous carcinoma in vitro and in vivo. Cancer Med. 2014;3:1256–65.
60. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9:669–76.
61. Kamat AA, et al. Clinical and biological significance of vascular endothelial growth factor in endometrial cancer. Clin Cancer Res. 2007;13:7487–95.
62. Hirai M, et al. Expression of vascular endothelial growth factors (VEGF-A/VEGF-1 and VEGF-C/VEGF-2) in postmenopausal uterine endometrial carcinoma. Gynecol Oncol. 2001;80:181–8.
63. Mazurek A, et al. Evaluation of angiogenesis, p-53 tissue protein expression and serum VEGF in patients with endometrial cancer. Neoplasma. 2004;51:193–7.
64. Aghajanian C, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011;29:2259–65.
65. Alvarez EA, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2013;129:22–7.
66. Paclitaxel, carboplatin, and bevacizumab or paclitaxel, carboplatin, and temsirolimus or ixabepilone, carboplatin, and bevacizumab in treating patients with stage III, stage IV, or recurrent endometrial cancer—full text view—ClinicalTrials.gov. https://clinicaltrials.gov/show/NCT00977574
67. Coleman RL, et al. Corrigendum to "A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study" [Gynecol Oncol 127 (2012) 538–543]. Gynecol Oncol. 2013;130.
68. Fuchs CS, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383:31–9.
69. Powell MA, et al. A phase II trial of brivanib in recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. Gynecologic. 2014;135:38–43. at <http://www.sciencedirect.com/science/article/pii/S0090825814011585>.
70. Kuhn E, et al. Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses. J Natl Cancer Inst. 2012;104:1503–13.
71. Welcker M, Clurman BE. FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer. 2008;8:83–93.
72. Mao J-H, et al. FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression. Science. 2008;321:1499–502.
73. Cassia R, et al. Cyclin E gene (CCNE) amplification and hCDC4 mutations in endometrial carcinoma. J Pathol. 2003;201:589–95.
74. Shih I-M, et al. Somatic mutations of PPP2R1A in ovarian and uterine carcinomas. Am J Pathol. 2011;178:1442–7.
75. Nagendra DC, Burke 3rd J, Maxwell GL, Risinger JI. PPP2R1A mutations are common in the serous type of endometrial cancer. Mol Carcinog. 2012;51:826–31.
76. Zhao S, et al. Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. Proc Natl Acad Sci U S A. 2013;110:2916–21.
77. Lin CL, Lin JK. Curcumin: a potential cancer chemopreventive agent through suppressing NF-κB signaling. J Cancer Mol. 2008;4:11–6. at <http://mupnet.com/JOCM%204(1)%2011-16.pdf>.
78. Bloom J, Pagano M. Deregulated degradation of the cdk inhibitor p27 and malignant transformation. Semin Cancer Biol. 2003;13.
79. Pagano M, et al. Role of the ubiquitin-proteasome pathway in regulating abundance of the cyclin-dependent kinase inhibitor p27. Science. 1995;269.
80. Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev. 1999;13.
81. Lahav-Baratz S. Decreased level of the cell cycle regulator p27 and increased level of its ubiquitin ligase Skp2 in endometrial carcinoma but not in normal secretory or in hyperstimulated endometrium. Mol Hum Reprod. 2004;10.
82. Miyamoto T, et al. Inverse correlation between Skp2 and p27Kip1 in normal endometrium and endometrial carcinoma. Gynecol Endocrinol. 2009. doi:10.1080/09513590903215482.
83. Oshita T, Shigemasa K, Nagai N, Ohama K. p27, cyclin E, and CDK2 expression in normal and cancerous endometrium. Int J Oncol. 2002. doi:10.3892/ijo.21.4.737.
84. Lecanda J, et al. Transforming growth factor-beta, estrogen, and progesterone converge on the regulation of p27Kip1 in the normal and malignant endometrium. Cancer Res. 2007;67:1007–18.
85. Chu IM, Hengst L, Slingerland JM. The Cdk inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy. Nat Rev Cancer. 2008;8.
86. Kamata Y, et al. High expression of skp2 correlates with poor prognosis in endometrial endometrioid adenocarcinoma. J Cancer Res Clin Oncol. 2005;131.

87. Wander SA, Zhao D, Slingerland JM. p27: a barometer of signaling deregulation and potential predictor of response to targeted therapies. Clin Cancer Res. 2010;17.
88. Davidovich S, Ben-Izhak O, Shapira M, Futerman B, Hershko DD. Over-expression of Skp2 is associated with resistance to preoperative doxorubicin-based chemotherapy in primary breast cancer. Breast Cancer Res. 2008;10.
89. Huang KT, Pavlides SC, Lecanda J, Blank SV, Mittal KR, Gold LI. Estrogen and progesterone regulate p27kip1 levels via the ubiquitin-proteasome system: pathogenic and therapeutic implications for endometrial cancer. PLoS One. 2012;7.
90. Di Cristofano A, Ellenson LH. Endometrial carcinoma. Annu Rev Pathol Mech Dis. 2007;445:53–7. at <http://www.annualreviews.org/doi/abs/10.1146/annurev.pathol.2.010506.091905>.
91. Ellenson LH, Wu T-C. Focus on endometrial and cervical cancer. Cancer Cell. 2004;5.
92. Shiozawa T, et al. Up-regulation of p27Kip1 by progestins is involved in the growth suppression of the normal and malignant human endometrial glandular cells. Endocrinology. 2001;142:4182–8.
93. Watanabe J, et al. Significance of p27 as a predicting marker for medroxyprogesterone acetate therapy against endometrial endometrioid adenocarcinoma. Int J Gynecol Cancer. 2006;16 Suppl 1:452–7.
94. An H-J, et al. Alteration of PTEN expression in endometrial carcinoma is associated with down-regulation of cyclin-dependent kinase inhibitor, p27. Histopathology. 2002;41:437–45.
95. Mamillapalli R, et al. PTEN regulates the ubiquitin-dependent degradation of the CDK inhibitor p27 (KIP1) through the ubiquitin E3 ligase SCF(SKP2). Curr Biol. 2001;11:263–7.
96. Mitsiades CS, Mitsiades N, Hideshima T, Richardson PG, Anderson KC. Proteasome inhibitors as therapeutics. Essays Biochem. 2005;41:205–18.
97. Kitagawa K, Kotake Y, Kitagawa M. Ubiquitin-mediated control of oncogene and tumor suppressor gene products. Cancer Sci. 2009;100:1374–81.
98. Hao B, et al. Structural basis of the Cks1-dependent recognition of p27(Kip1) by the SCF(Skp2) ubiquitin ligase. Mol Cell. 2005;20:9–19.
99. Cardozo T, Pagano M. Wrenches in the works: drug discovery targeting the SCF ubiquitin ligase and APC/C complexes. BMC Biochem. 2007;8 Suppl 1:S9.
100. Wu L, et al. Specific small molecule inhibitors of Skp2-mediated p27 degradation. Chem Biol. 2012;19:1515–24.
101. Denicourt C, Saenz CC, Datnow B, Cui X-S, Dowdy SF. Relocalized p27Kip1 tumor suppressor functions as a cytoplasmic metastatic oncogene in melanoma. Cancer Res. 2007;67:9238–43.
102. Larrea MD, Wander SA, Slingerland JM. p27 as Jekyll and Hyde: regulation of cell cycle and cell motility. Cell Cycle. 2009;8:3455–61.
103. Pavlides SC, et al. Inhibitors of SCF-Skp2/Cks1 E3 ligase block estrogen-induced growth stimulation and degradation of nuclear p27kip1: therapeutic potential for endometrial cancer. Endocrinology. 2013;154:4030–45.
104. Ungermannova D, et al. High-throughput screening AlphaScreen assay for identification of small-molecule inhibitors of ubiquitin E3 ligase SCFSkp2-Cks1. J Biomol Screen. 2013;18:910–20.
105. Rico-Bautista E, Wolf DA. Skipping cancer: small molecule inhibitors of SKP2-mediated p27 degradation. Chem Biol. 2012;19:1497–8.
106. Chan C-H, et al. Pharmacological inactivation of Skp2 SCF ubiquitin ligase restricts cancer stem cell traits and cancer progression. Cell. 2013;154:556–68.
107. Swift JG, Mukherjee TM, Rowland R. Intercellular junctions in hepatocellular carcinoma. J Submicrosc Cytol. 1983;15:799–810.
108. Morita K, Furuse M, Fujimoto K, Tsukita S. Claudin multigene family encoding four-transmembrane domain protein components of tight junction strands. Proc Natl Acad Sci U S A. 1999;96:511–6.
109. Santin AD, et al. Overexpression of claudin-3 and claudin-4 receptors in uterine serous papillary carcinoma: novel targets for a type-specific therapy using Clostridium perfringens enterotoxin (CPE). Cancer. 2007;109:1312–22.
110. Morin PJ. Claudin proteins in human cancer: promising new targets for diagnosis and therapy. Cancer Res. 2005;65:9603–6.
111. Hewitt KJ, Agarwal R, Morin PJ. The claudin gene family: expression in normal and neoplastic tissues. BMC Cancer. 2006;6:186.
112. Kavallaris M, et al. Taxol-resistant epithelial ovarian tumors are associated with altered expression of specific beta-tubulin isotypes. J Clin Invest. 1997;100:1282–93.
113. Vitolo MI, et al. Loss of PTEN induces microtentacles through PI3K-independent activation of cofilin. Oncogene. 2013;32:2200–10.
114. Magnani M, et al. The betaI/betaIII-tubulin isoforms and their complexes with antimitotic agents. Docking and molecular dynamics studies. FEBS J. 2006;273:3301–10.
115. Hari M, Yang H, Zeng C, Canizales M, Cabral F. Expression of class III beta-tubulin reduces microtubule assembly and confers resistance to paclitaxel. Cell Motil Cytoskeleton. 2003;56:45–56.
116. Roque DM, et al. Class III β-tubulin overexpression in ovarian clear cell and serous carcinoma as a maker for poor overall survival after platinum/taxane chemotherapy and sensitivity to patupilone. Am J Obstet Gynecol. 2013;209:62.e1–9.

117. Roque DM, et al. Tubulin-β-III overexpression by uterine serous carcinomas is a marker for poor overall survival after platinum/taxane chemotherapy and sensitivity to epothilones. Cancer. 2013;119: 2582–92.
118. Ferrandina G, et al. Class III beta-tubulin overexpression is a marker of poor clinical outcome in advanced ovarian cancer patients. Clin Cancer Res. 2006;12:2774–9.
119. Bollag DM, et al. Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action. Cancer Res. 1995;55: 2325–33.
120. English DP, Roque DM, Santin AD. Class III b-tubulin overexpression in gynecologic tumors: implications for the choice of microtubule targeted agents? Expert Rev Anticancer Ther. 2013; 13:63–74.
121. Carrara L, et al. Differential in vitro sensitivity to patupilone versus paclitaxel in uterine and ovarian carcinosarcoma cell lines is linked to tubulin-beta-III expression. Gynecol Oncol. 2012;125:231–6.
122. Paik D, et al. Higher sensitivity to patupilone versus paclitaxel chemotherapy in primary uterine serous papillary carcinoma cell lines with high versus low HER-2/neu expression in vitro. Gynecol Oncol. 2010;119:140–5.
123. Dizon DS, et al. Phase II trial of ixabepilone as second-line treatment in advanced endometrial cancer: gynecologic oncology group trial 129-P. J Clin Oncol. 2009;27:3104–8.
124. Duska LR, et al. A phase II evaluation of ixabepilone (IND #59699, NSC #710428) in the treatment of recurrent or persistent leiomyosarcoma of the uterus: an NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2014;135:44–8.

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